Health Quality Ontario

Ontario Health Technology Assessment Series

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

KEY MESSAGES

Each year in Ontario, more than 1,600 cancer patients experience severe pain at the end of life, even when they are given strong pain medications. One possible treatment for severe pain delivers drugs directly to the spinal fluid (called an *intrathecal drug delivery system*). The drugs are given using a pump connected to a small tube implanted in the spine. To see how effective intrathecal drug delivery systems are, we looked at studies comparing them with routine pain management. We found that patients had fewer drug side effects with intrathecal drug delivery systems, but they did not have less pain. We also found that routine pain management costs less than intrathecal drug delivery systems, unless the patient uses the system for 7 months or more. If the use of intrathecal drug delivery systems were paid for by the Ontario government, this would cost several hundred thousand dollars 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 cancer 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 due owing to cancer.

Methods

We searched Ovid MEDLINE, Ovid Embase, the Cochrane Library databases, 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 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.

The cost burden of publicly funding intrathecal drug delivery systems for cancer pain was estimated for a 5-year timeframe using a combination of published literature, information from the device manufacturer, administrative data, and expert opinion for the inputs.

Results

We included one randomized trial that examined effectiveness and harms, and one case series that reported an eligible economic evaluation. We found very low quality evidence that intrathecal drug delivery systems added to comprehensive pain management reduce overall drug toxicity; no significant reduction in pain scores was observed. Weak conclusions from economic evidence suggested that intrathecal drug delivery systems had the potential to be more cost-effective than high-cost oral therapy if administered for 7 months or longer. The cost burden of publicly funding this therapy is estimated to be $100,000 in the first year, increasing to $500,000 by the fifth year.

Conclusions

Current evidence could not establish the benefit, harm, or cost-effectiveness of intrathecal drug delivery systems compared with current standards of care for managing refractory cancer pain in adults. Publicly funding intrathecal drug delivery systems for cancer pain would result in a budget impact of several hundred thousand dollars per year.

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GRADE	Grading of Recommendations Assessment, Development, and Evaluation

BACKGROUND

Objective of Analysis

The objective of this analysis was to investigate 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 cancer.

Clinical Need and Target Population

Cancer is the leading cause of death in Canada: it was associated with an estimated 76,600 deaths in 2014.[1] However, despite the increasing incidence of cancer, patients are surviving longer thanks to advances in cancer treatment. Based on estimates for 2006 to 2008, 63% of Canadians diagnosed with cancer are now expected to survive for 5 years or more after diagnosis.[2] But although patients with incurable cancer are living longer, their quality of life may be compromised if they receive inadequate analgesia; about two thirds of patients with incurable cancer experience varying degrees of pain depending on cancer type, stage of illness, and clinical setting.[3]

Even with comprehensive and expert medical management, 10% to 30% of cancer patients receiving conventional pain therapies may have pain that is refractory (difficult to treat) or persistent at end of life.[3-6] Refractory pain and concerns about side effects from high doses of pain medications drive the search for alternative pain management options in cancer patients. Currently available options include opioid rotation, parenteral infusions, neuraxial analgesia, nerve blocks, and surgery.

Intrathecal drug delivery systems provide pain relief by directly infusing medication into the cerebrospinal fluid. An intrathecal drug delivery system includes the mechanical device and the catheter used to store and infuse analgesic medication. The intrathecal infusion of analgesics has been used for more than 20 years to treat chronic pain that is refractory to conventional therapies.[7] Implanted programmable pumps have been available in Canada since 1991.[8]

Because of a lack of high-quality evidence in support of intrathecal drug delivery systems, the European Palliative Care Research Collaborative has only weakly recommended the use of spinal opioids in adults with cancer pain.[9]

Cancer Care Ontario concluded that "insufficient evidence existed to recommend one particular intraspinal technique over another or to identify the optimal intraspinal medication. However, the evidence showed that intraspinal analgesia was effective in controlling pain in patients with cancer who could no longer achieve pain relief by other methods."[10,11] As a result, Cancer Care Ontario recommended that[11]:

- The intrathecal drug delivery system care team consist of interventional pain physicians, nurses, palliative care physicians, pharmacists, and primary care providers
- Institutions develop the necessary policies, procedures, and competencies to support health care professionals involved in the care of cancer patients

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience in association with actual or potential tissue damage, or described in terms of such damage."[12] 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."[13]

The principal indications for intrathecal drug delivery systems in chronic malignant (cancer) pain are[3,10]:

- Intractable (hard to control) pain despite adequate trials of more conservative management (equivalent to at least 200 mg of morphine orally per day)
- Dose-limiting side effects from conventional analgesics
- No procedure- or patient-related contraindications

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 (Medtronic Canada, email communication, January 7, 2015). These systems have also been recommended for the treatment of refractory pain by the British Pain Society and the 2012 Polyanalgesic Consensus Conference.[14,15]

Ontario Prevalence and Incidence

Accurate data indicating the burden of cancer pain in Ontario are not available. The calculations below are derived from the closest available statistics, but are likely underestimated because we used cancer deaths as a proxy for prevalent palliative cancer:

- 26,076 people died of cancer in Ontario in 2009[16]
- 64% of patients with advanced cancer experience some pain, of which 10% may be refractory[3,17]
- At least 1,669 patients in Ontario have refractory cancer pain that could be considered for intrathecal drug delivery system therapy (26,076 × 0.64 × 0.1)

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 time the 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.[3]

Regulatory Status

A 2005 evidence-based analysis[18] reported four intrathecal drug delivery system devices licensed by Health Canada for intrathecal baclofen infusion. However, only one of these devices is still available and selling on the Canadian market (Table 1) (Charles ElKhoury, product manager, Codman Neuro, J & J Medical Companies, personal communication January 7, 2015).

Table 1: Intrathecal Drug Delivery System Devices 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 systems 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[27]:

- 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-circuit
- The potential for misalignment and subsequent occlusion 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 malignant 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.)

Primary Studies Evaluating Effectiveness and Harms

A literature search was performed on April 22, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and the Cochrane Library (Wiley interface) (DSR, CENTRAL) for studies published from January 1, 2010, to April 22, 2014 (for Cochrane library, June 17, 2014). (Appendix 1 provides details of the search strategies.) Nine additional primary studies were identified from the systematic reviews above.

Systematic Reviews and Primary Studies for Economic Evaluation

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) (NHS EED) 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 malignant pain
- Studies of intrathecal drug delivery systems administering one or more of morphine, hydromorphone, fentanyl, bupivacaine, clonidine, and sufentanil; intrathecal drug delivery systems were one of the following three types:
  - Fixed rate
  - Programmable with a bolus option or personal therapy manager
  - Programmable without a bolus option or personal therapy manager
- Studies comparing standard pharmacologic (oral or parenteral analgesics) or nonpharmacologic pain management
- Studies with a duration ≥ 3 months
- 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 the incidence rates of harms related to the procedure or equipment, even noncomparative evidence may be relevant. To ensure timely completion of this analysis, we obtained noncomparative evidence from relevant extant systematic reviews.

