ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Intrathecal Drug Delivery Systems for Cancer Pain

A Health Technology Assessment

JANUARY 2024

Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Pain is one of the most common and most distressing symptoms for adults and children with cancer. There are different types of pain medication and different ways of delivering medication, for example, by mouth or through injection. However, for some patients, commonly available medications and delivery routes do not provide enough pain control or cause undesirable side effects at high doses.

An intrathecal drug delivery system (IDDS) directly infuses pain medication into a fluid-filled space around the spinal cord called the intrathecal space. A pump is implanted under the skin and stores pain medication that is delivered to the intrathecal space by a catheter (a thin tube). It requires much lower doses of medication compared with medication that is delivered in other ways. Because of this, the use of an IDDS may reduce side effects and allow for more rapid and effective pain relief.

This health technology assessment looked at how effective, safe, and cost-effective IDDSs are for managing cancer pain in adults and children. It also looked at the budget impact of publicly funding these devices; the experiences, preferences, and values of adults and children with cancer pain; and the ethical considerations that arise in the context of IDDSs for managing cancer pain in adults and children.

What Did This Health Technology Assessment Find?

Compared with other ways of delivering pain medication, intrathecal drug delivery likely reduces pain intensity and decreases the use of systemic opioids in adults with cancer pain who have a life expectancy greater than 6 months. It may also improve health-related quality of life, functional outcomes, and survival, although the evidence for survival is very uncertain. The clinical evidence for intrathecal drug delivery in children with cancer pain is very uncertain. The implantation of an intrathecal drug delivery device carries certain rare risks related to mechanical errors, drug-related side effects, and surgical complications.

Compared with other ways of delivering pain medication, intrathecal drug delivery may be a cost-effective option. We estimate that publicly funding IDDSs for patients with refractory cancer pain in Ontario over the next 5 years would cost an additional $1.34 million.

Patients with cancer pain and caregivers with whom we spoke described the debilitating nature of cancer pain and its negative impact on quality of life and mental health. They also spoke of the difficulty and frustration of having to try many options to find effective pain management. Those with experience of an IDDS spoke of its effectiveness in managing pain and its positive impact on quality of life and mental health.

Several ethical and equity considerations arise in the context of IDDSs, including disparities in the experiences and management of cancer pain, which can limit access to appropriate care; limitations in the evidence base, leading to uncertainties in decision-making for both patients and health systems; inequities in the clinical criteria used to identify eligible patients and the introduction of IDDSs into clinical practice; equity-of-access challenges related to geographic disparities and the significant resources needed for assessment, implantation, and ongoing care; and health system considerations related to any limitations to implement, deliver, and scale access to IDDSs in Ontario.

Acknowledgements

This report was developed by a multidisciplinary team from Ontario Health and the Canadian Agency for Drugs and Technologies in Health (CADTH). From Ontario Health, the primary clinical epidemiologist was Christine Lee, the secondary clinical epidemiologist was Kristen McMartin, the primary medical librarian was Corinne Holubowich, the secondary medical librarian was Caroline Higgins, the primary health economist was Jennifer Guo, the secondary health economist was Xuanqian Xie, and the primary patient engagement analyst was Jigna Mistry. From CADTH, the ethicist was Renata Axler.

The medical editor was Kara Cowan. Others from Ontario Health involved in the development and production of this report were Jamie Turnbull, Anisa Shire, Claude Soulodre, Susan Harrison, Sarah McDowell, Chunmei Li, Andrée Mitchell, Charles de Mestral, and Nancy Sikich. Others from CADTH involved in the development of this report were Jennifer Horton, Kendra Christiansen, Farah Husein, and Laura Weeks.

We would like to thank the following people and organizations for lending their expertise to the development of this report:

- Ehtesham Baig, University Health Network
- Anuj Bhatia, University Health Network
- Darren Cargill, Ontario Palliative Care Network
- Phillip Chan, St. Joseph's Healthcare Hamilton
- Collin Clarke, London Health Sciences Centre
- David Clinkard, Queen's University
- Sunit Das, University of Toronto
- Abha Gupta, The Hospital for Sick Children
- Pippa Hawley, BC Cancer
- Jenny Lau, University Health Network
- Nimish Mittal, University Health Network
- Dwight Moulin, London Health Sciences Centre
- Patricia Murphy-Kane, University Health Network
- Jill Osborn, Providence Health Care
- Vishal Varshney, Providence Health Care

We also thank our lived experience participants who generously gave their time to share their stories with us for this report.

The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

Citation

Ontario Health. Intrathecal drug delivery systems for cancer pain: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2024 Jan;24(2):1–162. Available from: hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/intrathecal-drug-delivery-systems-for-cancer-pain

Abstract

Background

Pain is a common and very distressing symptom for adults and children with cancer. Compared with other routes of delivery, infusing pain medication directly into the intrathecal space around the spinal cord may reduce the incidence of systemic side effects and allow for more rapid and effective pain relief. We conducted a health technology assessment of intrathecal drug delivery systems (IDDSs) for adults and children with cancer pain, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding IDDSs, patient preferences and values, and ethical considerations.

Methods

We performed a systematic literature search of the clinical evidence to retrieve systematic reviews, and we selected and reported results from 2 recent reviews that were relevant to our research questions. We complemented the chosen systematic reviews with a literature search to identify primary studies published after December 2020. We used the Risk of Bias in Systematic Reviews (ROBIS) tool to assess the risk of bias of each included systematic review. We assessed the quality of the body of evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted a cost-effectiveness analysis comparing IDDSs with standard care (i.e., non-IDDS methods of pain management) from a public payer perspective. We also analyzed the budget impact of publicly funding IDDSs in Ontario. To contextualize the potential value of IDDSs, we spoke with patients with cancer pain and with caregivers of patients with cancer pain. We explored ethical considerations from a review of published literature on the use of IDDSs for the management of cancer pain in adults and children as well as a review of the other components of this health technology assessment to identify ethical considerations relevant to the Ontario context.

Results

We included 2 systematic reviews (1 on adults and 1 on children) in the clinical evidence review. In adults with cancer pain who have a life expectancy greater than 6 months, intrathecal drug delivery was associated with a significant reduction in pain intensity compared with before implantation up to a 1-year follow-up (GRADE: Moderate to Low). Improved pain management appeared to be maintained beyond a 4-week follow-up. IDDSs likely decrease the use of systemic opioids (GRADE: Moderate to Low). They may also improve health-related quality of life (GRADE: Low), functional outcomes (GRADE: Low), and survival (GRADE: Low to Very low). In children with cancer pain, IDDSs may reduce pain intensity, improve functional outcomes, and improve survival, but the evidence is very uncertain (all GRADEs: Very low). IDDS implantation carries certain rare risks related to mechanical errors, drug-related side effects, and surgical complications. There are inherent limitations in conducting research in patients with refractory cancer pain; therefore, it is unlikely that higher-quality evidence will emerge in the next few years. Our primary economic evaluation found that IDDSs are more effective and more costly than standard care. The incremental cost-effectiveness ratio of IDDSs compared with standard care is $57,314 per quality-adjusted life-year (QALY) gained. The probability of IDDSs being cost-effective versus standard care is 43.46% at a willingness-to-pay of $50,000 per QALY gained and 72.54% at a willingness-to-pay of $100,000 per QALY gained. Publicly funding IDDSs in Ontario would cost an

additional $0.27 million per year, for a total of $1.34 million over the next 5 years. The patients with cancer pain and caregivers with whom we spoke described the debilitating nature of cancer pain and the difficulty of finding effective pain management options. Patients with experience of an IDDS spoke of its effectiveness and its positive impact on their quality of life and mental health. Implementing IDDSs for patients with cancer pain raises several ethical and equity considerations related to the experiences and management of cancer pain, how limitations in evidence may entail uncertainties in clinical and health system decision-making, as well as clinical, geographic, and health system access barriers.

Conclusions

Intrathecal drug delivery likely reduces pain intensity and decreases the use of systemic opioids in adults with cancer pain who have a life expectancy greater than 6 months. It may also improve health-related quality of life, functional outcomes, and survival, although the evidence for survival is very uncertain. The clinical evidence in children with cancer pain is very uncertain. IDDS implantation is reasonably safe. Intrathecal drug delivery is more effective and more costly than standard care. We estimate that funding IDDSs in Ontario will result in additional costs of $0.27 million per year, for a total of $1.34 million over the next 5 years. Considerations related to funding and implementing IDDSs for patients with cancer pain in Ontario will require explicit and focused attention to considerations of equity and access in the diagnosis and management of cancer pain and in the use, clinical uptake, and delivery of IDDS pain management.

Table of Contents

List of Tables

List of Figures

Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of implantable intrathecal drug delivery systems (IDDSs) for the management of cancer pain in adults and children. It also evaluates the budget impact of publicly funding implantable IDDSs; the experiences, preferences, and values of adults and children with cancer pain; and the ethical considerations that arise in the context of IDDSs for managing cancer pain in adults and children.

Background

Health Condition

Pain is one of the most common and most distressing symptoms for adults and children with cancer[1] and may negatively affect quality of life.[2] Cancer pain may be directly related to the primary tumour or metastatic disease, treatment (e.g., surgery, chemotherapy, radiation), or other causes not related to the malignancy.[3]

Clinical Need and Population of Interest

A systematic review in 2016 reported that the prevalence of cancer pain ranged from 33% in patients after curative treatment, to 55% in patients during anticancer treatment, and to 66% in patients with metastatic, advanced, or terminal disease.[4] Despite the development of clinical guidelines on pain management and the availability of opioids, the cancer pain of about 40% of patients with cancer is undertreated.[5] Advancements in cancer treatment have resulted in more patients receiving life-prolonging or curative treatment and more patients living longer after cancer diagnosis.[6] Many cancer survivors live with chronic pain conditions because of tumour-associated tissue damage and injury from treatment regimens.[7]

Current Treatment Options

The World Health Organization's 3-step analgesic "ladder" for cancer pain management is a stepwise model for the prescription of analgesic medications according to pain severity, ranging from acetaminophen and nonsteroidal anti-inflammatory drugs for mild pain to opioids for severe pain.[8] However, high doses of opioids are associated with undesirable side effects such as constipation, opioid use disorder, respiratory depression, sedation, and death.[9,10]

Pain medicine experts have suggested adding interventional procedures to the World Health Organization's analgesic ladder.[11,12] These include peripheral nerve blockade, neuraxial blocks, neurolytic blocks, radiofrequency ablation, sympathetic blocks, vertebral augmentation, neuromodulation, intrathecal drug delivery, and advanced neurosurgical procedures such as percutaneous cordotomy.[13]

Health Technology Under Review

Intrathecal drug delivery for refractory cancer pain (cancer pain no longer responding to conventional pain management) has been used in adult populations for more than 50 years.[14] Its use for cancer pain in children via implanted pump was first reported in the year 2000.[15] Before then, medications for refractory cancer pain in children were delivered into the intrathecal space through a catheter attached to an external pump.[16] The use of an external pump is still appropriate for patients at the end of life with a prognosis of 1 to 6 months.[17] However, intrathecal drug delivery via external pump was outside the scope of this health technology assessment. Except where specified, all references to intrathecal drug delivery and to IDDSs in this health technology assessment refer to intrathecal delivery via implanted pump.

An IDDS consists of a drug infusion device (a pump) and a catheter (a thin tube). The drug infusion device is implanted subcutaneously (under the skin) in the abdominal wall or the gluteal area (the buttocks). The device stores pain medication and delivers it through the catheter to the fluid-filled space around the spinal cord known as the intrathecal space. A drug reservoir in the drug infusion device is accessed percutaneously (through the skin) through a port to change or refill the medication.[18] The drug infusion device can be programmed to release medication at a fixed rate, thus delivering a constant flow of medication over a defined period, or at a variable rate, delivering different amounts of medication at different times of day. The drug infusion device also allows patients to administer boluses (additional doses) via patient-controlled programming.[19]

The direct infusion of medication into the intrathecal space circumvents the blood–brain barrier and allows the medication to bypass first-pass metabolism, thus allowing for direct absorption into the tissues of the central nervous system. As such, the use of an IDDS requires much lower doses of medication compared with oral, intravenous, transdermal, and epidural methods of drug delivery. By providing lower doses of medication and delivering medication directly into the cerebrospinal fluid, intrathecal drug delivery may reduce the incidence of systemic side effects and allow for more rapid and more effective pain relief.[20] However, intrathecal drug delivery does pose risks such as respiratory depression, pump or catheter infection, bleeding and epidural/spinal hematoma, spinal cord injury during initial catheter placement, wound dehiscence, and pocket seromas.[21]

The type and dose of medication and the frequency of its administration depend on the regimen of oral medications the patient is already being prescribed (E. Baig, MD, virtual communication, October 27, 2022). Both local anaesthetics and opioids are delivered intrathecally. The goal when transitioning a patient to an IDDS for cancer pain management is for all systemic opioid medications to be delivered intrathecally.

Regulatory Information

Three infusion pump systems for the intrathecal drug delivery of analgesic medications are licensed by Health Canada (Table 1). Two earlier-generation systems are no longer available on the market and have been replaced by the Synchromed Infusion II System (Medtronic Canada Inc., email communication, November 14, 2022).

Table 1: Intrathecal Drug Delivery Systems Licensed by Health Canada

System name	Manufacturer	Device class	Licence number	Licensed drugs	Available in Canada
Isomed System	Medtronic Canada Inc.	III	16579	Baclofen Morphine hydrochloride Morphine sulfate	No
Synchromed EL System	Medtronic Canada Inc.	III	934	Baclofen Morphine hydrochloride Morphine sulfate Ziconotide	No
Synchromed Infusion II System	Medtronic Canada Inc.	III	63074	Baclofen Morphine hydrochloride Morphine sulfate Ziconotide	Yes

There are 2 versions of the Synchromed Infusion II System, 1 with a reservoir size of 20 cc and 1 with a reservoir size of 40 cc (Medtronic Canada Inc., email communication, November 14, 2022). Although not specified as a pediatric pump, the system with the 20 cc reservoir is used in children because the pump is smaller.

The Prometra II programmable pump by Flowonix Medical Inc. is an IDDS available outside Canada.[22]

Ontario and Canadian Context

In 2016, based on a health technology assessment conducted by Health Quality Ontario,[23] the Ontario Health Technology Advisory Committee recommended "against the expansion of public funding for intrathecal drug delivery systems for patients with chronic pain due to advanced cancer," primarily because of low-quality evidence.[24] The clinical evidence review from the Health Quality Ontario health technology assessment[23] included 1 randomized controlled trial published in 2002[25] and 1 post-hoc analysis of that trial.[25] Since the publication of that health technology assessment in 2016, there has been no change in IDDS technology. However, new literature has emerged suggesting clinical efficacy and economic savings with the use of intrathecal drug delivery for the management of cancer pain.

Currently in Ontario, 1 hospital has an intrathecal drug delivery program for cancer pain management that uses implantable pumps; this program provides care for both adults and children (E. Baig, MD, virtual communication, October 27, 2022). Although there is no lower age limit for the program, adolescents are generally considered better candidates than children. A limited supply of IDDSs is

provided by the manufacturer. Patient eligibility is assessed by an interdisciplinary team including specialists in the areas of pain medicine, anaesthesiology, neurosurgery, oncology, radiation oncology, palliative care, physical medicine and rehabilitation, and nursing, based on the program's selection criteria, which are as follows.

Indications for the intrathecal drug delivery program include:

- Patients with severe cancer-related pain despite treatment with appropriate medical therapy, as well as patients who have achieved some analgesia with medical therapy but are unable to tolerate the side effects of these medications
- Patients with pain secondary to focal disease below the neck that is amenable to treatment with an intrathecal catheter. Pain resulting from diffuse metastatic disease is not amenable to this therapy
- Patients with a life expectancy of more than 6 to 9 months
- Patients who have been assessed by a multidisciplinary team including specialists in the areas of physical therapy, psychology, and nursing and who have been judged to be good candidates for intrathecal drug delivery. This step is necessary to address underlying psychological concerns and manage patient expectations
- Patients who have caregiver support to assist with device management at home
- Patients with sufficient mobility to enable follow-up visits for pump assessments and refills, unless reaching end of life

Absolute contraindications for the program include:

- Patients with systemic infection
- Patients with an uncorrectable or untreatable coagulopathy (however, being on anticoagulant therapy is not an absolute contraindication)
- Patients with an established allergy to any of the pump components
- Patients with a local infection at the site of catheter or pump insertion (however, another suitable site that is not infected could be considered)

Relative contraindications for the program include:

- Patients with psychological comorbidities including untreated depression, anxiety, ongoing drug or alcohol use disorder, and cognitive dysfunction. Psychosocial stressors such as excessive distress, unrealistic expectations, and caregiver access must also be addressed
- Patients with comorbid disease severe enough to preclude surgery and anaesthesia
- Patients with metastatic disease in the spine that would make catheter placement risky

The drug infusion device is implanted by a pain medicine physician or neurosurgeon in the operating room in an inpatient or outpatient setting (E. Baig, MD, virtual communication, October 27, 2022). Pain

management and ongoing care of the IDDS, including pump refills and programming, are done in an outpatient pain clinic or in patients' homes (for those at end of life) by a physician or nurse practitioner. An on-call system provides patients with after-hours support.

Considering the indications and contraindications of Ontario's intrathecal drug delivery program, it is estimated that approximately 60 patients with cancer pain (including adults and adolescents) are eligible for intrathecal drug delivery annually in Ontario (E. Baig, MD, virtual communication, October 27, 2022). Among these 60 patients, approximately 10% would be adolescents aged 12 to 17 years (E. Baig, MD, virtual communication, June 21, 2023).

Assessment for and the implantation of an IDDS should be performed in a tertiary care centre (a facility, often an academic teaching hospital, that provides specialized health care for inpatients) (E. Baig, MD, virtual communication, October 27, 2022). While virtual appointments can be used to monitor symptoms, in-person clinic visits are required to check the implantation site, adjust medication dose and frequency, and refill and program the pump. Clinic visits are more frequent in the first few weeks after implantation to transition systemic pain medications to the intrathecal route. Ongoing follow-up is based on patients' needs.

Currently, British Columbia is the only province in Canada that publicly funds IDDSs for the management of cancer pain. A health technology assessment of the neuromodulation of cancer and noncancer pain, including via IDDS, published by the Health Technology Assessment Office of British Columbia supported decision-making regarding public funding.[26]

We identified 4 international guidelines providing recommendations on the use of intrathecal drug delivery for the management of cancer pain (Table 2). Overall, these guidelines recommend that IDDSs should be strongly considered for patients with severe cancer pain that is not responding to conventional pain management. The Polyanalgesic Consensus Conference expert group also published recommendations for trialing intrathecal drug delivery therapy,[27] as well as guidance for improving the safety and mitigating the risks of intrathecal drug delivery.[28]

Table 2: Guideline Recommendations for Intrathecal Drug Delivery for the Management of Cancer Pain

Author, title, year	Recommendations
American Society of Pain and Neuroscience, "Best practices and guidelines for the interventional management of cancer-associated pain," 2021[29]	"Intrathecal drug delivery using an implantable pump should be strongly considered in patients with cancer-related pain that is not responding to conventional medical management" (evidence level I[a]; recommendation grade A[b])
Polyanalgesic Consensus Conference, "Recommendations on intrathecal drug infusion systems best practices and guidelines," 2017[30]	"Intrathecal therapy should be utilized for active cancer-related pain with opioids or ziconotide" (evidence level I[a]; recommendation grade A[b]; consensus strength strong)
NHS England, "Clinical commissioning policy: intrathecal pumps for treatment of severe cancer pain," 2015[31]	"Intrathecal drug delivery plays an important role in the treatment of intractable (hard to control) pain in a small group of appropriately selected patients, with an associated significant reduction in quality of life and that have no other treatment options. The needs of this population can be variable and as a consequence the selection process requires a highly specialised team to ensure appropriate selection and safety criteria as well as equity of access."
British Pain Society, "Intrathecal drug delivery for the management of pain and spasticity in adults: recommendations for best clinical practice," 2016[32]	"Intrathecal drug delivery is a recognized intervention for the management of chronic non-malignant pain, pain in patients with cancer and spasticity. The principal indication for using intrathecal drug delivery for pain in patients with cancer is failure of conventional routes of administration of analgesics to achieve satisfactory analgesia despite escalating doses of strong opioids and/or dose limiting side effects."

Abbreviation: NHS, National Health Service.

[a]Evidence based on at least 1 properly designed randomized controlled trial.

[b]Extremely recommendable.

Equity Context

Access to IDDSs for patients with cancer pain is currently limited to 1 hospital in Ontario that chose to adopt this technology through industry support. If effective, public funding may improve equity in access to the technology.

Expanding candidacy criteria to include patients who live alone and those who live far from a tertiary care centre but are otherwise deemed medically appropriate, with the support of community care, home care, and primary care, may improve access to this technology across the province.

Expert Consultation

We engaged with experts in the specialty areas of pain medicine, palliative care, neurosurgery, pediatric oncology, physical medicine and rehabilitation, and nursing to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence for intrathecal drug delivery for the management of cancer pain in Ontario.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD 42023393467), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the effectiveness and safety of implantable intrathecal drug delivery systems (IDDSs) compared with non-IDDS methods of pain management for the management of cancer pain in adults and children?

