Health Quality Ontario

Ontario Health Technology Assessment Series

Intrathecal Drug Delivery Systems for Noncancer Pain: A Health Technology Assessment

KEY MESSAGES

Some patients with chronic pain do not get adequate relief with the usual pain-relieving drugs, and sometimes not even with strong morphine-like drugs. A system that delivers drugs directly to the fluid surrounding the spinal cord (intrathecal space) is a possible treatment for pain that is difficult to control.

Drugs for pain can be given through a pump connected to a small tube implanted in the spine. This is known as an intrathecal drug delivery system. An intrathecal drug delivery system may be less likely to cause tiredness and confusion and can reduce pain; however, we don't know whether intrathecal drug delivery systems actually work better than routine pain drugs in patients with severe persistent pain not caused by cancer. To find out whether intrathecal drug delivery systems are better, we searched, reviewed, and collected evidence.

One study of very low quality compared intrathecal drug delivery systems with oral morphine-type drugs taken alone or as part of a rehabilitation program. Patients had lower pain scores with intrathecal drug delivery systems but did not seem to feel pain less or to be happier with treatment. No studies compared problems with intrathecal drug delivery systems and routine care.

We could not determine whether intrathecal drug delivery systems make sense when resources in a publicly funded health care system are scarce. If intrathecal drug delivery systems were paid for by the Ontario health care system, it would cost $1.5 to $5.0 million per year.

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HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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ABSTRACT

Background

Intrathecal drug delivery systems can be used to manage refractory or persistent chronic nonmalignant (noncancer) pain. We investigated the benefits, harms, cost-effectiveness, and budget impact of these systems compared with current standards of care for adult patients with chronic pain owing to nonmalignant conditions.

Methods

We searched Ovid MEDLINE, Ovid Embase, the Cochrane Library, and the National Health Service's Economic Evaluation Database and Tufts Cost-Effectiveness Analysis Registry from January 1994 to April 2014 for evidence of effectiveness, harms, and cost-effectiveness. We used existing systematic reviews that had employed reliable search and screen methods and also searched for studies published after the search date reported in the latest systematic review to identify studies. Two reviewers screened records and assessed study validity.

Results

We found comparative evidence of effectiveness and harms in one cohort study at high risk of bias (≥ 3-year follow-up, N = 130). Four economic evaluations of low to very low quality were also included.

Compared with oral opioid analgesia alone or a program of analgesia plus rehabilitation, intrathecal drug delivery systems significantly reduced pain (27% additional improvement) and morphine consumption. Despite these reductions, intrathecal drug delivery systems were not superior in patient-reported well-being or quality of life. There is no evidence of superiority of intrathecal drug delivery systems over oral opioids in global pain improvement and global treatment satisfaction. Comparative evidence of harms was not found. Cost-effectiveness evidence is of insufficient quality to assess the appropriateness of funding intrathecal drug delivery systems.

Evidence comparing intrathecal drug delivery systems with standard care was of very low quality.

Conclusions

Current evidence does not establish (or rule out) superiority or cost-effectiveness of intrathecal drug delivery systems for managing chronic refractory nonmalignant pain. The budget impact of funding intrathecal drug delivery systems would be between $1.5 and $5.0 million per year.

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LIST OF ABBREVIATIONS

GRADE	Grading of Recommendations Assessment, Development, and Evaluation
QALY	Quality-adjusted life-year

BACKGROUND

Objective of Analysis

This analysis investigated the benefits, harms, cost-effectiveness, and budget impact of intrathecal drug delivery systems compared with current standards of care for adult patients with chronic pain owing to nonmalignant (noncancer) conditions.

Clinical Need and Target Population

Options available to treat refractory pain include various painkillers—non-opioid analgesic medications, opioid analgesics, neuraxial analgesia—nerve blocks, and surgery. Multidisciplinary rehabilitation programs addressing physical, psychological, and social or occupational factors have also been found to reduce pain and improve function incremental to single-discipline rehabilitation or usual care.[1]

Intrathecal drug delivery provides pain relief by direct infusion of medication into the cerebrospinal fluid. An intrathecal drug delivery system includes the mechanical device and catheter used to both store and infuse analgesic medication into the central nervous system. Intrathecal infusions of analgesics have been used for more than 20 years to treat chronic pain that is refractory to conventional therapies.[2] Implanted programmable pumps have been available in Canada since 1991.[3] An intrathecal drug delivery system is, therefore, one option for treating refractory nonmalignant pain.

Intrathecal drug delivery systems are provided for chronic refractory nonmalignant and malignant pain in Quebec, Saskatchewan, British Columbia, Alberta, Manitoba, Ontario, Nova Scotia, New Brunswick, and Newfoundland (email communication from Kitty Zanata of Medtronic Canada to Dr. Catherine Smyth on January 7, 2015). Intrathecal drug delivery systems have also been recommended for the treatment of refractory pain by the British Pain Society and the 2012 Polyanalgesic Consensus Conference.[4,5]

Most of the existing systematic reviews and expert consensus recommendations have been informed by noncomparative evidence. It is unclear what evidence supports the use of intrathecal drug delivery systems in noncancer pain over continued comprehensive expert pain management in patients with persistent pain or treatment toxicity.

Pain is defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience in association with actual or potential tissue damage, or described in terms of such damage.”[6] Chronic pain is defined as “continuous or recurrent pain lasting longer than 3 months and resulting from either a chronic and ongoing physical condition or continuing beyond the expected healing time of an inciting disorder or cause.”[7] The target population with chronic noncancer pain eligible for intrathecal drug delivery systems includes[4,5]:

- Patients with severe refractory chronic pain
- Patients who have failed to receive adequate relief with physical, psychological, and pharmaceutical trials of therapy (biopsychosocial model)
- Patients with well-defined nociceptive or neuropathic pain conditions
- Patients who have no contraindications to an infusion pump (i.e., an untreated substance dependence, mental health conditions)
- Patients who have had a detailed interdisciplinary assessment, psychological evaluation, and favourable trial of intrathecal therapy before implantation

- Patients who have a relevant multiprofessional infrastructure for continuing care after implantation

Our targeted literature search did not identify global or Ontario-specific incidence or prevalence estimates for refractory noncancer pain or for inadequate pain control owing to emerging drug toxicity.

Technology/Technique

In the implantation of an intrathecal drug delivery system, a small incision is made adjacent to the spine; through this incision, an intrathecal catheter is placed into the cerebrospinal fluid. This procedure is guided using dynamic fluoroscopy, which is essentially an x-ray movie. Several factors affect which spinal level is chosen for the insertion of intrathecal catheters, such as the involvement of disease, a history of past spine surgery, any breakdown or radiation damage in the skin, the availability of magnetic resonance imaging for review, and the conus location. Next, a subcutaneous pocket tunnelled through the patient's abdominal wall connects the intrathecal catheter to the intrathecal drug delivery system. The system can weigh up to 215 g if it is filled with medication; it consists of a pump, a 20 or 40 mL reservoir, and a battery. The battery lasts 4 to 7 years, after which the intrathecal drug delivery system requires replacement.

The intrathecal drug delivery system delivers pain medication continuously. One system also allows patients to self-administer a bolus (single dose) of pain medication to handle severe pain via a personal therapy manager (myPTM, Medtronic of Canada Ltd, Montreal, Quebec) that is linked with the intrathecal drug delivery system. Clinicians program the bolus size, lockout period, and speed of intrathecal bolus injection according to individual patient needs. Several procedure-related harms have been previously reported; we have identified them as a priori harms of investigational interest to this evidence-based analysis.[8]

Regulatory Status

A 2005 evidence review[9] reported four intrathecal drug delivery system devices licensed by Health Canada for intrathecal baclofen infusion (Table 1). Only one of these devices is still available and selling on the Canadian market (Charles ElKhoury, product manager, Codman Neuro, J & J Medical Companies, personal communication, January 7, 2015).

Table 1: Intrathecal Drug Delivery Systems Licensed by Health Canada for Intrathecal Baclofen Infusion

Licence Name	Manufacturer's Name	Available on Canadian Market? (Yes/No)
Synchromed EL System, Synchromed System	Medtronic Inc.	No (Medtronic Canada, email communication, January 7, 2015)
Constant Flow M3000 Series Implantable Infusion Pump	Codman & Shurtleff Inc.	Yes (Johnson & Johnson companies, email communication, January 7, 2015)
Infusaid Constant Flow Implantable Infusion Pump	Codman & Shurtleff Inc.	No (Johnson & Johnson companies, email communication, January 7, 2015)
Archimedes Implantable Infusion Pump	Codman Neuro Sciences Sarl, a Johnson & Johnson Company	No (Johnson & Johnson companies, email communication, January 7, 2015)

Several types of intrathecal drug delivery system have been approved for use by Health Canada. A recent review of a Health Canada database (Mona Chauhan-Sahota, regulatory information officer, Medical Devices Bureau, Therapeutic Products Directorate, Health Canada, personal communication, December 16, 2014) revealed the devices listed in Table 2.

Table 2: Intrathecal Drug Delivery System Devices Approved by Health Canada

Licence Number	Licence Name	Manufacturer's Name	Available on Canadian Market? (Yes/No)
14493	Infusaid Constant Flow Implantable Infusion Pump	Codman & Shurtleff Inc.	No (Johnson & Johnson companies, email communication, January 7, 2015)
16579	Isomed System	Medtronic Inc.	No (Medtronic Canada, email communication, January 7, 2015)
63074	Synchromed II Infusion System	Medtronic Inc.	Yes (Medtronic Canada, email communication, January 7, 2015)

In June 2013, Medtronic, Inc., issued medical device recalls related to several SynchroMed Implantable Infusion System models. Reasons included[10]:

- Unintended delivery of drugs during the priming bolus procedure (presenting risks of respiratory depression, coma, and death)
- Motor stall or low-battery reset and alarm caused by electrical short circuiting
- The potential for misalignment and subsequent occlusion (blockage)for some sutureless connector catheters

Research Question

What are the benefits, harms, cost-effectiveness, and budget impact of intrathecal drug delivery systems compared with current standards of care for adult patients with chronic pain owing to nonmalignant conditions?

EVIDENCE REVIEW

Methods

Our methodologic approach to literature search and synthesis conformed to the Cochrane Collaboration's methods guidance and followed an a priori protocol. We first sought evidence from the most recent and relevant systematic reviews and health technology assessments as long as the documents included a broad and transparently reported search strategy, an appraisal of the validity of included studies, and a synthesis of the primary evidence aimed at minimizing bias. For an article to qualify as a systematic review and be assessed for methodologic rigour, it had to report databases searched, provide search end dates, and screen identified studies using predefined eligibility criteria.

If the synthesis of available reviews did not incorporate risk of bias but the literature search and screening were well conducted (i.e., a search of at least two databases, including MEDLINE; search end dates; and more than one reviewer), we used the most recent systematic review to identify relevant primary studies. We used subsequent bibliographic searches to update the original search, followed by a de novo synthesis of the originally included and newly identified studies.

We employed separate search strategies and study selection for effectiveness and harms and for cost-effectiveness. Titles and abstracts were screened by one reviewer, and a second reviewer rescreened excluded records for additional consideration. The full texts of included records were obtained and screened by two reviewers. Differences were resolved by consensus or by involving a third team member.

Literature Search

Systematic Reviews Evaluating Effectiveness and Harms

A literature search was performed on March 23, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and the Cochrane Library (Wiley interface) (DSR, DARE, CENTRAL, HTA) for studies published from January 1, 1994, to March 23, 2014. (Appendix 1 provides details of the search strategies.) Two additional records were nominated by reviewers.

Primary Studies Evaluating Effectiveness and Harms

A literature search was performed using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and the Cochrane Library (Wiley interface) (CENTRAL) for studies published from January 1, 2010, to April 23, 2014. (Appendix 1 provides details of the search strategies.) Twenty-three additional primary studies were identified from the systematic reviews above.

Systematic Reviews and Primary Studies for Economic Evaluation

A literature search was performed using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and the Cochrane Library (Wiley interface) (National Health Service's Economic Evaluation Database) for studies published from January 1, 1994, to March 23, 2014. (Appendix 1 provides details of the search strategies.) The Tufts Cost-Effectiveness Analysis Registry and the reference lists of included studies were also hand-searched.

Inclusion Criteria

- English-language full-text publications
- Studies involving adults with chronic nonmalignant pain
- Studies of intrathecal drug delivery systems administering one or more of morphine, hydromorphone, fentanyl, bupivacaine, clonidine, and sufentanil
- Studies comparing standard pharmacologic (oral or parenteral analgesics) or nonpharmacologic pain management
- Studies with a duration of at least 1 year
- Systematic reviews, independent group comparative experimental and observational studies, and full economic evaluations (i.e., cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses)

Note: When estimating incidence rates of procedure- or equipment-related harms, even noncomparative evidence could be relevant. However, to ensure timely completion of this analysis, we obtained noncomparative evidence from relevant extant systematic reviews.

Exclusion Criteria

- Studies of patients with pain caused by spasticity disorders
- Studies of ziconotide intrathecal therapy (not marketed in Canada)
- Studies involving epidural analgesia and intrathecal analgesia using an external pump
- Studies involving these comparisons:
    - Intrathecal drug delivery systems versus epidurals
    - Programmable versus fixed intrathecal drug delivery systems
    - One drug combination (or dose) administered via intrathecal drug delivery system versus another combination or dose administered via intrathecal drug delivery system
    - Intrathecal drug delivery systems versus rhizotomy or nerve blocks
- Studies with no independent comparator group

Outcomes of Interest

A priori outcomes of interest are outlined in Table 3.

Table 3: Outcomes of Interest

Outcome Domain[a]	Outcome Measure
Benefit	
Pain	• Pain intensity or relief • Total analgesic or opioid consumption • Rescue analgesia (or changes in the use of concomitant pain treatments)
Physical function	• Brief Pain Inventory interference items, Multidimensional Pain Inventory interference scale • Return to work
Emotional function	Depression, anxiety (Beck Depression Inventory, Profile of Mood States)
Drug-Related Harms	
Central nervous system toxicity	• Psychiatric abnormalities including suicidality • Chemical meningitis • Respiratory depression
Autonomic dysfunction	• Urinary retention • Hypotension
Treatment titration, modification, or discontinuation owing to intolerability or adverse events	Examples include severe or intractable nausea or vomiting, sedation, headaches, pruritus, addiction and tolerance, weight gain, allergy, or anaphylaxis
Procedure-Related Harms	
Paralysis or nerve injury	As measured/defined by investigators
Bleeding	As measured/defined by investigators
Seromas, hygromas, and granulomas	As measured/defined by investigators
Cerebrospinal fluid leaks, postdural puncture headaches	As measured/defined by investigators
Infections (surgical site or meningitis)	As measured/defined by investigators
Equipment-Related Harms	
Reoperation or reimplantation	NA
Catheter problems (tears, rupture, kinks, displacement)	NA
Remote or pump malfunction (overdosing, underdosing, or therapy cessation)	NA
All Serious Events	
Serious adverse events	As defined by the US Food and Drug Administration (FDA)
Mortality	NA
Aggregate (Patient's Overall Judgment About Balance of Benefits and Harms)	
Global improvement and treatment satisfaction	Patient global impression of change
Health-related quality of life	Measured via various questionnaires and scales
Economic	
Cost-effectiveness	Incremental cost-effectiveness ratio

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable.
[a]Outcome domains in bold underwent GRADE assessment for systematic reviewers' confidence.