Exclusion Criteria

- Studies involving ziconotide intrathecal therapy (not marketed in Canada)
- Studies of 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

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/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/vomiting, sedation, headaches, pruritus, addiction and tolerance, weight gain, or allergy/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/reimplantation	NA
Catheter problems (tears, ruptures, kinks, displacement)	NA
Remote/pump malfunction (overdosing or 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 the Balance of Benefits and Harms)	
Global improvement and treatment satisfaction	Patient Global Impression of Change
Health-related quality of life	Measured using 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 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[19] (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 size, when there were no important clinical and methodological 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 methodological quality of economic modelling.[19] 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 divided into three themes: structure, data, and consistency. Structure questions relate to the scope and mathematical construct of the model. Data questions focus on data identification methods and how uncertainty is addressed in 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; instead, we conducted a narrative synthesis. Where required, we calculated relative risk and confidence intervals for individual studies using a standard approach. We calculated hazard ratios from survival data following guidance from Parmar et al.[20]

For synthesis of the economic literature, we identified common methodological issues within studies and then assessed each study using a three-step process: initial assessment for validity; assessment of overall study quality (Philips checklist,[19] Appendix 2); and assessment of the study's quality and pertinence to the decision question. The focus was on the validity of evidence addressing the 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.[21] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

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.[21] For more detailed information, please refer to the latest series of GRADE articles.[21]

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 three systematic reviews with reliable search and screening methods.[9,10,22] However, the synthesis of the evidence was not rigorous in minimizing bias; as a result, none of the systematic reviews was included in this report. We searched for relevant primary literature using at least 3 months' overlap with the end search date of the latest and most comprehensive of the three reviews.[22] We also screened individual studies from the three reviews for eligibility. We identified no systematic reviews of economic evidence.

We included two primary studies on effectiveness and harms (three records, of which one was a companion study) and one economic evaluation in this report.[23-26] 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

Systematic Reviews Evaluating Effectiveness and Harms

The database search yielded 118 citations published between January 1, 1994, and March 23, 2014 (with duplicates removed). Articles were excluded based on information in the title and abstract. We obtained the full texts of potentially relevant articles for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis. Three reviews with reliable searches (two with acceptable quality and one with unclear quality) were identified, of which none presented outcome-specific results.[9,10,22] Consequently, no review was selected for updating. We used the last search date of one review to obtain primary studies for de novo synthesis.[22] The included primary studies in the three systematic reviews were also selected for screening.[9,10,22]

Primary Studies Evaluating Effectiveness and Harms

The database search yielded 470 citations published between January 1, 2010, and April 22, 2014 (for Cochrane Library, June 17, 2014) (with duplicates removed). We excluded articles based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis. We included two studies (three records,[23,25,26] of which one was a companion study) in this report.

Systematic Reviews and Primary Studies for Economic Evaluation

The database search yielded 425 citations published between January 1, 1994, and March 23, 2014 (with duplicates removed). Articles were excluded based on information in the title and abstract. We obtained the full texts of potentially relevant articles for further assessment.

Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis. We included one economic study in this report (Table 4).[24]

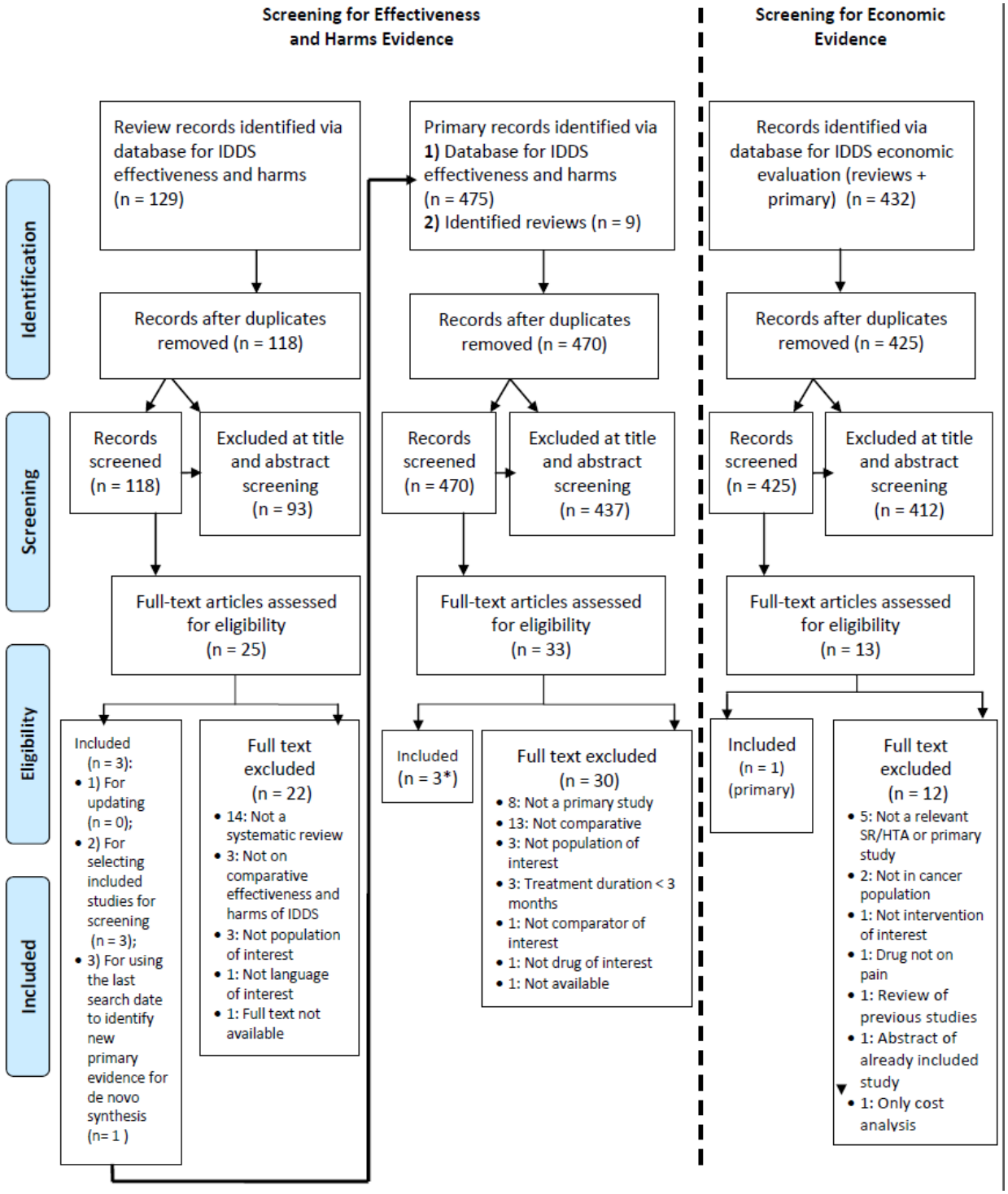

Figure 1: PRISMA Diagram—IDDS Effectiveness, Harms, and Economic Evaluation for Cancer Pain

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

*Two main studies, one of which had a companion.

Table 4: Body of Evidence Examined According to Study Design

Study Design	Eligible Studies (Effectiveness and Harms)	Eligible Studies (Cost-Effectiveness)
Randomized controlled trial	1	0
Cohort	1	0
Case series	0	1
Total	**2**	**1**

Effectiveness and Harms Evaluation

We identified two studies that met the inclusion criteria.[23,25,26] One study was available in only abstract form, and data regarding outcomes of interest could not be abstracted; therefore, we excluded the study by Bhatnager et al[23] from further analyses in this review.