Methods

Review Approach

To leverage existing evidence, we first systematically searched for a recent systematic review with high methodological quality that addressed our research question. More than 1 systematic review could have been chosen if each addressed different predefined populations or outcomes. We based the selection of the systematic reviews on the recency of the evidence, a risk-of-bias assessment, and the comprehensiveness of outcomes reported. Second, we ran a systematic literature search starting from the end date of the search of the earlier published of the 2 selected systematic reviews to identify any relevant primary studies published since that search had been conducted.

Clinical Literature Search

We performed a clinical literature search on December 19, 2022, by combining the population and intervention terminology with a methodological filter to retrieve systematic reviews, meta-analyses, and health technology assessments published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED).

Once the systematic reviews were selected, we updated the search starting from the end date of the earlier systematic review's search. We performed a literature search on January 26, 2023, using the same search strategy to capture the population and intervention terminology without a methodological filter to retrieve primary studies published from January 1, 2021, until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[33]

For both searches, we created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our clinical literature search strategy, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria – Systematic Reviews

- English-language full-text publications
- Studies published from database inception until December 19, 2022
- Systematic reviews, meta-analyses, and health technology assessments that included a systematic review of randomized controlled trials (RCTs) and comparative observational studies (including before-and-after studies), and that:
    - Specified well-defined research questions and inclusion and exclusion criteria
    - Used a reproducible literature search strategy of 2 or more electronic databases and provided information on databases searched, search terms, and search dates
    - Assessed and reported the methodological quality of the included studies (e.g., risk-of-bias assessment)

Inclusion Criteria – Primary Studies

- English-language full-text publications
- Studies published from January 1, 2021, until January 26, 2023
- RCTs and comparative observational studies (including before-and-after studies)

Exclusion Criteria – Systematic Reviews

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, primary studies, abstracts, editorials, letters, case reports, case series, and commentaries

Exclusion Criteria – Primary Studies

- Animal and in vitro studies
- Reviews, abstracts, editorials, letters, case reports, case series, and commentaries

Participants

- Adults and children with cancer-related pain who are indicated for intrathecal drug delivery using an implantable pump (see description of indications and contraindications in the “Ontario and Canadian Context Section” above)

Intervention

- IDDS as the sole route of delivery for pain medication

Comparator

- Conventional medical management via nonintrathecal drug delivery; e.g., oral pain medications, methadone, subcutaneous opioids, periodic blocks

Outcome Measures

- Pain intensity
- Functional outcomes (e.g., activities of daily life)
- Health-related quality of life
- Health care use (e.g., hospital visits)
- Types and doses of pain medications
- Drug-related side effects
- Device-related side effects

Timing

- After diagnosis of cancer with a life expectancy of more than 6 months

Setting

- Inpatient and outpatient

Literature Screening

Prior to screening all titles and abstracts, 2 reviewers assessed the eligibility of a sample of 100 citations until sufficient agreement (> 80%) was reached. If this threshold was not met, the eligibility criteria were clarified, and the validation exercise was repeated with another 50 citations. Once the internal validation was successful and all disagreements were resolved, the primary reviewer screened all remaining citations using Covidence[34] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The primary reviewer then examined the full-text articles and selected studies eligible for inclusion. The primary reviewer also examined the reference lists of the included studies for any additional relevant studies not identified through the search. Citation flow and reasons for the exclusion of full-text articles were reported according to the PRISMA statement.[35]

Data Extraction

For systematic reviews, the primary reviewer extracted data on populations, interventions, comparators, outcomes, and literature search information to guide the selection of the best-quality systematic reviews.

From the chosen systematic reviews, data on study characteristics, outcome results, and follow-up duration of each included study were extracted as reported.

Since the only eligible primary study was included in the chosen systematic review, we used the data extracted by that systematic review.

Equity Considerations

We used PROGRESS-Plus, a health equity framework recommended by the Campbell and Cochrane Equity Methods Group[36] to explore potential inequities for this health technology assessment. Factors that could lead to disadvantage or inequities in the framework include place of residence; race, ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes.

We sought but did not identify any equity considerations relevant to the use of IDDSs for the management of cancer pain across different populations defined by the PROGRESS-Plus categories.[37] However, equity considerations may exist that were not identified as part of our analysis.

Statistical Analysis

Since the primary study[38] that we identified was included in 1 of our selected systematic reviews,[39] we did not perform a de novo synthesis. We reported all statistical analyses as they were presented in that systematic review.[39]

Critical Appraisal of Evidence

We assessed risk of bias in the included systematic reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool[40] (Appendix 2, Table A1). We reported the risk of bias of the primary studies included in the systematic reviews as reported by the authors of the systematic reviews.

We evaluated the quality of the body of evidence for each outcome based on the risk of bias as reported by the authors of the included systematic reviews and based on expert consultation. We made our evaluations according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[41] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search for Systematic Reviews

The database search of clinical literature for systematic reviews yielded 90 citations published between database inception and December 19, 2022, including grey literature searches and after duplicates were removed. We identified no additional eligible studies from other sources. In total, we identified 6 studies (4 systematic reviews[39,42-44] and 2 health technology assessments[23,45]) that met our inclusion criteria. See Appendix 3 for a list of selected systematic reviews excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search for systematic reviews.

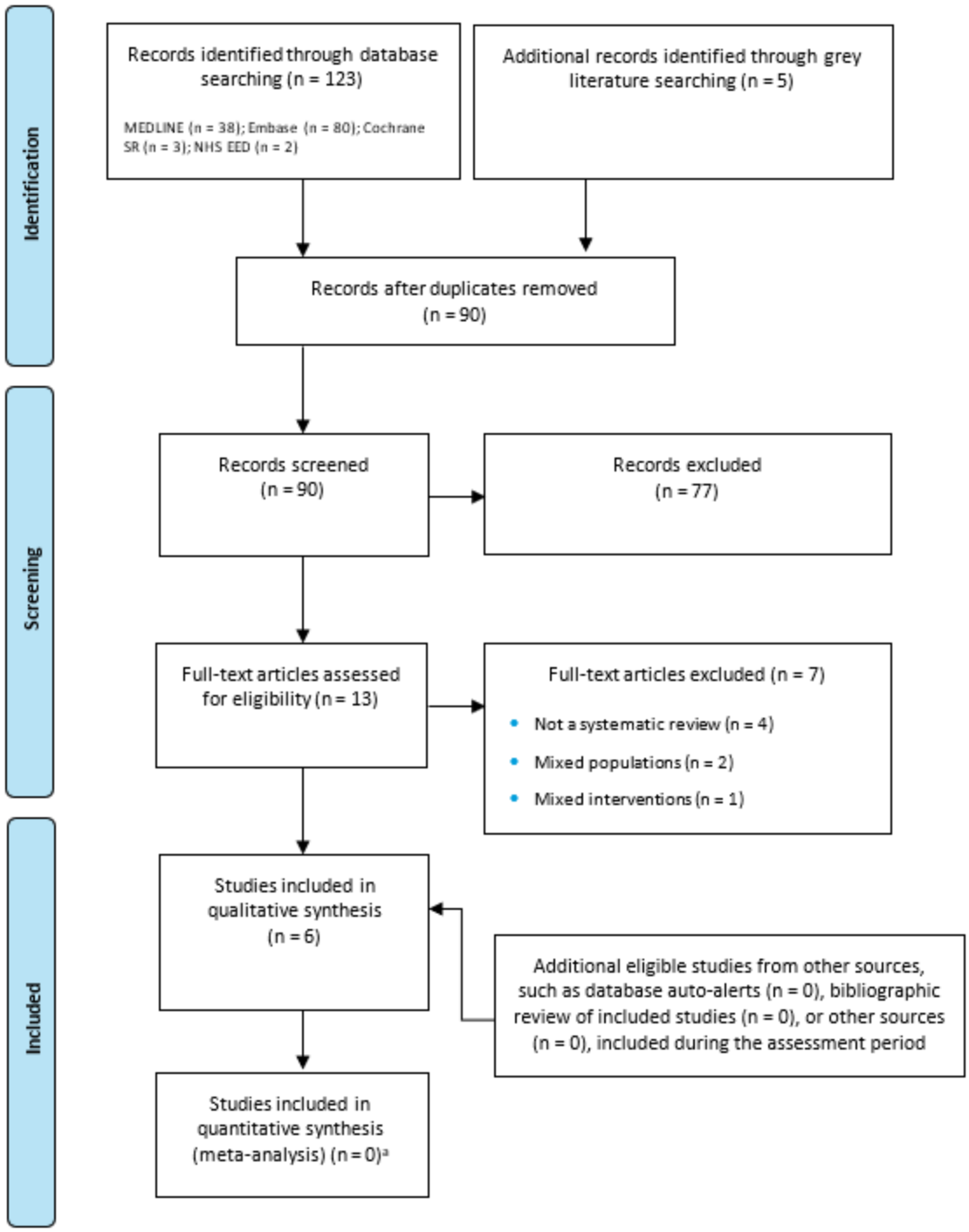

Figure 1: PRISMA Flow Diagram – Clinical Search Strategy for Systematic Reviews

PRISMA flow diagram showing the clinical search strategy for systematic reviews. The database search of systematic reviews yielded 90 citations published between database inception and December 19, 2022, including grey literature searches and after duplicates were removed. We identified no additional eligible studies from other sources. We screened the abstracts of the 90 identified studies and excluded 77. We assessed the full text of 13 articles and excluded a further 7. In the end, we included 6 articles in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
[a]The purpose of the systematic review search was to identify recent high-quality systematic reviews that addressed the clinical research question to leverage existing evidence; therefore, the included systematic reviews were not meta-analyzed.
Source: Adapted from Page et al.[35]

Characteristics of Identified Systematic Reviews

Four systematic reviews[39,42-44] and 2 health technology assessments[23,45] initially met our eligibility criteria. One systematic review was conducted in pediatric populations,[42] and the others were conducted in adult populations.[23,39,43-45] The reviews were published between 2011 and 2022. The more recent reviews captured newer primary studies that had not been included in the 2016 health technology assessment by Health Quality Ontario.[23] See Appendix 2, Table A1, for the risk-of-bias assessment of the identified systematic reviews using the ROBIS tool.

We excluded 4 systematic reviews.[23,43-45] Among those, the 2012 health technology assessment by the Belgian Health Care Knowledge Centre[45] had a low risk of bias, but its literature search was outdated. The 2011 systematic review by Hayek et al[43] and the 2016 health technology assessment by Health Quality Ontario[23] did not provide references of excluded full-text articles, and both literature searches were outdated. The systematic review by Perruchoud et al[44] included both external and implantable IDDSs as interventions in its primary meta-analyses, and the heterogeneity statistics included studies with either intervention. The authors reported subgroup analyses for implantable IDDSs for several few outcomes, including change in pain level, systemic opioid consumption, infection, and survival. However, they did not conduct a risk-of-bias assessment of the included studies, and the end date of their literature search was January 2019. Appendix 4, Table A7, summarizes the design and characteristics of the systematic reviews that we identified but then excluded.

For our analysis, we ultimately selected 2 systematic reviews: 1 in adult populations by Duarte et al[39] published in 2022 (with a literature search end date of March 2021) and 1 in pediatric populations by Kenfield et al[42] published in 2021 (with a literature search end date of December 2020). Table 3 describes the characteristics of the selected systematic reviews.

The review by Duarte et al[39] was rated at low risk of bias using the ROBIS tool. Although this systematic review included implantable IDDSs and spinal cord stimulation as interventions, the authors pooled studies on implantable IDDSs in meta-analyses for the primary outcome of pain intensity and presented summary estimates and heterogeneity statistics. The authors included a predefined review protocol and reported comprehensive literature search strategies. They also provided detailed information about the characteristics of study populations, outcomes, and risk-of-bias assessment for each included study, as well as an assessment of the quality of the body of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.

The review by Kenfield et al[42] is the only systematic review published on IDDSs for the management of cancer pain in pediatric populations to date. Despite its high risk of bias, we elected to include this review to highlight the scarcity of literature and the challenges of conducting research in this population.

Table 3: Characteristics of Included Systematic Reviews

Author, year, literature search end date	Populations	Interventions	Comparators	Outcomes	Study designs
Duarte et al, 2022,[39] March 2021	Adult patients aged ≥ 18 y with pain related to cancer or its treatment	Implantable IDDS and/or SCS (implantable IDDS results analyzed and reported separately)	Any comparators or no comparators	Change in pain intensity Health-related quality of life Functional outcomes Reduction in systemic opioid intake Survival Device-related complications Side effects	RCTs, case-control studies, cohort studies, uncontrolled single-arm studies, registry studies with sample size ≥ 20 participants
Kenfield et al, 2021,[42] December 2020	Patients aged < 21 y (no lower age limit)	External and implantable IDDS (implantable IDDS results reported separately)	Any comparators or no comparators	Satisfaction with analgesia Functional benefits	All study designs

Abbreviations: IDDS, intrathecal drug delivery system; RCT, randomized controlled trial; SCS, spinal cord stimulation.

Clinical Literature Search for Primary Studies

The database search of clinical literature for primary studies yielded 82 citations published between January 1, 2021, and January 26, 2023, after duplicates were removed. We identified no additional studies from other sources. In total, we identified 1 retrospective observational study that met our inclusion criteria. Figure 2 presents the PRISMA flow diagram for the clinical literature search for primary studies.

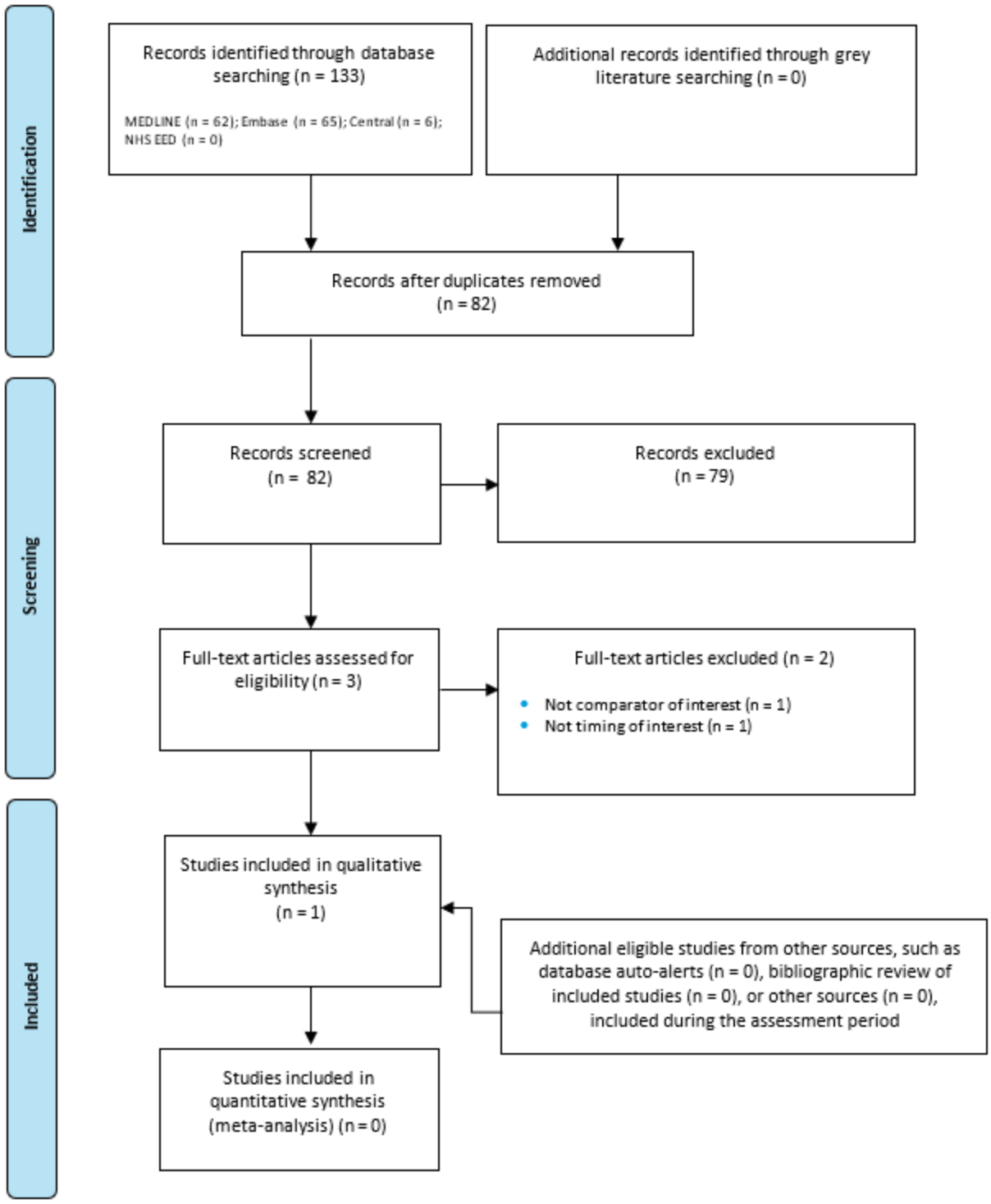

Figure 2: PRISMA Flow Diagram – Clinical Search Strategy for Primary Studies

PRISMA flow diagram showing the clinical search strategy for primary studies. The database search of primary studies yielded 82 citations published from January 1, 2021, to January 26, 2023, including grey literature searches and after duplicates were removed. We identified no additional eligible studies from other sources. We screened the abstracts of the 82 identified studies and excluded 79. We assessed the full text of 3 articles and excluded a further 2. In the end, we included 1 article in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[35]

Characteristics of Identified Primary Study

One retrospective observational study met our inclusion criteria.[38] It was first published online on July 8, 2020, and then published in print in March 2021. This study, by Spiegel et al,[38] was included in the systematic review by Duarte et al[39] and was also captured in our literature search for primary studies. Since Duarte et al[39] had extracted the data from, assessed the risk of bias of, and analyzed the results of this primary study, we leveraged their findings.

Characteristics of Included Studies

In their systematic review focusing on adults, Duarte et al[39] identified 1 RCT that compared IDDSs with comprehensive medical management.[46] (Subsequently, 2 post-hoc analyses of this RCT were published.[25,47]) Duarte et al[39] also included 19 observational studies[38,48-65] that evaluated only IDDSs for the management of cancer pain in adults. Among these studies, 7 were prospective[59-65] and 12 were retrospective.[38,48-58] The follow-up duration of the included studies ranged from 7 days to 16 months. The included studies examined various types of cancer, including breast, colorectal, gastrointestinal, hepatobiliary, lung, ovarian, pancreatic, prostate, sarcoma, urinary tract, and uterus. This systematic review included IDDSs and/or spinal cord stimulation as interventions. Given our scope, we extracted only the data and results pertaining to IDDSs.

In the systematic review by Kenfield et al focusing on pediatric populations,[42] the authors included 6 studies[15,16,66-69] reporting results on the use of IDDSs for the management of cancer pain in children. A total of 7 patients were included in these studies, among which 5 were case reports[15,16,66-68] and 1 was a case series.[69] The patients' ages ranged from 15 to 18 years. The follow-up duration ranged from 5 weeks to 5 months, although at the time of publication, the follow-up period of 1 study[16] remained ongoing. This systematic review included both external and implantable IDDSs as interventions. Given our scope, we extracted only the data and results pertaining to implantable IDDSs.

Table 4 describes the characteristics of the studies included in the selected systematic reviews.

Quality of Evidence

In the systematic review by Duarte et al,[39] the authors considered the overall risk of bias of the included RCT as high owing to concerns with deviation from intended interventions, outcome measurements, and selection of reported results. The authors considered the overall risk of bias of the included observational studies as high owing to concerns with the generalizability of results among centres, considerable differences in baseline systemic opioid dose, and various practices in opioid reduction.

In the systematic review by Kenfield et al,[42] the authors acknowledged that all data had been extracted from case series and case reports, which constitute a low quality of evidence. The authors considered the included studies as being at high risk of bias owing to a lack of randomization, blinding, and control groups, as well as potential selection and reporting biases.

The quality of evidence for each outcome in the selected systematic reviews is included in the following sections discussing the outcomes of all studies.