Risk of Bias Assessment

We assessed the risk of bias for primary studies using the Cochrane tool for randomized controlled trials; for observational studies using a generic assessment of selection bias, confounding, and information bias (for a hypothetical target trial); and for primary economic evaluations using the Philips checklist[11] (Appendix 2). For outcomes that were to undergo a Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment, publication bias was investigated when more than 10 studies contributed data for an outcome, when studies were of unequal sizes, when there were no important clinical and methodologic differences between smaller and larger studies, and when quantitative results were reported with accompanying measures of dispersion.

The Philips checklist provides a validated and well-accepted framework that can be used to inform the critical appraisal of the methodologic quality of economic modelling.[11] It has been used extensively by bodies engaged in health technology assessment including the National Institute for Health and Care Excellence in the United Kingdom. The checklist is subdivided into three themes: structure, data, and consistency. Structural questions relate to the scope and mathematical construct of the model. Data questions focus on data identification methods and how uncertainty is addressed within the model. Consistency questions address the overall quality of the model.

Synthesis of Evidence

Because of a lack of comparative evidence, we could not perform a meta-analysis. For synthesis of the economic literature, we identified common methodologic issues within studies and then assessed each study through a three-step process: initial assessment for validity, assessment of overall study quality (Philips checklist,[11] Tables A4–A7), and assessment of the study's quality and pertinence to the research question. We focused on the validity of evidence addressing cost-effectiveness of intrathecal drug delivery systems compared with current standards of care. We also attempted to identify optimal patient subpopulations.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria.[12] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural method.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, three main factors that may raise the quality of evidence were considered: the large magnitude of effect, the dose-response gradient, and any residual confounding factors.[12] For more detailed information, please refer to the latest series of GRADE articles.[12]

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

Results

For evidence of effectiveness and harms, we identified four systematic reviews with reliable search and screening methods.[13-18] Synthesis of evidence was judged not to be very rigorous in minimizing bias: no review was formally selected for updating. With at least 3 months' overlap with the end search date of the latest (i.e., December 2012) and most comprehensive of the four reviews,[14,15,17] we searched for relevant primary literature. We added studies included in the four reviews to records retrieved through our searches and screened each for eligibility. No systematic review was identified for economic evidence.

In this report, we included two primary study records on effectiveness and harms and four records on economic evaluation of intrathecal drug delivery systems.[19-24] Specific search yields are reported in more detail below and in the associated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1).

Search Yields

The search yields are presented separately for evidence on intrathecal drug delivery system effectiveness and harms (reviews and primary) and for the economic evaluation.

Systematic Reviews Evaluating Effectiveness and Harms

The database search yielded 352 citations published between 1994 and March 23, 2014 (with duplicates removed). We excluded articles on the basis of information in the title and abstract. Full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows when and for what reason citations were excluded from the analysis. We identified four reviews with acceptable quality and reliable searches, of which none presented outcome-specific results.[13-18] Consequently, no review was selected for updating. We used the last search date of one review (with two companion records) to obtain primary studies for de novo synthesis.[14,15,17] The included primary studies and three other reviews with reliable searches were also selected for screening.

Primary Studies Evaluating Effectiveness and Harms

The database search yielded 683 citations published between 2010 and April 23, 2014 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. We obtained the full texts of potentially relevant articles for further assessment. Figure 1 shows when and for what reason citations were excluded from the analysis. We included two studies in this report.[21,24]

Systematic Reviews and Primary Studies for Economic Evaluation

The database search yielded 659 citations published between 1994 and March 23, 2014 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. We obtained the full texts of potentially relevant articles for further assessment. One record was identified when the reference lists of included studies were searched; however, we later excluded it because it was an abstract of an already-included study with no further information.[25] Figure 1 shows when and for what reason citations were excluded from the analysis. We included four studies in this report (Table 4).[19,20,22,23]

Table 4: Body of Evidence Examined According to Study Design

Study Design	No. of Eligible Studies (Effectiveness and Harms Evaluation)	No. of Eligible Studies (Economic Evaluation)
Randomized controlled trials	0	1
Cohort	2	1 (before-after)
Modelling studies	0	2
Total	**2**	**4**

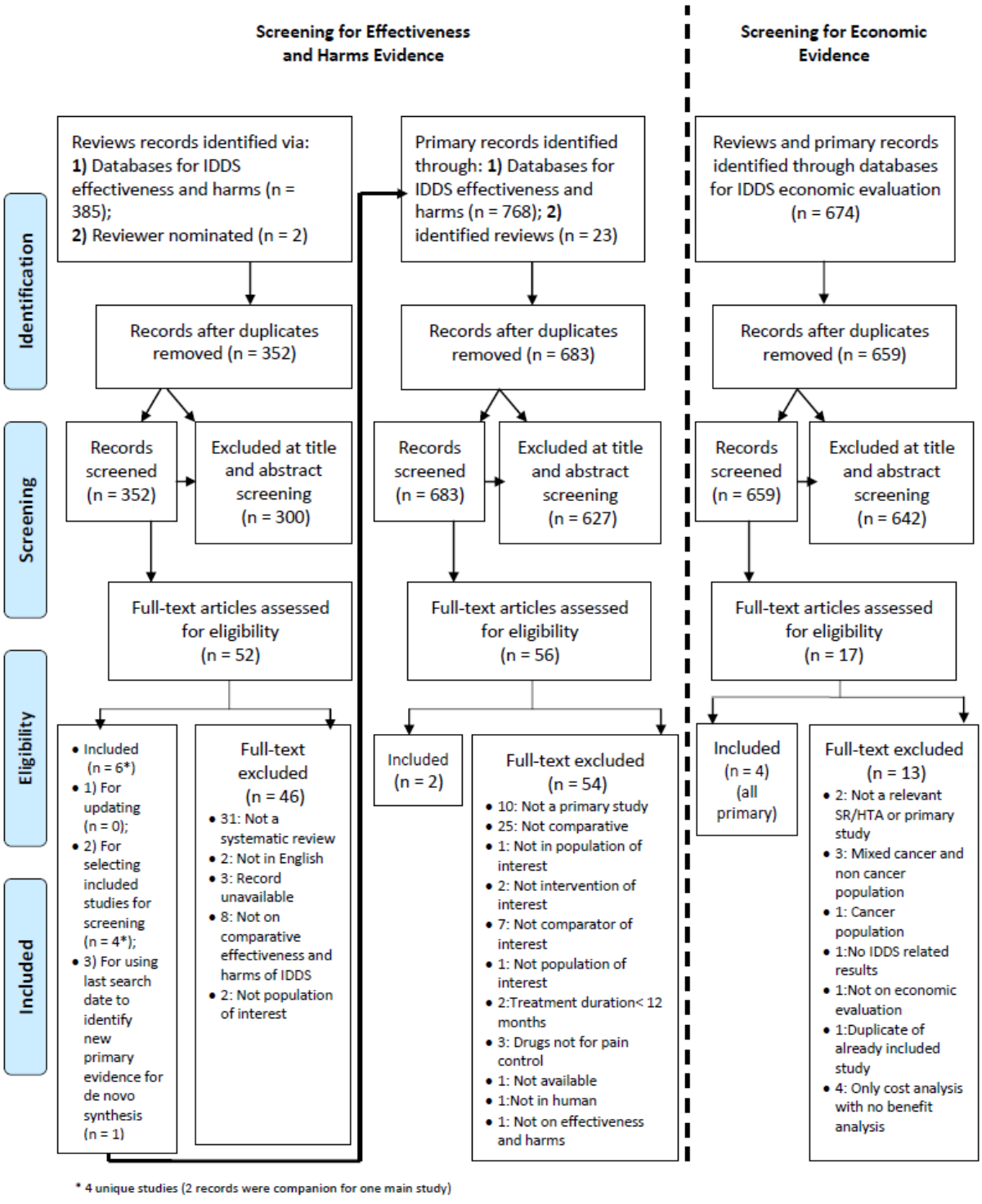

Figure 1: PRISMA Diagram–IDDS Effectiveness, Harms, and Economic Evaluation for Noncancer Pain

Abbreviations: HTA, health technology assessment; IDDS, intrathecal drug delivery system; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SR, systematic review.

Effectiveness and Harms Evaluation

We identified one retrospective and one prospective comparative cohort study. The study by Thimineur et al[24] included patients who failed eligibility for an intrathecal drug delivery system in their comparator group, thus introducing a high risk of selection bias. We therefore excluded it from further analysis in this review.

The retrospective cohort study involved 140 patients with failed back surgery syndrome (Table 5).[21] Three populations comprised the three treatment groups that were analyzed—a programmable intrathecal drug delivery system delivering opioid therapy; oral opioid analgesia; and a 4-week psychosocial, educational, and behavioural rehabilitation program with routine pain medication. Study characteristics and effectiveness and harms outcomes are presented in Tables 5 and 6. Outcome-specific judgments about the certainty of the estimate of effect are reported in the GRADE tables (Appendix 2).

Table 5: Characteristics of Included Studies Reporting on IDDS for Noncancer Pain

				Study Groups			
Study	**N**	**Population**	**Inclusion Criteria**	**IDDS**	**Oral Opioid**	**Rehabilitation Program**	**Follow-Up Period**
Doleys et al, 2006[21]	140	Mean age: 47.8 years[a] 34% female	Failed back surgery syndrome with ongoing pain for at least 2 years	Programmable IDDS[b]	Oral opioid therapy	4-week psychosocial, educational, and behavioural rehabilitation program + routine pain medication	3 years

Abbreviation: IDDS, intrathecal drug delivery system.
[a]Calculated as a mean of the means of the reported ages in the three study groups.
[b]Delivery of opioids after successful trialling.

Table 6: Outcomes of Effectiveness and Harms With Intrathecal Drug Delivery System Use

Outcome	IDDS	Oral Opioids	Rehabilitation Program
Pain			
Mean total opioid consumption post-intervention	21.17 mg/d (SD 2.16)	126.4 mg/d (SD 18.0)	42.7 mg/d (SD 13.3)
Mean change in opioid consumption post-intervention	Decrease of 108.43 mg/d (SD not calculable)	Increase of 56.20 mg/d (SD not calculable)	Increase of 5.80 mg/d (SD not calculable)
Mean % improvement in 10-point VAS scores of pain post-intervention	35.5 (SD 0.28)	8.5 (SD 0.22)	8.0 (SD 0.28)
Mean decrease on a 10-point VAS score of pain post-intervention	2.78 (SD not calculable)	0.60 (SD not calculable)	0.50 (SD not calculable)
Mean post-intervention VAS pain score on a 10-point scale	5.12	6.5	6.3
Physical Functioning			
Post-intervention mean score on Oswestry Disability Questionnaire	49.4 (SD 2.5)	53.5 (SD 2.7)	48.5 (SD 3.5)
% of people employed	26	10	23
Emotional Functioning			
Post-intervention Beck Depression Inventory score	13.7 (SD 1.6)	22.1 (SD 2.4)	19.3 (SD 2.5)
Health-Related Quality of Life			
Post-intervention McGill Pain Questionnaire score	34.5 (SD 2.5)	40.1 (SD 2.8)	36.8 (SD 3.1)
SF-36 physical component score	26.5 (SD 1.5)	24.2 (SD 1.3)	25.4 (SD 1.5)
SF-36 mental component score	44.8 (SD 2.1)	35.7 (SD 2.4)	42.8 (SD 2.3)
Global Pain Improvement			
% improvement in pain	64	52	27

Abbreviations: IDDS, intrathecal drug delivery system; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; VAS, visual analogue scale.

Mean opioid consumption was statistically lower in the intrathecal drug delivery system group compared with the study groups that consumed opioids orally (Table 6). Doleys et al[21] indicated that the group mean consumption for the intrathecal drug delivery system had the potency of 6,357 morphine equivalents per day when using a 300:1 conversion factor. This translates to the intrathecal drug delivery system group having a benefit that is equivalent to much higher doses than the actual drug consumption.

The mean pain score decreased by a statistically significant amount in the intrathecal drug delivery system group, but not in the other two study groups (Table 6). The post-intervention mean pain score in the intrathecal drug delivery system group was the lowest of the three groups, at 5.12 out of a possible 10. However, this is still higher than the pre-determined clinically meaningful threshold, which indicates that patients remained in the category of extreme pain.[21]

In addition to the outcomes presented in Table 6, this study also reported patient satisfaction, by the percentage of patients who reported feeling satisfied with their care. Patient satisfaction with their treatment was 88% for the intrathecal drug delivery system group, 97% for the oral opioid group, and 51% for the rehabilitation program group.

Evidence indicates that intrathecal drug delivery systems may be superior to oral opioids and rehabilitation in reducing pain; however, that superiority is not clearly evident in terms of overall well-being or quality of life. Given limitations in the power, applicability, and validity of the evidence, our confidence in findings is very low (Appendix 2).

Adverse events were not reported in the study by Doleys et al.[21] Non-comparative evidence from underpowered, uncontrolled case series captured in extant systematic reviews suggest that:

- For intrathecal opioids, discontinuation rates because of side effects may be 8.9% (95% confidence interval 4.0%–26.1%); this is from a meta-analysis of five studies with a total of 86 participants[16]
- 5% of patients may undergo pump removal; 27% re-implantation; 5% mechanical or battery failure; 19% catheter kinking, breakage, or obstruction; 12% catheter dislodgment; 17% pump malposition; 12% wound infection; and 2% meningitis. These were crude unweighted meta-analytic estimates of incidence rates derived from a body of evidence with a duration greater than 6 months, fewer than 150 participants, and fewer than 8 studies[18]
- The incidence of serious adverse events requiring surgical treatment owing to device-related issues (e.g., catheter migration, catheter obstruction, pump failure) varies from 10% to 33% (across six case series)[13]

Cost-Effectiveness Evaluation

Study Design

Of the four studies relating to nonmalignant conditions, three specified a population of patients with low back pain,[19,20,22] while the fourth had a population that was predominantly patients with low back pain.[23] Each study was nominally a comparison of intrathecal drug delivery systems and conventional pain therapy (Table 7).

Kumar et al compared intrathecal drug delivery systems with conventional pain therapy in a cost-minimization analysis with a randomized design.[22] The population totalled 88 patients with low back pain: 44 received conventional pain therapy and 44 received an intrathecal drug delivery system. Because 21 patients in the intrathecal drug delivery system group who did not respond to a trial bolus of intrathecal morphine were excluded from the analysis, the results of this study can be considered insufficiently valid. Resource use included preplacement costs including diagnostic imaging, placement procedure costs, pump maintenance costs, physician visits, pharmacotherapy, and adjunct therapies. Costs were estimated from patient flow charts. Over a 5-year period, intrathecal drug delivery systems were found to be dominant over conventional pain therapy: they were cheaper ($29,410 vs. $38,000) and at least equally effective. Limited sensitivity analyses were conducted, and results were not sensitive to changes in certain assumptions.