Smith et al[25] conducted a randomized controlled trial of programmable intrathecal drug delivery systems added to comprehensive medical management versus comprehensive medical management alone (Table 5).

Table 5: Characteristics of Included Studies Reporting on Intrathecal Drug Delivery Systems for Cancer Pain

Study	N	Locations	Population	Inclusion Criteria	Intervention	Control	Follow-Up Period
Smith et al[25,26]	200	16 United States 1 Australia 4 Europe	Mean age: 57 years 44% female	• Intractable cancer-associated pain[a] • Expected lifespan ≥3 months	Programmable intrathecal drug delivery system	Comprehensive medical management	6 months

[a]Patients with a baseline pain score of ≥ 5 on a 10-point visual analogue scale despite 200 mg/d of oral morphine equivalents, or those with intolerable side effects. All had an expected lifespan of ≥ 3 months.

Patients were randomly allocated to receive either an intrathecal drug delivery system or medical management. There was no difference in baseline characteristics among patients randomly assigned to the study groups ($P > .05$). Results for the outcomes of pain and toxicity are summarized in Table 6.

Table 6: Pain and Drug Toxicity at 12 Weeks

Outcome	IDDS (N = 57)	CMM (N = 45)	Significance
Proportion of patients with an improvement of ≥ 20% in pain **or** reduced toxicity (10-point VAS)	82.5%	77.8%	*P* = .55
Proportion of patients with an improvement of ≥ 20% in pain **and** reduced toxicity[a]	57.9%	33.3%	*P* = .01
Pain relief[b]—proportion of patients with an improvement in pain score from baseline	47% Mean pain score on 10-point VAS: Baseline, 7.81 At 12 weeks, 3.89	42% Mean pain score on 10-point VAS: Baseline, 7.21 At 12 weeks, 4.53	*P* = .23
Toxicity score[b]—proportion of patients with an improvement in toxicity score[b] from baseline	66% Mean comprehensive toxicity score: Baseline, 6.68 At 12 weeks, 2.30	37% Mean comprehensive toxicity score: Baseline, 6.73 At 12 weeks, 4.13	*P* = .01

Abbreviations: CMM, comprehensive medical management; IDDS, intrathecal drug delivery system; VAS, visual analogue scale.
[a]Toxicity was determined utilizing a 15-item scoring system that included fatigue, confusion, and depression; the full list available in the original study by Smith et al.[26]
[b]Adjusted for confounding patient characteristics with regression modelling.

Outcome-specific assessments were considered to be of very low quality of evidence. Details of the assessments are reported in the GRADE tables (Appendix 2).

Patients were allowed to cross over to the therapy they were not initially randomized to; so, a patient who was assigned to intrathecal drug delivery system could refuse it, and a patient who was assigned to conventional medical management could get the system implanted during the study duration. While there were no statistically significant differences reported between patient groups at baselines, when examining the baseline data of patients who crossed over, those who were allocated to comprehensive medical management but opted to receive an intrathecal drug delivery system had the highest morphine consumption per day (320 mg/d vs. < 280 mg/d), and patients who were randomized to the intrathecal drug delivery system group but opted to undergo comprehensive medical management had the lowest baseline pain (6.9 vs. > 7.4 on a 10-point visual analogue scale). This may indicate that while patients were not statistically significantly different, there may have been marked differences between patients who ultimately received the intrathecal delivery systems and those who did not.

By 12 weeks' post-randomization, there were 12 patients allocated to the intrathecal drug delivery system group who had not been implanted, while 19 patients in the conventional medical management group had crossed over to receive an intrathecal drug delivery system. Compared with their results in the conventional medical management group, these 19 implanted patients showed statistically significant net improvements from baseline on both pain and toxicity scores. Their pain scores (standard deviation) on a 10-point visual analogue scale were reduced from 6.2 (2.8) to 4.5 (2.7) (*P* = .011), and their toxicity scores (standard deviation) decreased from 7.6 (4.8) to 3.8 (4.2) (*P* < .0001).

Adverse events were not reported in any study that met the inclusion criteria of this review. However, the study by Smith et al[25,26] did report adverse event and survival data for 4 weeks: 131 patients reported a serious adverse event (as per International Conference on Harmonization Good Clinical Practice standards; relative risk = 0.87, 95% confidence interval 0.71–1.07). Procedure- or equipment-related harms were estimated at 25% (95% confidence interval 14.4–38.4). Examples of harms related to the intrathecal drug delivery system included infections, wound dehiscence, hematoma, seroma, cerebrospinal fluid leaks, pump flipping, pump migration, catheter kinking, and occlusion (blockage). The incidence rate of intrathecal granuloma is unclear. Survival at 6 months was calculated to have a hazard ratio of 1.22 (95% confidence interval 0.78–1.89).

Very low quality of evidence suggests that the use of an intrathecal drug delivery system plus comprehensive pain management may reduce overall drug toxicity over a 12-week period when compared with comprehensive pain management alone; however, no statistically significant difference was observed in pain scores.[26] For the composite outcome of reduction in pain and drug toxicity, very low quality of evidence favours the use of intrathecal drug delivery systems (Appendix 2).

Cost-Effectiveness Evaluation

We included one study in the cost-effectiveness evaluation.[24] This study involved a retrospective chart review that assessed costs and pain scores in 36 patients before and after intrathecal drug delivery system implantation compared with conventional pain therapy. Given the narrow focus of the study and the before-and-after study design, this study was of inadequate validity (Appendix 2, Table A3).

The study by Brogan et al[24] assessed patients with cancer-related chronic pain before pump placement and 4 to 6 weeks after pump placement. Six patients underwent pump placement but died or were admitted to a hospice before the follow-up period and were excluded from analysis. Costs included the initial pump placement and pain medications. Comparators were conventional pain therapy and pain therapy through intrathecal drug delivery system. The analysis of data for conventional pain therapy involved stratifying patients into high-cost drug therapy (parenteral drugs, brand pain therapies, and/or high-dose morphine) and low-cost drug therapy (all others).

The average cost of pump placement was estimated to be $35,601. The median monthly drug cost for an intrathecal drug delivery system was $487, compared with $631 for all patients receiving conventional pain therapy. For such patients on low-cost drugs, the median monthly drug cost was $399, compared with $5,246 for high-cost conventional pain therapy. For those receiving low-cost conventional pain therapy, intrathecal drug delivery system therapy would not be cost-effective. For those receiving high-cost conventional pain therapy, intrathecal drug delivery system therapy would be cost-effective if given for at least 7.6 months. Pain scores improved post-placement. The average survival after placement was less than 7 months.

This study had a number of methodological weaknesses. The before-and-after study design was of low validity. The exclusion of the six patients who had pump placement but subsequently died or were admitted to a hospice likely biased the results. The authors provided limited details about how pain scores were assessed, making it impossible to assess the quality of this study component. The stratification of patients by low- or high-cost conventional pain therapy was not incorporated into the comparison of conventional pain therapy and intrathecal drug delivery systems, so conclusions about this stratification were not possible. No sensitivity analysis was

provided. Costs of drug therapies were presented as medians rather than means, which is inappropriate for economic studies. The authors also provided limited details about the statistical methods for deriving median costs, and it was unclear if they adequately adjusted for differential survival.