Table 4: Characteristics of Studies Included in the Selected Systematic Reviews

Author, year, country	Study design	Intervention	Comparator	No. patients (sex), age	Types of cancer	Follow-up duration	Funding source(s)
Studies included in the systematic review by Duarte et al[39] (adults)							
Smith et al, 2002,[46] Australia, Italy, Spain, Switzerland, United States	RCT	IDDS	CMM	IDDS n = 101 (M = 52, F = 49) Mean age: 56.2 ± 13.2 y CMM n = 99 (M = 59, F = 40) Mean age: 57.8 ± 13.7 y	IDDS: breast, colon, lung, pancreas, prostate CMM: breast, colon, lung, pancreas, prostate	Primary end point on pain intensity at 4 wk Survival at 6 mo	In part by Medtronic
Smith et al, 2005,[25] Australia, Italy, Spain, Switzerland, United States	Post-hoc analysis of RCT	IDDS	Non-IDDS methods of pain management	IDDS n = 101 (M = 52, F = 49) Mean age: 56.2 ± 13.2 y CMM n = 99 (M = 59, F = 40) Mean age: 57.8 ± 13.7 y	IDDS: breast, colon, lung, pancreas, prostate Non-IDDS: breast, colon, lung, pancreas, prostate	Primary end point on pain intensity at 4 and 12 wk Survival at 6 mo	In part by Medtronic
Smith et al, 2005,[47] Australia, Italy, Spain, Switzerland, United States	Post-hoc analysis of RCT	IDDS after failing CMM	NA	n = 30 (M = 16, F = 14) Mean age: 56.0 ± 13.4 y	Breast, colon, lung, pancreas, prostate	Primary end point on pain intensity at 4 wk Survival at 6 mo	In part by Medtronic
Brogan et al, 2015,[59] United States	Prospective observational	IDDS	NA	n = 58 (M = 40, F = 18) Mean age: 56.8 ± 14.6 y	Breast, colorectal, lung, pancreas, prostate,	41.7 ± 25.7 d (range: 14–82 d)	No financial support
Brogan et al, 2020,[60] United States	Prospective observational	IDDS	NA	n = 51 (M = 33, F = 18) Mean age: 56.6 ± 14.3 y	Breast, lung, pancreatic, prostate, sarcoma	8 wk	Department of Anesthesiology, University of Utah
Carvajal et al, 2018,[61] France	Prospective observational	IDDS	NA	n = 70 (M = 39, F = 31) Median age: 62.5 y (IQR: 51.5–68 y)	Pancreatic	3 mo	No financial support

Author, year, country	Study design	Intervention	Comparator	No. patients (sex), age	Types of cancer	Follow-up duration	Funding source(s)
Cheng et al, 2020,[62] China	Prospective observational	IDDS	NA	n = 33 (M = 21, F = 12) Mean age: 58.6 ± 7.0 y	Breast, gastrointestinal, hepatobiliary, lung, pancreatic	12 mo	Jiangsu Provincial Medical Youth Talents Program and the National Natural Science Foundation of China
Dupoiron et al, 2011,[63] France	Prospective observational	IDDS	NA	n = 97 (M = 52, F = 45) Mean age: 59.8 y (range: 25–88 y)	Breast, colorectal, pancreatic, prostate, uterus	3 mo	No financial support
Rauck et al, 2003,[64] United States and international sites	Prospective observational	IDDS	NA	n = 119 (M = 60, F = 59) Mean age: 60.6 ± 13.5 y	Breast, colorectal, lung, prostate	16 mo	Medtronic
Stearns et al, 2020,[65] Europe, Latin America, United States,	Prospective observational	IDDS	NA	n = 1,403 (M = 609, F = 794) Mean age: 59 y (range 13–93 y)	Breast, colon/rectal, Lung, pancreatic, prostate	12 mo	Medtronic
Becker et al, 2000,[48] Germany	Retrospective observational	IDDS	NA	n = 43 (M = 24, F = 19) Mean age: 64 y (range: 40–84 y)	Breast, lower gastrointestinal tract, lung, prostate gland, urinary tract	Neuropathic pain: median 2.5 mo Nociceptive pain: median 5 mo	NR
Brogan et al, 2011,[49] United States	Retrospective observational	IDDS	NA	n = 31 (M = 20, F = 11) Mean age: 55.2 ± 12.5 y	Colorectal, lung, pancreatic, prostate, sarcoma	4–6 wk	No financial support
Chen et al, 2020,[50] United States	Retrospective observational	IDDS	NA	n = 43 (M = 19, F = 24) Median age: 59 y	Breast, ovarian, pancreatic, renal, sarcoma	Mean: 8.9 d; median: 4 d	MSK Cancer Center Support Grant and Department of Anesthesiology and Critical Care

Author, year, country	Study design	Intervention	Comparator	No. patients (sex), age	Types of cancer	Follow-up duration	Funding source(s)
Dupoiron et al, 2019,[51] France	Retrospective observational	IDDS	NA	n = 108 (M = 59, F = 49) Mean age: 61 ± 11 y	Digestive tract, gynecologic tract, lung, urologic tract, other	7 d	NR
Erdine et al, 1996,[52] Turkey	Retrospective observational	IDDS	NA	n = 54 (M = 39, F = 15) Mean age: 56.0 ± 11.3 y	Breast, gastrointestinal, lung, urogenital, other	235.4 ± 140.4 d (range: 70–727 d)	NR
Onofrio et al, 1990,[53] United States	Retrospective observational	IDDS	NA	n = 53 (M = 24, F = 29) Mean age: 58.4 ± 1.6 y	Cervical, colon, lung, pancreas, rectal	4 mo	NR
Reig et al, 2009,[54] Spain	Retrospective observational	IDDS	NA	n = 64 (M = 34, F = 30) Median age: 57.5 y (IQR: 16–77 y)	NR	Median: 6.37 mo (IQR: 1–59 mo)	NR
Sayed et al, 2018,[55] United States	Retrospective observational	IDDS	NA	n = 160 (M = 83, F = 77) Median age: 58 y (IQR: 18–79 y)	Pancreatic	12 mo	No financial support
Scanlon et al, 2017,[56] United States	Retrospective observational	IDDS	NA	n = 64 (M = 29, F = 35) Mean age: 60 y	NR	12 mo	NR
Sindt et al, 2020,[57] United States	Retrospective observational	IDDS	NA	n = 173 (M = 96, F = 77) Mean age: 54.5 ± 15.3 y	Breast, lung, pancreas, prostate, other	30 d	No financial support
Spiegel et al, 2021,[38] United States	Retrospective observational	IDDS	NA	n = 50 (M = 22, F = 28) Median age: 61 y	Mostly breast and gastrointestinal	6 months	MSK Cancer Center Support Grant and the Department of Anesthesiology and Critical Care
Yegul et al, 1999,[58] Turkey	Retrospective observational	IDDS	NA	n = 58	Not specified for IDDS patients separately	Mean: 3.2 mo	NR

Author, year, country	Study design	Intervention	Comparator	No. patients (sex), age	Types of cancer	Follow-up duration	Funding source(s)
Studies included in the systematic review by Kenfield et al[42] (pediatric populations)							
Galloway et al, 2000,[15] United States	Case report	IDDS	NA	n = 1 (M), 15 y	Recurrent primitive neuroectodermal tumour encasing right ilium and sacrum	5 mo	NR
Tobias et al, 2000,[66] United States	Case report	IDDS	NA	n = 1 (M), 16 y	Metastatic adenocarcinoma of the colon	5 wk	NR
Saroyan et al, 2005,[67] United States	Case report	IDDS	NA	n = 1 (F), 15 y	Recurrent high-grade pleomorphic osteogenic sarcoma of right knee and left pelvis	2 mo	NR
Bengali et al, 2014,[68] United States	Case report	IDDS	NA	n = 1 (F), 15 y	Metastatic squamous cell cancer of the anus with vulvar-perianal condyloma	4.5 mo	NR
Kim et al, 2018,[69] United States	Case series	IDDS	NA	n = 2 (M), 17 y and 18 y	Avascular necrosis of hip secondary to acute leukemia, meningioma	NR	NR
Mele et al, 2021,[16] United States	Case report	IDDS	NA	n = 1 (F), 16 y	Ewing-like sarcoma of pelvis	Ongoing, months	NR

Abbreviations: CMM, comprehensive medical management; F, female; IDDS, intrathecal drug delivery system; IQR, intraquartile range; M, male; MSK, Memorial Sloan Kettering; NA, not applicable; NR, not reported; RCT, randomized controlled trial.

Note: Outcomes are presented in subsequent tables and sections.

Pain Intensity

Adults

In adults, the systematic review by Duarte et al[39] consistently showed an overall improvement in pain relief after IDDS implantation despite included studies using different measures of pain intensity. Aside from the 1 included RCT,[46] most included studies were before-and-after studies comparing pain intensity at baseline and follow-up. The follow-up duration ranged from 1 to 12 months.

Qualitatively, most the included studies showed a reduction in pain scores of approximately 30% to 50% after IDDS implantation at follow-ups ranging from 1 to 12 months (Table 5). This magnitude of effect represents a clinically important pain reduction.[70] The results of 3 observational studies suggested maintenance of improved pain management beyond the 4-week follow-up.[60,64,65]

Quantitatively, a meta-analysis of 4 prospective studies[46,59,60,63] and 2 retrospective studies[49,50] including 325 participants implanted with an IDDS showed a significant reduction in pain intensity (as measured by a visual analog scale or numeric rating scale) at a follow-up of up to 1 month compared with baseline, with a mean difference of −3.53 (95% confidence interval [CI]: −4.06, −3.00). Another meta-analysis of 6 prospective studies[46,59,60,62,63,65] and 2 retrospective studies[49,50] including 405 participants implanted with an IDDS also showed a significant reduction in pain intensity at the latest follow-up compared with baseline, with a mean difference of −3.31 (95% CI: −4.18, −2.45). There was substantial heterogeneity (I^2: 62.7–90.6%) between studies, which was not explained by study design (i.e., prospective vs. retrospective).

Based on 1 RCT and 16 observational studies, the GRADE quality of the evidence for pain intensity in adults was considered Moderate (RCT) to Low (observational studies), upgraded due to the large magnitude of effects (Appendix 2, Table A2).

Children

In children, the systematic review by Kenfield et al[42] reported that all 7 patients reported satisfactory analgesia after IDDS implantation (Table 5).

Based on 5 case reports and 1 case series summarized by Kenfield et al,[42] the GRADE quality of the evidence for pain intensity in children was considered Very low (case reports and case series), downgraded due to risk of bias and serious imprecision (Appendix 2, Table A3).

Table 5: Pain Intensity

Author, year	Pain intensity
Studies included in the systematic review by Duarte et al[39] (adults)	
Smith et al, 2002[46]	*VAS, mean ± SD* IDDS (n = 71) Baseline: 7.57 ± 1.79 Reduction at 4 wk: 3.90 ± 3.42 CMM (n = 72) Baseline: 7.81 ± 1.63 Reduction at 4 wk: 3.05 ± 3.16
Smith et al, 2005[25]	Pain scores significantly better with IDDS compared with non-IDDS at 4 wk (p = 0.002) but not at 12 wk (p = 0.23)
Smith et al, 2005[47]	*VAS, mean ± SD* Baseline: 6.2 ± 2.8 4 wk: 4.5 ± 2.7 (improvement, p = 0.011)
Brogan et al, 2015[59]	*NRS, mean ± SD* Worst pain Baseline (n = 57): 8.32 ± 1.73 Follow-up (n = 53): 4.98 ± 2.92 (improvement, p < 0.001) ≥ 50% pain reduction: 44%
Brogan et al, 2020[60]	*NRS, mean ± SD* Worst pain Baseline (n = 51) 8.00 ± 1.80 4 wk (n = 32): 5.70 ± 2.5 8 wk (n = 24): 6.67 ± 2.73 Average pain Baseline (n = 51): 5.86 ± 1.8 4 wk (n = 32): 4.00 ± 2.44 8 wk (n = 24): 4.54 ± 2.72
Carvajal et al, 2018[61]	*NRS, median (IQR)* Baseline: 8 (7 to 9) Difference from baseline: 1 wk (n = 69): −6 (−7 to −4) 4 wk (n = 66): −5 (−6 to −4) 3 mo (n = 32): −5.5 (−7 to −4) ≥50% pain reduction: 1 wk: 59/69 (85.5%) 4 wk: 52/66 (78.8%) 3 mo: 25/32 (78.1%)
Cheng et al, 2020[62]	*NRS, mean ± SD* Baseline: 7.76 ± 1.15
Dupoiron et al, 2011[63]	*NRS, mean ± SE* Baseline: 7.97 ± 0.2 4 wk: 3.65 ± 0.46

Author, year	Pain intensity
Rauck et al, 2003[64]	Mean NAS decreased from 6.1 at baseline to 4.2 at 1 mo (improvement, $p < 0.01$) and remained decreased through 13 mo (improvement, $p < 0.05$) ≥50% pain reduction 1 mo (n = 99): 37% 2 mo (n = 74): 42% 3 mo (n = 59): 42% 4 mo (n = 47): 43%
Stearns et al, 2020[65]	*NRS, mean ± SD* Baseline (n = 283): 6.8 ± 2.4 6 mo (n = 103): 5.5 ± 2.6 12 mo (n = 55): 5.4 ± 2.5 (improvement, $p < 0.01$)
Becker et al, 2000[48]	*Neuropathic VRS, median* Baseline (n = 20): 9 2.5 mo (n = 13): 8 *Nociceptive VRS, median* Baseline (n = 23): 9 5 mo (n = 13): 3
Brogan et al, 2011[49]	*NRS, mean ± SD* Baseline (n = 29): 6.5 ± 2.1 Follow-up (n = 29): 3.1 ± 2.0 (improvement, $p < 0.001$)
Chen et al, 2020[50]	*VAS, mean ± SD* Baseline: 6.5 ± 2.0 (range: 0–10) Follow-up: 2.7 ± 2.3 (range: 0–8)
Dupoiron et al, 2019[51]	*Minimum NRS, median* Baseline: 5 (range: 0–8) *Maximum NRS, median* Baseline: 8 (range: 1–10) 67.8% decrease of mean NRS between day 0 and day 7 after IDDS implantation
Reig et al, 2009[54]	*NRS, median (IQR)* Baseline: 8.23 (6–10) Follow-up: 2.6 (1–10) ≥ 50% pain reduction: 78.12%
Sayed et al, 2018[55]	*Pain score, median (IQR)* Baseline (n = 152): 7.1 (6–8) 1 mo (n = 83): 5 (2–6) (improvement, $p < 0.0001$) *Pain score, mean* 3 mo (n = 43): 4.47 (did not differ significantly from 1 mo, $p = 0.384$) 6 mo (n = 19): 4.11 12 mo (n = 7): 4.86
Spiegel et al, 2021[38]	*VAS, mean* Baseline (n = 50): 6.6 1 mo (n = 38): 4.4 3 mo (n = 29): 3.6 6 mo (n = 20): 3.4
Studies included in the systematic review by Kenfield et al[42] (pediatric populations)	
Galloway et al, 2000[15]	Satisfactory analgesia

Author, year	Pain intensity
Tobias et al, 2000[66]	Satisfactory analgesia
Saroyan et al, 2005[67]	Satisfactory analgesia
Bengali et al, 2014[68]	Satisfactory analgesia
Kim et al, 2018[69]	Satisfactory analgesia
Mele et al, 2021[16]	Satisfactory analgesia

Abbreviations: CMM, comprehensive medical management; IDDS, intrathecal drug delivery system; IQR, intraquartile range; NAS, numerical analog scale; NRS, numerical rating scale; SD, standard deviation; SE: standard error; VAS, visual analog scale; VRS, verbal rating scale.

Use of Systemic Opioids

Adults

All studies included in the systematic review by Duarte et al[39] that assessed the use of systemic opioids showed a reduction in opioid dosage following IDDS implantation. In the single RCT,[46] the daily morphine oral equivalent doses were 50 mg in the IDDS group compared with 290 mg in the comprehensive medical management group at a 4-week follow-up (Table 6). There was a sustained lower use of systemic opioids after IDDS implantation.

Based on 1 RCT and 11 observational studies, the GRADE quality of the evidence for use of systemic opioids in adults was considered Moderate (RCT) to Low (observational studies), downgraded due to risk of bias (Appendix 2, Table A2).

Table 6: Use of Systemic Opioids

Author, year	Use of systemic opioids
Studies included in the systematic review by Duarte et al[39] (adults)	
Smith et al, 2002[46]	*Daily MOED, median* IDDS Baseline: 250 mg 4 wk: 50 mg CMM Baseline: 272 mg 4 wk: 290 mg
Smith et al, 2005[47]	*Daily MOED, median (IQR)* Baseline: 320 mg (120–1,240 mg)
Brogan et al, 2015[59]	*Daily MOED, mean ± SD* Baseline: 805.28 ± 1,085.81 mg (range: 0–5,760 mg) Follow-up: 128.18 ± 387.55 mg (range: 0–2,160 mg) (improvement, $p < 0.001$) 84% reduction in daily MOED
Brogan et al, 2020[60]	*Daily MOED, mean* Baseline: 375 mg (range: 0–3,160 mg) 4 wk: 28/32 (87.5%) discontinued all non-intrathecal opioids 8 wk: 22/24 (92%) remained off all non-intrathecal opioids
Carvajal et al, 2018[61]	*Daily MOED, median* Baseline: 385.5 mg (range: 265–600 mg)

Author, year	Use of systemic opioids
Dupoiron et al, 2011[63]	Baseline mean daily MOED of 567 mg reduced to 5.35 mg following IDDS implantation
Rauck et al, 2003[64]	*Daily MOED, mean ± SD* Baseline: 106.5 ± 135.3 mg At 3, 4, and 13 mo, more than 50% of patients reported no use of systemic opioids At each visit through 13 mo, more than 70% of patients reported a reduction of 50% or more in systemic opioid use from baseline (improvement, $p < 0.01$)
Brogan et al, 2011[49]	*Daily MOED, mean* Baseline: 796 mg (range: 0–4,320 mg) Follow-up: 64 mg (range: 0–803.8 mg) (improvement, $p < 0.001$) 92% reduction in daily MOED
Chen et al, 2020[50]	*Daily MOED, mean ± SD* Baseline: 1,041 ± 1,267 mg (range: 24–5,560 mg) Follow-up: 307 ± 543 mg (range: 0–2,545 mg) 71% reduction in daily MOED
Dupoiron et al, 2019[51]	*Daily MOED, median* Baseline: 300 mg (range: 24–2,000 mg)
Sindt et al, 2020[57]	*Daily MOED, mean ± SD* Baseline: 305 ± 279 mg Follow-up: 19 ± 57 mg (improvement, $p < 0.0001$) 94% reduction in daily MOED
Spiegel et al, 2021[38]	*Daily MOED, median* Baseline: 503 mg (range 35–5,560 mg) 1 mo: 128 mg (range: 0–3,034 mg) 3 mo: 120 mg (range: 0–4,320 mg) 6 mo: 105 mg (range: 0–2,880 mg)

Abbreviations: CMM, comprehensive medical management; IDDS, intrathecal drug delivery system; IQR, intraquartile range; MOED, morphine oral equivalent dose; SD, standard deviation.

Health-Related Quality of Life

Adults

One study[65] included in the systematic review by Duarte et al[39] reported health-related quality of life as an outcome using the EQ-5D, a health-related quality-of-life measure. The average EQ-5D index score improved significantly from baseline to a 6-month follow-up. This improvement was considered clinically important. The minimal clinically important difference in EQ-5D utility score (US version) in cancer was approximately 0.07.[71] However, there was no significant change at a 12-month follow-up[65] (Table 7). This finding is likely explained by the progression of cancer in most patients.

Based on 1 observational study, the GRADE quality of the evidence for health-related quality of life in adults was considered Low (observational studies) (Appendix 2, Table A2).

Table 7: Health-Related Quality of Life

Author, year	Health-related quality of life
Study included in the systematic review by Duarte et al[39] (adults)	
Stearns et al, 2020[65]	*EQ-5D index score, mean ± SD* Baseline (n = 139): 0.386 ± 0.252 6 mo (n = 41): 0.556 ± 0.252 Average change: 0.171 (95% CI: 0.069–0.273) Improvement: *p* = 0.0016 at 6 mo but no significant change at 12 mo

Abbreviation: SD, standard deviation.

Functional Outcomes

Adults

In the systematic review by Duarte et al,[39] observational evidence showed that pain management by IDDS was associated with improved symptom severity and less symptom interference with quality of life[59,60] compared with before IDDS implantation, and more patients were able to ambulate instead of requiring bedrest after IDDS implantation[53] (Table 8).

In the systematic review by Kenfield et al,[42] all 7 patients reported improved functional outcomes after IDDS implantation, such as returning to school and participating in physical activities (Table 8).

Based on 4 observational studies, the GRADE quality of the evidence for functional outcomes in adults was considered Low (observational studies) (Appendix 2, Table A2).

Children

In the systematic review by Kenfield et al,[42] all 7 patients reported improved functional outcomes after IDDS implantation, such as returning to school and participating in physical activities (Table 8).

Based on 5 case reports and 1 case series summarized by Kenfield et al,[42] the GRADE quality of the evidence for functional outcomes in children was considered Very low (case reports and case series), downgraded due to risk of bias and serious imprecision (Appendix 2, Table A3).