The study by de Lissovoy and colleagues was also a cost-minimization analysis.[20] The lack of transparency with respect to the modelling and data extraction for this study limits its validity. De Lissovoy and colleagues used a computer simulation model that had the characteristics of a Markov model.[20] The model provided monthly estimates of the total costs of care with intrathecal drug delivery systems and conventional pain therapy for a hypothetical cohort of 1,000 patients over a 5-year period. Resource use was based on expert opinion. Costs were based on charges through access to billing data. Over a 5-year period, intrathecal drug delivery systems were found to be dominant over conventional pain therapy in that they were cheaper ($82,893 vs. $85,186) and at least equally effective. Results were sensitive to changes in certain assumptions.

The other two studies were cost-utility analyses.[19,23] The second study by Kumar et al[23] analyzed data from a retrospective chart review for a simple model of three states (optimal, suboptimal, and death). Outcomes were modelled for a 10-year period. The primary data source was 169 patients, 125 of which were selected to receive an intrathecal drug delivery system; the other 44 patients had either failed a trial of intrathecal therapy or refused a trial. Patients in the intrathecal drug delivery system group who did not respond to a trial of intrathecal pain therapy were excluded from this group and subsequently included in the conventional pain therapy group. This factor limits the validity of the study results. (Further detailed assessment of each study using the Philips checklist[11] is reported in Appendix 2.) Quality-of-life data were collected 6 months after placement. Resource data relating to preplacement, placement procedure, pump maintenance, adjunct therapy, pharmacotherapy, and hospitalizations were included. It is unclear for what period resource use data were monitored and how they were collected. The intrathecal drug delivery system was more effective (quality-adjusted life-year [QALY] gain of 1.15) and more costly (increase of $13,034). This leads to an incremental cost per QALY gained of $11,326 for intrathecal drug delivery systems versus conventional pain therapy.

The study by Biggs et al[19] was a before-and-after study of 12 patients. Although the reporting for this study was clear, certain aspects of the methodology were poor, suggesting the validity of the study is limited. Costs in the 2 years before placement were compared with costs in the

2 years after placement. Resource use was estimated on the basis of chart review, and appropriate costing was applied. Utility values were estimated using the European Quality of Life 5-Domain questionnaire (EQ-5D) prior to intrathecal drug delivery system implantation and 1 year afterward. On an annual basis, intrathecal drug delivery systems were more effective (QALY gain of 0.31) and more costly (increase of £9,049). This leads to an incremental cost per QALY gained of £29,030 for intrathecal drug delivery systems versus conventional pain therapy.

Table 7: Cost-Effectiveness of IDDS Versus CPT for Nonmalignant Conditions

Study	Quality Assessment			Results		Quality
	Design	Structural	Data	Base Case	Sensitivity Analyses	
Kumar et al, 2002[22]	Randomized design	Very serious limitations	Very serious limitations	• Expected cost of IDDS over 5 years = $29,410 • Expected cost of CPT over 5 years = $38,000 • After 28 months, IDDS will be cost saving • At 5 years, IDDS dominates CPT as both cost saving and more effective	• Increasing cost of pump by 50% would increase time to cost saving to 33 mo • Results were not influenced by increasing battery time • If complications were reduced by 50%, time to cost saving would be 26 months	Very low
de Lissovoy et al, 1997[20]	Simulation model	Serious limitations	Very serious limitations	• Expected cost of IDDS over 5 years = $82,893 ($1,382/month) • Expected cost of CPT/month = $1,573 • After 22 months, IDDS will be cost saving • At 5 years, IDDS dominates CPT as both cost saving and more effective	Results varied when assumptions relating to costs, discount rates, and adverse event rates varied. In many instances, IDDS was no longer cost saving after 5 years	Low
Kumar et al, 2013[23]	Markov model	Very serious limitations	Very serious limitations	• Expected cost of IDDS over 10 years = $61,442 • Expected cost of CPT over 10 years = $48,408 • Incremental effectiveness of IDDS = 1.15 QALYs • Incremental cost per QALY gained for IDDS vs. CPT = $11,326	Results were sensitive to the costs of CPT, the efficacy of IDDS and CPT, and assumptions relating to the utility with CPT	Very low
Biggs et al, 2011[19]	Before-and-after study	Serious limitations	Serious limitations	• Annual costs = £13,135 for IDDS, £4,086 for CPT • Annual QALYs = 0.65 for IDDS, 0.33 for CPT • Incremental cost per QALY gained for IDDS vs. CPT = £29,030	NA	Low

Abbreviations: CPT, conventional pain therapy; IDDS, intrathecal drug delivery system; NA, not applicable; QALY, quality-adjusted life-year.

Study Weaknesses

The cost-minimization analysis by Kumar and colleagues had several methodologic weaknesses and is of limited validity.[22] It is unclear whether the study was truly a randomized controlled trial. The description of the methodology suggests both randomization and case-matching were conducted, which seems contradictory. The study excluded 21 patients who failed to gain adequate pain relief from a trial bolus of intrathecal morphine; ideally these patients would be included within the intrathecal drug delivery system group. The source for resource use data relating to physician visits was unclear and appeared to be primarily a hypothesis. Assumptions appeared biased in favour of intrathecal drug delivery systems; for example, the annual number of family physician visits was assumed to be four for intrathecal drug delivery systems and 24 for conventional pain therapy. Other assumptions relating to hospitalizations, diagnostic procedures, and adjunct therapies suffered from a similar bias. Sensitivity analysis was inadequate to address the limitations of the analysis. In addition, the independence of the study is in doubt given that the primary author was a paid consultant for Medtronic, Inc., the manufacturer of the intrathecal drug delivery system.

The study by de Lissovoy and colleagues had several weaknesses.[20] The study was based on a computer simulation model described with insufficient clarity to understand the design. There were not enough details to validate the resource use estimates used within the study. The costs of resources were based on charges and not on actual costs. The study was not independent, as it was funded by Medtronic, Inc., the manufacturer of the intrathecal drug delivery system.

The cost-utility analysis by Kumar and colleagues had several methodologic weaknesses and is of inadequate validity.[23] The study compared two groups of patients: those who had a successful trial of intrathecal therapy and those who had an unsuccessful trial or refused a trial. This comparison is inappropriate to assess the cost-effectiveness of intrathecal drug delivery systems versus conventional pain therapy. A lack of randomization means that the study could not control for any confounding between the two groups. The source for resource use data provided insufficient details to assess validity. Baseline utility was not assessed, which raises the question of whether any differences in utility resulted from treatment or were a function of baseline values. In addition, the use of differential utility values for optimal care between those receiving an intrathecal drug delivery system and those receiving conventional pain therapy is inappropriate. Optimal health was defined as having a European Quality of Life 5-Domain questionnaire score of at least 0.5, yet the utility value for conventional pain therapy with optimal health was 0.489. In addition, we have the same concerns over the independence of the study that we have for the earlier study by Kumar and colleagues.[22]

The study by Biggs and colleagues[19] was clearly reported, and certain aspects of the methodology (costing of resource use and estimation of utility values) were appropriate. However, other aspects of the methodology were poor, suggesting the validity of the study is limited. The study's before-and-after design is liable to bias given the likely cyclical nature of pain. The major methodologic weakness was in the analysis of utility values, where only two time points were available. The authors should have employed an area-under-the-curve methodology to estimate the QALYs for the postimplant procedure. This method would necessarily have halved the QALY gains from intrathecal drug delivery systems and, hence, doubled the incremental cost per QALY gained.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis to determine the estimated cost burden of intrathecal drug delivery for adult patients with chronic pain owing to nonmalignant conditions. The analysis considers the budget impact over the next 5 years and is from the perspective of the Ontario Ministry of Health and Long-Term Care. All costs are reported in 2015 Canadian dollars.

Objective

The objective of this analysis was to determine the budget impact of intrathecal drug delivery systems compared with current standards of care for adult patients with chronic pain owing to nonmalignant conditions.

Methods

Target Population

The number of Ontarians with nonmalignant conditions who would receive an implantation of an intrathecal drug delivery system for chronic pain is estimated to be 30 to 50 in the first year if the technology were funded (Dr. Anuj Bhatia, personal communication, September 3, 2015). This number may increase to 100 to 200 surgeries per year in 5 to 10 years' time.

As a base case, we assumed that there would be 40 surgeries per year in the first year of technology funding and that the demand would increase linearly to 100 over 5 years' time. In the sensitivity analysis, we calculated minimum and maximum volume scenarios within the ranges of numbers provided by the clinical expert (Table 8).

Table 8: One-Year and Five-Year Volumes for Different Budget Impact Scenarios

Scenario	1-Year Volumes	5-Year Volumes
Base case	40	100
Minimum volumes	30	50 (assuming 100 surgeries in 10 years)
Maximum volumes	50	200

The volume of incident cases for the years in between were estimated using linear interpolation (Table 9).

Table 9: Estimated Annual Volumes

Scenario	1-Year Volumes	2-Year Volumes	3-Year Volumes	4-Year Volumes	5-Year Volumes
Base case	40	55	70	85	100
Minimum volumes	30	35	40	45	50
Maximum volumes	50	88	125	163	200

Resources and Costs

We determined the incremental budget impact of intrathecal drug delivery systems by calculating the initial and maintenance costs of implantation of an intrathecal drug delivery system per person versus the cost of conventional treatment per person. The costs for intrathecal drug delivery can be stratified into initial hospitalization costs, infusion pump equipment costs, maintenance and follow-up costs, and standard pump replacement costs.

Initial Hospitalization Costs

The initial in-patient hospitalization costs were calculated using Ontario IntelliHEALTH system administrative data for the years 2006 to 2013. We used a specific procedure code (Table 10) as a filter to identify hospitalizations where an intrathecal drug delivery system was implanted.

Table 10: Canadian Codes for Intrathecal Drug Delivery System Procedures

Description	Code	Source of Code
Implantation of internal device, spinal canal and meninges of infusion pump	1.AX.53.LA.QK	*Canadian Classification of Health Interventions*[26]

To identify incident cases, we excluded codes for most responsible diagnosis if they specified that the purpose of the procedure was to (1) adjust the infusion pump or (2) address a complication resulting from the installation of the infusion pump (Table 11).

Table 11: Codes for Intrathecal Drug Delivery System Procedures to Adjust the Pump or Address Complications

Description	Code	Source of Code
Adjustment and management of implanted device	Z45	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Complications of other internal prosthetic devices, implants, and grafts	T85	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Cerebrospinal fluid leak	G96.0	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]

We found 23 cases. We reviewed the most responsible diagnosis codes to ensure that the cases identified involved chronic pain. We excluded cases that were related to conditions that might have required intrathecal drug therapy for spasticity (Table 12).

Table 12: Codes for Intrathecal Drug Delivery System Procedures for Treating Spasticity

Description	Code	Source of Code
Multiple sclerosis	G35	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Cerebral palsy	G80	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Spastic quadriplegia	G824	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Spastic paraplegia	G821	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Hereditary spastic paraplegia	G114	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Motor neuron disease	G122	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Guillain-Barré syndrome	G610	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]
Cramp and spasm	R252	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[27]

After all exclusions, a total of five cases remained. Resource use intensity for each in-patient hospitalization was reported in the administrative data as resource intensity weights. We converted these weights to cost for hospitalization using the most recent cost of a standard hospital stay.[28] The resource intensity weights reported in the administrative data exclude physician costs; therefore, this was calculated separately. Physician fee codes were collected for all claims made during the observation period. The actual amounts paid for each claim were not available in the administrative database. Instead, we estimated the cost by matching the fee code with the corresponding cost in the Ontario Ministry of Health and Long-Term Care physician schedule of benefits.[29]

Intrathecal Drug Delivery Pump Costs

We obtained drug pump costs from the manufacturer supplying this device to Canadian consumers (Medtronic Canada, personal communication, October 2, 2015).

Maintenance and Follow-Up Costs

We extracted the follow-up health care costs post-implantation from a cost-effectiveness study comparing intrathecal drug delivery with conventional treatment for chronic nonmalignant pain from the perspective of the Saskatchewan health care system.[23] We included costs for physicians, nurses, complications, medication, and hospitalizations for acute pain exacerbations. The authors reported costs stratified by mono-, dual, and triple drug therapy for individuals with utility values above and below 0.5. We used the average of these values for the base case. Though follow-up data were collected for the Ontario patient cohort identified in administrative data as receiving intrathecal drug delivery pump implantation, most of these patients were being treated for a malignant condition. As a result, we did not use follow-up data for this analysis.

Standard Pump Replacement Costs

Intrathecal drug delivery pumps are replaced every 5 years. For our analysis, we assumed that the hospital and physician costs for replacement of the pump would be the same as those for the initial implantation.

Conventional Treatment Costs

We extracted the cost of conventional treatment from the intrathecal drug delivery system cost-effectiveness study from Saskatchewan.[23] We included costs for health professionals, imaging, and medication. Costs were reported for individuals above and below 0.5 utility values. We used the average for the base case.

Mortality

We did not include mortality in our analysis because we assumed that individuals eligible for intrathecal drug delivery for chronic nonmalignant pain would not have a higher death rate than that of the general population. Over the timeframe of our analysis, the mortality rate would be low.

Analysis

Cost inputs were based on the best estimates available. We also calculated lower and upper limit estimates based on the smallest and largest inputs found in the literature, or on expert opinion. In these calculations, the volumes were the same as in the base case. Finally, we calculated lower and upper limit estimates based on the lower and upper limits of patient volumes. In these calculations, the cost inputs remained the same. Where a smaller or larger value was not identified in published literature, we used the minimum and maximum values identified in the administrative data. We converted all costs extracted from literature to Canadian currency using the Organisation for Economic Co-operation and Development purchasing power parities data.[30] We then inflated costs to 2015 dollars using the Bank of Canada inflation calculator.[31] The estimates used for each analysis are presented in Table 13. In summary, there were five calculations: base case; lower and upper limits based on minimum and maximum cost inputs with volumes remaining the same; and lower and upper limits based on minimum and maximum patient volumes with cost inputs remaining the same.

Table 13: Cost Inputs for Budget Impact Analysis

	Base		Minimum		Maximum	
Cost Input	**Value ($)**	**Source**	**Value ($)**	**Source**	**Value ($)**	**Source**
Intrathecal drug delivery system						
Initial hospitalization	27,320	Ontario administrative data[a]	11,248	Kumar et al, 2002[22] (less pump and drug cost)	54,350	Ontario administrative data
Intrathecal pump	10,505	Device manufacturer[b]	10,505	Device manufacturer[b]	10,505	Device manufacturer[b]
Annual maintenance/follow-up costs	9,330	Kumar et al, 2013[23] (mean cost of intrathecal drug treatment)	1,402	Kumar et al, 2002[22]	10,496	Kumar et al, 2013[23] (triple-drug treatment with suboptimal health-related quality of life)
5-year expected pump replacement	27,320	Assumed same as initial hospitalization	11,169	Kumar et al, 2002[22]	54,350	Assumed same as initial hospitalization
Conventional therapy						
Annual costs	10,277	Kumar et al, 2013[23] (mean cost of conventional therapy)	9,684	Kumar et al, 2002[22] (mean of alternating year cost)	10,394	Kumar et al, 2013[23] (suboptimal health-related quality of life)

[a]Ontario Ministry of Health and Long-Term Care: IntelliHEALTH Ontario.
[b]Medtronic Canada, personal communication, October 2, 2015.