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 malignant 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 malignant conditions.

Methods

Target Population

The number of Ontarians with malignant conditions expected to receive an intrathecal drug delivery system implant for chronic pain is estimated to be five in the first year and up to 30 in the fifth year if the procedure were publicly funded (Dr. Catherine Smyth, personal communication, September 2, 2015). We calculated the expected number of surgeries from 2 to 4 years using linear interpolation. The results are presented in Table 7. We estimate that in total, 88 individuals would receive intrathecal drug delivery pump implantation over a 5-year timeframe. These 88 individuals represent our analysis cohort.

Table 7: Annual Volumes for Intrathecal Drug Delivery System Implantation for Chronic Pain

Scenario	1-Year Volumes	2-Year Volumes	3-Year Volumes	4-Year Volumes	5-Year Volumes
Base case	5	11	18	24	30

Resources and Costs

We determined the incremental budget impact of intrathecal drug delivery system use 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, infusion pump equipment, maintenance and follow-up, and standard pump replacement.

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 as a filter to identify hospitalizations where an intrathecal drug delivery system was implanted (Table 8).

Table 8: 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*[28]

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 9).

Table 9: 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)[29]
Complications of other internal prosthetic devices, implants, and grafts	T85	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]
Cerebrospinal fluid leak	G96.0	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]

A total of 23 cases were found. 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 10).

Table 10: 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)[29]
Cerebral palsy	G80	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]
Spastic quadriplegia	G824	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]
Spastic paraplegia	G821	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]
Hereditary spastic paraplegia	G114	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]
Motor neuron disease	G122	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]
Guillain-Barré syndrome	G610	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]
Cramp and spasm	R252	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10-CA)[29]

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 hospitalization costs using the most recent cost of a standard hospital stay ($5,283).[30] 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 costs by matching the fee code with the corresponding cost in the Ontario Ministry of Health and Long-Term Care physician schedule of benefits.[31]

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

Patients who have undergone intrathecal drug delivery system implantation in Ontario were followed up for 2 months. Most individuals identified in the cohort were being treated for a malignant condition. Therefore, follow-up costs collected in the administrative databases were used for our analysis. Follow-up costs at 2 months included additional in-patient hospitalizations, outpatient hospital visits, physician visits, home care, and in-patient rehabilitation costs.

Standard Pump Replacement Costs

Standard pump replacement costs were not included in our analysis since nobody in our analysis cohort was expected to survive to the complete 5-year life cycle of the intrathecal pump.

Conventional Treatment Costs

In this analysis, we assumed that individuals eligible for intrathecal drug delivery would continue to have similar health care–related costs if they did not receive this treatment. Health care costs for the 6 months prior to intrathecal drug delivery system implantation were recorded in the administrative data cohort. We used the mean monthly cost as the monthly conventional treatment cost.

Mortality

We based mortality rates on a cost analysis of intrathecal therapy for refractory chronic pain in a cancer cohort.[24] At the 4- to 6-week follow-up, the mean survival of this patient cohort was 5.6 months (standard deviation 4.5 months). For our analysis, we added 4 weeks to the total survival time to account for the period prior to follow-up.

Analysis

Costs were calculated monthly for this analysis given the short life expectancy of the patient cohort. The volume of patients expected to receive intrathecal drug therapy in each year was further interpolated with monthly time points. This resulted in patients entering the analysis in a gradual fashion. For example, from 1 year to 2 years, 11 patients were estimated to receive intrathecal drug delivery pump implantation. Interpolated to monthly time points, that translates to one implantation per month. For each individual in our analysis cohort of 88 patients, we determined life expectancy by randomly sampling from the normal distribution using the mean and standard deviations observed by Brogan and colleagues.[24]

To determine the cost accrued for each patient, we collected the cost inputs identified above. We converted all costs extracted from literature to Canadian currency using the Organisation for Economic Co-operation and Development purchasing power parities data.[32] We then inflated costs to 2015 dollars using the Bank of Canada inflation calculator.[33] The estimates used for each analysis are presented in Table 11.

Table 11: 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[34] (less pump and drug cost)	54,350	Ontario administrative data[a] (maximum value)
Intrathecal pump	10,505	Device manufacturer[b]	10,505	Device manufacturer[b]	10,505	Device manufacturer[b]
Monthly maintenance/follow-up costs	2,317	Ontario administrative data[a]	117	Kumar et al, 2002[34] (annual cost converted to monthly cost)	8,460	Ontario administrative data[a] (maximum value)
Conventional therapy						
Monthly costs	4,920	Ontario administrative data[a] (mean 6-month cost prior to surgery)	830	Brogan et al, 2013[24] (mean cost of conventional therapy)	28,230	Ontario administrative data[a] (maximum value)

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

To determine the total cost of intrathecal drug delivery system use in our analysis cohort, we assigned each individual first-month costs consisting of initial hospitalization and pump expenses. After the first month, individuals accrued monthly maintenance and follow-up costs for their remaining life expectancy. To calculate the total cost of conventional treatment in the same analysis cohort, each individual was assigned the monthly conventional treatment cost for the same duration. The incremental cost of publicly funding intrathecal drug delivery systems for chronic pain was calculated by subtracting conventional treatment costs from the total intrathecal drug delivery system costs. Monthly costs were summed and reported as annual costs.

Results

The base case analysis for the budget impact of intrathecal drug delivery system over a 5-year timeframe is presented in Table 12. The budget impact varies with the cost inputs used; the results of calculations using minimum and maximum values are presented in Table 13.

Table 12: Base Case Budget Impact of Intrathecal Drug Delivery Systems

	Annual Cost ($ Million)				
Treatment Option	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Intrathecal drug delivery system	0.2	0.5	0.9	1.2	1.5
Conventional treatment	0.1	0.3	0.5	0.8	1.0
Incremental cost of intrathecal drug delivery[a]	0.1	0.3	0.4	0.4	0.5

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

Table 13: 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	0.1	0.2	0.4	0.5	0.7
Conventional treatment	0.01	0.04	0.1	0.1	0.2
Incremental cost of intrathecal drug delivery[a]	0.1	0.2	0.3	0.4	0.5
Upper-limit cost inputs					
Intrathecal drug delivery system	0.4	1.1	2.0	2.7	3.4
Conventional treatment	0.5	1.4	3.0	4.5	5.6
Incremental cost of intrathecal drug delivery[a]	−0.05	−0.4	−1.1	−1.8	−2.3

[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 malignant adult population would be $100,000 in the first year and would reach

$500,000 by the fifth year. Reanalyzing using maximum cost values illustrates that the budget impact might represent cost savings.