Table 8: Functional Outcomes

Author, year	Functional outcomes
Studies included in the systematic review by Duarte et al[39] (adults)	
Brogan et al, 2015[59]	*MDASI SS, mean ± SD* Baseline: 4.98 ± 1.67 Follow-up: 3.72 ± 1.80 (improvement, $p < 0.0001$) *MDASI SI, mean ± SD* Baseline: 6.53 ± 2.22 Follow-up: 4.37 ± 2.54 (improvement, $p < 0.001$)
Brogan et al, 2020[60]	*MDASI SS, mean ± SD* Baseline (n = 51): 5.13 ± 1.90 4 wk (n = 32): 3.70 ± 2.13 8 wk (n = 24): 4.29 ± 1.89 *MDASI SI, mean ± SD* Baseline (n = 51): 5.88 ± 2.63 4 wk (n = 32): 3.92 ± 2.82 8 wk (n = 24): 4.22 ± 3.00 *MDASI fatigue score, mean ± SD* Baseline (n = 51): 7.84 ± 1.90 4 wk (n = 32): 5.78 ± 2.80 8 wk (n = 24): 6.96 ± 2.76
Cheng et al, 2020[62]	KPS baseline, mean ± SD: 72.27 ± 10.66 SAS baseline, mean ± SD: 57.91 ± 11.82 SDS baseline, mean ± SD: 62.12 ± 11.64
Onofrio et al, 1990[53]	*Baseline ambulatory index:* Bedfast, n = 21 Sits/walks sparingly, n = 12 Walking, n = 18 *3 to 6 wk after implantation:* Bedfast, n = 14 Sits/walks sparingly, n = 8 Walking, n = 29
Studies included in the systematic review by Kenfield et al[42] (pediatric populations)	
Galloway et al, 2000[15]	Patient was able to achieve goals of staying lucid and returning to school. With implanted pump, patient was able to participate in school activities with minimal pain
Saroyan et al, 2005[67]	Patient was able to return to home country essentially pain free
Bengali et al, 2014[68]	Patient was discharged home and was able to return school, attend a Halloween party, and spend the winter holidays with family and friends
Kim et al, 2018[69]	Patients were bedridden prior to IDDS implantation but were able to return to school after IDDS placement
Mele et al, 2021[16]	Patient was previously inpatient for management of acute pain crisis. Following IDDS implantation, she was able to return home and enjoy physical activities, including swimming, boating, painting, and playing online video games with friends

Abbreviations: IDDS, intrathecal drug delivery system; KPS, Karnofsky Performance Status Scale; MDASI SI, MD Anderson Symptom Inventory Symptom Interference with Quality of Life; MDASI SS, MD Anderson Symptom Inventory Symptom Severity; SAS, Self-Rating Anxiety Scale; SD, standard deviation; SDS, Self-Rating Depression Scale.

Survival

Adults

The systematic review by Duarte et al[39] showed that in a single RCT, pain management by IDDS may lead to improvement in survival compared with comprehensive medical management in adults. Cumulative survival at 6 months in the RCT was 53.9% for the IDDS group compared with 37.2% in the comprehensive medical management group.[46] Other included observational studies reported survival using different measures (Table 9).

In the systematic review by Kenfield et al,[42] 5 out of 7 pediatric patients died within the follow-up periods (Table 9). Many factors affect survival outcomes in patients with cancer, and it is uncertain how the use of IDDSs may affect survival.

Based on 1 RCT and 10 observational studies, the GRADE quality of the evidence for survival in adults was considered Low (RCT) to Very low (observational studies), downgraded due to risk of bias and imprecision (Appendix 2, Table A2).

Children

In the systematic review by Kenfield et al,[42] 5 out of 7 pediatric patients died within the follow-up periods (Table 9). Many factors affect survival outcomes in patients with cancer, and it is uncertain how the use of IDDSs may affect survival.

Based on 5 case reports and 1 case series summarized by Kenfield et al,[42] the GRADE quality of the evidence for survival in children was considered Very low (case reports and case series), downgraded due to risk of bias and serious imprecision (Appendix 2, Table A3).

Table 9: Survival

Author, year	Survival
Studies included in the systematic review by Duarte et al[39] (adults)	
Smith et al, 2002[46]	*Cumulative survival at 6 mo* IDDS: 53.9% CMM: 37.2% ($p < 0.06$ log-rank test)
Smith et al, 2005[25]	*Survival at 6 mo* IDDS, no implant: 59.2% IDDS, implant: 54.3% CMM, implant: 51.8% CMM, no implant: 31.5%
Smith et al, 2005[47]	Cumulative survival, 6 mo follow-up: 44% Survival after IDDS implantation, median: 103 d
Carvajal et al, 2018[61]	Overall survival, median: 91 d (95% CI: 83–111)
Cheng et al, 2020[62]	8 patients died during the 12 mo follow-up period
Stearns et al, 2020[65]	*Post-implantation survival* 0.5 y: 39% 1 y: 24% 2 y: 16% 3 y: 11% 10 y: 5%
Brogan et al, 2011[49]	Survival, mean ± SD: 3.5 ± 1.9 mo
Dupoiron et al, 2019[51]	Overall survival, median: 142 d (range: 9–1,460 d)
Sayed et al, 2018[55]	Overall survival, mean: 138 d; median 65 d
Scanlon et al, 2017[56]	51 patients died during the 12 mo follow-up period
Spiegel et al, 2021[38]	27 patients died during the 6 mo follow-up period
Studies included in the systematic review by Kenfield et al[42] (pediatric populations)	
Galloway et al, 2000[15]	Patient died during the follow-up period
Tobias et al, 2000[66]	Patient died during the follow-up period
Saroyan et al, 2005[67]	Patient died during the follow-up period
Bengali et al, 2014[68]	Patient died during the follow-up period
Kim et al, 2018[69]	1 of 2 patients died during the follow-up period
Mele et al, 2021[16]	Patient alive, on palliative chemotherapy

Abbreviations: CI, confidence interval; CMM, comprehensive medical management; IDDS, intrathecal drug delivery system; IQR, intraquartile range; SD, standard deviation.

Complications and Side Effects

Adults

The systematic review by Duarte et al[39] summarized that postdural puncture headache was the most reported procedural complication, whereas urinary retention, nausea, and vomiting were commonly

reported pharmacological side effects. Death directly related to IDDS was uncommon. Three studies each reported 1 death: 1 caused by pneumonia after IDDS implantation,[48] 1 caused by pulmonary embolism,[61] and 1 caused by acute renal failure owing to obstructive uropathy following pump infection, which required explantation and intravenous antibiotic therapy.[59] Stearns et al[65] reported 2 deaths (out of 1,141 patients with follow-up) that may have been associated with IDDS: 1 was reported as infection with death secondary to postoperative pneumonia after IDDS implantation, and the other was caused by pulmonary embolus occurring in the context of drug withdrawal resulting from a missed pump refill (Table 10).

In the systematic review by Kenfield et al,[42] focusing on pediatric patients, 4 out of 7 patients reported no IDDS-related complications or side effects. None of the reported IDDS-related side effects were life-threatening (Table 10).

Based on 1 RCT and 16 observational studies, the GRADE quality of the evidence for complications and side effects in adults was considered Moderate to Low, downgraded due to risk of bias (Appendix 2, Table A2).

Children

In the systematic review by Kenfield et al,[42] focusing on pediatric patients, 4 out of 7 patients reported no IDDS-related complications or side effects. None of the reported IDDS-related side effects were life-threatening (Table 10).

Based on 5 case reports and 1 case series summarized by Kenfield et al,[42] the GRADE quality of the evidence for complications and side effects in children was considered Very low (case reports and case series), downgraded due to risk of bias and serious imprecision (Appendix 2, Table A3).

Table 10: Complications and Side Effects

Author, year	Complications and side effects
Studies included in the systematic review by Duarte et al[39] (adults)	
Smith et al, 2002[46]	*IDDS* All SAEs (n = 62) IDDS-related SAEs (n = 14) Pocket problems (n = 4) Infections (n = 1) Pump migration (n = 1) Lumbar site (n = 5) Catheter problems (n = 5) CSF leak (n = 1) *CMM* All SAEs (n = 69) IDDS-related SAEs (n = 2) Pocket problems (n = 2) Infections (n = 1) Pump migration (NA) Lumbar site (NA) Catheter problems (NA) Cerebrospinal fluid leak (NA)
Brogan et al, 2015[59]	Based on 98 pumps implanted, rather than the 58 in the final study group: 1 pump infection required explant and intravenous antibiotic therapy 3 patients (3.1%) developed postdural puncture headache Several patients developed mild, transient, lower-extremity weakness after patient-controlled intrathecal analgesia dosing Several patients reported urinary hesitancy
Brogan et al, 2020[60]	No infectious complications during the study period 2 patients developed a postdural puncture headache that did not respond to conservative therapy and required an epidural blood patch
Carvajal et al, 2018[61]	Postlumbar puncture headache (n = 30; 32.3%) Catheter/pump malfunction (n = 3; 3.2%) Surgical wound dehiscence (n = 2; 2.1%) Pump pocket infection (n = 1; 1.1%) Bacterial meningitis (n = 1; 1.1%) Subdural hematoma (n = 1; 1.1%) Minor spinal cord puncture (n = 1; 1.1%) Pocket hematoma (n = 1; 1.1%) Pulmonary embolism (n = 1; 1.1%)
Cheng et al, 2020[62]	Nausea and vomiting (n = 11; 33.3%) Drowsiness (n = 8; 24.2%) Constipation (n = 5; 15.2%) Dizziness (n = 4; 12.1%) Skin reactions (n = 3; 9.1%) Hypotension (n = 2; 6.1%) Diarrhea (n = 1; 3.0%)

Author, year	Complications and side effects
Dupoiron et al, 2011[63]	Postdural puncture headache (n = 52; 54%) Urinary retention (n = 16; 16%) Withdrawal syndrome (n = 38; 39%) Infection (n = 5; 5%) Hematoma (n = 3; 3%) Rotation of pump in site (n = 3; 3%)
Rauck et al, 2003[64]	63 SAEs in 40 patients 7 device-related SAEs in 7 patients 55 procedure-related SAEs in 36 patients 1 SAE related to intercurrent illness or injury in 1 patient
Stearns et al, 2020[65]	2 deaths (1 from postoperative pneumonia, 1 from pulmonary embolus) possibly related to IDDS out of 1,141 patients 68 SAEs in 54/706 patients (7.7%) 17 infections and infestation events in 17 patients (2.4%) 5 psychiatric disorder events in 4 patients (0.6%) 9 nervous system disorder events in 9 patients (1.3%) 29 general disorders and administration site conditions in 23 patients (3.3%) 6 injury, poisoning, and procedural complications in 6 patients (0.9%) 2 respiratory, thoracic, and mediastinal disorders in 2 patients (0.28%) 279/706 (40%) experienced ≥ 1 adverse event related to the device components, implant procedure, or delivery of therapy The most frequently occurring AEs were adverse drug reaction (24.5%; 95% CI: 21.5–27.8) and medical device site pain (10.1%; 95% CI: 8.1–12.5)
Becker et al, 2000[48]	Transient side effects (n = 23; 53.5%) Nausea and vomiting (n = 15; 34.9%) Procedure-related (n = 5; 11.6%) Spinal catheter malfunction (n = 3; 6.9%) Hematoma (n = 1; 2.3%) Postoperative pneumonia (n = 1; 2.3%)
Brogan et al, 2011[49]	1 patient had an increase in pain after the catheter had backed out of the intrathecal space Several patients reported urinary hesitancy
Chen et al, 2020[50]	Numbness and urinary retention (n = 7; 16.2%) Postdural puncture headache (n = 3; 6.9%)
Erdine et al, 1996[52]	Urinary retention (n = 21; 38.9%) Leakage-related headache (n = 16; 29.6%) Nausea and vomiting (n = 10; 18.5%) Pruritus (n = 8; 14.8%) Infection (n = 5; 9.3%) Disconnection (n = 4; 7.4%) Migration (n = 3; 5.6%)

Author, year	Complications and side effects
Reig et al, 2009[54]	22% test period complications (most frequent: postdural puncture headache and urinary retention) 16% mechanical complications (most frequent: catheter dislodgement) 8% surgical complications (mostly postdural puncture headache) 33% medication-related complications (mostly nausea, vomiting, constipation)
Sayed et al, 2018[55]	5 patients (3.1%) had their pumps explanted because of infection
Scanlon et al, 2017[56]	Surgical site infection (n = 4; 6.2%) Of these, 3 were pocket site infections, and 1 was a meningitis infection
Spiegel et al, 2021[38]	Numbness (n = 8) Urinary retention (n = 7) Postdural puncture headache (n = 5) Light-headedness (n = 2) Sedation (n = 1) Weakness (n = 1)
Yegul et al, 1999[58]	Nausea and vomiting (n = 10; 17.2%) Constipation (n = 6; 10.3%) Headache (n = 6; 10.3%) Urinary retention (n = 5; 8.6%) Seroma (n = 4; 6.9%) Pruritus (n = 4; 6.9%) Infection (n = 2; 3.4%) Respiratory depression (n = 2; 3.4%)
Systematic review by Kenfield et al[42] (pediatric populations)	
Galloway et al, 2000[15]	None reported
Tobias et al, 2000[66]	Patient initially satisfied with pain relief with bupivacaine alone but reported concern regarding motor blockade. Concentration of bupivacaine was decreased and sufentanil (lipophilic opioid) was added to provide additional analgesia
Saroyan et al, 2005[67]	None reported
Bengali et al, 2014[68]	None reported
Kim et al, 2018[69]	Of the 10 patients with IDDS placement (for cancer and noncancer pain): 2 patients developed seromas, which were percutaneously drained 1 patient developed a postdural puncture headache, which resolved after a blood patch 1 patient with severe contractures and body deformities experienced pump erosion through the skin requiring the pump to be surgically repositioned 1 patient experienced sedation, confusion, and severe vomiting after the basal infusion of hydromorphone was increased by 30%
Mele et al, 2021[16]	None reported

Abbreviations: CMM, comprehensive medical management; IDDS, intrathecal drug delivery system; NA, not applicable; SAE, serious adverse event.

Ongoing Studies

We are aware of the following ongoing studies that have potential relevance to this review.

On ClinicalTrials.gov, we identified 1 ongoing observational study:

- "Prospective evaluation of intrathecal targeted drug delivery for cancer associated pain" (NCT 05674240) (accrual start date: December 2022; estimated study completion date: December 2025)

In PROSPERO, we identified 1 ongoing systematic review:

- "The effectiveness of implanted intrathecal opioid pump in improving quality of life and reducing time admitted to hospital in patients with a diagnosis of advanced cancer" (CRD42022310678)

Discussion

In this clinical evidence review, we based our evidence synthesis on data reported in published reviews. In adults, most studies included in the selected systematic review consistently showed a reduction in pain intensity by 30% to 50% after IDDS implantation. This magnitude of pain reduction was clinically meaningful in patients with severe refractory cancer pain. Other positive outcomes associated with IDDS implantation included decreased use of systemic opioids, improved health-related quality of life, improved functional outcomes, and improved survival. However, the evidence was of low to very low quality owing to methodological weakness (e.g., lack of randomization, lack of blinding), small sample size, and short follow-up duration. In children, the studies included in the selected systematic review also reported favourable outcomes; however, the literature was restricted to anecdotal evidence from case studies and case series and included only 7 patients.

Many systematic reviews and observational studies have been published on the use of IDDSs for adults with cancer pain. However, we found only 1 RCT, which was published more than 2 decades ago. The scarcity of rigorous evidence on this topic is likely because of the ethical issues (e.g., double-blinding, randomization, sham procedure) involved in conducting research in patients with advanced cancer experiencing severe refractory pain and poor quality of life. These patients may also have a limited life expectancy, which curtails the length of follow-up possible.[31] The evidence base in pediatric populations is even more limited. It has been proposed that evidence synthesized from case reports and case series could be used to inform decision-making when no higher-quality evidence is available.[72]

In the 2010 *Declaration of Montreal*, representatives of the International Association for the Study of Pain declared that "access to pain management is a fundamental human right."[73] Although it has not been included in the World Health Organization's analgesic ladder, intrathecal drug delivery may have a role to play in improving pain management for patients with refractory cancer pain owing to the smaller doses of analgesic medication required and the reduced incidence of systemic side effects compared with conventional opioid-based treatment. However, intrathecal drug delivery does carry certain rare risks of complications and side effects. The needs of the cancer patient populations that may be appropriate for intrathecal drug delivery for pain management are quite diverse (aside from all having refractory cancer pain), making it difficult to clearly define selection criteria for the use of IDDSs. A

specialized multidisciplinary team must compare potential effectiveness versus harm on an individual basis to ensure appropriate selection prior to IDDS implantation.

In summary, intrathecal drug delivery can provide adequate pain relief and improve quality of life and functional outcomes for appropriately selected patients with refractory cancer pain.

Conclusions

Intrathecal Drug Delivery Systems for Cancer Pain in Adults

Compared with nonintrathecal drug delivery in adults with cancer pain who have a life expectancy greater than 6 months, intrathecal drug delivery:

- Likely reduces pain intensity (GRADE: Moderate to Low)
- Likely decreases the use of systemic opioids (GRADE: Moderate to Low)
- May improve health-related quality of life (GRADE: Low)
- May improve functional outcomes (GRADE: Low)
- May improve survival; however, the evidence is very uncertain (GRADE: Low to Very low)

Intrathecal Drug Delivery Systems for Cancer Pain in Children

Compared with nonintrathecal drug delivery in children with cancer pain, intrathecal drug delivery may reduce pain intensity, improve functional outcomes, and improve survival; however, the evidence is very uncertain (all GRADEs: Very low).

Safety of Intrathecal Drug Delivery Systems for Cancer Pain

IDDS implantation carries certain rare risks related to mechanical errors, drug-related side effects, and surgical complications (GRADE: Moderate to Low for adults; Very low for children).

Economic Evidence

Research Question

What is the cost-effectiveness of implantable intrathecal drug delivery systems (IDDSs) compared with non-IDDS methods of pain management for the management of cancer pain in adults and children?

Methods

Economic Literature Search

We performed an economic literature search on December 20, 2022, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied. In addition to the databases used for the clinical search, we also used the Ovid interface in the Cochrane Central Register of Controlled Trials.

We created database auto-alerts in MEDLINE and Embase and monitored them until May 10, 2023. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See the clinical literature search for further details on methods used. See Appendix 1 for our economic literature search strategy, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from inception until the search date
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Narrative reviews, editorials, case reports, commentaries, and abstracts

Population

- Adults and children with cancer pain who are indicated for intrathecal drug delivery using an implantable pump (see description of indications and contraindications in the “Ontario and Canadian Context” section)

Intervention

- IDDS as the sole route of delivery for pain medications

Comparator

- Conventional medical management via nonintrathecal drug delivery; e.g., oral pain medications, methadone, subcutaneous opioids, periodic blocks

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[35] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[74] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into 2 sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the

second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly applicable.

Results

Economic Literature Search

The database search of the economic literature yielded 105 citations published between database inception and December 20, 2022, including grey literature searches and after duplicates were removed. We identified no additional eligible studies from other sources, including database alerts (monitored until May 10, 2023). In total, we identified 4 studies that met our inclusion criteria. See Appendix 5 for a list of selected studies excluded after full-text review. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

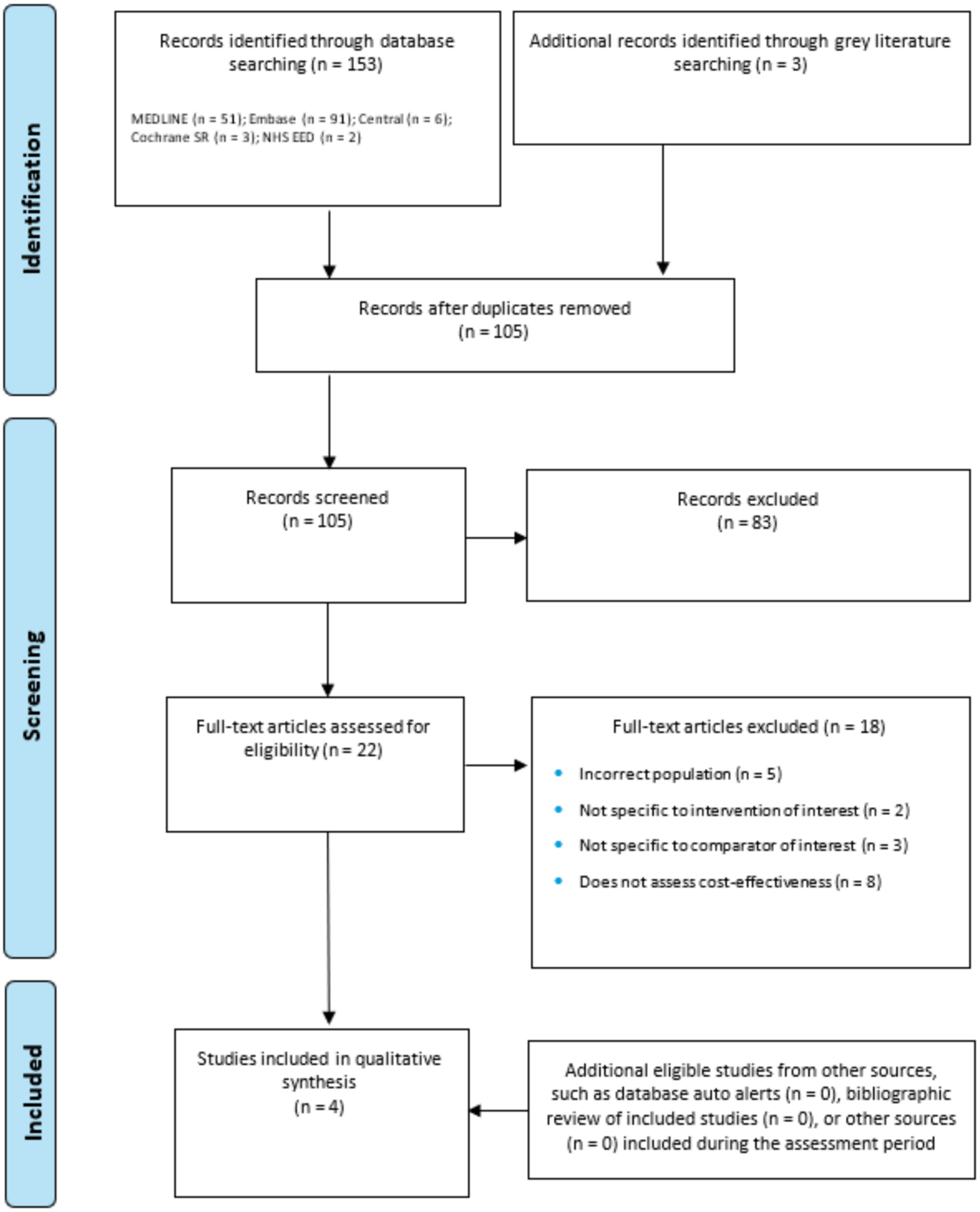

Figure 3: PRISMA Flow Diagram – Economic Search Strategy

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 153 citations published between database inception and December 20, 2022. We identified 3 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 105 studies and excluded 83. We assessed the full text of 22 articles and excluded a further 18. In the end, we included 4 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[35]

Overview of Included Economic Studies

We identified a total of 4 studies that met our inclusion criteria (Table 11).[75-78] One was a cost-effectiveness analysis,[26] and 3 were costing studies.[76-78] None of the identified studies included children in their study population.