We multiplied the number of annual incident cases taken from the estimated volumes by the first-year costs. These cases would accrue follow-up costs each year. We calculated the total annual budget impact by summing the incident and prevalent cohort costs for each corresponding year. The incident (year 1) and prevalent (years 2–5) costs for individuals with intrathecal drug delivery system and for conventional treatment are presented in Table 14. We calculated an incremental cost of publicly funding intrathecal drug delivery system for chronic pain from the difference in total intrathecal drug delivery system costs and conventional treatment costs.

Table 14: Incident and Prevalent Cohort Costs for Individuals for Base Case and Minimum and Maximum Values

		Limits Based on Patient Volumes		Limits Based on Cost Inputs	
Description	**Base Case**	**Lower**	**Upper**	**Lower**	**Upper**
Intrathecal drug delivery system					
Cost year 1 ($)	47,155	47,155[a]	47,155[a]	23,155	75,351
Annual cost years 2–4 ($)	9,330	9,330	9,330	1,402	10,496
Cost year 5 (includes pump replacement) ($)	47,155	47,155	47,155	23,075	75,351
Conventional treatment					
Annual cost ($)	10,277	10,277	10,277	9,684	10,394

[a]Note that lower and upper limit calculations based on patient volumes retained the cost inputs of the base case.

Results

Table 15 outlines the base case budget impact analysis. The lower and upper limits based on patient volumes and on cost inputs are presented in Tables 16 and 17, respectively.

Table 15: Base Case Budget Impact of Intrathecal Drug Delivery Systems

	Annual Cost ($ Millions)				
Treatment Option	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Intrathecal drug delivery system	1.9	3.0	4.2	5.5	8.7
Conventional treatment	0.4	1.0	1.7	2.6	3.6
Incremental cost of intrathecal drug delivery[a]	1.5	2.0	2.5	3.0	5.0

[a]Incremental costs may not match the difference in the two totals above because of rounding.

Table 16: Budget Impact of Intrathecal Drug Delivery Systems Based on Maximum and Minimum Patient Volumes

	Annual Cost ($ Millions)				
Treatment Option	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Lower-limit patient volume					
Intrathecal drug delivery system	1.4	1.9	2.5	3.1	4.9
Conventional treatment	0.3	0.7	1.1	1.5	2.1
Incremental cost of intrathecal drug delivery[a]	1.1	1.3	1.4	1.6	2.8
Upper-limit patient volume					
Intrathecal drug delivery system	2.4	4.6	7.2	10.1	15.3
Conventional treatment	0.5	1.4	2.7	4.4	6.4
Incremental cost of intrathecal drug delivery[a]	1.8	3.2	4.5	5.7	8.9

[a]Incremental costs may not match the difference in the two totals above because of rounding.

Table 17: Budget Impact of Intrathecal Drug Delivery Systems Based on Maximum and Minimum Cost Inputs

	Annual Cost ($ Millions)				
Treatment Option	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Lower-limit cost inputs					
Intrathecal drug delivery system	0.9	1.3	1.8	2.2	3.5
Conventional treatment	0.4	0.9	1.6	2.4	3.4
Incremental cost of intrathecal drug delivery[a]	0.5	0.4	0.2	−0.2	0.1
Upper-limit cost inputs					
Intrathecal drug delivery system	3.0	4.6	6.3	8.1	12.7
Conventional treatment	0.4	1.0	1.7	2.6	3.6
Incremental cost of intrathecal drug delivery[a]	2.6	3.6	4.6	5.5	9.1

[a]Incremental costs may not match the difference in the two totals above because of rounding.

Discussion

We estimate that the budget impact of publicly funding intrathecal drug delivery systems for chronic pain in a nonmalignant adult population would be $1.5 million the first year and reach $5.0 million by the fifth year. The annual cost after this time would remain high and continue to increase since there would be a cohort of individuals every year requiring a pump replacement after 5 years of intrathecal treatment. Costs would also increase as the volume of patients eligible for implantation increased, until we reached the upper threshold of health care resources for implantation.

There are several limitations to our analysis. First, the initial hospitalization cost included in this analysis was based on a small sample identified in administrative data. As a result, we are uncertain whether the costs calculated would be reflective of a larger cohort if the technology were publicly funded. Second, many of the cost inputs were based on a study from Saskatchewan,[23] and the costs may be different in Ontario. Also the data extracted for maintenance and follow-up costs from the Saskatchewan study included medications that could not be excluded. Medication costs in Ontario are covered by private insurance unless the individual is older than 65 or on social assistance. Therefore, the maintenance and follow-up costs we used may be higher than would be expected in Ontario. Third, we assumed that all patients would need the pump replaced in 5 years' time, and that the cost would be identical to the initial implantation cost. The actual cost may be lower because replacing a pump might be less complicated than implanting one. Fourth, projected volumes for intrathecal drug delivery for chronic pain were based on expert opinion and may be inaccurate. Volumes may differ depending on the extent of implementation—limitations in staff capable of conducting the implantation and in facility resources may result in lower volumes than anticipated. Finally, although this analysis attempted to capture the main incremental cost for intrathecal drug delivery systems, there may be other cost inputs that were not accounted for.

The strengths of our analysis include the sources of data used in this budget impact. Most of the costs were from a Canadian health system. Estimated patient volumes were based on information from clinical experts who are aware of the potential limitations in treatment uptake in Ontario.

Overall, the cost of funding intrathecal drug delivery for chronic pain in a nonmalignant population is expected to be several million dollars a year. There is a large level of uncertainty in the calculation inputs resulting in an annual cost that can range from cost savings to double the base case. Thus, the results from our analysis should be interpreted with caution.

CONCLUSIONS

There was very low quality of evidence that demonstrated that patients who received intrathecal drug delivery systems experienced a significant reduction in pain and opioid consumption. However, there was no difference in quality of life and well-being compared with patients who received only oral opioids or a rehabilitation program.

We did not find reliable estimates in the literature regarding the cost-effectiveness of intrathecal drug delivery systems for chronic non-malignant pain; given the poor quality evidence, we elected not to conduct a formal economic evaluation.

The annual budget impact of publicly funding intrathecal drug delivery systems for chronic pain in a nonmalignant population from the perspective of the Ontario Ministry of Health and Long-Term Care is between $1.5 and $5.0 million per year. Results need to be interpreted with caution because of the uncertainty around the numbers we used in our calculations.

APPENDICES

Appendix 1: Literature Search Strategies

Literature Search Strategies for Reviews Evidence for Effectiveness and Harms Evaluation

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2014 Week 12>:

Date: March 23, 2014

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1 Morphine/ (109753)
2 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or "l-Morphine" or "M-Eslon" or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or "MS Contin" or Nepenthe or "Oramorph SR" or Roxanol or "SDZ 202-250" or "SDZ202-250" or Sevredol or Skenan).mp. (136290)
3 57-27-2.rn. (72386)
4 Hydromorphone/ (7045)
5 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7761)
6 466-99-9.rn. (5709)
7 exp Fentanyl/ (57002)
8 (Duragesic or Durogesic or Durotep or Fentanest or fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys).mp. (64959)
9 437-38-7.rn. (41334)
10 Bupivacaine/ (37209)
11 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41490)
12 38396-39-3.rn. (2080)
13 Bupivacaine.rn. (35740)
14 Clonidine/ (46603)
15 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155").mp. (52703)
16 4205-90-7.rn. (33399)
17 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9426)
18 56030-54-7.rn. (6522)
19 or/1-18 (264061)
20 Analgesics, Opioid/ (42084)
21 opioid*.tw. (125625)
22 Pain Management/ (56091)
23 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (207999)
24 or/20-23 (362185)
25 exp Infusion Pumps/ (17063)
26 (infusion* or infusor* or perfusion* or perfusor*).tw. (695749)
27 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (69800)
28 (SynchroMed* or InfusAid* or Codman$1).tw. (1157)
29 exp Injections, Spinal/ (35775)
30 (intrathecal* or intra-thecal*).tw. (39785)

31 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) adj5 (inject* or infus* or administ* or deliver* or therapy or therapies)).tw. (20944)
32 or/25-31 (831487)
33 Chronic Pain/ (35494)
34 ((chronic* or constant* or continu* or persist*) adj5 (pain or painful* or ache or aches or aching)).tw. (120511)
35 ((noncancer* or non-cancer or nonmalignan* or non-malignan* or nononcolog* or non-oncolog*) adj10 pain*).tw. (4720)
36 (CNMP or CNCP).tw. (438)
37 or/33-36 (130850)
38 Fibromyalgia/ (18910)
39 (fibromyalgia* or fibrosit*).tw. (17251)
40 exp Neuralgia/ (81909)
41 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII).tw. (28149)
42 Myalgia/ (32971)
43 (myalgia* or myodynia*).tw. (14307)
44 chronic compartment syndrome*.tw. (299)
45 Polymyalgia Rheumatica/ (5738)
46 polymyalgia rheumati*.tw. (4396)
47 exp Back Pain/ (93467)
48 (backache* or dorsalgia* or (failed back adj2 syndrome*) or lumbago*).tw. (8239)
49 exp Headache Disorders/ (222021)
50 Headache/ (155134)
51 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*).tw. (138075)
52 exp Migraine Disorders/ (62537)
53 migrain*.tw. (57451)
54 Neck Pain/ (16807)
55 (neckache* or cervicalgia* or cervicodynia*).tw. (228)
56 exp Myofascial Pain Syndromes/ (12284)
57 ((myofascial pain or temporomandibular joint dysfunction or TMJ or Costen's or Costens) adj syndrome*).tw. (1617)
58 exp Arthralgia/ (42882)
59 (arthralgia* or polyarthralgia* or poly-arthralgia* or arthrodynia* or joint pain*).tw. (25289)
60 exp Arthritis, Rheumatoid/ (230606)
61 (rheumatism or rheumatoid or rheumarthrit* or rheum arthrit*).tw. (211128)
62 ((Caplan* or Felty* or Sjogren* or Sicca) adj syndrome*).tw. (26075)
63 ("adult-onset" adj1 (still$1 adj disease*)).tw. (1844)
64 or/38-63 (839511)
65 exp Pain/ or (pain or painful*).tw. (1523690)
66 Pain Management/ or exp Analgesia/ or exp Analgesics/ (1121179)
67 65 or 66 (2377293)
68 64 and 67 (502998)
69 37 or 68 (589058)
70 (19 or 24) and 32 and 69 (9101)
71 exp Animals/ not (exp Animals/ and Humans/) (7833335)
72 70 not 71 (7841)
73 limit 72 to systematic reviews [Limit not valid in Embase; records were retained] (5486)
74 meta analysis.pt. (45861)

75 meta-analysis/ (122598)
76 exp meta-analysis as topic/ (25740)
77 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (142496)
78 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (173666)
79 exp Technology assessment, biomedical/ (20449)
80 (cochrane or health technology assessment or evidence report).jw. (24148)
81 or/74-80 (353772)
82 72 and 81 (353)
83 73 or 82 (5507)
84 (comment or editorial or interview or letter or news).pt. (2753659)
85 83 not 84 (5388)
86 limit 85 to yr="1994-current" (4642)
87 86 use prmz (193)
88 Morphine/ (109753)
89 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or "l-Morphine" or "M-Eslon" or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or "MS Contin" or Nepenthe or "Oramorph SR" or Roxanol or "SDZ 202-250" or "SDZ202-250" or Sevredol or Skenan).mp. (136290)
90 57-27-2.rn. (72386)
91 Hydromorphone/ (7045)
92 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7761)
93 466-99-9.rn. (5709)
94 fentanyl/ (55117)
95 (Duragesic or Durogesic or Durotep or Fentanest or fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys).mp. (64959)
96 437-38-7.rn. (41334)
97 Bupivacaine/ (37209)
98 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41490)
99 38396-39-3.rn. (2080)
100 Bupivacaine.rn. (35740)
101 Clonidine/ (46603)
102 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155").mp. (52703)
103 4205-90-7.rn. (33399)
104 Sufentanil/ (8333)
105 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9426)
106 56030-54-7.rn. (6522)
107 or/88-106 (263183)
108 narcotic analgesic agent/ (14311)
109 opioid*.tw. (125625)
110 analgesia/ (87193)
111 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (207999)

112 or/108-111 (366320)
113 exp infusion pump/ (17063)
114 (infusion* or infusor* or perfusion* or perfusor*).tw. (695749)
115 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (69800)
116 (SynchroMed* or InfusAid* or Codman$1).tw. (1157)
117 exp intraspinal drug administration/ (22511)
118 (intrathecal* or intra-thecal*).tw. (39785)
119 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) adj5 (inject* or infus* or administ* or deliver* or therapy or therapies)).tw. (20944)
120 or/113-119 (826697)
121 chronic pain/ (35494)
122 ((chronic* or constant* or continu* or persist*) adj5 pain*).tw. (121215)
123 ((noncancer* or non-cancer or nonmalignan* or non-malignan* or nononcolog* or non-oncolog*) adj10 pain*).tw. (4720)
124 (CNMP or CNCP).tw. (438)
125 or/121-124 (131482)
126 exp myalgia/ (68584)
127 (myalgia* or fibromyalgia* or fibrosit*).tw. (31248)
128 exp neuralgia/ (81909)
129 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII).tw. (28149)
130 myodynia*.tw. (7)
131 chronic compartment syndrome*.tw. (299)
132 polymyalgia rheumati*.tw. (4396)
133 exp backache/ (93467)
134 (backache* or dorsalgia* or (failed back adj2 syndrome*) or lumbago*).tw. (8239)
135 exp "headache and facial pain"/ (196066)
136 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*).tw. (138075)
137 migrain*.tw. (57451)
138 neck pain/ (16807)
139 (neckache* or cervicalgia* or cervicodynia*).tw. (228)
140 myofascial pain syndrome*.tw. (1171)
141 ((temporomandibular joint dysfunction or TMJ or Costen's or Costens) adj syndrome*).tw. (448)
142 arthralgia/ (40152)
143 (arthralgia* or polyarthralgia* or poly-arthralgia* or arthrodynia* or joint pain*).tw. (25289)
144 exp rheumatoid arthritis/ (230606)
145 (rheumatism or rheumatoid or rheumarthrit* or rheum arthrit*).tw. (211128)
146 ((Caplan* or Felty* or Sjogren* or Sicca) adj syndrome*).tw. (26075)
147 ("adult-onset" adj1 (still$1 adj disease*)).tw. (1844)
148 or/126-147 (835121)
149 exp Pain/ or (pain or painful*).tw. (1523690)
150 exp analgesia/ or exp analgesic agent/ (1108662)
151 149 or 150 (2375753)
152 148 and 151 (503640)
153 125 or 152 (590769)
154 (107 or 112) and 120 and 153 (8810)
155 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36733737)