There are several limitations to our analysis. First, we used administrative data from a small cohort for several inputs in this analysis. As a result, we are uncertain whether the costs calculated would be reflective of a larger cohort if the technology were publicly funded. Second, there were very few follow-up data available in the administrative data cohort. As such, there is also some uncertainty regarding the accuracy of the maintenance and follow-up costs in our analysis. Third, we based several cost inputs on studies from different jurisdictions (Saskatchewan and the United States).[24,34] There may be differences in how health care is administered in these jurisdictions, resulting in different costs compared with Ontario. Fourth, projected volumes for intrathecal drug delivery 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 we 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. Although the administrative data cohort was small, the data represent Ontario patients receiving intrathecal drug delivery for chronic pain. Also, most of the cost inputs in our analysis were from a Canadian health system. Estimated patient volumes were from a clinical expert in consultation with experts at other the academic hospitals that would handle the bulk of intrathecal drug delivery system implantation in Ontario.

Overall, the cost of funding intrathecal drug delivery for chronic pain in a malignant population is expected to be a few hundred thousand dollars a year from the perspective of the Ontario Ministry of Health and Long-Term Care. The small budget impact is owing to the limited eligible population and the short life expectancy of the individuals. There is uncertainty in the calculation inputs. As a result, there is a potential to save money by publicly funding intrathecal drug delivery for chronic malignant pain. However, with the level of uncertainty in this analysis, the results should be interpreted with caution.

CONCLUSIONS

Very low quality evidence demonstrates that compared with comprehensive pain management alone, intrathecal drug delivery systems reduce overall drug toxicity; however, a significant reduction in pain scores was not observed. The risk of serious harm related to the procedure and equipment for intrathecal drug delivery systems may be as low as 14% or as high as 38%, over a 4-week period.

Intrathecal drug delivery systems are likely to be more costly than low-cost conventional pain therapy; however, their use has the potential, if given for a long enough duration, to be less costly than high-cost conventional pain therapy—a proposition less realistic for the subpopulation of cancer patients who are routinely treated with high-dose conventional treatment (chemotherapy).

The annual budget impact of publicly funding intrathecal drug delivery systems for chronic pain in a malignant population from the perspective of the Ontario Ministry of Health and Long-Term Care is between $100,000 and $500,000 per year. Results need to be interpreted with caution owing to the uncertainty of the calculation inputs.

APPENDICES

Appendix 1: Literature Search Strategies

Literature Search Strategies for Evidence Review 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
---
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 exp Neoplasms/ (5688767)
34 exp Pain/ or (pain or painful*).tw. (1523690)
35 Pain Management/ or exp Analgesia/ or exp Analgesics/ (1121179)
36 33 and (34 or 35) (293868)
37 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) adj10 pain*).tw. (52910)
38 36 or 37 (312607)
39 (19 or 24) and 32 and 38 (5193)
40 exp Animals/ not (exp Animals/ and Humans/) (7833335)
41 39 not 40 (5005)
42 limit 41 to systematic reviews [Limit not valid in Embase; records were retained] (3241)
43 meta analysis.pt. (45861)
44 meta-analysis/ (122598)
45 exp meta-analysis as topic/ (25740)
46 (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)
47 (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)
48 exp Technology assessment, biomedical/ (20449)
49 (cochrane or health technology assessment or evidence report).jw. (24148)
50 or/43-49 (353772)
51 41 and 50 (126)
52 42 or 51 (3250)
53 (comment or editorial or interview or letter or news).pt. (2753659)
54 52 not 53 (3185)
55 limit 54 to yr="1994-current" (2477)
56 55 use prmz (52)
57 Morphine/ (109753)
58 (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)
59 57-27-2.rn. (72386)
60 Hydromorphone/ (7045)
61 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7761)
62 466-99-9.rn. (5709)
63 fentanyl/ (55117)
64 (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)
65 437-38-7.rn. (41334)
66 Bupivacaine/ (37209)
67 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41490)
68 38396-39-3.rn. (2080)
69 Bupivacaine.rn. (35740)
70 Clonidine/ (46603)

71 (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)
72 4205-90-7.rn. (33399)
73 sufentanil/ (8333)
74 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9426)
75 56030-54-7.rn. (6522)
76 or/57-75 (263183)
77 narcotic analgesic agent/ (14311)
78 opioid*.tw. (125625)
79 analgesia/ (87193)
80 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (207999)
81 or/77-80 (366320)
82 exp infusion pump/ (17063)
83 (infusion* or infusor* or perfusion* or perfusor*).tw. (695749)
84 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (69800)
85 (SynchroMed* or InfusAid* or Codman$1).tw. (1157)
86 exp intraspinal drug administration/ (22511)
87 (intrathecal* or intra-thecal*).tw. (39785)
88 ((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)
89 or/82-88 (826697)
90 cancer pain/ (14246)
91 exp neoplasm/ (5688767)
92 exp Pain/ or (pain or painful*).tw. (1523690)
93 exp analgesia/ or exp analgesic agent/ (1108662)
94 91 and (92 or 93) (293698)
95 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) adj10 pain*).tw. (52910)
96 90 or 94 or 95 (315274)
97 (76 or 81) and 89 and 96 (5321)
98 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36733737)
99 exp humans/ or exp human experimentation/ or exp human experiment/ (27772668)
100 98 not 99 (8962609)
101 97 not 100 (5120)
102 limit 101 to "reviews (maximizes specificity)" (81)
103 meta-analysis/ (122598)
104 "systematic review"/ (72076)
105 "meta analysis (topic)"/ (12209)
106 (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)
107 (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)
108 biomedical technology assessment/ (19351)
109 (cochrane or health technology assessment or evidence report).jw. (24148)
110 or/103-109 (361161)
111 101 and 110 (134)

112 102 or 111 (143)
113 (editorial or letter).pt. (2450057)
114 112 not 113 (141)
115 limit 114 to yr="1994-current" (136)
116 115 use emez (97)
117 56 or 116 (149)
118 remove duplicates from 117 (114) [UNIQUE RECORDS]
119 118 use prmz (47) [UNIQUE MEDLINE RECORDS]
120 118 use emez (67) [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 Neoplasms] 49382
#27 [mh Pain] 31409
#28 (pain or painful*):ti,ab,kw 65640
#29 [mh "Pain Management"] 1399
#30 [mh Analgesia] 5931
#31 [mh Analgesics] 15151
#32 #26 and (#27 or #28 or #29 or #30 or #31) 3375
#33 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) near/10 pain*):ti,ab,kw 2836
#34 #32 or #33 4683
#35 (#12 or #17) and #25 and #34 Publication Date from 1994 to 2014 251

DSR - 10
DARE – 4
CENTRAL – 234 (not part of Pt 1 screening)
HTA – 1

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>:

Date: April 22, 2014

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1 Morphine/ (110639)
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. (137409)
3 57-27-2.rn. (72570)
4 Hydromorphone/ (7135)
5 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7870)
6 466-99-9.rn. (5745)
7 exp Fentanyl/ (57290)
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. (65314)
9 437-38-7.rn. (41469)
10 Bupivacaine/ (37443)
11 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41744)
12 38396-39-3.rn. (2154)
13 Bupivacaine.rn. (35840)
14 Clonidine/ (46719)
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. (52852)