The cost-effectiveness analysis[26] was conducted in a Canadian setting and used a Markov model to estimate the cost-effectiveness of IDDSs compared with non-IDDS methods of pain management (i.e., conventional medical management) among patients with cancer pain. It used a 4-year time horizon and reported outcomes as cost per life-year gained. This study found that over a time horizon of 4 years, compared with conventional medical management, IDDSs achieved an ICER of $126,925 per additional life-year gained.

The 3 costing studies[76-78] were conducted in the United States, and all used a 1-year time horizon. Two[76,77] of the 3 studies used propensity-score-matched analyses to compare costs between patients who received an IDDS and those who remained on conventional medical management at 2, 6, and 12 months. Both propensity-score-matched analyses[76,77] found that IDDSs were associated with cost savings at 12 months. However, 1[79] found that cost savings occurred only at 6 and 12 months (with a total cost savings of $3,195 at 12 months), whereas the other[80] found cost savings at all points of follow-up (with a total cost savings of $62,498 at 12 months).

The third costing study[81] was a retrospective chart review of 36 patients who underwent IDDS implantation. Costs at 6 months before undergoing IDDS implantation were collected and projected over time as if the patients had continued with conventional medical management with no change in drug regimen until death. The actual cost data for patients with an IDDS were then collected and compared against the projected costs of conventional medical management to determine when cost equivalence would be attained. The study[81] found that patients who received an IDDS achieved cost equivalence with patients who received a high-cost analgesic regimen under conventional medical management at 7.6 months but did not reach cost equivalence with those who received a low-cost analgesic regimen under conventional medical management within the study time horizon.

Across all studies,[75-78] IDDSs were associated with higher initial costs due to the cost of the device and implantation procedure but lower health care use costs over time. Notably, the cost-effectiveness study[26] also found that IDDSs were associated with 0.29 incremental life-years gained over a 4-year time horizon compared with conventional medical management.

Table 11: Results of Economic Literature Review – Summary

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Stearns et al, 2019, United States[80]	Analytic technique: cost analysis Study design: retrospective propensity score-matched cohort Perspective: payer perspective Time horizon: 2, 6, 12 mo Discount rate: NA Currency and cost year: USD, 2015	Cancer patients with IDDS *Before matching:* Total N: 376 Age, mean (SD): 51.88 y (9.98 y) Male, n (%): 160 (42.6) *After matching:* Total N: 268 Age, mean (SD): 51.91 y (10.20 y) Male (%): 115 (42.9) Cancer patients with CMM *Before matching:* Total N: 4,839 Age (SD): 51.52 y (11.16 y) Male, n (%): 1,834 (37.9) *After matching:* Total N: 268 Age, mean (SD): 52.27 y (11.19 y) Male (%): 116 (43.3)	Intervention: IDDS Comparator: CMM	Total QALYs (mean per person): NA Mean difference: NA	*Total costs (mean per person)* IDDS 2 mo: $55,353 6 mo: $102,377 12 mo: $126,211 CMM 2 mo: $70,495 6 mo: $121,954 12 mo: $189,709 *Mean difference, IDDS vs. CMM* 2 mo: –$15,142 6 mo: –$19,577 (not statistically significant) 12 mo: –$63,498	Compared with CMM, IDDS was associated with a mean total cost savings of $15,142 at 2 mo and $62,498 at 12 mo IDDS was also associated with a mean total cost savings of $19,577 at 6 mo, although this was not statistically significant No sensitivity analyses conducted

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
University of Calgary, 2018, Canada[26]	Analytic technique: cost-effectiveness analysis Study design: decision tree plus Markov model Perspective: Canadian public health care system Time horizon: 4 y Discount rate: 1.5% on costs and effects Currency and cost year: CAD, 2017	Cancer patients with IDDS Cancer patients with CMM	Intervention: IDDS Comparator: CMM	*Total LYs (4 y)* IDDS: 0.76 CMM: 0.47 Mean difference, IDDS vs. CMM: 0.29	*Total costs (4 y)* IDDS: $65,408 CMM: $28,145 Mean difference, IDDS vs. CMM: $37,263	ICER: $126,925/ additional LY gained PSA found that 94.8% of 4,000 iterations resulted in IDDS having greater costs and greater life years than CMM Highly sensitive to costs associated with CMM medications and intrathecal pump medications and refills
Stearns et al, 2016, United States[79]	Analytic technique: cost analysis Study design: retrospective propensity score-matched cohort Perspective: payer perspective Time horizon: 2, 6, 12 mo Discount rate: NA Currency and cost year: USD, 2006–2010 (costs recorded in USD in the years services were incurred without adjusting for inflation)	Cancer patients with IDDS *Before matching* Total N: 142 Age, mean: 51.92 y Male, n: 55 Cancer patients with CMM *Before matching* Total N: 3,188 Age, mean: 51.55 y Male, n: 1,168 *After matching* Total N: 73 pairs	Intervention: IDDS Comparator: CMM	Total QALYs (mean per person): NA Mean difference: NA	*Total costs (mean per person)* IDDS 2 mo: $58,209 6 mo: $97,761 12 mo: $126,407 CMM 2 mo: $ 55,157 6 mo: $103,306 12 mo: $129,602 *Mean difference, IDDS vs. CMM* 2 mo: $3,052 6 mo: –$5,545	Compared with CMM, IDDS was associated with higher costs at 2 mo ($3,052) but lower costs at 6 and 12 mo (cost savings of $5,545 and $3,195, respectively) No sensitivity analyses conducted

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
		Age, mean: NR Male, %: NR			12 mo: –$3,195	
Brogan et al, 2013, United States[78]	Analytic technique: cost analysis Study design: retrospective chart review Perspective: US hospital Time horizon: 1 y Discount rate: NA Currency and cost year: USD, 2011	Cancer patients with IDDS[a] Total N: 36 Age, mean (SD): 54.5 y (14.9 y) Male (%), n: 67%	Intervention: IDDS Comparator: CMM, low-cost and high-cost	Total QALYs (mean per person): NA Mean difference: NA	*Total costs (mean per person)* IDDS: $630.71/mo, $7,568.55/y Low-cost CMM: $399.98/mo, $4,799.75/y High-cost CMM: $5,245.96/mo, $62.951.55/y *Mean difference, IDDS vs. CMM* Low-cost CMM: $230.02/mo High-cost CMM: –$4,615.25/mo	IDDS achieved cost equivalence with high-cost CMM at 7.6 mo; IDDS did not achieve cost equivalence with low-cost CMM No sensitivity analyses conducted

Abbreviations: CMM, conventional medical management; ICER, incremental cost-effectiveness ratio; IDDS, intrathecal drug delivery system; LY, life-year; NA, not applicable; NR, not reported; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SD, standard deviation.

[a]Patients were randomly assigned to a high-cost or low-cost conventional regimen based on their preimplantation analgesic regimen. The high-cost conventional regimen (n = 12) included patients who had received parenteral drug administration, those on a nongeneric regimen, and those on a high-dose regimen (i.e., oral morphine equivalence > 1,000 mg/day). The low-cost conventional regimen (n = 24) included patients on a generic regimen and those who used few or no opioids.

Applicability and Limitations of the Included Studies

Appendix 6 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. All 4 studies[75-78] were deemed partially applicable to the research question. We assessed the limitations of these studies and found that 3[75-77] had potentially serious limitations and 1[81] had very serious limitations.

Discussion

Our economic evidence review found that IDDS pain management was associated with varied results compared with conventional medical management, ranging from being cost-saving to having increased costs and increased life-years gained, to achieving cost equivalence only with high-cost analgesic regimens. There was uncertainty surrounding the results of all included studies, but only 1 study[26] conducted a sensitivity analysis. The studies that did not conduct sensitivity analyses were the retrospective chart review[81] and the 2 propensity-score-matched analyses.[76,77]

The study population of the retrospective chart review[81] was restricted to patients who had undergone IDDS implantation. This study[81] assumed that the costs incurred 6 months before implantation would remain unchanged until death if these patients had remained on conventional medical management. This assumption was used in lieu of actual cost data collected post-implantation. This study[81] may therefore have underestimated the medical costs associated with conventional medical management for patients with poorly controlled cancer pain because it did not consider dose escalation or possible increases in hospital admissions or emergency department visits for pain management over time. Because the size of the study population (n = 36) was small, the results of the study[81] may also not be representative of the overall mean cost of health care use for patients with an IDDS. Similarly, the medical costs of the patients who were stratified to high-cost (n = 12) and low-cost (n = 24) analgesic regimens may not be representative of their respective groups. Last, disaggregated costs were not provided for the initial costs associated with IDDS implantation. As such, it was unclear whether the costs reported for the placement of the intrathecal pump (i.e., equipment, operating room time, and professional fees) included the cost of the device. It was therefore unclear whether all relevant costs were included in this study.[81]

The 2 studies that conducted propensity-score-matched analyses[4,5] applied the same methodology and used the same data source (i.e., a large US claims database). The earlier study[4] included patients who had an IDDS implanted between 2006 and 2010, and the later study[5] included patients who underwent implantation between 2009 and 2015. During the time of the earlier study,[4] IDDS implantation was largely performed as an inpatient procedure. The later study[5] was initiated because of several shifts in health care use. First, IDDS implantation was then being done more often as an outpatient procedure. Second, there was an overall decrease in inpatient hospitalizations and an increase in the use of lower-acuity services for both patients with an IDDS and those who remained on conventional medical management. These differences in health care use since 2006 likely contributed to the wide range in the reported cost savings associated with IDDS implantation, with cost savings at 12 months of $3,195 reported for the earlier study[4] and $62,498 reported for the later study.[5]

Both studies may also have underestimated costs associated with the experience of cancer pain in both the IDDS and conventional medical management groups.[4,5] While propensity-score matching is a common method used to reduce bias and improve causal inference in observational studies, it may sometimes have the opposite effect.[82] Specifically, to balance retreatment confounders between a

treated group (i.e., IDDS) and an untreated group (i.e., conventional medical management), propensity-score matching will match individuals from both groups on a key set of baseline characteristics and, in doing so, effectively prune the worst-matched observations.[82] For instance, in the later study,[80] we observed that patients with an IDDS before matching experienced greater health care use (i.e., number of hospitalizations, length of stay, and emergency department visits) compared with patients with an IDDS post-match. This finding suggests that this study[80] may have excluded the more severe cases of cancer pain from its matched observations, as there were no suitable matches in the untreated group. Last, both studies[76,77] declared conflicts of interest, and the impact of these on the study results is unknown.

The cost-effectiveness analysis[26] was conducted using a Canadian (British Columba) public payer perspective. It assessed health outcomes using only life-years. While 1 randomized controlled trial[46] found that intrathecal drug delivery may improve overall survival, the intended use of this intervention is to provide pain relief and better quality of life. As such, by omitting quality-adjusted life-years, this study[3] may not have adequately captured all meaningful health effects. This cost-effectiveness analysis[26] also derived its costs from a retrospective chart review.[81] As such, it is subject to the limitations associated with that retrospective chart review. Additionally, because that review[81] was a study of 36 patients in the United States, its generalizability to the context of the Canadian health care system is unclear.

Conclusions

We found 4 economic analyses[75-78] that compared IDDSs with non-IDDS methods of pain management (i.e., conventional medical management) for the management of cancer pain in adults. The studies used different methods and had conflicting results. Therefore, the cost-effectiveness of IDDSs compared with conventional medical management for adults with cancer pain remained unclear. Owing to these limitations, we conducted a primary economic evaluation in the context of Ontario.

Primary Economic Evaluation

Research Question

What is the cost-effectiveness of implantable intrathecal drug delivery systems (IDDSs) compared with non-IDDS methods of pain management for the management of cancer pain in adults from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[83] The content of this report is based on a previously developed economic project plan.

Type of Analysis

We conducted a cost–utility analysis because this is the recommended reference case approach and adheres to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines.[84] We reported results as the incremental cost per quality-adjusted life-years (QALYs) gained.

Population of Interest

The population of interest was adults with refractory cancer pain who are indicated for intrathecal drug delivery using an implantable pump. These are individuals who have severe pain related to their cancer (either from a primary tumour or metastatic disease), treatments (e.g., surgery, chemotherapy, radiation), or other causes and whose pain is poorly managed despite receiving appropriate medical therapy.[3] This population also includes individuals who are unable to tolerate the side effects of systemic opioid analgesia. Individuals who are indicated for intrathecal drug delivery should have pain related to focal disease below the neck, which is amenable to this type of therapy, rather than pain due to diffuse metastatic disease (E. Baig, MD, telephone communication, October 27, 2022). Further, because IDDS implantation is an invasive procedure, physicians may include a life expectancy of more than 6 to 9 months in the eligibility criteria for appropriate patient selection (E. Baig, MD, telephone communication, October 27, 2022). We did not include children in our population of interest because the clinical evidence review reported that the clinical evidence for the use of IDDS pain management in children is very uncertain, with the quality of evidence rated as very low according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group criteria.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Intervention and Comparator

We conducted evaluations comparing IDDSs with non-IDDS methods of pain management (i.e., conventional medical management, referred to as “standard care” in this evaluation). Table 12 summarizes the interventions evaluated in the economic model.

Table 12: Disease Interventions and Comparators to Be Evaluated in the Primary Economic Model

Intervention	Comparator	Population	Outcomes
IDDS	Non-IDDS methods of pain management[a] (i.e., standard care)	Adults with cancer pain indicated for intrathecal drug delivery using an implantable pump	Incremental cost Incremental QALYs ICER ($/QALY)

Abbreviations: ICER, incremental cost-effectiveness ratio; IDDS, intrathecal drug delivery system; QALY, quality-adjusted life-year.
[a]Includes oral pain medications, methadone, subcutaneous opioids, and periodic blocks.

In the intervention arm, adults with refractory cancer pain are assessed for eligibility for an IDDS by a multidisciplinary team of health care providers, and suitable candidates then undergo implantation.

In the standard care arm, adults with refractory cancer pain are managed with systemic prescription opioids as guided by the World Health Organization's 3-step ladder of cancer pain analgesia.[8] However, despite treatment with opioid analgesia, patients in the standard care arm are considered not to have achieved adequate pain control and continue to experience refractory cancer pain.

Time Horizon and Discounting

We used a 1-year time horizon in our reference case analysis. This short time horizon is appropriate as it is sufficient to capture meaningful differences between the intervention and comparator. Also, the mean survival post-implantation for individuals with an IDDS is reported to be less than 1 year.[39,44] Further, we did not identify any studies that reported outcomes on health utility for our population of interest beyond 1 year. Because the time horizon is not more than 1 year, we did not apply a discount rate to either costs or QALYs. The model included monthly intervals to reflect a clinically meaningful period of time.[85]

Main Assumptions

In the reference case, the model's main assumptions were as follows:

- There will be no difference in overall survival between the intervention and standard care arms. While 1 randomized controlled trial (RCT)[46] reported outcomes suggesting intrathecal drug delivery improved survival compared with standard care (with a cumulative survival at 6 months of 53.9% in patients with an IDDS compared with 37.2% in patients who continued with standard care), survival was not the primary end point of this study; as such, this study's survival outcomes should be interpreted with caution. Further, this RCT[46] used an "as treated" approach and explicitly allowed crossovers. Therefore, while the possible improvement in survival for individuals with IDDSs may be attributed to better pain management and reduced drug toxicity, it may also be attributed to a poorer prognosis that precluded certain patients from being eligible for IDDS implantation or simply to chance alone

- The health utilities of individuals in the standard care arm will remain unchanged between baseline (i.e., when they enter the model) and death. This assumption was made because no published RCTs have compared patient-reported quality-of-life outcome measures in patients with an IDDS versus patients receiving standard care. As such, health utilities could be derived only from observational studies conducted with patients before and after implantation.[65] Given that individuals indicated for intrathecal drug delivery are those whose pain is poorly managed despite receiving appropriate medical therapy and those who cannot tolerate the side effects of systemic opioid analgesia, it may be reasonable to assume that continuing conventional medical management under standard care will not provide improved pain relief over time
- Individuals with IDDSs will experience improved health utilities shortly after implantation. This improvement will be sustained up to 1 year or until death
- IDDS implantation will be a day surgery. While this interventional procedure can be performed either as a day surgery or inpatient surgery based on the discretion of the physician, it is recommended that, in general, it should be performed as a day surgery in Ontario (E. Baig, MD, telephone communication, October 27, 2022)
- Following IDDS implantation, no patients will require explantation for the remainder of their life. We made this simplifying assumption because the expected life span of the intrathecal pump and its battery life are greater than the average life expectancy of a patient post-implantation, at 5 and 6 to 7 years, respectively. The intrathecal catheter similarly has a life span longer than the average overall survival of a patient post-implantation (Medtronic Canada Inc., email communication, November 2022). As such, the likelihood of requiring device removal due to failure to relieve pain is expected to be very low
- The average daily systemic opioid use (which includes oral, transdermal, and subcutaneous medications) or the morphine oral equivalent dose (MOED) for individuals in the standard care arm is 300 mg per day. This assumption was based on the 1 RCT[46] of the use of IDDSs in adults with cancer pain, which found that the average MOED for individuals after 4 weeks of standard care was 290 mg per day. This average MOED was considered to reflect the average daily MOED of cancer patients who are candidates for intrathecal drug delivery in Ontario (E. Baig, MD, email communication, January 8, 2023)
- The average daily systemic opioid use in the intervention arm is an MOED of 50 mg per day. This is a conservative assumption based on the RCT[46] described previously, which found that the average MOED for individuals with IDDSs 4 weeks post-implantation was 50 mg per day. While the treatment goal for individuals with IDDSs is to convert all systemic opioids to intrathecal drug delivery, we made the conservative assumption that some individuals may continue to receive systemic opioid medications via non-intrathecal delivery following implantation[57]
- The use of an IDDS may reduce health care resource use related to inpatient hospitalizations for poorly managed pain or severe side effects of systemic opioids

Model Structure

We developed a decision-analytic model with 2 health states: alive and dead (Figure 4). Patients in the alive state would either receive IDDS (i.e., the new intervention) or non-IDDS pain management (i.e., standard care). Depending on the treatment arm, patients incur different costs and utilities (i.e., health-related quality of life). We estimated the proportion of patients in the alive state using published survival data.[65]

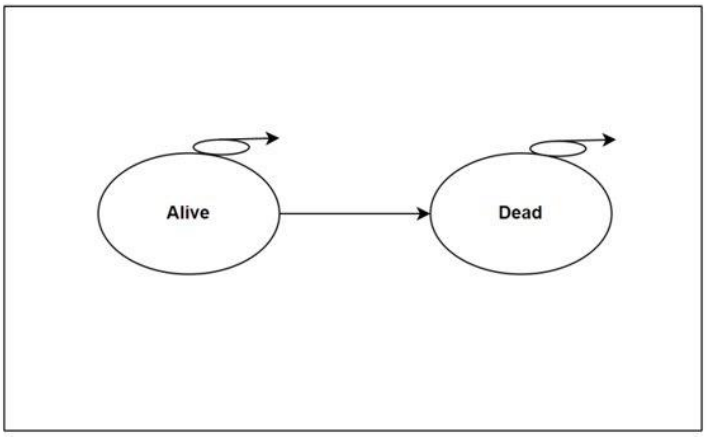

Figure 4: Model Structure

Clinical Outcomes and Utility Parameters

We obtained the clinical and utility parameters from the clinical evidence review whenever possible and validated these with clinical experts to ensure that they reflected real-world clinical practice in Ontario.

We derived our clinical and utility parameters from a recent prospective multicentre study by Stearns et al.[65] The average age of study participants was 59 years, and 56.5% of participants were female. The types of cancer of participants included lung, breast, colon/rectal, pancreatic, prostate, and bladder, though 45.1% of the study population were reported as having other or unknown types of cancer.[65] This study[65] examined the survival and patient-reported outcomes of patients with an IDDS using registry data. The patient-reported outcomes included the EQ-5D index value, which can be directly converted to health utilities in economic evaluations.