156 exp humans/ or exp human experimentation/ or exp human experiment/ (27772668)
157 155 not 156 (8962609)
158 154 not 157 (7512)
159 limit 158 to "reviews (maximizes specificity)" (216)
160 meta-analysis/ (122598)
161 "systematic review"/ (72076)
162 "meta analysis (topic)"/ (12209)
163 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (142496)
164 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (173666)
165 biomedical technology assessment/ (19351)
166 (cochrane or health technology assessment or evidence report).jw. (24148)
167 or/160-166 (361161)
168 158 and 167 (332)
169 159 or 168 (346)
170 (editorial or letter).pt. (2450057)
171 169 not 170 (346)
172 limit 171 to yr="1994-current" (342)
173 172 use emez (234)
174 87 or 173 (427)
175 remove duplicates from 174 (325) [UNIQUE RECORDS]
176 175 use prmz (187) [UNIQUE MEDLINE RECORDS]
177 175 use emez (138) [UNIQUE EMBASE RECORDS]

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Cochrane Library (Wiley interface)
Date: March 23, 2014
ID Search Hits
#1 [mh Morphine] 3473
#2 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or "l-Morphine" or "M-Eslon" or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or "MS Contin" or Nepenthe or "Oramorph SR" or Roxanol or "SDZ 202-250" or "SDZ202-250" or Sevredol or Skenan):ti,ab,kw 6808
#3 [mh Hydromorphone] 176
#4 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone):ti,ab,kw 331
#5 [mh Fentanyl] 3907
#6 (Duragesic or Durogesic or Durotep or Fentanest or Fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys):ti,ab,kw 7220
#7 [mh Bupivacaine] 3414
#8 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402"):ti,ab,kw 6515
#9 [mh Clonidine] 1552
#10 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155"):ti,ab,kw 2677

#11 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso):ti,ab,kw 1297
#12 or/1-11 20267
#13 [mh "Analgesics, Opioid"] 5063
#14 opioid*:ti,ab,kw 9922
#15 [mh "Pain Management"] 1399
#16 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) near/5 pain*):ti,ab,kw 25869
#17 {or #13-#16} 31880
#18 [mh "Infusion Pumps"] 956
#19 (infusion* or infusor* or perfusion* or perfusor*):ti,ab,kw 37730
#20 ((implant* or intravenous*) near/5 (device* or pump or pumps or deliver* or system*)):ti,ab,kw 2528
#21 (SynchroMed* or InfusAid* or Codman*):ti,ab,kw 31
#22 [mh "Injections, Spinal"] 1273
#23 (intrathecal* or intra-thecal*):ti,ab,kw 2381
#24 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) near/5 (inject* or infus* or administ* or deliver* or therapy or therapies)):ti,ab,kw 2754
#25 or/18-24 43161
#26 [mh "Chronic Pain"] 221
#27 ((chronic* or constant* or continu* or persist*) near/5 pain*):ti,ab,kw 6276
#28 ((noncancer* or (non next cancer*) or nonmalignan* or (non next malignan*) or nononcolog* or (non next oncolog*)) near/10 pain*):ti,ab,kw 290
#29 CNMP or CNCP:ti,ab,kw 9
#30 or/26-29 6303
#31 [mh Fibromyalgia] 585
#32 (fibromyalgia* or fibrosit*):ti,ab,kw 1057
#33 [mh Neuralgia] 729
#34 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII):ti,ab,kw 1522
#35 [mh Myalgia] 0
#36 (myalgia* or myodynia*):ti,ab,kw 1406
#37 ("chronic compartment" next syndrome*) or (polymyalgia next rheumati*):ti,ab,kw 67
#38 [mh "Polymyalgia Rheumatica"] 46
#39 [mh "Back Pain"] 2700
#40 (backache* or dorsalgia* or ("failed back" near/2 syndrome*) or lumbago*):ti,ab,kw 1005
#41 [mh "Headache Disorders"] 1983
#42 [mh Headache] 1566
#43 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*):ti,ab,kw 11958
#44 [mh "Migraine Disorders"] 1646
#45 migrain*:ti,ab,kw 2958
#46 [mh "Neck Pain"] 531
#47 (neckache* or cervicalgia* or cervicodynia*):ti,ab,kw 5
#48 [mh "Myofascial Pain Syndromes"] 330
#49 (("myofascial pain" or "temporomandibular joint dysfunction" or TMJ or "Costen's" or Costens) next syndrome*):ti,ab,kw 421
#50 [mh Arthralgia] 784

#51 (arthralgia* or polyarthralgia* or (poly next arthralgia*) or arthrodynia* or (joint* near/1 pain*)):ti,ab,kw 2062
#52 [mh "Arthritis, Rheumatoid"] 4005
#53 (rheumatism or rheumatoid or rheumarthrit* or (rheum next arthrit*)):ti,ab,kw 6223
#54 ((Caplan* or Felty* or Sjogren* or Sicca) next syndrome*):ti,ab,kw 74
#55 ("adult-onset" near/1 (still* next disease*)):ti,ab,kw 1
#56 28-#55 27571
#57 [mh Pain] 31409
#58 (pain or painful*):ti,ab,kw 65640
#59 [mh "Pain Management"] 1399
#60 [mh Analgesia] 5931
#61 [mh Analgesics] 15151
#62 {or #57-#61} 78420
#63 #56 and #62 14431
#64 #30 or #63 18462
#65 (#12 or #17) and #25 and #64 Publication Date from 1994 to 2014 708

DSR - 31
DARE – 22
CENTRAL – 641 (not part of Pt 1 screening)
HTA – 7

Literature Search Strategies for Primary Evidence for Effectiveness and Harms Evaluation

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2014 Week 16> Search Strategy:

Date: April 23, 2014

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1 Morphine/ (110654)
2 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or "l-Morphine" or "M-Eslon" or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or "MS Contin" or Nepenthe or "Oramorph SR" or Roxanol or "SDZ 202-250" or "SDZ202-250" or Sevredol or Skenan).mp. (137427)
3 57-27-2.rn. (72570)
4 Hydromorphone/ (7139)
5 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7875)
6 466-99-9.rn. (5745)
7 exp Fentanyl/ (57295)
8 (Duragesic or Durogesic or Durotep or Fentanest or fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys).mp. (65323)
9 437-38-7.rn. (41469)
10 Bupivacaine/ (37449)
11 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41749)
12 38396-39-3.rn. (2154)
13 Bupivacaine.rn. (35846)
14 Clonidine/ (46721)

15 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155").mp. (52854)
16 4205-90-7.rn. (33458)
17 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9469)
18 56030-54-7.rn. (6541)
19 or/1-18 (265819)
20 Analgesics, Opioid/ (42595)
21 opioid*.tw. (127321)
22 Pain Management/ (57300)
23 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (210340)
24 or/20-23 (366314)
25 exp Infusion Pumps/ (17191)
26 (infusion* or infusor* or perfusion* or perfusor*).tw. (699886)
27 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (70533)
28 (SynchroMed* or InfusAid* or Codman$1).tw. (1162)
29 exp Injections, Spinal/ (36067)
30 (intrathecal* or intra-thecal*).tw. (40037)
31 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) adj5 (inject* or infus* or administ* or deliver* or therapy or therapies)).tw. (21094)
32 or/25-31 (836793)
33 Chronic Pain/ (36183)
34 ((chronic* or constant* or continu* or persist*) adj5 (pain or painful* or ache or aches or aching)).tw. (122004)
35 ((noncancer* or non-cancer or nonmalignan* or non-malignan* or nononcolog* or non-oncolog*) adj10 pain*).tw. (4806)
36 (CNMP or CNCP).tw. (446)
37 or/33-36 (132456)
38 Fibromyalgia/ (19076)
39 (fibromyalgia* or fibrosit*).tw. (17406)
40 exp Neuralgia/ (82579)
41 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII).tw. (28294)
42 Myalgia/ (33203)
43 (myalgia* or myodynia*).tw. (14406)
44 chronic compartment syndrome*.tw. (299)
45 Polymyalgia Rheumatica/ (5757)
46 polymyalgia rheumati*.tw. (4408)
47 exp Back Pain/ (94173)
48 (backache* or dorsalgia* or (failed back adj2 syndrome*) or lumbago*).tw. (8260)
49 exp Headache Disorders/ (223557)
50 Headache/ (156267)
51 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*).tw. (139158)
52 exp Migraine Disorders/ (62861)
53 migrain*.tw. (57808)
54 Neck Pain/ (16966)
55 (neckache* or cervicalgia* or cervicodynia*).tw. (230)
56 exp Myofascial Pain Syndromes/ (12300)

57 ((myofascial pain or temporomandibular joint dysfunction or TMJ or Costen's or Costens) adj syndrome*).tw. (1623)
58 exp Arthralgia/ (43297)
59 (arthralgia* or polyarthralgia* or poly-arthralgia* or arthrodynia* or joint pain*).tw. (25508)
60 exp Arthritis, Rheumatoid/ (231580)
61 (rheumatism or rheumatoid or rheumarthrit* or rheum arthrit*).tw. (211997)
62 ((Caplan* or Felty* or Sjogren* or Sicca) adj syndrome*).tw. (26195)
63 ("adult-onset" adj1 (still$1 adj disease*)).tw. (1856)
64 or/38-63 (844550)
65 exp Pain/ or (pain or painful*).tw. (1536220)
66 Pain Management/ or exp Analgesia/ or exp Analgesics/ (1128229)
67 65 or 66 (2394215)
68 64 and 67 (506571)
69 37 or 68 (593724)
70 (19 or 24) and 32 and 69 (9257)
71 exp Animals/ not (exp Animals/ and Humans/) (7870616)
72 70 not 71 (7966)
73 limit 72 to systematic reviews [Limit not valid in Embase; records were retained] (5589)
74 meta analysis.pt. (47102)
75 meta-analysis/ (124808)
76 exp meta-analysis as topic/ (26398)
77 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (145199)
78 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (176520)
79 exp Technology assessment, biomedical/ (20503)
80 (cochrane or health technology assessment or evidence report).jw. (24550)
81 or/74-80 (359180)
82 72 and 81 (356)
83 73 or 82 (5610)
84 (comment or editorial or interview or letter or news).pt. (2769818)
85 83 not 84 (5491)
86 limit 85 to yr="1994-current" (4745)
87 (controlled clinical trial or randomized controlled trial).pt. (454371)
88 clinical trials as topic.sh. (169424)
89 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1388250)
90 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (283657)
91 trial.ti. (279677)
92 or/87-91 (1779511)
93 72 and 92 (2050)
94 controlled clinical trial.pt. (88179)
95 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (479650)
96 (control* adj2 trial*).tw. (315513)
97 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (71875)
98 (nRCT or nRCTs or non-RCT$1).tw. (634)
99 (control* adj3 ("before and after" or "before after")).tw. (5787)
100 time series.tw. (33122)
101 (pre- adj3 post-).tw. (106080)
102 (pretest adj3 posttest).tw. (6127)

103 (control* adj2 stud$3).tw. (336278)
104 Control Groups/ (60095)
105 (control$ adj2 group$1).tw. (719107)
106 trial.ti. (279677)
107 or/94-106 (1941418)
108 72 and 107 (1693)
109 exp Cohort Studies/ (1500054)
110 cohort$1.tw. (659069)
111 Retrospective Studies/ (825085)
112 (longitudinal or prospective or retrospective).tw. (1673259)
113 ((followup or follow-up) adj (study or studies)).tw. (81440)
114 Observational study.pt. (1809)
115 (observation$2 adj (study or studies)).tw. (108560)
116 ((population or population-based) adj (study or studies or analys#s)).tw. (25066)
117 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (169)
118 Comparative Study.pt. (1671337)
119 ((comparative or comparison) adj (study or studies)).tw. (167663)
120 exp Case-Control Studies/ (735864)
121 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (140189)
122 or/109-121 (4836974)
123 72 and 122 (1860)
124 93 or 108 or 123 (3395)
125 124 not (71 or 84) (3383)
126 125 not 85 (1129)
127 (201209* or 201210* or 201211* or 201212* or 2013* or 2014*).ed. (1693309)
128 126 and 127 (147)
129 128 use prmz (147)
130 Morphine/ (110654)
131 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or "l-Morphine" or "M-Eslon" or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or "MS Contin" or Nepenthe or "Oramorph SR" or Roxanol or "SDZ 202-250" or "SDZ202-250" or Sevredol or Skenan).mp. (137427)
132 57-27-2.rn. (72570)
133 Hydromorphone/ (7139)
134 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7875)
135 466-99-9.rn. (5745)
136 fentanyl/ (55403)
137 (Duragesic or Durogesic or Durotep or Fentanest or fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys).mp. (65323)
138 437-38-7.rn. (41469)
139 Bupivacaine/ (37449)
140 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41749)
141 38396-39-3.rn. (2154)
142 Bupivacaine.rn. (35846)
143 Clonidine/ (46721)
144 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155").mp. (52854)

145 4205-90-7.rn. (33458)
146 Sufentanil/ (8367)
147 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9469)
148 56030-54-7.rn. (6541)
149 or/130-148 (264939)
150 narcotic analgesic agent/ (14423)
151 opioid*.tw. (127321)
152 analgesia/ (88201)
153 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (210340)
154 or/150-153 (370258)
155 exp infusion pump/ (17191)
156 (infusion* or infusor* or perfusion* or perfusor*).tw. (699886)
157 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (70533)
158 (SynchroMed* or InfusAid* or Codman$1).tw. (1162)
159 exp intraspinal drug administration/ (22736)
160 (intrathecal* or intra-thecal*).tw. (40037)
161 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) adj5 (inject* or infus* or administ* or deliver* or therapy or therapies)).tw. (21094)
162 or/155-161 (831969)
163 chronic pain/ (36183)
164 ((chronic* or constant* or continu* or persist*) adj5 pain*).tw. (122709)
165 ((noncancer* or non-cancer or nonmalignan* or non-malignan* or nononcolog* or non-oncolog*) adj10 pain*).tw. (4806)
166 (CNMP or CNCP).tw. (446)
167 or/163-166 (133089)
168 exp myalgia/ (69022)
169 (myalgia* or fibromyalgia* or fibrosit*).tw. (31501)
170 exp neuralgia/ (82579)
171 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII).tw. (28294)
172 myodynia*.tw. (7)
173 chronic compartment syndrome*.tw. (299)
174 polymyalgia rheumati*.tw. (4408)
175 exp backache/ (94173)
176 (backache* or dorsalgia* or (failed back adj2 syndrome*) or lumbago*).tw. (8260)
177 exp "headache and facial pain"/ (197437)
178 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*).tw. (139158)
179 migrain*.tw. (57808)
180 neck pain/ (16966)
181 (neckache* or cervicalgia* or cervicodynia*).tw. (230)
182 myofascial pain syndrome*.tw. (1177)
183 ((temporomandibular joint dysfunction or TMJ or Costen's or Costens) adj syndrome*).tw. (448)
184 arthralgia/ (40537)
185 (arthralgia* or polyarthralgia* or poly-arthralgia* or arthrodynia* or joint pain*).tw. (25508)
186 exp rheumatoid arthritis/ (231580)
187 (rheumatism or rheumatoid or rheumarthrit* or rheum arthrit*).tw. (211997)
188 ((Caplan* or Felty* or Sjogren* or Sicca) adj syndrome*).tw. (26195)