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. (9465)
18 56030-54-7.rn. (6541)
19 or/1-18 (265783)
20 Analgesics, Opioid/ (42567)
21 opioid*.tw. (127315)
22 Pain Management/ (57274)
23 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (210349)
24 or/20-23 (366286)
25 exp Infusion Pumps/ (17189)
26 (infusion* or infusor* or perfusion* or perfusor*).tw. (699870)
27 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (70521)
28 (SynchroMed* or InfusAid* or Codman$1).tw. (1163)
29 exp Injections, Spinal/ (36059)
30 (intrathecal* or intra-thecal*).tw. (40032)
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. (21095)
32 or/25-31 (836757)
33 exp Neoplasms/ (5729041)
34 exp Pain/ or (pain or painful*).tw. (1536156)
35 Pain Management/ or exp Analgesia/ or exp Analgesics/ (1127999)
36 33 and (34 or 35) (296618)
37 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) adj10 pain*).tw. (53448)
38 36 or 37 (315538)
39 (19 or 24) and 32 and 38 (5270)
40 exp Animals/ not (exp Animals/ and Humans/) (7868655)
41 39 not 40 (5075)
42 (comment or editorial or interview or letter or news).pt. (2769617)
43 41 not 42 (4961)
44 limit 43 to systematic reviews [Limit not valid in Embase; records were retained] (3236)
45 meta analysis.pt. (46983)
46 meta-analysis/ (124689)
47 exp meta-analysis as topic/ (26385)
48 (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. (145164)
49 (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. (176504)
50 exp Technology assessment, biomedical/ (20501)
51 (cochrane or health technology assessment or evidence report).jw. (24552)
52 or/45-51 (359135)
53 43 and 52 (127)
54 44 or 53 (3245)
55 (controlled clinical trial or randomized controlled trial).pt. (453961)
56 clinical trials as topic.sh. (169353)
57 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1388198)
58 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (283628)
59 trial.ti. (279643)

60 or/55-59 (1779284)
61 43 and 60 (844)
62 controlled clinical trial.pt. (88158)
63 Controlled Clinical Trial/ or Controlled Clinical Trials as Topic/ (479625)
64 (control* adj2 trial*).tw. (315498)
65 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (71881)
66 (nRCT or nRCTs or non-RCT$1).tw. (635)
67 (control* adj3 ("before and after" or "before after")).tw. (5791)
68 time series.tw. (33110)
69 (pre- adj3 post-).tw. (106089)
70 (pretest adj3 posttest).tw. (6125)
71 (control* adj2 stud$3).tw. (336252)
72 Control Groups/ (60095)
73 (control$ adj2 group$1).tw. (719076)
74 trial.ti. (279643)
75 or/62-74 (1941315)
76 43 and 75 (706)
77 exp Cohort Studies/ (1498588)
78 cohort$1.tw. (659081)
79 Retrospective Studies/ (824459)
80 (longitudinal or prospective or retrospective).tw. (1673206)
81 ((followup or follow-up) adj (study or studies)).tw. (81444)
82 Observational study.pt. (1710)
83 (observation$2 adj (study or studies)).tw. (108581)
84 ((population or population-based) adj (study or studies or analys#s)).tw. (25062)
85 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (169)
86 Comparative Study.pt. (1670681)
87 ((comparative or comparison) adj (study or studies)).tw. (167656)
88 exp Case-Control Studies/ (735007)
89 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (140178)
90 or/77-89 (4835784)
91 43 and 90 (941)
92 61 or 76 or 91 (1593)
93 92 not 54 (625)
94 limit 93 to yr="2010-current" (117)
95 94 use prmz (117)
96 Morphine/ (110639)
97 (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. (137409)
98 57-27-2.rn. (72570)
99 Hydromorphone/ (7135)
100 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7870)
101 466-99-9.rn. (5745)
102 fentanyl/ (55399)
103 (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. (65314)
104 437-38-7.rn. (41469)

105 Bupivacaine/ (37443)
106 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41744)
107 38396-39-3.rn. (2154)
108 Bupivacaine.rn. (35840)
109 Clonidine/ (46719)
110 (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. (52852)
111 4205-90-7.rn. (33458)
112 sufentanil/ (8366)
113 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9465)
114 56030-54-7.rn. (6541)
115 or/96-114 (264903)
116 narcotic analgesic agent/ (14423)
117 opioid*.tw. (127315)
118 analgesia/ (88197)
119 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (210349)
120 or/116-119 (370251)
121 exp infusion pump/ (17189)
122 (infusion* or infusor* or perfusion* or perfusor*).tw. (699870)
123 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (70521)
124 (SynchroMed* or InfusAid* or Codman$1).tw. (1163)
125 exp intraspinal drug administration/ (22736)
126 (intrathecal* or intra-thecal*).tw. (40032)
127 ((intraspinal* or intra-spinal* or spinal* or subarachnoid* or sub-arachnoid*) adj5 (inject* or infus* or administ* or deliver* or therapy or therapies)).tw. (21095)
128 or/121-127 (831937)
129 cancer pain/ (14346)
130 exp neoplasm/ (5729041)
131 exp Pain/ or (pain or painful*).tw. (1536156)
132 exp analgesia/ or exp analgesic agent/ (1115323)
133 130 and (131 or 132) (296446)
134 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) adj10 pain*).tw. (53448)
135 129 or 133 or 134 (318210)
136 (115 or 120) and 128 and 135 (5398)
137 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36942014)
138 exp humans/ or exp human experimentation/ or exp human experiment/ (27940966)
139 137 not 138 (9002594)
140 136 not 139 (5190)
141 limit 140 to "reviews (maximizes specificity)" (82)
142 meta-analysis/ (124689)
143 "systematic review"/ (73257)
144 "meta analysis (topic)"/ (12725)
145 (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. (145164)

146 (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. (176504)
147 biomedical technology assessment/ (19400)
148 (cochrane or health technology assessment or evidence report).jw. (24552)
149 or/142-148 (366680)
150 140 and 149 (135)
151 141 or 150 (144)
152 (editorial or letter).pt. (2462910)
153 151 not 152 (142)
154 randomized controlled trial/ or controlled clinical trial/ (926794)
155 exp "clinical trial (topic)"/ (99831)
156 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1388198)
157 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (283628)
158 trial.ti. (279643)
159 or/154-158 (1908545)
160 140 and 159 (934)
161 controlled clinical trial/ (472182)
162 "controlled clinical trial (topic)"/ (2730)
163 (control* adj2 trial*).tw. (315498)
164 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (71881)
165 (nRCT or nRCTs or non-RCT$1).tw. (635)
166 (control* adj3 ("before and after" or "before after")).tw. (5791)
167 time series analysis/ (13676)
168 time series.tw. (33110)
169 pretest posttest control group design/ (200)
170 (pre- adj3 post-).tw. (106089)
171 (pretest adj3 posttest).tw. (6125)
172 controlled study/ (4290196)
173 (control* adj2 stud$3).tw. (336252)
174 control group/ (60095)
175 (control$ adj2 group$1).tw. (719076)
176 trial.ti. (279643)
177 or/161-176 (5552997)
178 140 and 177 (952)
179 cohort analysis/ (327784)
180 cohort$1.tw. (659081)
181 retrospective study/ (824459)
182 longitudinal study/ (150010)
183 prospective study/ (608518)
184 (longitudinal or prospective or retrospective).tw. (1673206)
185 follow up/ (785205)
186 ((followup or follow-up) adj (study or studies)).tw. (81444)
187 observational study/ (55713)
188 (observation$2 adj (study or studies)).tw. (108581)
189 population research/ (66900)
190 ((population or population-based) adj (study or studies or analys#s)).tw. (25062)
191 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (169)
192 exp comparative study/ (2619496)
193 ((comparative or comparison) adj (study or studies)).tw. (167656)
194 exp case control study/ (735007)