Clinical Parameters

Stearns et al[65] found that for its study population (n = 1,403), the survival of patients 1 year post-implantation was 24%. We estimated the total life-years per patient over the model time horizon using the area under the survival curve. Our approach was as follows:

- Step 1: We digitized the survival curve from the source publication[80] using the online platform Automeris.io[86] (Figure 5)

- Step 2: A dataset was created based on the digitized points, from which we estimated the proportion of people who remain surviving at each monthly interval
- Step 3: We calculated the total life-years per patient over the model time horizon (i.e., the area under the survival curve) after adjusting for a half-cycle correction

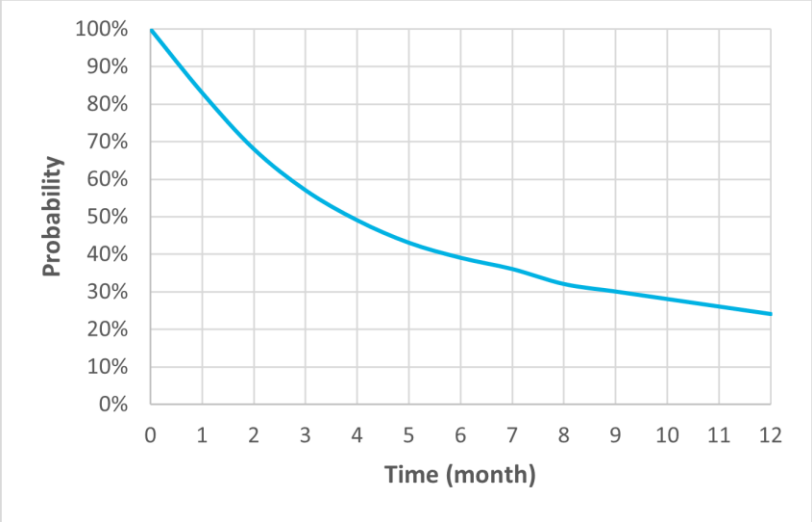

Figure 5: One-Year Post-IDDS Implantation Survival

Health State Utility Parameters

Patient-reported outcomes were collected from only a subset of the study population at baseline (month 0) and at follow-up (month 6 [n = 41] and month 12 [n = 25]). At baseline, the average EQ-5D index value was 0.39 (SD, 0.252), which improved to 0.56 (SD, 0.252) at month 6. While there was also an improvement in EQ-5D index values at month 12 compared with baseline, it was not statistically significant.

Based on local clinical experience, patients who receive an IDDS begin to experience pain relief relatively shortly after implantation, and pain continues to be well controlled with intrathecal opioids until end of life (E. Baig, MD, written communication, February 2023). We therefore assumed that individuals in the IDDS arm will have improved health utilities in month 1 (0.56) and that this improvement will remain stable for the remainder of the model time horizon or until transition to death. Comparatively, we assumed that individuals in the standard care arm will remain at the baseline utility (0.39) for the remainder of the model time horizon or until transition to death (Table 13). It should be noted that this assumption may overestimate the health utility gains associated with the use of IDDSs because Stearns et al[65] did not observe a statistically significant difference in EQ-5D index values at 12 months.

Table 13: Utilities Used in the Economic Model

Health state	Utility	Reference
IDDS		
Alive with reduced pain	0.56	Stearns et al, 2020[65]
Standard care		
Alive with refractory cancer pain	0.39	Stearns et al, 2020[65]

Abbreviation: IDDS, intrathecal drug delivery system.

Cost Parameters

All costs are reported in 2023 Canadian dollars (Table 14).

Device

The cost of the IDDS device was provided by the manufacturer. The main components of an IDDS include the programmable drug infusion device and the intrathecal catheter. The 1-time costs are $9,550 for the programmable drug infusion device and $800 for the intrathecal catheter (Medtronic Canada Inc., email communication, November 15, 2022). While the actual costs of these components may vary from site to site depending on the volume of IDDS implantations performed at a given hospital, variation in cost is not expected to exceed 10% of the listed prices (Medtronic Canada Inc., email communication, November 15, 2022). A tablet referred to as the "clinician programmer," which is compatible with the programmable infusion device, is provided to the hospital and used by physicians to manage all patients with IDDSs. It is priced at $1,995 but provided free of charge by the manufacturer. Patients with IDDSs have access to the myPTM ("Personal Therapy Manager") app and handset, which allow them to activate bolus doses within limits set by their physicians. The myPTM app and handset are priced at $1,295 but also provided free of charge by the manufacturer (Medtronic Canada Inc., email communication, November 15, 2022).

Device Implantation

We derived the cost of IDDS implantation and associated costs from the Ontario Schedule of Benefits[87] and the National Ambulatory Care Reporting System (NACRS) via IntelliHealth. Based on an average procedure time of 2.5 hours (E. Baig, MD, email communication, January 8, 2023), the physician (surgeon and anaesthesiologist) billing for implantation (billing code N555) is estimated to be around $1,024 (Appendix 7, Table A13).

In addition to physician billing fees, other medical costs are associated with this procedure, including the cost of the operating room, recovery room, and other staff (e.g., nurses) involved in the patient's surgical care. We calculated these costs from a search of incident cases of this procedure in NACRS, which provides cost data for day surgeries in Ontario. We searched for procedures performed from January 2015 to March 2022 using a specific procedure code (Appendix 7, Table A14) to identify cases involving IDDS implantation. Using this approach, we found that the total cost of IDDS implantation is $12,335.

Post-implantation Follow-Up

Following implantation, patients should be followed up on days 3, 7, and 10 postoperatively to wean them off systemic opioid medications and to appropriately program their infusion device (E. Baig, MD, email communication, January 8, 2023). Programming likely takes place 1 to 2 times out of these 3 visits (E. Baig, MD, email communication, January 8, 2023). As such, we estimated that the cost of follow-up in the immediate postoperative period is $407.25 (including 3 follow-up visits [billing code A013] and 1.5 visits to program the infusion device [billing code: Z943]) (Appendix 7, Table A13).

Long-Term (1-Year) Follow-Up

The average frequency of pump refills is once every 3 months. (E. Baig, MD, telephone communication, October 27, 2022) A refill requires a physician visit to program the infusion pump (billing code: Z943) and the use of a refill kit (Appendix 7, Table A13). The refill kit, excluding drugs but including scrub materials (e.g., syringe) is priced at $31 (Medtronic Canada Inc., email communication, November 15, 2022).

Prescription Pain Medication

Standard Care

For the standard care arm, the average use of systemic opioid medication by individuals with refractory cancer pain is assumed to be an MOED of 300 mg per day (see “Main Assumptions”). Oral is typically the preferred route of administration. Individuals unable to take opioids orally (e.g., because of the severity of side effects or inability to swallow) may be transitioned to transdermal or subcutaneous administration.[88]

We therefore further assumed that 60%, 10%, and 30% of individuals in the standard care arm are on oral opioids, transdermal opioids, and subcutaneous opioid infusions using an external pump (e.g., the continuous ambulatory delivery device [CADD] pump), respectively (E. Baig, MD, written communication, May 31, 2023). To calculate the average monthly cost of pain medications, we first searched the unit prices of the most commonly recommended prescription opioids for moderate to severe cancer pain in the Ontario Drug Benefit (ODB) formulary.[89]

Oral opioids include morphine, hydromorphone, oxycodone, and methadone (E. Baig, MD, telephone communication, March 21, 2023).[89] Where available, we included both short- and long-acting formulations of these opioids because individuals with refractory cancer pain are typically prescribed both (E. Baig, MD, telephone communication, March 21, 2023). Transdermal opioids include fentanyl patches. Subcutaneous opioids include morphine and hydromorphone.

Each opioid drug (whether delivered orally, transdermally, or subcutaneously) is associated with a particular strength (e.g., milligrams per tablet, milligrams per millilitre). We multiplied the strength of each drug by its respective opioid equianalgesic conversion ratio to identify the quantity required per day to achieve an MOED of 300 mg per day. We then multiplied this number by the unit price of each drug to obtain the daily cost, and then by 30.437 to approximate the monthly cost. For each drug, we also incorporated pharmacy markup[90] and dispensing fees.[91] Last, we summed the average costs of oral, transdermal, and subcutaneous opioids multiplied by their proportion of use (Appendix 7, Table A15). For subcutaneous opioids, we also added the cost of the external CADD pump, estimated to be $6,616.72 per unit.[92]

We therefore estimated that the cost of systemic opioid use for individuals receiving standard care is $270 per month. In practice, the type of opioid prescribed for cancer pain varies from person to person and is based on the needs of the individual patient. Further, pain medications can be prescribed as either monotherapy or combination therapy.

IDDS Treatment

For the intervention arm, we assumed that individuals with an IDDS will largely be transitioned to intrathecal opioids and remain on a substantially reduced daily dose of systemic oral opioids at an MOED of 50 mg per day. We calculated the daily intrathecal dose based on the pre-implantation MOED amount using an oral-to-intrathecal dose ratio of 100:1. Based on individual need, additional patient-controlled doses can be programmed at one-tenth the daily intrathecal dose.[30] As such, based on the pre-implantation MOED of 250 mg (300 mg – 50 mg) a day, the intrathecal dose for individuals with an IDDS is 2.5 mg per day plus an available on-demand (bolus) dose of 0.25 mg. For simplicity, however, we did not consider the costs of patient-controlled doses. This is because the bolus option is not always activated (e.g., if adequate pain relief is achieved without it). In addition, the bolus dose is a relatively small volume of opioids; as such, we did not expect this cost to be substantial. Currently, only morphine and baclofen are approved for IDDSs by Health Canada. However, intrathecal baclofen is unlikely to be used for cancer pain. Because intrathecal opioid refills take place in hospital rather than at a pharmacy, we did not consider pharmacy markup or dispensing fees for intrathecal opioids. Overall, we estimated that the total cost of opioid use for individuals in the IDDS arm is $111 per month.

Additional Health Care Resource Use for Poorly Managed Pain or Severe Side Effects of Systemic Opioids

A recent retrospective study by Stearns et al[80] using propensity-score-matched analysis found that patients on intrathecal drug delivery incurred less health care resource use than patients receiving standard care. Because imbalances in patient characteristics (e.g., age, cancer type, comorbidities, treatment patterns for cancer and pain at baseline) were accounted for in the matched cohorts, differences in health care resource use may be attributed the difference in pain-related outcomes between the 2 groups. This study[80] found that at 12 months, individuals receiving standard care had a significantly higher number of inpatient hospital visits compared with individuals with an IDDS (2.3; 95% CI, 1.2–3.4, $p < 0.001$).

We therefore derived the cost of additional pain-related health care resource use in the standard care arm by multiplying the 12-month mean difference in number of inpatient hospital visits (2.3) by the average total estimated cost of an additional hospitalization for pain management ($7,483). We derived this cost using the Canadian Institute for Health Information (CIHI) patient cost estimator to identify the case mix group for adults using health care resources for pain management.[93] We thus estimated that the total cost of additional hospitalizations for pain management under standard care is $17,210 ($7,483 × 2.3).

Table 14: Costs Used in the Economic Model

Variable	Unit cost, $	Quantity	Total cost, $	Reference
IDDS				
Device (1-time costs)				
Programmable drug infusion device	$9,550	1	$9,550	Medtronic Canada Inc., email communication, November 15, 2022
Intrathecal catheter	$800	1	$800	Medtronic Canada Inc., email communication, November 15, 2022
Implantation procedure and post-procedure follow-up (1-time costs)				
Procedure (physician billing)	$1,024	1	$1,024	Schedule of Benefits[87]
Hospital costs for IDDS implantation[a]	$12,335	1	$12,335	NACRS
Post-procedure follow-up visits (physician billing)	$64.65	3	$193.95	Schedule of Benefits[87]
Infusion pump programming (physician billing)	$142.20	1.5	$213.30	Schedule of Benefits[87]
Long-term (1-year) follow-up				
Infusion pump programming (physician billing)	$142.20	4	$568.80	Schedule of Benefits[87]
Refill kit	$31	4	$124	Medtronic Canada Inc., email communication, November 15, 2022
Prescription pain medication (monthly costs)				
Intrathecal opioids[b]	NA	NA	$76	Calculated (Appendix 7, Table A15)
Systemic opioids[c]	NA	NA	$35	Calculated (Appendix 7, Table A15)

Variable	Unit cost, $	Quantity	Total cost, $	Reference
Standard care				
Prescription pain medication (monthly costs)				
Systemic opioids[d]	NA	NA	$270	Calculated (Appendix 7, Table A15)
External pump for subcutaneous administration of pain medication (1-time costs)				
CADD pump[e]	$6,617	30%	$1,985	Thunder Bay Regional Health Sciences Foundation[92]
Additional health care resource use for poorly managed pain or severe side effects of systemic opioids (1-year costs)				
Additional yearly hospitalizations for poorly managed pain or severe side effects of systemic opioids	$7,483 per hospitalization	2.3 per year	$17,210	Stearns et al, 2019[80]; CIHI Patient Cost Estimator, 2015/16 to 2019/20[93]

Abbreviations: CADD, continuous ambulatory delivery device; CIHI, Canadian Institute for Health Information; IDDS, intrathecal drug delivery system; MOED, morphine oral equivalent dose; NA, not applicable; NACRS, National Ambulatory Care Reporting System.

[a]We identified 21 cases in NACRS using the specific procedure code (Appendix 7, Table A14) to identify cases involving IDDS implantation. We then excluded cases specifying that the purpose of the procedure was to adjust the infusion pump or to address a complication resulting from the installation of the infusion pump. We further filtered cases by centre to identify IDDS cases, as there is currently only 1 centre in Ontario that performs this interventional procedure. After these exclusions, 1 case remained. Based on this case, we estimated that the total cost associated with the IDDS implantation procedure is $12,335.

[b]Based on an MOED of 2.5 mg/day.

[c]Based on an MOED of 50 mg/day.

[d]Based on the weighted-average cost of oral, transdermal, and subcutaneous opioids for an MOED of 300 mg/day (see Appendix 7, Table A15 for further details).

[e]Based on the assumption that 30% of systemic opioids in standard care would be administered subcutaneously via external pump.

Internal Validation

The secondary health economist conducted formal internal validation. This process included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis

Our reference case and sensitivity analyses adhered to the CADTH guidelines[84] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions.

We calculated the reference case of this analysis by running 5,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters that were expected to vary. We set distributions for variables within the model. Tables A11 and A12 in Appendix 7 list the model variables and corresponding distributions. Appendix 8 details the methods used for simulating survival data for

probabilistic analysis. We calculated mean costs with credible intervals and mean QALYs with credible intervals for each intervention assessed. We also calculated the mean incremental costs with credible intervals, incremental QALYs with credible intervals, and incremental cost-effectiveness ratios (ICERs) for IDDSs versus standard care.

The results of the probabilistic analysis are presented in a scatter plot on a cost-effectiveness plane (Figure 6) and in a cost-effectiveness acceptability curve (Figure 7). Although not used as definitive willingness-to-pay (WTP) thresholds, including graphical indications of the location of the results relative to guideposts of $50,000 per QALY and $100,000 per QALY facilitates interpretation of the findings and comparison with historical decisions. We also present uncertainty quantitatively as the probability that an intervention is cost-effective at the previously mentioned WTP guideposts. This uncertainty is also presented qualitatively in 1 of 5 categories defined by the Ontario Decision Framework[94]: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely not to be cost-effective (20%–39% probability), or highly likely not to be cost-effective (0%–19% probability).

Scenario Analyses

We explored 11 scenario analyses by modifying various parameter inputs and applying alternative assumptions (Table 15).

In scenario 1, we considered a scenario in which IDDS implantation is performed as an inpatient procedure. We included this scenario because this procedure has historically been performed as an inpatient procedure. However, as clinicians gained more experience and expertise in the procedure, the 1 centre providing IDDS pain management in Ontario is now performing the procedure more often on an outpatient basis (E. Baig, MD, telephone communication, March 21, 2023). We considered that if IDDSs were publicly funded for the management of cancer pain, other centres that begin to provide IDDS care are likely to begin by performing implantation as an inpatient procedure (D. Moulin, MD, telephone communication, March 15, 2023). We derived the hospitalization costs associated with inpatient IDDS implantation by searching for incident cases of this procedure in the Discharge Abstract Database (DAD), which provides cost data for acute inpatient care. We searched for data from January 2015 to March 2022 and used the same procedure code as in the reference case to identify cases involving IDDS implantation (Appendix 7, Table A14). As in the reference case, we excluded cases specifying that the purpose of the procedure was to adjust the infusion pump or address a complication of implantation. As only 1 centre in Ontario currently performs IDDS implantation for cancer pain, we further excluded cases not performed at this centre, as such cases would be related to the use of IDDSs for noncancer pain. After these exclusions, 29 cases remained. Based on these cases, we estimated that the mean total cost of inpatient IDDS implantation is $21,127.

Because the range of the average MOED in individuals with refractory cancer pain varies widely in the published literature and was also described as varying widely in consultations with clinical experts (E. Baig, MD, telephone communication, March 21, 2023), we explored a scenario that considered a substantially lower MOED of 100 mg per day (scenario 2) and 1 that considered a substantially higher MOED of 600 mg per day (scenario 3).

In scenarios 4 and 5, we assumed that the total cost of the IDDS device (including the programmable drug infusion device and the intrathecal catheter) would be reduced or increased by 10% of its list price, respectively. This value was chosen because variation in device cost was not expected to exceed 10% of the list price (Medtronic Canada Inc., email communication, November 15, 2022).

In scenario 6, we assumed that 3.2% of individuals with an IDDS would experience an infection requiring surgical intervention, such as device explantation, device replacement, pocket revision, and/or irrigation and debridement. This assumption is based on the study by Stearns et al[65] from which we derived the clinical and utility parameters for the reference case analysis. This study[65] found that 3.2% of its study population (n = 1,403) reported infection requiring surgical intervention. We then used the same approach as in the reference case to identify incident cases involving IDDS implantation in NACRS via IntelliHealth, but we filtered for cases specifying that the purpose of the procedure was to adjust the infusion pump or address a complication of implantation. After applying the filter, 4 cases remained. Based on these cases, we estimated that the mean total cost associated with an infection requiring surgical intervention for patients with an IDDS is about $6,193.

In scenario 7, we assumed that individuals with an IDDS would have improved survival outcomes compared with individuals receiving standard care. This assumption was based on the RCT by Smith et al,[46] which reported a 6-month cumulative survival of 53.9% in the IDDS group and 37.2% in the standard care group. In this scenario, we calculated the monthly probability of death from this survival outcome and extrapolated it to the entire 1-year time horizon of our model.

In scenario 8, we assumed that IDDSs would be associated with improved health-related utilities only until 6 months, after which point these utilities would return to baseline. We included this scenario because Stearns et al[65] reported that individuals with an IDDS experienced a significant improvement in EQ-5D index scores compared with individuals receiving standard care only at the 6-month follow-up.

In scenario 9, we assumed that standard care would not be associated with any additional health care resource use for poorly managed pain or severe side effects of systemic opioids.

Scenarios 10 and 11 assumed that lower percentages of systemic opioids (20% and 15%, respectively) would be administered subcutaneously using an external pump under standard care.

Table 15: Variables Varied in Scenario Analyses

Parameter	Reference case	Reference	Scenario analysis	Reference
Scenario 1: IDDS implantation performed as an inpatient procedure				
Initial hospitalization costs	$12,335	NACRS	$21,127	DAD
Scenario 2: Systemic opioid use in standard care is an average MOED of 100 mg/day				
Systemic opioids, monthly cost (standard care)	$270	Calculated	$102	Calculated
Scenario 3: Systemic opioid use in standard care is an average MOED of 600 mg/day				
Systemic opioids, monthly cost (standard care)	$270	Calculated	$522	Calculated
Scenario 4: IDDS device cost reduced by 10% of list price				
Device cost (programmable drug infusion device + intrathecal catheter)	$10,350	Medtronic Canada Inc., email communication, November 15, 2022	$9,315	Calculated
Scenario 5: IDDS device cost increased by 10% of list price				
Device cost (programmable drug infusion device + intrathecal catheter)	$10,350	Medtronic Canada Inc., email communication, November 15, 2022	$11,385	Calculated
Scenario 6: 3.2% of IDDS patients will have an infection requiring surgical intervention				
Cost of infection requiring surgical intervention	NA	NA	$6,193	NACRS
Proportion of IDDS patients requiring surgery	NA	NA	3.2%	Stearns et al, 2020[65]
Scenario 7: IDDS is associated with improved survival compared with standard care				
Monthly probability of death in standard care arm	NA	NA	0.152	Smith et al, 2022[46]
Monthly probability of death in IDDS arm	NA	NA	0.098	Smith et al, 2022[46]
Scenario 8: IDDS is associated with improved health-related utilities only until 6 months				
Health utilities in IDDS arm, months 7 to 12	0.56	Stearns et al, 2020[65]	0.39	Assumption

Parameter	Reference case	Reference	Scenario analysis	Reference
Scenario 9: Standard care is not associated with any additional health care resource use for poorly managed pain or severe side effects of systemic opioids				
Cost of additional inpatient hospital visits in standard care arm	$17,210	Stearns et al, 2019[80]; CIHI Patient Cost Estimator, 2015/16 to 2019/20[93]	$0	Assumption
Scenario 10: 20% of systemic opioids in standard care administered subcutaneously				
Percentage of systemic opioids administered subcutaneously	30%	E. Baig, MD, written communication, May 31, 2023	20%	Assumption
Scenario 11: 15% of systemic opioids in standard care administered subcutaneously				
Percentage of systemic opioids administered subcutaneously	30%	E. Baig, MD, written communication, May 31, 2023	15%	Assumption

Abbreviations: CIHI, Canadian Institute of Health Information; DAD, discharge abstract database; IDDS, intrathecal drug delivery system; MOED, morphine oral equivalent dose; NACRS, National Ambulatory Care Reporting System.