189 (''adult-onset'' adj1 (still$1 adj disease*)).tw. (1856)
190 or/168-189 (840171)
191 exp Pain/ or (pain or painful*).tw. (1536220)
192 exp analgesia/ or exp analgesic agent/ (1115537)
193 191 or 192 (2392661)
194 190 and 193 (507232)
195 167 or 194 (595455)
196 (149 or 154) and 162 and 195 (8954)
197 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36953909)
198 exp humans/ or exp human experimentation/ or exp human experiment/ (27950900)
199 197 not 198 (9004555)
200 196 not 199 (7628)
201 limit 200 to "reviews (maximizes specificity)" (218)
202 meta-analysis/ (124808)
203 "systematic review"/ (73257)
204 "meta analysis (topic)"/ (12725)
205 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (145199)
206 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (176520)
207 biomedical technology assessment/ (19402)
208 (cochrane or health technology assessment or evidence report).jw. (24550)
209 or/202-208 (366720)
210 200 and 209 (334)
211 201 or 210 (348)
212 (editorial or letter).pt. (2463154)
213 211 not 212 (348)
214 limit 213 to yr="1994-current" (344)
215 randomized controlled trial/ or controlled clinical trial/ (927204)
216 exp "clinical trial (topic)"/ (99831)
217 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1388250)
218 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (283657)
219 trial.ti. (279677)
220 or/215-219 (1908716)
221 200 and 220 (2075)
222 controlled clinical trial/ (472203)
223 "controlled clinical trial (topic)"/ (2730)
224 (control* adj2 trial*).tw. (315513)
225 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (71875)
226 (nRCT or nRCTs or non-RCT$1).tw. (634)
227 (control* adj3 (''before and after'' or ''before after'')).tw. (5787)
228 time series analysis/ (13676)
229 time series.tw. (33122)
230 pretest posttest control group design/ (200)
231 (pre- adj3 post-).tw. (106080)
232 (pretest adj3 posttest).tw. (6127)
233 controlled study/ (4290196)
234 (control* adj2 stud$3).tw. (336278)

235 control group/ (60095)
236 (control$ adj2 group$1).tw. (719107)
237 trial.ti. (279677)
238 or/222-237 (5553100)
239 200 and 238 (1997)
240 cohort analysis/ (328035)
241 cohort$1.tw. (659069)
242 retrospective study/ (825085)
243 longitudinal study/ (150128)
244 prospective study/ (608948)
245 (longitudinal or prospective or retrospective).tw. (1673259)
246 follow up/ (785205)
247 ((followup or follow-up) adj (study or studies)).tw. (81440)
248 observational study/ (55812)
249 (observation$2 adj (study or studies)).tw. (108560)
250 population research/ (66900)
251 ((population or population-based) adj (study or studies or analys#s)).tw. (25066)
252 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (169)
253 exp comparative study/ (2620152)
254 ((comparative or comparison) adj (study or studies)).tw. (167663)
255 exp case control study/ (735864)
256 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (140189)
257 or/240-256 (5987218)
258 200 and 257 (2200)
259 221 or 239 or 258 (3685)
260 259 not 199 (3685)
261 260 not 212 (3660)
262 ("201237" or "201238" or "201239" or "201240" or "201241" or "201242" or "201243" or "201244" or "201245" or "201246" or "201247" or "201248" or "201249" or "201250" or "201251" or "201252" or 2013* or 2014*).em. (3701259)
263 261 and 262 (657)
264 263 use emez (570)
265 129 or 264 (717)
266 remove duplicates from 265 (640) [TOTAL UNIQUE HITS]
267 266 use prmz (141) [MEDLINE UNIQUE HITS]
268 266 use emez (499) [EMBASE UNIQUE HITS]

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Cochrane Library (Wiley interface)
Date: April 23, 2014
ID Search Hits
#1 [mh Morphine] 3495
#2 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or "l-Morphine" or "M-Eslon" or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or "MS Contin" or Nepenthe or "Oramorph SR" or Roxanol or "SDZ 202-250" or "SDZ202-250" or Sevredol or Skenan):ti,ab,kw 6818
#3 [mh Hydromorphone] 176
#4 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone):ti,ab,kw 330
#5 [mh Fentanyl] 3930

#6 (Duragesic or Durogesic or Durotep or Fentanest or Fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys):ti,ab,kw 7203
#7 [mh Bupivacaine] 3434
#8 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402"):ti,ab,kw 6508
#9 [mh Clonidine] 1558
#10 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155"):ti,ab,kw 2651
#11 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso):ti,ab,kw 1296
#12 or/1-11 20253
#13 [mh "Analgesics, Opioid"] 5142
#14 opioid*:ti,ab,kw 10059
#15 [mh "Pain Management"] 1559
#16 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) near/5 pain*):ti,ab,kw 26984
#17 {or #13-#16} 33057
#18 [mh "Infusion Pumps"] 995
#19 (infusion* or infusor* or perfusion* or perfusor*):ti,ab,kw 38260
#20 ((implant* or intravenous*) near/5 (device* or pump or pumps or deliver* or system*)):ti,ab,kw 2468
#21 (SynchroMed* or InfusAid* or Codman*):ti,ab,kw 31
#22 [mh "Injections, Spinal"] 1300
#23 (intrathecal* or intra-thecal*):ti,ab,kw 2312
#24 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) near/5 (inject* or infus* or administ* or deliver* or therapy or therapies)):ti,ab,kw 2752
#25 or/18-24 43620
#26 [mh "Chronic Pain"] 341
#27 ((chronic* or constant* or continu* or persist*) near/5 pain*):ti,ab,kw 6528
#28 ((noncancer* or (non next cancer*) or nonmalignan* or (non next malignan*) or nononcolog* or (non next oncolog*)) near/10 pain*):ti,ab,kw 294
#29 CNMP or CNCP:ti,ab,kw 11
#30 or/26-29 6556
#31 [mh Fibromyalgia] 629
#32 (fibromyalgia* or fibrosit*):ti,ab,kw 1097
#33 [mh Neuralgia] 760
#34 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII):ti,ab,kw 1545
#35 [mh Myalgia] 2
#36 (myalgia* or myodynia*):ti,ab,kw 1319
#37 ("chronic compartment" next syndrome*) or (polymyalgia next rheumati*):ti,ab,kw 68
#38 [mh "Polymyalgia Rheumatica"] 47
#39 [mh "Back Pain"] 2867
#40 (backache* or dorsalgia* or ("failed back" near/2 syndrome*) or lumbago*):ti,ab,kw 954
#41 [mh "Headache Disorders"] 2031
#42 [mh Headache] 1593

#43 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*):ti,ab,kw 11199
#44 [mh "Migraine Disorders"] 1680
#45 migrain*:ti,ab,kw 2983
#46 [mh "Neck Pain"] 572
#47 (neckache* or cervicalgia* or cervicodynia*):ti,ab,kw 5
#48 [mh "Myofascial Pain Syndromes"] 357
#49 (("myofascial pain" or "temporomandibular joint dysfunction" or TMJ or "Costen's" or Costens) next syndrome*):ti,ab,kw 445
#50 [mh Arthralgia] 885
#51 (arthralgia* or polyarthralgia* or (poly next arthralgia*) or arthrodynia* or (joint* near/1 pain*)):ti,ab,kw 2090
#52 [mh "Arthritis, Rheumatoid"] 4081
#53 (rheumatism or rheumatoid or rheumarthrit* or (rheum next arthrit*)):ti,ab,kw 6517
#54 ((Caplan* or Felty* or Sjogren* or Sicca) next syndrome*):ti,ab,kw 76
#55 ("adult-onset" near/1 (still* next disease*)):ti,ab,kw 1
#56 28-#55 27443
#57 [mh Pain] 32778
#58 (pain or painful*):ti,ab,kw 66940
#59 [mh "Pain Management"] 1559
#60 [mh Analgesia] 6099
#61 [mh Analgesics] 15436
#62 {or #57-#61} 79987
#63 #56 and #62 14466
#64 #30 or #63 18633
#65 (#12 or #17) and #25 and #64 Publication Date from 2012 to 2014 157

Reviews – 15 (*did not download*)
DARE – 8 (*did not download*)
CENTRAL – 128
HTA – 3 records (*did not download*)
NHS EED – 3 records (*did not download*)

Literature Search Strategies for Reviews and Primary Evidence for Economic Evaluation
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2014 Week 12> Search Strategy:
Date: March 23, 2014
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1 Morphine/ (109753)
2 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or "I-Morphine" or "M-Eslon" or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or "MS Contin" or Nepenthe or "Oramorph SR" or Roxanol or "SDZ 202-250" or "SDZ202-250" or Sevredol or Skenan).mp. (136290)
3 57-27-2.rn. (72386)
4 Hydromorphone/ (7045)
5 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7761)
6 466-99-9.rn. (5709)
7 exp Fentanyl/ (57002)

8 (Duragesic or Durogesic or Durotep or Fentanest or fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys).mp. (64959)
9 437-38-7.rn. (41334)
10 Bupivacaine/ (37209)
11 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41490)
12 38396-39-3.rn. (2080)
13 Bupivacaine.rn. (35740)
14 Clonidine/ (46603)
15 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155").mp. (52703)
16 4205-90-7.rn. (33399)
17 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9426)
18 56030-54-7.rn. (6522)
19 or/1-18 (264061)
20 Analgesics, Opioid/ (42084)
21 opioid*.tw. (125625)
22 Pain Management/ (56091)
23 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (207999)
24 or/20-23 (362185)
25 exp Infusion Pumps/ (17063)
26 (infusion* or infusor* or perfusion* or perfusor*).tw. (695749)
27 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (69800)
28 (SynchroMed* or InfusAid* or Codman$1).tw. (1157)
29 exp Injections, Spinal/ (35775)
30 (intrathecal* or intra-thecal*).tw. (39785)
31 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) adj5 (inject* or infus* or administ* or deliver* or therapy or therapies)).tw. (20944)
32 or/25-31 (831487)
33 Chronic Pain/ (35494)
34 ((chronic* or constant* or continu* or persist*) adj5 (pain or painful* or ache or aches or aching)).tw. (120511)
35 ((noncancer* or non-cancer or nonmalignan* or non-malignan* or nononcolog* or non-oncolog*) adj10 pain*).tw. (4720)
36 (CNMP or CNCP).tw. (438)
37 or/33-36 (130850)
38 Fibromyalgia/ (18910)
39 (fibromyalgia* or fibrosit*).tw. (17251)
40 exp Neuralgia/ (81909)
41 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII).tw. (28149)
42 Myalgia/ (32971)
43 (myalgia* or myodynia*).tw. (14307)
44 chronic compartment syndrome*.tw. (299)
45 Polymyalgia Rheumatica/ (5738)
46 polymyalgia rheumati*.tw. (4396)
47 exp Back Pain/ (93467)

48 (backache* or dorsalgia* or (failed back adj2 syndrome*) or lumbago*).tw. (8239)
49 exp Headache Disorders/ (222021)
50 Headache/ (155134)
51 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*).tw. (138075)
52 exp Migraine Disorders/ (62537)
53 migrain*.tw. (57451)
54 Neck Pain/ (16807)
55 (neckache* or cervicalgia* or cervicodynia*).tw. (228)
56 exp Myofascial Pain Syndromes/ (12284)
57 ((myofascial pain or temporomandibular joint dysfunction or TMJ or Costen's or Costens) adj syndrome*).tw. (1617)
58 exp Arthralgia/ (42882)
59 (arthralgia* or polyarthralgia* or poly-arthralgia* or arthrodynia* or joint pain*).tw. (25289)
60 exp Arthritis, Rheumatoid/ (230606)
61 (rheumatism or rheumatoid or rheumarthrit* or rheum arthrit*).tw. (211128)
62 ((Caplan* or Felty* or Sjogren* or Sicca) adj syndrome*).tw. (26075)
63 (''adult-onset'' adj1 (still$1 adj disease*)).tw. (1844)
64 or/38-63 (839511)
65 exp Pain/ or (pain or painful*).tw. (1523690)
66 Pain Management/ or exp Analgesia/ or exp Analgesics/ (1121179)
67 65 or 66 (2377293)
68 64 and 67 (502998)
69 37 or 68 (589058)
70 (19 or 24) and 32 and 69 (9101)
71 exp Animals/ not (exp Animals/ and Humans/) (7833335)
72 70 not 71 (7841)
73 exp ''Costs and cost analysis''/ (425969)
74 exp *Economics/ (272329)
75 ec.fs. (3802042)
76 (cost or costs or costing or economic*).tw. (957134)
77 (cost-benefit* or cost-effective* or cost-utilit*).tw. (189480)
78 sensitivity analys*.tw. (35119)
79 (pharmacoeconomic* or pharmaco-economic*).tw. (9727)
80 ''Quality of Life''/ (357651)
81 quality-adjusted life years/ (18432)
82 (life qualities or life quality or quality adjusted or adjusted life or qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).tw. (95829)
83 or/73-82 (5201724)
84 72 and 83 (1150)
85 limit 84 to yr=''1994-current'' (1111)
86 85 use prmz (190)
87 Morphine/ (109753)
88 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or ''l-Morphine'' or ''M-Eslon'' or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or ''MS Contin'' or Nepenthe or ''Oramorph SR'' or Roxanol or ''SDZ 202-250'' or ''SDZ202-250'' or Sevredol or Skenan).mp. (136290)
89 57-27-2.rn. (72386)
90 Hydromorphone/ (7045)
91 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7761)

92 466-99-9.rn. (5709)
93 fentanyl/ (55117)
94 (Duragesic or Durogesic or Durotep or Fentanest or fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys).mp. (64959)
95 437-38-7.rn. (41334)
96 Bupivacaine/ (37209)
97 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41490)
98 38396-39-3.rn. (2080)
99 Bupivacaine.rn. (35740)
100 Clonidine/ (46603)
101 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155").mp. (52703)
102 4205-90-7.rn. (33399)
103 Sufentanil/ (8333)
104 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9426)
105 56030-54-7.rn. (6522)
106 or/87-105 (263183)
107 narcotic analgesic agent/ (14311)
108 opioid*.tw. (125625)
109 analgesia/ (87193)
110 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (207999)
111 or/107-110 (366320)
112 exp infusion pump/ (17063)
113 (infusion* or infusor* or perfusion* or perfusor*).tw. (695749)
114 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (69800)
115 (SynchroMed* or InfusAid* or Codman$1).tw. (1157)
116 exp intraspinal drug administration/ (22511)
117 (intrathecal* or intra-thecal*).tw. (39785)
118 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) adj5 (inject* or infus* or administ* or deliver* or therapy or therapies)).tw. (20944)
119 or/112-118 (826697)
120 chronic pain/ (35494)
121 ((chronic* or constant* or continu* or persist*) adj5 pain*).tw. (121215)
122 ((noncancer* or non-cancer or nonmalignan* or non-malignan* or nononcolog* or non-oncolog*) adj10 pain*).tw. (4720)
123 (CNMP or CNCP).tw. (438)
124 or/120-123 (131482)
125 exp myalgia/ (68584)
126 (myalgia* or fibromyalgia* or fibrosit*).tw. (31248)
127 exp neuralgia/ (81909)
128 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII).tw. (28149)
129 myodynia*.tw. (7)
130 chronic compartment syndrome*.tw. (299)
131 polymyalgia rheumati*.tw. (4396)
132 exp backache/ (93467)