195 ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (140178)
196 or/179-195 (5986160)
197 140 and 196 (1168)
198 160 or 178 or 197 (1897)
199 198 not 152 (1881)
200 199 not 153 (1768)
201 limit 200 to yr="2010-current" (552)
202 201 use emez (440)
203 95 or 202 (557)
204 remove duplicates from 203 (462) [UNIQUE RECORDS]
205 204 use prmz (113) [MEDLINE UNIQUE HITS]
206 204 use emez (349) [EMBASE UNIQUE HITS]

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Database: Cochrane Library (Wiley interface)
Date: June 17, 2014
ID Search Hits
#1 [mh Morphine] 3505
#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 6888
#3 [mh Hydromorphone] 176
#4 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone):ti,ab,kw 343
#5 [mh Fentanyl] 3937
#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 7298
#7 [mh Bupivacaine] 3442
#8 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402"):ti,ab,kw 6583
#9 [mh Clonidine] 1561
#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 2673
#11 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso):ti,ab,kw 1315
#12 {or #1-#11} 20469
#13 [mh "Analgesics, Opioid"] 5177
#14 opioid*:ti,ab,kw 10183
#15 [mh "Pain Management"] 1583
#16 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) near/5 pain*):ti,ab,kw 27457
#17 {or #13-#16} 33603
#18 [mh "Infusion Pumps"] 997
#19 (infusion* or infusor* or perfusion* or perfusor*):ti,ab,kw 38609
#20 ((implant* or intravenous*) near/5 (device* or pump or pumps or deliver* or system*)):ti,ab,kw 2514
#21 (SynchroMed* or InfusAid* or Codman*):ti,ab,kw 31

#22 [mh "Injections, Spinal"] 1311
#23 (intrathecal* or intra-thecal*):ti,ab,kw 2341
#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 2813
#25 {or #18-#24} 44076
#26 [mh Neoplasms] 51865
#27 [mh Pain] 32964
#28 (pain or painful*):ti,ab,kw 68222
#29 [mh "Pain Management"] 1583
#30 [mh Analgesia] 6131
#31 [mh Analgesics] 15517
#32 #26 and (#27 or #28 or #29 or #30 or #31) 3553
#33 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) near/10 pain*):ti,ab,kw 2972
#34 #32 or #33 4914
#35 (#12 or #17) and #25 and #34 Publication Year from 2010 to 2014 67

DSR – 8
DARE – 2
CENTRAL – 55 (primary studies)
HTA – 1
NHS EED -1

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>:
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 exp Neoplasms/ (5688767)
34 exp Pain/ or (pain or painful*).tw. (1523690)
35 Pain Management/ or exp Analgesia/ or exp Analgesics/ (1121179)
36 33 and (34 or 35) (293868)
37 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) adj10 pain*).tw. (52910)
38 36 or 37 (312607)
39 (19 or 24) and 32 and 38 (5193)
40 exp Animals/ not (exp Animals/ and Humans/) (7833335)
41 39 not 40 (5005)
42 exp "Costs and cost analysis"/ (425969)
43 exp *Economics/ (272329)
44 ec.fs. (3802042)
45 (cost or costs or costing or economic*).tw. (957134)
46 (cost-benefit* or cost-effective* or cost-utilit*).tw. (189480)
47 sensitivity analys*.tw. (35119)
48 (pharmacoeconomic* or pharmaco-economic*).tw. (9727)
49 "Quality of Life"/ (357651)
50 quality-adjusted life years/ (18432)
51 (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)
52 or/42-51 (5201724)
53 41 and 52 (784)
54 limit 53 to yr="1994-current" (713)
55 54 use prmz (136)
56 Morphine/ (109753)
57 (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)
58 57-27-2.rn. (72386)
59 Hydromorphone/ (7045)
60 (Dihydromorphinone or Dilaudid or DiMo or Dimorphone or Hydromorphon or Hydromorphone or Novolaudon or Palladone).mp. (7761)
61 466-99-9.rn. (5709)
62 fentanyl/ (55117)
63 (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)
64 437-38-7.rn. (41334)
65 Bupivacaine/ (37209)
66 (Anekain or Bupivacain or Bupivacaine or Carbostesin or Exparel or Marcain or Marcaine or Sensorcaine or "SKY 0402").mp. (41490)
67 38396-39-3.rn. (2080)
68 Bupivacaine.rn. (35740)
69 Clonidine/ (46603)
70 (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)
71 4205-90-7.rn. (33399)
72 sufentanil/ (8333)
73 (Chronogesic or Sufenta or Sufentanil or Sufentanilum or Sulfentanil or Sulfentanyl or "R 30,730" or "R-30730" or Zalviso).mp. (9426)
74 56030-54-7.rn. (6522)
75 or/56-74 (263183)
76 narcotic analgesic agent/ (14311)
77 opioid*.tw. (125625)
78 analgesia/ (87193)
79 ((alleviat* or manag* or control* or reduc* or relief* or reliev*) adj5 pain*).tw. (207999)
80 or/76-79 (366320)
81 exp infusion pump/ (17063)
82 (infusion* or infusor* or perfusion* or perfusor*).tw. (695749)
83 ((implant* or intravenous*) adj5 (device* or pump$1 or deliver* or system*)).tw. (69800)
84 (SynchroMed* or InfusAid* or Codman$1).tw. (1157)
85 exp intraspinal drug administration/ (22511)
86 (intrathecal* or intra-thecal*).tw. (39785)
87 ((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)
88 or/81-87 (826697)
89 cancer pain/ (14246)
90 exp neoplasm/ (5688767)
91 exp Pain/ or (pain or painful*).tw. (1523690)
92 exp analgesia/ or exp analgesic agent/ (1108662)
93 90 and (91 or 92) (293698)
94 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) adj10 pain*).tw. (52910)
95 89 or 93 or 94 (315274)
96 (75 or 80) and 88 and 95 (5321)

97 exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (36733737)
98 exp humans/ or exp human experimentation/ or exp human experiment/ (27772668)
99 97 not 98 (8962609)
100 96 not 99 (5120)
101 exp "cost"/ (425969)
102 exp *economics/ (272329)
103 (cost or costs or costing or economic*).tw. (957134)
104 (cost-benefit* or cost-effective* or cost-utilit*).tw. (189480)
105 sensitivity analys*.tw. (35119)
106 (pharmacoeconomic* or pharmaco-economic*).tw. (9727)
107 exp "quality of life"/ (372965)
108 (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)
109 or/101-108 (1700875)
110 100 and 109 (591)
111 limit 110 to yr="1994-current" (524)
112 111 use emez (395)
113 55 or 112 (531)
114 remove duplicates from 113 (430) [UNIQUE RECORDS]
115 114 use prmz (133) [UNIQUE MEDLINE RECORDS]
116 114 use emez (297) [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	2-#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 25-#24 43161
#26 [mh Neoplasms] 49382
#27 [mh Pain] 31409
#28 (pain or painful*):ti,ab,kw 65640
#29 [mh "Pain Management"] 1399
#30 [mh Analgesia] 5931
#31 [mh Analgesics] 15151
#32 #26 and (#27 or #28 or #29 or #30 or #31) 3375
#33 ((cancer* or carcinoma* or malignan* or neoplasm* or oncolog* or tumor* or tumour*) near/10 pain*):ti,ab,kw 2836
#34 #32 or #33 4683
#35 (#12 or #17) and #25 and #34 Publication Date from 1994 to 2014 251