Results

Reference Case Analysis

The mean total costs for IDDSs and standard care arms were $25,053 and $20,571, respectively. Although the IDDS strategy had a higher overall incremental cost of $4,482 because of the upfront costs of the device, implantation, and hospitalization for implantation, this additional cost was partially offset by savings associated with a reduction in inpatient hospital visits for poorly managed pain or severe side effects of systemic opioids under standard care. To a lesser extent, the reduced cost of monthly prescription opioids in the intervention arm also partially offset the upfront costs of IDDS implantation.

The mean total effect was 0.26 QALYs for the IDDS strategy and 0.18 QALYs for standard care; treatment with IDDSs thus resulted in a small increase of 0.08 QALYs versus standard care over the duration of the model. Given the short time horizon of the model (1 year), the small difference in QALYs was expected. Treatment with IDDSs compared with standard care resulted in an ICER of $57,314 per QALY over 1 year. Table 16 provides the details of the reference case analysis results.

Table 16: Reference Case Analysis Results

Strategy	Average total costs, $ (95% CrI)	Incremental cost, $[a,b,c] (95% CrI)	Average total QALYs (95% CrI)	Incremental QALYs,[c,d] (95% CrI)	ICER[c] ($/QALY)
Standard care	20,571 (13,298 to 29,834)	–	0.18 (0.14 to 0.21)	–	–
IDDS	25,053 (21,637 to 29,048)	4,482 (−5,395 to 12,823)	0.26 (0.22 to 0.29)	0.08 (0.03 to 0.13)	57,314

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; IDDS, intrathecal drug delivery system; QALY, quality-adjusted life-year.

[a]Incremental cost = average cost (strategy B) − average cost (strategy A).

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[d]Incremental effect = average effect (strategy B) − average effect (strategy A).

Sensitivity Analysis

The results of our probabilistic analysis are presented in a scatter plot on a cost-effectiveness plane (Figure 6) and in a cost-effectiveness acceptability curve (Figure 7). The results of this analysis show that 99.86% of simulations found that IDDSs generated more QALYs than standard care. Of these simulations, 83.82% also found IDDSs to be more costly than standard care, whereas 16.18% found this strategy to be less costly than standard care.

Figure 6: Scatter Plot of Probabilistic Results

Scatter plot of probabilistic results with 5,000 iterations of the incremental cost-effectiveness ratio between the intervention and comparator arms. Each dot represents the joint distribution of incremental cost and effectiveness for 1 simulation.

When the results of the probabilistic analysis were plotted in a cost-effectiveness curve (Figure 7), we found that at the commonly used WTP of $50,000 per QALY, the probability of IDDSs being cost-effective was 43.46%, meaning the cost-effectiveness of this strategy is uncertain. The likelihood of its being cost-effective increased as the WTP increased. At the commonly used WTP of $100,000 per QALY, the probability of IDDSs being cost-effective was 72.54%, or moderately likely to be cost-effective.

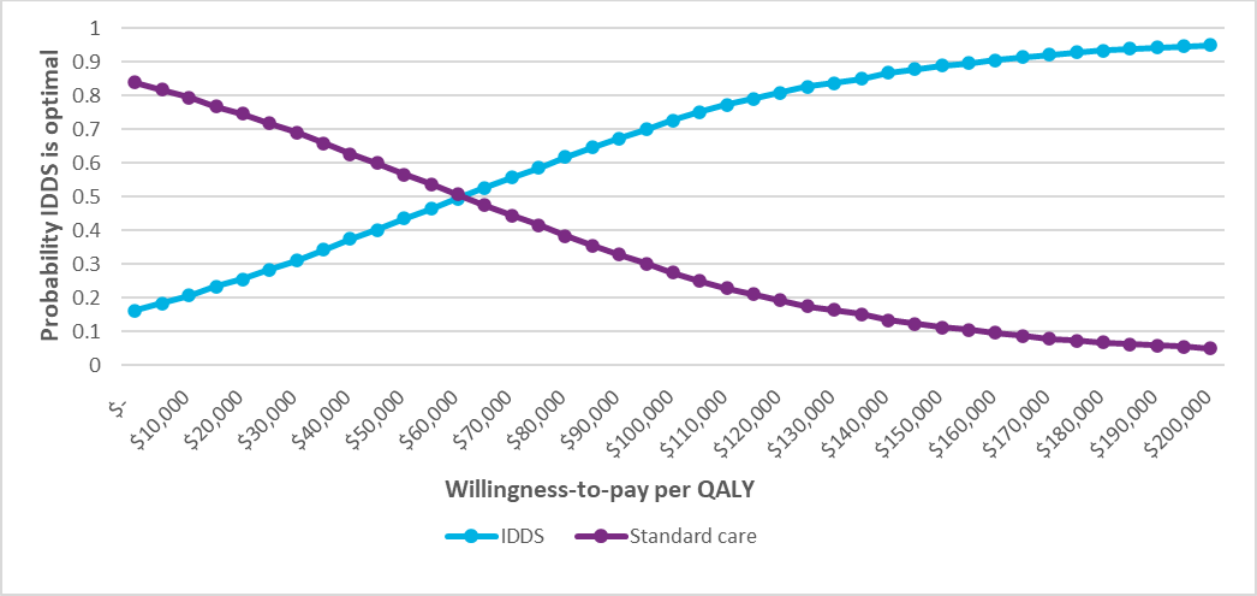

Figure 7: Cost-Effectiveness Acceptability Curve

Our scenario analyses showed that some parameters affected the results of our reference case more substantially than others. For instance, 6 scenarios yielded results with higher ICERs than in the reference case:

- Scenario 2: Systemic opioid use in standard care is an average MOED of 100 mg per day
- Scenario 5: The cost of the IDDS device is increased by 10% of the list price
- Scenario 6: 3.2% of patients with an IDDS acquire an infection requiring surgical intervention
- Scenario 8: IDDSs are associated with improved health-related utilities only until 6 months
- Scenarios 10 and 11: A lower percentage (20% and 15%, respectively) of systemic opioids are administered subcutaneously in standard care

However, few scenarios resulted in changes to the ICER as substantially as the following:

- Scenario 1: IDDS implantation is performed as an inpatient procedure
- Scenario 9: Standard care is not associated with additional health care resource use for poorly managed pain or severe side effects of systemic opioids

In contrast, our reference case ICER decreased in the following scenarios:

- Scenario 3: Systemic opioid use in standard care is an average MOED of 600 mg per day
- Scenario 4: The cost of the IDDS device is reduced by 10% of the list price
- Scenario 7: IDDSs are associated with improved survival compared with standard care

Overall, the cost-effectiveness results were most sensitive to the following:

- IDDS implantation being performed as an inpatient procedure
- IDDSs being associated with improved survival compared with standard care
- Standard care not being associated with additional health care resource use for poorly managed pain or severe side effects of systemic opioids

Table 17 provides a summary of the results of the scenario analyses.

Table 17: Scenario Analysis Results

Strategy	Average total costs, $	Incremental cost, $[a,b,c]	Average total effects, QALYs	Incremental effect, QALYs[c,d]	ICER ($/QALY)[c]
Reference case	SC: 20,571 IDDS: 25,053	4,482	SC: 0.18 IDDS: 0.26	0.08	57,314
Scenario 1: IDDS implantation performed as an inpatient procedure	SC: 20,685 IDDS: 33,828	13,143	SC: 0.18 IDDS: 0.26	0.08	167,698
Scenario 2: Systemic opioid MOED in SC: 100 mg/day	SC: 19,740 IDDS: 24,998	5,258	SC: 0.18 IDDS: 0.26	0.08	67,223
Scenario 3: Systemic opioid MOED in SC: 600 mg/day	SC: 20,657 IDDS: 25,001	2,935	SC: 0.18 IDDS: 0.26	0.08	37,772
Scenario 4: IDDS device cost reduced by 10% of list price	SC: 18,590 IDDS: 24,058	3,401	SC: 0.18 IDDS: 0.26	0.08	43,491
Scenario 5: IDDS device cost increased by 10% of list price	SC: 20,676 IDDS: 26,084	5,408	SC: 0.18 IDDS: 0.26	0.08	68,673
Scenario 6: 3.2% of IDDS patients will have an infection requiring surgical intervention	SC: 20,638 IDDS: 25,233	4,595	SC: 0.18 IDDS: 0.26	0.08	58,827
Scenario 7: IDDS associated with improved survival compared with SC	SC: 20,697 IDDS: 25,050	4,353	SC: 0.17 IDDS: 0.32	0.15	28,800

Strategy	Average total costs, $	Incremental cost, $[a,b,c]	Average total effects, QALYs	Incremental effect, QALYs[c,d]	ICER ($/QALY)[c]
Scenario 8: IDDS associated with improved health-related utilities only until 6 months	SC: 20,699 IDDS: 25,105	4,405	SC: 0.18 IDDS: 0.23	0.06	79,840
Scenario 9: SC not associated with any additional health care resource use for poorly managed pain or severe side effects of systemic opioids	SC: 3,467 IDDS: 25,056	21,589	SC: 0.18 IDDS: 0.26	0.08	273,517
Scenario 10: 20% of systemic opioids in SC administered subcutaneously	SC: 19,848 IDDS: 67,272	5,214	SC: 0.18 IDDS: 0.26	0.08	67,272
Scenario 11: 15% of systemic opioids in SC administered subcutaneously	SC: 19,343 IDDS: 25,024	5,681	SC: 0.18 IDDS: 0.26	0.08	72,179

Abbreviations: ICER, incremental cost-effectiveness ratio; IDDS, intrathecal drug delivery system; MOED, morphine oral equivalent dose; QALY, quality-adjusted life-year; SC, standard care.

[a]Incremental cost = average cost (strategy B) − average cost (strategy A).

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[d]Incremental effect = average effect (strategy B) − average effect (strategy A).

Discussion

Our reference case results show that despite initial upfront costs associated with the device, implantation, and hospitalization, the overall cost of cancer pain management with an IDDS was partially offset by the savings associated with the reduced cost of health care resource use (i.e., inpatient hospitalizations) for poorly managed pain or severe side effects of systemic opioids and, to a lesser extent, by the lower monthly cost of opioid analgesics.

However, several important considerations should be taken into account when interpreting the results of our analysis. First, while IDDSs have historically been considered a last resort for individuals with refractory cancer pain, there is a growing shift in the medical community to offer this pain management modality to patients earlier, before their pain becomes severe. It has been considered unethical to wait for potentially eligible patients to experience an acute pain crisis before offering the option of an IDDS (E. Baig, MD, telephone communication, October 27, 2023; J. Osborn, MD, telephone communication, April 12, 2023; V. Varshney, MD, telephone communication, April 25, 2023). As such, while a higher average MOED in individuals indicated for an IDDS will result in a lower ICER (scenario 3; MOED: 600 mg/day), it may be unethical to wait to offer an IDDS to individuals until they have reached the point of requiring such a high dose of systemic opioids. Similarly, while our analysis showed that

performing IDDS implantation as an inpatient procedure was not cost-effective at the commonly used WTPs of $50,000/QALY and $100,000/QALY (scenario 1), the decision to perform this procedure on an inpatient or outpatient basis should be made based on clinical judgement. This is because patient characteristics, including age, comorbidities, and overall health condition, will inform whether better outcomes can be achieved through an inpatient or outpatient procedure (P. Hawley, MD, telephone communication, May 8, 2023).

Second, individuals transitioning from systemic to intrathecal opioids may have a more substantial effect on outcomes that were out of scope for our analysis. For instance, over the past decade, there has been a steady increase in opioid-related harms (e.g., hospitalizations and emergency department [ED] visits for opioid poisoning) in Ontario.[95] In 2021 alone, more than 2,800 people in Ontario died from opioid-related causes.[95] Opioid poisoning can occur when an individual administers an opioid not as prescribed, for example through overdose, accidental ingestion, or purposeful self-inflicted harm.[96] Additionally, the possibility of opioid-related harms is not limited to the individual for whom opioid medications are prescribed. A North American review paper[97] found that the majority of individuals in the general population who engaged in the nonmedical use of prescription opioids had sourced the medication from friends or family. As such, a reduction in prescribed opioids may naturally reduce the risks of both opioid poisoning and misuse.[97]

In Ontario, opioid-related harms may also disproportionally affect some regions more than others. For instance, in 2021, the rates of opioid-related ED visits per 100,000 people were highest in the North East (260,9 per 100,000), North West (224.3 per 100,000), Hamilton Niagara Haldimand Brant (163.4 per 100,000), South West (154.5 per 100,000), North Simcoe Muskoka (149.3 per 100,000), and Erie St. Clair (134.2 per 100,000) Local Health Integration Networks. Overall, the rate of opioid-related ED visits in Ontario in 2021 was 114 per 100,000 people.[95] As such, ensuring that access to cancer pain management via IDDS is available across the province may help mitigate the disproportionately higher rates of opioid-related harms in some regions.

It is important to consider the barriers to accessing cancer pain management via IDDS in Ontario. As described in the clinical evidence review, the assessment of eligibility for and performance of IDDS implantation require a highly specialized multidisciplinary health care team. If IDDSs are publicly funded, it is likely that this procedure will continue to be performed only at large, well-resourced tertiary care centres, which are typically located in large urban centres, which can limit access for many patients. However, if follow-up care, including device programming and refills, can take place at satellite centres by appropriately trained health care professionals, then some travel-related and out-of-pocket costs may be mitigated for some individuals.

Overall, our reference case and scenario analyses showed that the incremental QALY gains for IDDSs compared with standard care were small. While this result was expected given the short time horizon of our model, it is important to consider that our population of interest is palliative. The valuation of QALYs for palliative care continues to be debated in the cost-effectiveness literature, for example, in terms of whether a QALY gained at end of life is equivalent to a QALY gained earlier in life.[98] Some experts have argued that society has shown a WTP for palliative care interventions is higher than what is typically considered “rational.”[98]

Strengths and Limitations

To our knowledge, our analysis is the first to evaluate the cost–utility of IDDSs compared with standard care for adults with refractory cancer pain. Before this analysis, no study had adequately captured all meaningful health effects related to the use of IDDSs despite the intended use of this intervention being to provide pain relief and better quality of life. We were able to capture QALY gains associated with the use of IDDSs by deriving utility parameters from the recently published study by Stearns et al,[65] which included the EQ-5D index values for patient-reported health outcomes.

The clinical evidence review found that while most studies have reported the use of IDDSs being associated with positive outcomes in terms of reduced pain intensity, survival, functional outcomes, health-related quality of life, and decreased use of systemic opioids, the evidence is largely of low quality owing to methodological weakness. In our analyses, we took into consideration the scarcity of rigorous evidence on this topic and made conservative assumptions in our reference case, including that IDDSs would not be associated with improved survival and that individuals with an IDDS would continue to receive some systemic opioids.

To ensure that our results were generalizable to the context of health care in Ontario and Canada, we ensured that our cost parameters were largely derived from local sources, including the Ontario Schedule of Benefits, the Canadian IDDS list price, Canadian administrative health databases, the publicly available Ontario Drug Benefit (ODB) formulary, and published costing estimates from CIHI.

Some limitations to our analysis should be noted, however. First, while we were able to derive utility values from the EQ-5D index values reported by Stearns et al,[65] the subset of study participants for which these values were reported was very small (n = 41). Therefore, there is some uncertainty in the generalizability of these data to our broader population of interest.

Second, we derived the cost parameter for pain-related health care resource use from another study by Stearns et al,[80] which was a propensity-matched analysis that found that standard care was associated with a higher number of inpatient hospitalizations than pain management via IDDS. However, this study did not report the causes for hospitalization. We reasoned that this difference may have resulted from pain being better managed by IDDSs because the amount of health care resource use required by our population of interest to manage their disease (e.g., intensive palliative care, regular nursing and physician visits, home care services) is not expected to change substantially based on pain management modality, regardless of how well pain is managed. While this may be a reasonable simplifying assumption, there is uncertainty around this cost parameter because it is a key driver of cost-effectiveness for IDDSs (as seen in scenario 9).

Third, we used the ODB formulary to estimate the costs of outpatient drugs. However, some individuals in our population of interest may not be eligible under the ODB program and may or may not have drug coverage under private insurance. While the percentage of people not covered by a public drug plan is unknown, we did not expect this figure to substantially affect our reference case results because our scenario analyses showed that drug costs were not a key driver of cost-effectiveness.

Last, based on the clinical evidence review, which found that the evidence for IDDSs compared with standard care in children was very uncertain, we limited our economic evaluation to adults.

Conclusions

Our cost–utility analysis showed that compared with standard care, IDDS generated 0.08 additional QALYs and cost an additional $4,482, resulting in an ICER of $57,314 per QALY over a 1-year time horizon. These results were most sensitive to IDDS implantation being performed as an inpatient procedure, IDDSs not being associated with improved survival outcomes, and standard care not being associated with additional health care resource use for poorly managed pain or severe side effects of systemic opioids. If IDDSs become publicly funded for the management of cancer pain, future implementation considerations should address access barriers.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding implantable intrathecal drug delivery systems (IDDSs) for the management of cancer pain in adults and children?

Methods

Analytic Framework

We estimated the budget impact of publicly funding IDDSs for the management of cancer pain in adults and children using the cost difference between 2 scenarios: (1) current clinical practice without public funding for IDDSs (the current scenario) and (2) anticipated clinical practice with public funding for IDDSs (the new scenario). Figure 8 presents the model schematic.

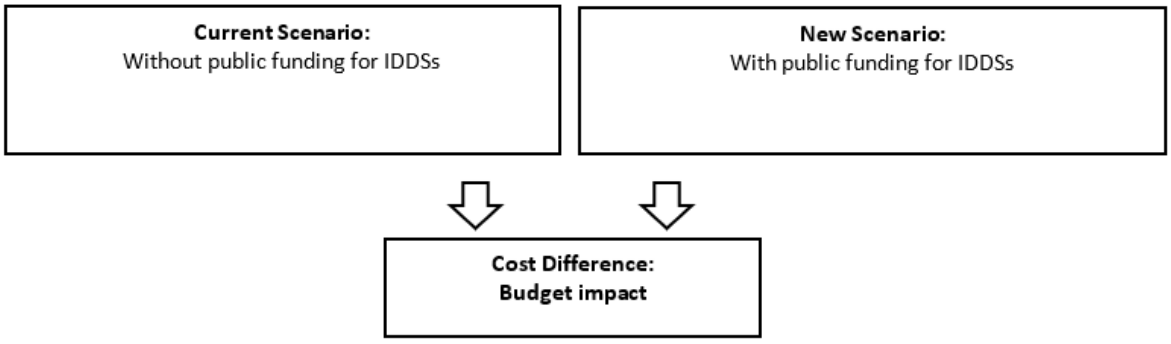

Figure 8: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. The current scenario would explore resource use and total costs without public funding for IDDS. The new scenario would explore resource use and total costs *with* public funding for IDDS. The budget impact would represent the difference in costs between the 2 scenarios.

Key Assumptions

The model's main assumptions included all those used in the primary economic evaluation plus the following:

- About 60 people will receive an IDDS each year, about 10% of whom will be children (E. Baig, MD, telephone communication, October 27, 2022; June 27, 2023)
- For simplicity, we assumed that the number of people undergoing IDDS implantation will remain constant over the next 5 years
- For simplicity, we assumed that children will incur the same per-person costs as adults

Population of Interest

According to a systematic review[4] published in 2016, the prevalence of cancer pain ranges from 33% in patients who have undergone curative treatment to 64% in patients whose cancers are metastatic, advanced, or terminal. Despite the availability of clinical guidelines on pain management, cancer pain is considered to be undertreated in around 40% of patients.[5] Of the patients who continue to experience chronic refractory pain, interventional procedures, such as intrathecal drug delivery, may be offered as a treatment option to achieve better pain management. However, eligibility for intrathecal drug delivery should be assessed carefully by a multidisciplinary health care team (including specialists in the areas of pain medicine, anaesthesiology, neurosurgery, oncology, radiation oncology, palliative care, physical medicine and rehabilitation, and nursing) to increase the likelihood of treatment success[30] (E. Baig, MD, telephone communication, October 27, 2022).

The selection process should involve careful consideration of cancer stage, life expectancy, patient characteristics, and comorbidities that may influence the risks and side effects of opioid analgesics (e.g., sleep apnea, pulmonary disease, cardiac disease, metabolic syndrome), as well as overall psychological state.[99,100] Because of the complex interplay among these variables in identifying potential candidates for intrathecal drug delivery, we were unable to derive an estimated number of individuals eligible for IDDS implantation in Ontario from administrative databases or the published literature. As such, we estimated the annual volume of our population of interest based on clinical expert opinion. As noted, we estimated that about 60 people (including adults and children) will receive an IDDS each year over the next 5 years (Table 18) (E. Baig, MD, telephone communication, October 27, 2022).