133 (backache* or dorsalgia* or (failed back adj2 syndrome*) or lumbago*).tw. (8239)
134 exp "headache and facial pain"/ (196066)
135 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*).tw. (138075)
136 migrain*.tw. (57451)
137 neck pain/ (16807)
138 (neckache* or cervicalgia* or cervicodynia*).tw. (228)
139 myofascial pain syndrome*.tw. (1171)
140 ((temporomandibular joint dysfunction or TMJ or Costen's or Costens) adj syndrome*).tw. (448)
141 arthralgia/ (40152)
142 (arthralgia* or polyarthralgia* or poly-arthralgia* or arthrodynia* or joint pain*).tw. (25289)
143 exp rheumatoid arthritis/ (230606)
144 (rheumatism or rheumatoid or rheumarthrit* or rheum arthrit*).tw. (211128)
145 ((Caplan* or Felty* or Sjogren* or Sicca) adj syndrome*).tw. (26075)
146 ("adult-onset" adj1 (still$1 adj disease*)).tw. (1844)
147 or/125-146 (835121)
148 exp Pain/ or (pain or painful*).tw. (1523690)
149 exp analgesia/ or exp analgesic agent/ (1108662)
150 148 or 149 (2375753)
151 147 and 150 (503640)
152 124 or 151 (590769)
153 (106 or 111) and 119 and 152 (8810)
154 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36733737)
155 exp humans/ or exp human experimentation/ or exp human experiment/ (27772668)
156 154 not 155 (8962609)
157 153 not 156 (7512)
158 exp "cost"/ (425969)
159 exp *economics/ (272329)
160 (cost or costs or costing or economic*).tw. (957134)
161 (cost-benefit* or cost-effective* or cost-utilit*).tw. (189480)
162 sensitivity analys*.tw. (35119)
163 (pharmacoeconomic* or pharmaco-economic*).tw. (9727)
164 exp "quality of life"/ (372965)
165 (life qualities or life quality or quality adjusted or adjusted life or qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).tw. (95829)
166 or/158-165 (1700875)
167 157 and 166 (813)
168 limit 167 to yr="1994-current" (787)
169 168 use emez (624)
170 86 or 169 (814)
171 remove duplicates from 170 (667) [UNIQUE RECORDS]
172 171 use prmz (187) [UNIQUE MEDLINE]
173 171 use emez (480) [UNIQUE EMBASE]

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Cochrane Library (Wiley interface)
Date: March 23, 2014
ID Search Hits

#1 [mh Morphine] 3473
#2 (Aguettant or DepoDur or Dimorf or Duramorph or Duromorph or "l-Morphine" or "M-Eslon" or Morfina or Morphia or Morphin or Morphina or Morphine or Morphinum or Morphium or Moscontin or "MS Contin" or Nepenthe or "Oramorph SR" or Roxanol or "SDZ 202-250" or "SDZ202-250" or Sevredol or Skenan):ti,ab,kw 6808
#3 [mh Hydromorphone] 176
#4 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone):ti,ab,kw 331
#5 [mh Fentanyl] 3907
#6 (Duragesic or Durogesic or Durotep or Fentanest or Fentamyl or Fentanyl or Fentanylum or Fentora or IONSYS or Lazanda or Matrifen or Phentanyl or "R-4263" or Sublimase or Sublimaze or Subsys):ti,ab,kw 7220
#7 [mh Bupivacaine] 3414
#8 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402"):ti,ab,kw 6515
#9 [mh Clonidine] 1552
#10 (Catapres or Catapresan or Catapressan or Clonidine or Chlophazolin or Clofelin or Clopheline or Dixarit or Gemiton or Hemiton or Isoglaucon or Klofelin or Klofenil or "M-5041T" or "ST-155"):ti,ab,kw 2677
#11 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso):ti,ab,kw 1297
#12 or/1-11 20267
#13 [mh "Analgesics, Opioid"] 5063
#14 opioid*:ti,ab,kw 9922
#15 [mh "Pain Management"] 1399
#16 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) near/5 pain*):ti,ab,kw 25869
#17 {or #13-#16} 31880
#18 [mh "Infusion Pumps"] 956
#19 (infusion* or infusor* or perfusion* or perfusor*):ti,ab,kw 37730
#20 ((implant* or intravenous*) near/5 (device* or pump or pumps or deliver* or system*)):ti,ab,kw 2528
#21 (SynchroMed* or InfusAid* or Codman*):ti,ab,kw 31
#22 [mh "Injections, Spinal"] 1273
#23 (intrathecal* or intra-thecal*):ti,ab,kw 2381
#24 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) near/5 (inject* or infus* or administ* or deliver* or therapy or therapies)):ti,ab,kw 2754
#25 or/18-24 43161
#26 [mh "Chronic Pain"] 221
#27 ((chronic* or constant* or continu* or persist*) near/5 pain*):ti,ab,kw 6276
#28 ((noncancer* or (non next cancer*) or nonmalignan* or (non next malignan*) or nononcolog* or (non next oncolog*)) near/10 pain*):ti,ab,kw 290
#29 CNMP or CNCP:ti,ab,kw 9
#30 or/26-29 6303
#31 [mh Fibromyalgia] 585
#32 (fibromyalgia* or fibrosit*):ti,ab,kw 1057
#33 [mh Neuralgia] 729
#34 (neuralgia* or neurodynia* or piriformis syndrome* or pudendal canal entrapment or pudendal nerve entrapment or pudendal neuropath* or sciatica or causalgia* or "CRPS-II" or CRPSII):ti,ab,kw 1522
#35 [mh Myalgia] 0

#36 (myalgia* or myodynia*):ti,ab,kw 1406
#37 ("chronic compartment" next syndrome*) or (polymyalgia next rheumati*):ti,ab,kw 67
#38 [mh "Polymyalgia Rheumatica"] 46
#39 [mh "Back Pain"] 2700
#40 (backache* or dorsalgia* or ("failed back" near/2 syndrome*) or lumbago*):ti,ab,kw 1005
#41 [mh "Headache Disorders"] 1983
#42 [mh Headache] 1566
#43 (headache* or cephalea* or cephalalgia* or cephalgia* or cephalodynia* or cranialgia* or hemicrania*):ti,ab,kw 11958
#44 [mh "Migraine Disorders"] 1646
#45 migrain*:ti,ab,kw 2958
#46 [mh "Neck Pain"] 531
#47 (neckache* or cervicalgia* or cervicodynia*):ti,ab,kw 5
#48 [mh "Myofascial Pain Syndromes"] 330
#49 (("myofascial pain" or "temporomandibular joint dysfunction" or TMJ or "Costen's" or Costens) next syndrome*):ti,ab,kw 421
#50 [mh Arthralgia] 784
#51 (arthralgia* or polyarthralgia* or (poly next arthralgia*) or arthrodynia* or (joint* near/1 pain*)):ti,ab,kw 2062
#52 [mh "Arthritis, Rheumatoid"] 4005
#53 (rheumatism or rheumatoid or rheumarthrit* or (rheum next arthrit*)):ti,ab,kw 6223
#54 ((Caplan* or Felty* or Sjogren* or Sicca) next syndrome*):ti,ab,kw 74
#55 ("adult-onset" near/1 (still* next disease*)):ti,ab,kw 1
#56 28-#55 27571
#57 [mh Pain] 31409
#58 (pain or painful*):ti,ab,kw 65640
#59 [mh "Pain Management"] 1399
#60 [mh Analgesia] 5931
#61 [mh Analgesics] 15151
#62 {or #57-#61} 78420
#63 #56 and #62 14431
#64 #30 or #63 18462
#65 (#12 or #17) and #25 and #64 Publication Date from 1994 to 2014 708

DSR - 31
DARE – 22
CENTRAL – 641 (not part of Pt 1 screening)
HTA – 7
NHS EED - 7

Appendix 2: Evidence Quality Assessment

Table A1: GRADE Evidence Profile for Comparison of Programmable Intrathecal Drug Delivery Systems and Oral Opioid Analgesia

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Percentage reduction in pain (follow-up mean 4 years; measured with 10-point numerical pain rating scale; range of scores: 0–100; better indicated by higher values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	Other considerations (+1)[e]	⊕ Very Low
Mean daily morphine consumption (mg) (follow-up mean 4 years; better indicated by lower values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None[f]	⊕ Very Low
Post-treatment Oswestry Disability Questionnaire percentage scores (follow-up mean 4 years; range of scores: 0–100; better indicated by lower values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None[f]	⊕ Very Low
Percentage employment (follow-up mean 4 years)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Very serious limitations (−1)[g]	Undetected	None	⊕ Very Low
Quality of well-being (follow-up mean 4 years; measured with Quality of Well-Being Scale Self-Administered 1.04; range of scores: 0–1; better indicated by higher values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very Low
Physical component summary, SF-36 (follow-up mean 4 years; measured with Quality of Well-Being Scale Self-Administered 1.04; range of scores: 0–100; better indicated by higher values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None[f]	⊕ Very Low
Mental component summary, SF-36 (follow-up mean 4 years; measured with Quality of Well-Being Scale Self-Administered 1.04; range of scores: 0–100; better indicated by higher values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None[f]	⊕ Very Low
Global pain improvement (follow-up mean 4 years)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Very serious limitations (−1)[g]	Undetected	None	⊕ Very Low

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Global treatment satisfaction (follow-up mean 4 years)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Very serious limitations (−1)[g]	Undetected	None	⨁ Very Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SF-36, 36-Item Short Form Health Survey.

[a]Subjects were from three distinct treatment populations matched by age, education, pain and treatment duration, and number of spinal surgeries but not by intensity of pain, pretreatment opioid use, disability, or pain refractoriness.

[b]Unclear risk of selection bias, information bias, and confounding by co-interventions; moderate risk of confounding by indication.

[c]Patients did not necessarily have refractory pain or intolerable/unacceptable side effects but had higher pretreatment opioid consumption.

[d]Narrow confidence interval, but small sample size.

[e]27% additional improvement with an intrathecal drug delivery system.

[f]Although patients treated with an intrathecal drug delivery system were consuming more opioids at baseline, evidence is still not upgraded here because of concerns about other confounding factors and selection bias.

[g]Wide confidence interval and small sample size.

Table A2: GRADE Evidence Profile for Comparison of Programmable Intrathecal Drug Delivery Systems and Rehabilitation Program Plus Routine Pain Medication

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Percentage reduction in pain (follow-up mean 4 years; measured with 10-point numerical pain rating scale; range of scores: 0–100; better indicated by higher values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	Other considerations (+1)[e]	⊕ Very Low
Mean daily morphine consumption (mg) (follow-up mean 4 years; better indicated by lower values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None[f]	⊕ Very Low
Post-treatment Oswestry Disability Questionnaire percentage scores (follow-up mean 4 years; range of scores: 0–100; better indicated by lower values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very Low
Percentage employment (follow-up mean 4 years)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Very serious limitations (−2)[g]	Undetected	None	⊕ Very Low
Quality of well-being (follow-up mean 4 years; measured with Quality of Well-Being Scale Self-Administered 1.04; range of scores: 0-1; better indicated by higher values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None	⊕ Very Low
Physical component summary, SF-36 (follow-up mean 4 years; measured with Quality of Well-Being Scale Self-Administered 1.04; range of scores: 0–100; better indicated by higher values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None[f]	⊕ Very Low
Mental component summary, SF-36 (follow-up mean 4 years; measured with Quality of Well-Being Scale Self-Administered 1.04; range of scores: 0-100; better indicated by higher values)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None[f]	⊕ Very Low
Global pain improvement (follow-up mean 4 years)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Serious limitations (−1)[d]	Undetected	None[f]	⊕ Very Low
Global treatment satisfaction (follow-up mean 4 years)							
1 (observational)[a]	Very serious limitations (−2)[b]	No serious limitations	Serious limitations (−1)[c]	Very serious limitations (−2)[g]	Undetected	None[f]	⊕ Very Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SF-36, 36-Item Short Form Health Survey.

[a]Subjects were from three distinct treatment populations matched by age, education, pain and treatment duration, and number of spinal surgeries but not intensity of pain, pretreatment opioid use, disability, or pain refractoriness.

[b]Unclear risk of selection bias, information bias, and confounding by co-interventions; moderate risk of confounding by indication.
[c]Patients did not necessarily have refractory pain or intolerable (or unacceptable) side effects but had higher pretreatment opioid consumption.
[d]Narrow confidence interval, but small sample size.
[e]27% additional improvement with an intrathecal drug delivery system.
[f]Although patients treated with an intrathecal drug delivery system were consuming more opioids at baseline, evidence is still not upgraded here because of concerns about other confounding factors and selection bias.
[g]Wide confidence interval and small sample size.

Table A3: Risk of Bias Among Observational Studies for the Comparison of IDDS Versus Oral Opioid Therapy and of IDDS Versus Rehabilitation Program Plus Routine Pain Medication

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Doleys et al, 2006[21]	Unclear limitations[a]	Unclear limitations[b]	Unclear limitations[c]	Limitations[d]	Unclear limitations[e]

Abbreviation: IDDS, intrathecal drug delivery system.

[a]Risk of nonrandom patient selection is unclear.

[b]Reliability of outcome measurement is unclear.

[c]Risk of information bias is unclear: no blinding of outcome assessment; risk for contamination by alternative treatments is unclear.

[d]Moderate risk for confounding by indication: subjects were from three distinct treatment populations matched by age, education, pain and treatment duration, and number of spinal surgeries but not by intensity of pain, pretreatment opioid use, disability, or refractory pain. Nonetheless, those using IDDS had a longer mean duration of pain and more surgeries.
Risk for confounding by co-interventions (e.g., muscle relaxants, anxiolytics, and antidepressants; oral opioid intake by IDDS patients) is unclear.

[e]Risk of selection bias is unclear: included patients had to receive active treatment for at least 3 years (dropouts, noncompliant patients, and non-responders—e.g., after unsuccessful trial—cannot be estimated because of unreported information).