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Appendix 2: Evidence Quality Assessment

Table A1: GRADE Evidence Profile for Comparison of Intrathecal Drug Delivery System Plus CMM Versus CMM Alone

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
% Reduction in Pain Scores at 12 Weeks							
1 (RCT)	Very serious limitations (−2)[a]	No serious limitations	Serious limitations (−1)[b]	Very serious limitations (−2)[c]	NA	NA	⊕ Very Low
% Reduction in Composite Drug Toxicity Scores at 12 Weeks							
1 (RCT)	Very serious limitations (−2)[a]	Serious limitations (−1)[d]	Serious limitations (−1)[b]	Very serious limitations (−2)[e]	NA	NA	⊕ Very Low
≥ 20% Relief of Pain *or* Toxicity at 12 Weeks							
1 (RCT)	Very serious limitations (−2)[a]	No serious limitations	Serious limitations (−1)[b]	Very serious limitations (−2)[c]	NA	NA	⊕ Very Low
≥ 20% Relief of Pain *and* Toxicity at 12 Weeks							
1 (RCT)	Very serious limitations (−2)[a]	No serious limitations	Serious limitations (−1)[b]	Serious limitations (−1)[f]	NA	NA	⊕ Very Low
Survival at 6 Months							
1 (RCT)	Very serious limitations (−2)[g]	No serious limitations	Serious limitations (−1)[b]	Very serious limitations (−2)[c]	NA	NA	⊕ Very Low

Abbreviations: CMM, comprehensive medical management; GRADE, Grading of Recommendations Assessment, Development, Evaluation; NA, not applicable; RCT, randomized controlled trial.

[a]High risk of detection bias, selection bias, and confounding.

[b]Patients did not exclusively have refractory pain or intolerable side effects.

[c]Wide confidence interval and small analyzed sample.

[d]Reductions in individual drug toxicities were not statistically significant.

[e]Small sample size and fragile results. Also, lower bound approached “no clinically important difference.”

[f]Small number analyzed and fragile results.

[g]High risk of selection bias and confounding.

Table A2: Risk of Bias Among Randomized Controlled Trials for the Comparison of IDDS Plus CMM Versus CMM Alone

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Smith et al, 2002[26] and 2005[25]	Limitations[a]	Limitations[b]	Limitations[c]	Limitations[d]	Limitations[e]

Abbreviations: CMM, comprehensive medical management; IDDS, intrathecal drug delivery system.

[a]Unclear risk: insufficient information about the method of randomization and adequate allocation concealment.

[b]Unclear risk of performance bias (adequacy of CMM because adherence rates were not reported; balanced on various types of cancer treatments). High risk of detection bias for patient-reported outcomes of pain, quality of life, toxicity, and opioid consumption. Low risk for others.

[c]Unclear risk: by 4 weeks, 28% versus 24% of patients had missing values for various reasons. No appropriate adjustment for missing values was conducted.

[d]High risk for serious adverse events, procedure-related adverse events, and equipment-related adverse events for the 3- to 6-month time period. Although there were no major differences in baseline characteristics of randomized groups, there remained a serious concern about important prognostic imbalance at baseline because the intention-to-treat analysis in a companion paper revealed that more patients died in the control arm. In the as-treated analysis, investigators adjusted for a baseline imbalance in confounders but did not adjust for an imbalance owing to follow-up time-varying confounders and time-varying treatment. Moreover, it was unclear whether postrandomization intraspinal trialling for selection of IDDS patients was all intrathecal or a mix of intrathecal and epidural (the latter may not have correctly identified potential responders). Concerns also existed about an imbalance in the use of antidepressants, impacting pain and quality-of-life assessment. Lastly, IDDS person-time was variable, which could have challenged the validity of toxicity assessment in analyses that did not account for this.

[e]High risk: the as-treated analysis did not account for substantial crossover. By 6 months, about 30% of patients in both arms had crossed over from the contralateral treatment arm. The analysis did not account for crossover, leading to unit-of-analysis error. Because the crossover was conditional on failure (i.e., not everyone crossed over), very serious concerns about selection bias existed. Additional concerns about selection bias included the fact that trialling was undertaken postrandomization. As such, those who did not respond would not have received IDDS. The IDDS arm was likely loaded with potential responders, unlike the CMM arm. The direction of selection bias could not be ascertained without a formal analysis on patient-level data.

Table A3: Philips Checklist[19] for Quality Assessment of Brogan, 2013[24]

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?	No	
	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	Not a model
	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?	Unclear	
S3	Has the evidence regarding the model structure been described?	No	
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Unclear	
	Are the sources of data used to develop the structure of the model specified?	Yes	
S4	Are the structural assumptions transparent and justified?	NA	Not a model
	Are the structural assumptions reasonable given the overall objective, perspective, and scope of the model?	NA	Not a model
S5	Is there a clear definition of the options under evaluation?	No	
	Is there justification for the exclusion of feasible options?	No	Not discussed
S6	Is the chosen model type appropriate given the decision problem and specified causal relationship within the model?	NA	Not a model
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	NA	Not a model
	Are the time horizon of the model, the duration of treatment, and the duration of treatment effect described and justified?	NA	Not a model
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	Not a model
S9	Is the cycle length defined and justified in terms of the natural history of disease?	NA	Not a model
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	
	Where choices have been made between data sources, are these justified appropriately?	No	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	Has particular attention been paid to identifying data for the important parameters in the model?	NA	Not a model
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	Unclear	
	Has the quality of the data been assessed appropriately?	Unclear	
	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?	Unclear	
D2a	Is the choice of baseline data described and justified?	NA	Not a model
	Are transition probabilities calculated appropriately?	NA	Not a model
	Has a half-cycle correction been applied to both cost and outcome?	NA	Not a model
	If not, has this omission been justified?	NA	Not a model
D2b	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	NA	No relative treatment effects included
	Have the methods and assumptions to extrapolate short-term results to final outcomes been documented and justified?	No	Problems with before-and-after study design not addressed
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	NA	No extrapolation of data
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	NA	No extrapolation of data
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?	Yes	
	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	No	

Quality Criteria	Questions for Critical Appraisal	Response	Comments
	uncertainty been justified?		
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	No sensitivity analyses
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	NA	No sensitivity analyses
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	NA	
C2	Are the conclusions valid given the data presented?	No	Analysis fails to consider survival estimates alongside cost estimates
	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?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	No	Results not put into context with previous literature

Abbreviations: C, consistency; D, data; NA, not applicable; S, structure.

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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.

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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.

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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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