Table A4: Philips Checklist[11] for Quality Assessment of de Lissovoy, 1997[20]

Quality Criteria	Questions for Critical Appraisal	Response	Comments
S1	Is there a clear statement of the decision problem?	No	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	NA	
	Is the primary decision maker specified?	No	
S2	Is the perspective of the model stated clearly?	No	
	Are the model inputs consistent with the stated perspective?	NA	
	Has the scope of the model been stated and justified?	No	
	Are the outcomes of the model consistent with the perspective, scope, and overall objective of the model?	NA	
S3	Has the evidence regarding the model structure been described?	Yes	
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Unclear	Consideration of other resource items not given
	Are the sources of data used to develop the structure of the model specified?	No	"Representative patterns of care"
S4	Are the structural assumptions transparent and justified?	No	
	Are the structural assumptions reasonable given the overall objective, perspective, and scope of the model?	NA	
S5	Is there a clear definition of the options under evaluation?	Yes	Intrathecal morphine therapy and medical management using other treatments
	Is there justification for the exclusion of feasible options?	NA	
S6	Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	Yes	Given focus on costs—yes
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	Yes	
	Are the time horizon of the model, the duration of treatment, and the duration of treatment effect described and justified?	Partially	Treatment effects not modelled
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Partially	The pathway for IDDS is appropriate, though no description of the model structure is provided. No pathway for CPT provided
S9	Is the cycle length defined and justified in terms of the natural history of disease?	No	No description of the model structure is provided

Quality Criteria	Questions for Critical Appraisal	Response	Comments
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	No	
	Where choices have been made between data sources, are these justified appropriately?	NA	None discussed
	Has particular attention been paid to identifying data for the important parameters in the model?	NA	None discussed
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	NA	None discussed
	Has the quality of the data been assessed appropriately?	No	
	Where expert opinion has been used, are the methods described and justified?	No	
D2	Is the premodel data analysis methodology based on justifiable statistical and epidemiologic techniques?	No	
D2a	Is the choice of baseline data described and justified?	No	
	Are transition probabilities calculated appropriately?	Unclear	None discussed
	Has a half-cycle correction been applied to both cost and outcome?	No	
	If not, has this omission been justified?	NA	
D2b	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	NA	
	Have the methods and assumptions to extrapolate short-term results to final outcomes been documented and justified?	NA	
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	NA	
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	NA	
D2c	Are the utilities incorporated into the model appropriate?	No	
	Is the source for the utility weights referenced?	NA	
	Are the methods of derivation for the utility weights justified?	NA	
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	No	
	Has the use of mutually inconsistent data been justified (i.e., are assumptions and choices appropriate)?	NA	
	Is the process of data incorporation transparent?	No	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	NA	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	
D4	Have the four principal types of uncertainty been addressed?	No	
	If not, has the omission of particular forms of uncertainty been justified?	No	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	No	
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	No	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	No	Too limited in parameters considered
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	No	No justification for ranges provided
C1	Is there evidence that the mathematical logic of the model was tested thoroughly before use?	No	
C2	Are the conclusions valid given the data presented?	Partially	
	Are any counterintuitive results from the model explained and justified?	NA	
	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	Yes	

Abbreviations: CPT, conventional pain therapy; IDDS, intrathecal drug delivery system; NA, not applicable.

Table A5: Philips Checklist[11] for Quality Assessment of Kumar, 2002[22]

Quality Criteria	Questions for Critical Appraisal	Response	Comments
S1	Is there a clear statement of the decision problem?	Yes	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	No	Objective relates to comparing those who respond to intrathecal therapy with those who respond to CPT. It should compare intrathecal therapy with CPT
	Is the primary decision-maker specified?	No	Assumed provincial ministry of health
S2	Is the perspective of the model stated clearly?	No	
	Are the model inputs consistent with the stated perspective?	NA	
	Has the scope of the model been stated and justified?	NA	Not a model—comparative study
	Are the outcomes of the model consistent with the perspective, scope, and overall objective of the model?	NA	
S3	Has the evidence regarding the model structure been described?	NA	Not a model—comparative study
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	NA	Not a model—comparative study
	Are the sources of data used to develop the structure of the model specified?	NA	Not a model—comparative study
S4	Are the structural assumptions transparent and justified?	No	
	Are the structural assumptions reasonable given the overall objective, perspective, and scope of the model?	NA	
S5	Is there a clear definition of the options under evaluation?	Yes	Intrathecal pain therapy through IDDS and CPT; however, the former comparator includes only those who had a successful trial of intrathecal therapy
	Is there justification for the exclusion of feasible options?	No	Comparator should have been all those commencing a trial of intrathecal therapy
S6	Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	NA	
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	Yes	Time horizon for the comparison is 5 years
	Is the time horizon of the model, the duration of treatment, and the duration of treatment effect described and justified?	Yes	
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect	NA	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	the underlying biological process of the disease in question and the impact of interventions?		
S9	Is the cycle length defined and justified in terms of the natural history of disease?	NA	
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	No	Methods for estimation of resource use lack clarity, and estimates appear biased
	Where choices have been made between data sources, are these justified appropriately?	NA	None discussed
	Has particular attention been paid to identifying data for the important parameters in the model?	NA	None discussed
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	NA	None discussed
	Has the quality of the data been assessed appropriately?	No	
	Where expert opinion has been used, are the methods described and justified?	No	
D2	Is the premodel data analysis methodology based on justifiable statistical and epidemiological techniques?	No	
D2a	Is the choice of baseline data described and justified?	No	
	Are transition probabilities calculated appropriately?	NA	
	Has a half-cycle correction been applied to both cost and outcome?	NA	
	If not, has this omission been justified?	NA	
D2b	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	NA	
	Have the methods and assumptions to extrapolate short-term results to final outcomes been documented and justified?	NA	
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	NA	
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	NA	
D2c	Are the utilities incorporated into the model appropriate?	No	
	Is the source for the utility weights referenced?	NA	
	Are the methods of derivation for the utility weights justified?	NA	
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	No	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	Has the use of mutually inconsistent data been justified (i.e., are assumptions and choices appropriate)?	NA	
	Is the process of data incorporation transparent?	No	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	NA	
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	
D4	Have the four principal types of uncertainty been addressed?	No	
	If not, has the omission of particular forms of uncertainty been justified?	No	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	No	
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	No	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	No	None provided
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	NA	
C1	Is there evidence that the mathematical logic of the model was tested thoroughly before use?	No	
C2	Are the conclusions valid given the data presented?	Partially	
	Are any counterintuitive results from the model explained and justified?	NA	
	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	No	

Abbreviations: CPT, conventional pain therapy; IDDS, intrathecal drug delivery system; NA, not applicable.

Table A6: Philips Checklist[11] for Quality Assessment of Biggs, 2011[19]

Quality Criteria	Questions for Critical Appraisal	Response	Comments
S1	Is there a clear statement of the decision problem?	No	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	NA	
	Is the primary decision-maker specified?	No	
S2	Is the perspective of the model stated clearly?	No	
	Are the model inputs consistent with the stated perspective?	NA	
	Has the scope of the model been stated and justified?	NA	Study is a before-and-after study comparing costs for 12 patients before and after IDDS placement
	Are the outcomes of the model consistent with the perspective, scope, and overall objective of the model?	Unclear	Outcome is incremental cost per QALY gained with costs from the public payer perspective. The perspective and decision problem are not stated
S3	Has the evidence regarding the model structure been described?	NA	Not a model
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	NA	
	Are the sources of data used to develop the structure of the model specified?	NA	Data obtained from chart reviews
S4	Are the structural assumptions transparent and justified?	NA	
	Are the structural assumptions reasonable given the overall objective, perspective, and scope of the model?	NA	
S5	Is there a clear definition of the options under evaluation?	Partially	The “before” period relates to conventional pain therapy, and “after” to the use of an IDDS; however, details of what the “before” stage involved are limited
	Is there justification for the exclusion of feasible options?	Unclear	Unclear if there would be patients who had a trial of intrathecal therapy and failed to benefit. Their exclusion would bias study conclusions
S6	Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	NA	
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	Possibly	Study follow-up is 2 years

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	Is the time horizon of the model, the duration of treatment, and the duration of treatment effect described and justified?	Partially	Described but not justified
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	NA	
S9	Is the cycle length defined and justified in terms of the natural history of disease?	NA	
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	The estimations of resource use and of utility values are transparent
	Where choices have been made between data sources; are these justified appropriately?	NA	
	Has particular attention been paid to identifying data for the important parameters in the model?	No	
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	No	
	Has the quality of the data been assessed appropriately?	No	
	Where expert opinion has been used, are the methods described and justified?	Unclear	
D2	Is the premodel data analysis methodology based on justifiable statistical and epidemiological techniques?	No	Estimation of QALYs during IDDS is flawed and should be based on area under-the-curve methodology
D2a	Is the choice of baseline data described and justified?	Partially	
	Are transition probabilities calculated appropriately?	NA	
	Has a half-cycle correction been applied to both cost and outcome?	NA	
	If not, has this omission been justified?	NA	
D2b	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	NA	The before-and-after study design may be inappropriate in assessing cost differences owing to the cyclical nature of pain
	Have the methods and assumptions to extrapolate short-term results to final outcomes been documented and justified?	NA	
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	NA	
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	No	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
D2c	Are the utilities incorporated into the model appropriate?	Partially	The derivation of utility values is appropriate, but the analysis is flawed
	Is the source for the utility weights referenced?	Yes	From study participants using the EQ-5D
	Are the methods of derivation for the utility weights justified?	Yes	
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	No	The actual resource use is not provided
	Has the use of mutually inconsistent data been justified (i.e., are assumptions and choices appropriate)?	Not applicable	
	Is the process of data incorporation transparent?	No	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	NA	
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	
D4	Have the four principal types of uncertainty been addressed?	No	
	If not, has the omission of particular forms of uncertainty been justified?	No	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	No	
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	No	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	NA	No formal sensitivity analyses have been provided
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	NA	
C1	Is there evidence that the mathematical logic of the model was tested thoroughly before use?	No	
C2	Are the conclusions valid given the data presented?	No	The flaw in the estimation of QALY values suggests that the true incremental cost per QALY gained could be double the result presented
	Are any counterintuitive results from the model explained and justified?	NA	
	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	Have the results of the model been compared with those of previous models and any differences in results explained?	No	

Abbreviations: EQ-5D, European Quality of Life 5-Domain questionnaire; IDDS, intrathecal drug delivery system; NA, not applicable; QALY, quality-adjusted life-year.

Table A7: Philips Checklist[11] for Quality Assessment of Kumar, 2013[23]

Quality Criteria	Questions for Critical Appraisal	Response	Comments
S1	Is there a clear statement of the decision problem?	Yes	
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Yes	
	Is the primary decision-maker specified?	Yes	Provincial ministry of health
S2	Is the perspective of the model stated clearly?	Yes	Provincial ministry of health
	Are the model inputs consistent with the stated perspective?	Yes	
	Has the scope of the model been stated and justified?	Yes	
	Are the outcomes of the model consistent with the perspective, scope, and overall objective of the model?	Yes	Outcome is incremental cost per QALY gained with costs from the public payer perspective
S3	Has the evidence regarding the model structure been described?	Yes	3-state model—optimal health, suboptimal health, and death
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	Additional health states may have been preferred
	Are the sources of data used to develop the structure of the model specified?	Partially	It is unclear if resource use is based on actual or hypothesized resource use. If the former, the method for estimation lacks clarity
S4	Are the structural assumptions transparent and justified?	No	No discussion of why only 3 states
	Are the structural assumptions reasonable given the overall objective, perspective, and scope of the model?	Possible	Additional health states for different levels of pain may be preferable.
S5	Is there a clear definition of the options under evaluation?	No	Intrathecal pain therapy through IDDS and CPT; however, the latter comparator group includes those who had an unsuccessful trial of intrathecal therapy
	Is there justification for the exclusion of feasible options?	NA	
S6	Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	Unclear	Markov model, 20 treatment cycles of 6 mo with time horizon of 10 y; however probabilities relate only to initial probability of successful intrathecal therapy trial and pain relief. No long-term transition probabilities applied; assume long-term retention of treatment effect
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	Yes	Assumed long-term retention of treatment effect

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	Is the time horizon of the model, the duration of treatment, and the duration of treatment effect described and justified?	No	No justification of assumption of long-term retention of treatment effect
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Partially	Additional health states for different levels of pain may be preferable
S9	Is the cycle length defined and justified in terms of the natural history of disease?	Yes	
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	No	Limited information provided on how short-term transition probabilities and resource use were obtained. No basis for assumption of long-term retention of treatment effect
	Where choices have been made between data sources, are these justified appropriately?	NA	
	Has particular attention been paid to identifying data for the important parameters in the model?	No	
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	No	
	Has the quality of the data been assessed appropriately?	No	
	Where expert opinion has been used, are the methods described and justified?	No	Details of resource use estimation are scarce and are likely based on expert opinion
D2	Is the premodel data analysis methodology based on justifiable statistical and epidemiological techniques?	No	Utility values were only estimated at 6 mo, so no baseline adjustment was possible
			Analysis assumed long-term retention of treatment effect—no justification provided
D2a	Is the choice of baseline data described and justified?	No	Baseline data for utility values were not provided
	Are transition probabilities calculated appropriately?	Unclear	Details of calculation of initial probabilities are poorly reported
	Has a half cycle correction been applied to both cost and outcome?	Unclear	
	If not, has this omission been justified?	Unclear	
D2b	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	Unclear	Details of calculation of initial probabilities are poorly reported
	Have the methods and assumptions to extrapolate short-term results to final outcomes been documented and justified?	No	Analysis assumed long-term retention of treatment effect—no justification provided
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	No	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	No	
D2c	Are the utilities incorporated into the model appropriate?	Yes	
	Is the source for the utility weights referenced?	Yes	Utility values were assessed at 6 mo with the EQ-5D questionnaire
	Are the methods of derivation for the utility weights justified?	No	Baseline utility values were not assessed. It is unclear if differences in utility values are caused by differences in baseline values or in treatment
			Assumption of differences in utility value between CPT and IDDS patients in the same health state is inappropriate
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	No	Details regarding the transition probabilities and resource use are unclear
	Has the use of mutually inconsistent data been justified (i.e., are assumptions and choices appropriate)?	No	
	Is the process of data incorporation transparent?	No	
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	No	Appear appropriate
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Yes	
D4	Have the four principal types of uncertainty been addressed?	No	Structural uncertainty is not explored
	If not, has the omission of particular forms of uncertainty been justified?	No	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	No	
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	No	
D4d	Are the methods of assessment of parameter uncertainty appropriate?	Yes	
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	No	
C1	Is there evidence that the mathematical logic of the model was tested thoroughly before use?	No	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
C2	Are the conclusions valid given the data presented?	No	The many limitations with respect to patient inclusion, transition probabilities, utilities, and costs are not reflected in the conclusions
	Are any counterintuitive results from the model explained and justified?	No	
	If the model has been calibrated against independent data, have any differences been explained and justified?	No	
	Have the results of the model been compared with those of previous models and any differences in results explained?	No	

Abbreviations: CPT, conventional pain therapy; EQ-5D, European Quality of Life 5-Domain questionnaire; IDDS, intrathecal drug delivery system; NA, not applicable; QALY, quality-adjusted life-year.

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

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