Table 18: Estimated Number of People Receiving Standard Care and IDDSs in the Current and New Scenarios

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Standard care, n	60	60	60	60	60	300
New scenario						
IDDS, n	60	60	60	60	60	300
Standard care, n	0	0	0	0	0	0

Abbreviation: IDDS, intrathecal drug delivery system.

Current Intervention Mix

In the current scenario, standard care is conventional medical management via non-IDDS methods of pain management as guided by the World Health Organization's 3-step analgesic ladder for cancer pain management.[8] This framework recommends the stepwise prescription of pain medications based on pain severity from nonsteroidal anti-inflammatory drugs for mild pain to weak prescription opioids (e.g., codeine) for moderate pain to strong prescription opioids (e.g., morphine) for severe pain. Since individuals indicated for intrathecal drug delivery are those experiencing chronic refractory cancer pain, it is likely that they are managing their cancer pain with strong systemic prescription opioids.

Uptake of the New Intervention and New Intervention Mix

In the new scenario, individuals with chronic refractory cancer pain may be eligible for IDDSs implantation. Given that there is currently just 1 centre (with 2 sites) in Ontario performing IDDS implantation, it is likely that this centre would continue to perform all procedures were IDDS implantation to be publicly funded (E. Baig, MD, telephone communication, October 27, 2022). However, over time, the procedure could become available at other sites with established pain centres with the appropriate neurosurgical and pain expertise, such as member partners of the Toronto Academic Pain Medicine Institute (E. Baig, MD, telephone communication, October 27, 2022).

Because implantation will initially be performed at only 1 centre, travel and cost may pose access barriers for some patients. However, follow-up appointments for pump programming and refills could be done locally by trained health care professionals. As such, training should be provided to health care professionals across the province to reduce travel and cost barriers for patients post-implantation.

Resources and Costs

We included all health care costs in our budget impact analysis by running the companion cost-effectiveness analyses previously described over the time horizon of the budget impact analysis (without discounting) to obtain the relevant costs. We also included disaggregated costs by key cost categories (e.g., device, drug, hospital).

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

The scenarios examined in our sensitivity analysis were as follows:

- Scenario 1: The annual uptake of IDDS implantation is gradual, from 20% in year 1, increasing to 100% in year 5
- Scenario 2: IDDS implantation is performed as an inpatient procedure
- Scenario 3: Systemic opioid use in standard care is an average MOED of 100 mg per day
- Scenario 4: Systemic opioid use in standard care is an average MOED of 600 mg per day
- Scenario 5: The cost of the IDDS device is reduced by 10% of its list price
- Scenario 6: The cost of the IDDS device is increased by 10% of its list price
- Scenario 7: 3.2% of IDDS patients will experience an infection requiring surgical intervention
- Scenario 8: IDDSs are associated with improved survival compared with standard care
- Scenario 9: IDDSs are associated with improved health-related utilities only until 6 months

- Scenario 10: Standard care is not associated with additional health care resource use for poorly managed pain or severe side effects of systemic opioids
- Scenario 11: 20% of systemic opioids in standard care are administered subcutaneously
- Scenario 12: 15% of systemic opioids in standard care are administered subcutaneously
- Scenario 13: More patients (100) receive an IDDS each year

Results

Reference Case

Table 19 summarizes the total costs associated with IDDS implantation over the next 5 years. We found that the budget impact was an additional $0.27 million per year, for a total of $1.34 million over 5 years.

Table 19: Budget Impact Analysis Results

Scenario	Budget impact, $ million[a,b,c]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Current scenario	1.23	1.23	1.23	1.23	1.23	6.17
Additional pain-related hospitalizations	1.03	1.03	1.03	1.03	1.03	5.13
Prescription pain medication	0.21	0.21	0.21	0.21	0.21	1.04
New scenario	1.50	1.50	1.50	1.50	1.50	7.52
IDDS device	0.62	0.62	0.62	0.62	0.62	3.10
Hospital cost for IDDS implantation procedure	0.74	0.74	0.74	0.74	0.74	3.70
Physician fees[d]	0.11	0.11	0.11	0.11	0.11	0.53
Prescription pain medication	0.04	0.04	0.04	0.04	0.04	0.18
Budget impact[b,c]	0.27	0.27	0.27	0.27	0.27	1.34

Abbreviation: IDDS, intrathecal drug delivery system.
[a]In 2023 Canadian dollars.
[b]All costs were calculated using the mean cost from the primary economic evaluation's probabilistic results.
[c]Results may appear inexact due to rounding.
[d]During and following implantation.

Sensitivity Analysis

Table 20 summarizes the results of the 13 scenarios analyses. Compared with the reference case, scenarios that considered an increase or decrease in IDDS-associated costs resulted in a higher or lower budget impact, respectively. For instance, assuming that IDDS implantation is performed as an inpatient procedure (scenario 2) resulted in an annual budget impact of an additional $0.79 million and a total 5-year budget impact of an additional $3.94 million. The budget impact also increased, but to a lesser extent, in scenarios in which the cost of the IDDS device was increased by 10% of its list price (scenario 6) and in which a small number of IDDS patients experienced an infection requiring surgical intervention

(scenario 7). In contrast, the budget impact decreased in the scenario in which the cost of the IDDS device was reduced by 10% of its list price (scenario 5).

While the direct cost of IDDS implantation (i.e., the total cost of the device) remained the same for scenarios that considered a lower and higher average MOED in standard care (scenarios 3 and 4), a lower percentage of systemic opioids being administered subcutaneously in standard care (scenarios 11 and 12), and standard care not being associated with additional health care resource use for poorly managed pain or severe side effects of systemic opioids (scenario 10), each of these scenarios incurred a change to the overall budget impact. For instance, when systemic opioid use in standard care was assumed to be an average MOED of 100 mg per day (scenario 3), the overall budget impact increased to an additional $0.32 million a year, for a total 5-year budget impact of $1.58 million. When we assumed that 20% of systemic opioids in standard care are administered subcutaneously (rather than 30%, as in the reference case) (scenario 11), the overall budget impact increased to an additional $0.31 million a year, for a total 5-year budget impact of $1.56 million. But when systemic opioid use in standard care was assumed to be an average MOED of 600 mg per day (scenario 4), the overall budget impact decreased to an additional $0.18 million a year, for a total 5-year budget impact of $0.88 million.

Scenarios that assumed that IDDS implantation was associated with improved survival (scenario 8) and that IDDS implantation was associated with improved health-related utilities only until 6 months (scenario 9) resulted in relatively similar budget impact results as in the reference case.

Assuming a gradual annual uptake of IDDS implantation, from 20% in year 1, increasing to 100% in year 5 (scenario 1), resulted in a lower budget impact that increased over time. However, the budget impact increased when we assumed a higher annual number of patients undergoing IDDS implantation (scenario 13).

Table 20: Budget Impact Analysis Results – Sensitivity Analyses

Scenario	Budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Reference case	0.27	0.27	0.27	0.27	0.27	1.34
Scenario 1: Gradual annual uptake rate, from 20% in year 1, increasing to 100% in year 5	0.05	0.11	0.16	0.22	0.27	0.81
Scenario 2: IDDS implantation performed as an inpatient procedure	0.79	0.79	0.79	0.79	0.79	3.94
Scenario 3: Systemic opioid use in standard care is an average MOED of 100 mg/day	0.32	0.32	0.32	0.32	0.32	1.58
Scenario 4: Systemic opioid use in standard care is an average MOED of 600 mg/day	0.18	0.18	0.18	0.18	0.18	0.88
Scenario 5: IDDS device cost reduced by 10% of list price	0.20	0.20	0.20	0.20	0.20	1.02
Scenario 6: IDDS device cost increased by 10% of list price	0.32	0.32	0.32	0.32	0.32	1.62
Scenario 7: 3.2% of IDDS patients will have an infection requiring surgical intervention	0.28	0.28	0.28	0.28	0.28	1.38
Scenario 8: IDDSs associated with improved survival outcomes compared with standard care	0.26	0.26	0.26	0.26	0.26	1.31
Scenario 9: IDDSs associated with improved utilities only until 6 months	0.26	0.26	0.26	0.26	0.26	1.32
Scenario 10: Standard care not associated with additional health care resource use due to poorly managed pain or severe side effects of systemic opioids	1.30	1.30	1.30	1.30	1.30	6.48
Scenario 11: 20% of systemic opioids in standard care administered subcutaneously	0.31	0.31	0.31	0.31	0.31	1.56
Scenario 12: 15% of systemic opioids in standard care administered subcutaneously	0.34	0.34	0.34	0.34	0.34	1.71

Scenario	Budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Scenario 13: More patients (100) receive an IDDS each year	0.45	0.45	0.45	0.45	0.45	2.24

Abbreviations: IDDS, intrathecal drug delivery system; MOED, morphine oral equivalent dose.

[a]In 2023 Canadian dollars.

[b]Results may appear inexact due to rounding.

[c]Includes the direct costs of the device, implantation procedure, initial hospitalization for procedure, post-procedure follow-up, drug costs, device programming, and medication refills over 1 year.

Discussion

IDDS implantation is associated with additional costs that are partially offset by the cost savings associated with reduced hospitalizations for poorly managed pain or severe side effects of systemic opioids and, to a lesser extent, by a reduction in the cost of prescription opioids.

Based on expert opinion, we assumed that if publicly funded, about 60 IDDS implantation procedures would be performed each year over the next 5 years (E. Baig, MD, virtual communication, October 27, 2022). It is important to note that currently, many potentially eligible patients are not referred for IDDS implantation or are referred too late because of a lack of awareness of this technology among health care professionals (J. Osborn, MD, telephone communication, April 12, 2023; V. Varshney, MD, telephone communication, April 25, 2023). In British Columbia, the only province where IDDS implantation is currently publicly funded, the low number of referrals and subsequent low annual volume of IDDS implantations have been partially attributed to a lack of clinician familiarity with intrathecal drug delivery in the context of cancer pain (J. Osborn, MD, telephone communication, April 12, 2023; V. Varshney, MD, telephone communication, April 25, 2023). As such, future implementation considerations should include investments in education and training in IDDS care for both patients and health care professionals, in particular those specializing in palliative care. An increase in awareness may lead to an increase in the number of eligible patients referred for IDDS implantation, as well as a subsequent increase in the budget impact.

Strengths and Limitations

The estimates for our budget impact analysis were derived from our cost-effectiveness analysis, which obtained its clinical parameters from the clinical evidence review, and the cost parameters were largely derived from Canadian sources. Further, we validated our assumptions and estimates with clinical experts with expertise in the use of IDDSs for the management of cancer pain.

Notably, we relied on consultation with clinical experts to obtain estimates for the annual volume of IDDS implantations and for the uptake rate because this information was unavailable in the published literature and because we were unable to derive these estimates from alternative sources given the complexity in assessing eligibility for IDDS implantation and the recent shift in clinical practice to offer IDDS implantation earlier in a patient's experience of cancer, before their pain progresses in severity.

Conclusions

We estimate that publicly funding IDDSs in Ontario for the management of cancer pain in adults and children would lead to an additional cost of $0.27 million per year, for a total of $1.34 million over the next 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of cancer pain, as well as the preferences and perceptions of patients and caregivers regarding implantable intrathecal drug delivery systems (IDDSs).

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[101-103] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of patients with cancer pain, caregivers, and health care providers in 2 ways:

- A review by Ontario Health of the quantitative evidence on patient, caregiver, and health care provider preferences and values
- Direct engagement by Ontario Health with patients with cancer pain, caregivers, and health care providers through interviews

Quantitative Evidence

Research Questions

- What are the relative preferences of patients, caregivers, and health care providers for implantable IDDSs compared with nonintrathecal drug delivery for the management of cancer pain?
- What is the relative importance of key attributes of implantable IDDSs, and what trade-offs between attributes are patients and health care providers willing to make?

Methods

Literature Search

We performed a literature search for quantitative evidence of preferences and values on January 4, 2023, to retrieve studies published from database inception until the search date. We used the Ovid interface to search MEDLINE and the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

The search was based on the population and intervention of the clinical search strategy with a methodological filter applied to limit retrieval to quantitative evidence of preferences and values (modified from Selva et al).[104] The final search strategy was peer-reviewed using the PRESS Checklist.[33]

We created database auto-alerts in MEDLINE and CINAHL and monitored them for the duration of the assessment period. See Appendix 1 for our quantitative preferences and values literature search strategy, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published since database inception
- Key study designs (e.g., surveys, discrete choice experiments)
- Studies on patient and health care provider preferences for IDDSs for cancer pain management that use quantitative measures:
    - Utility measures
        - Direct techniques: standard gamble, time trade-off, rating scales, conjoint analysis (e.g., discrete choice experiment, contingent valuation and willingness-to-pay, probability trade-off)
        - Indirect techniques: prescored multi-attributable instruments (e.g., 36-Item Short Form Health Survey, EQ-5D, Health Utilities Index)
    - Nonutility measures
        - Direct-choice techniques: decision aids, surveys, questionnaires

Exclusion Criteria

- Qualitative studies, editorials, commentaries, case reports, conferences abstracts, letters
- Animal and in vitro studies

Results

Literature Search

The literature search for quantitative evidence of preferences and values yielded 64 citations published between database inception and January 4, 2023, after duplicates were removed. We identified no additional studies from other sources. No studies met our inclusion criteria. Figure 9 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the literature search for quantitative evidence of preferences and values.

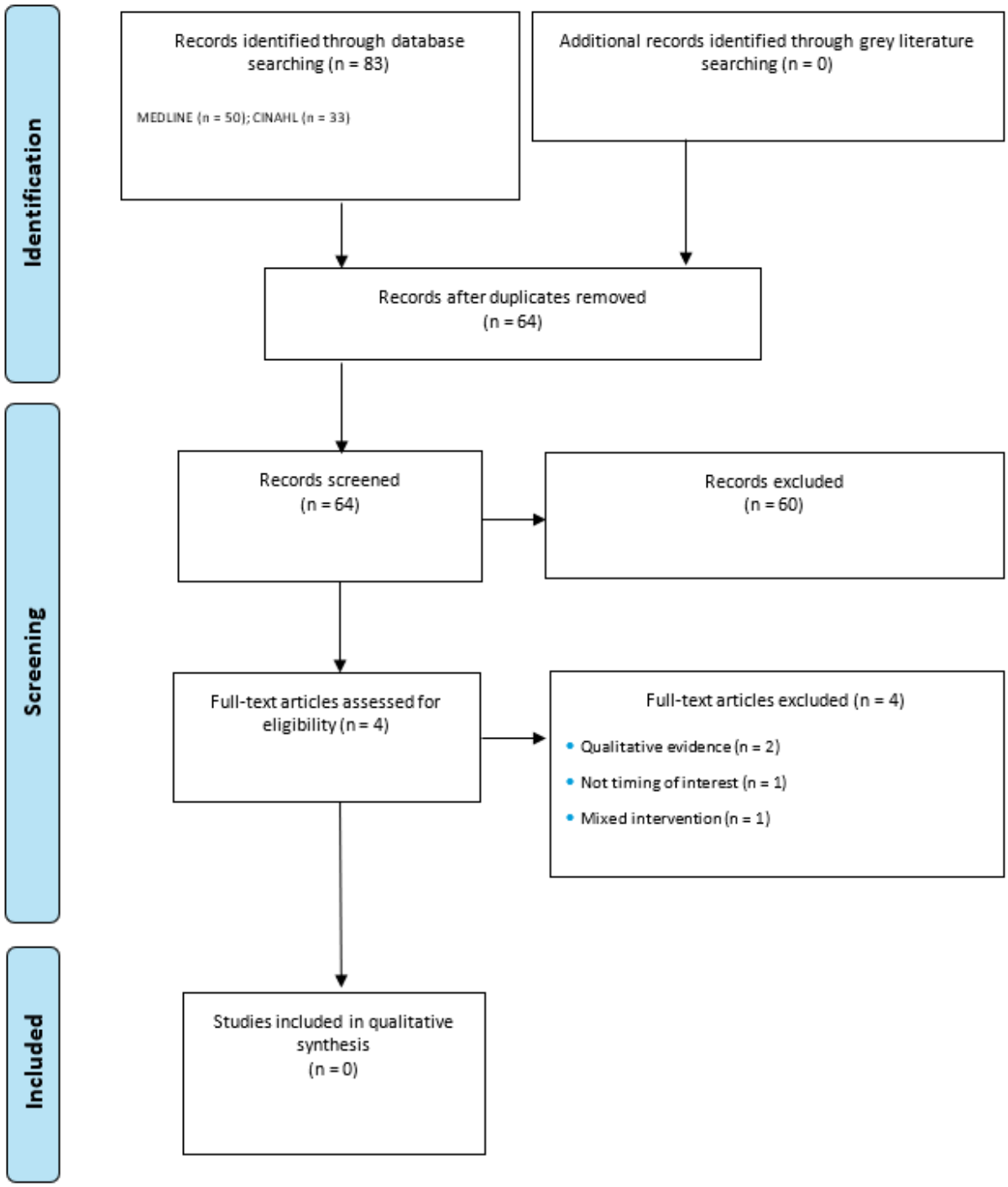

Figure 9: PRISMA Flow Diagram – Quantitative Evidence of Preferences and Values Search Strategy

PRISMA flow diagram showing the quantitative evidence of preferences and values search strategy. The database search of the preferences and values literature yielded 83 citations published between database inception and January 4, 2023. We identified no additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 64 studies and excluded 60. We assessed the full text of 4 articles and excluded all 4. In the end, we included no articles in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[35]

Conclusions

We identified no studies on the quantitative preferences and values of patients, caregivers, or health care providers for IDDSs compared with other routes of medication delivery for the management of cancer pain that were applicable to Ontario context.

Direct Patient Engagement

Methods

Partnership Plan

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with cancer pain and their family members and caregivers. We engaged people via telephone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with cancer pain, as well as those of their families and caregivers.[105] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

Participant Outreach

We used an approach called purposive sampling,[106-109] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of community organizations, clinical experts, and community-based health programs in Ontario that support people affected by cancer to spread the word about this engagement activity and to contact people with cancer pain, family members, and caregivers, including those with experience of IDDSs.

Inclusion Criteria

We sought to speak with adults with lived experience of cancer pain. We included those who had undergone IDDS implantation, those who were planning to undergo IDDS implantation, and those without direct experience of IDDS implantation.

Exclusion Criteria

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

Participants

For this project, we spoke with 7 people living in Ontario, 5 of whom had lived experience of cancer pain. The remaining participants were a caregiver of an adolescent with cancer pain and a family member of an adult with cancer pain. Two participants had direct experience with an IDDS, and 1 had experience with an IDDS as a caregiver for a patient using the device.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 9). We then obtained participants' verbal consent before starting the interview. With the participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 30 to 60 minutes. The interview was semistructured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[110] Questions focused on the impact of cancer pain on the quality of life of people with cancer, their experiences with treatments to manage cancer pain, their experiences with IDDSs, and their perceptions of the benefits or limitations of IDDSs, as well as the impact of the person's cancer pain and treatments on family members and caregivers. See Appendix 10 for our interview guide.

For this review, we also leveraged a 2003 Global News segment on the use of IDDSs for the management of cancer pain that included a patient interview.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[111,112] We used the qualitative data analysis software program NVivo[113] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of cancer pain and pain management on the people we interviewed.

Results

Note: For clarity and simplicity in this section, participants with cancer are referred to as "patients," as are the people cared for by the caregiver and family member participants. The caregiver and family member are referred to as "caregivers." Where both patients and caregivers are being referred to, "participants" is used.

Living With Cancer Pain

Patients experienced various forms of cancer pain. Some spoke of widespread pain, whereas others spoke of pain being concentrated in a specific area. The experience and progression of pain were often unique to the individual. Patients reported beginning to experience pain around the time of their cancer diagnosis and that the pain got worse over time. For patients whose cancer spread to other parts of their bodies, the pain also spread. Patients and caregivers described the intensity of the pain, its debilitating effect, and the complexity of its episodic nature.

> *At the beginning, I was experiencing bad lower back pain … then I started having nerve pain down in the perineal area, and it was painful and very strange.*

One patient received their cancer diagnosis after experiencing a sprain that was not healing and caused pain that worsened over time.

> *One week it would be better; then, when we think that he is getting better, he would kind of sprain it over again. And it kept getting worse.*

Some patients described what their pain felt like, including the intensity of the sensation and how unbearable and excruciating it was.

> *The tumour was pressing on all the nerves at the base of the spine … and compressing the sciatic nerve. And it was causing extreme, extreme pain.*

> *It feels like somebody's drilling into your bone. And it won't stop, and it can be excruciating sometimes.*

> *It feels like it's almost like someone kicked me in the back, and my hips feel like I fell and [like] they're bruised, but you're touching the bruise.*

The patient interviewed in the 2003 Global News segment described their pain as follows:

> *The pain was just so intense, I simply could not sit, not even for a minute. I would just scream. I didn't mean to scream; it was just so intense.*

Participants spoke of their pain progressing over time and the negative impact it had on patients' quality of life. As the pain increased in severity, it became increasingly difficult for them to carry out daily activities, which had a substantial negative impact on patients' day-to-day lives. In most cases, health-promoting activities such as eating or sleeping were negatively affected.

> *The pain was so bad, it was keeping me up at night, and I couldn't function.*

> *[The pain] was [so] bad that he lost his appetite. So, he was losing a lot of weight and muscle because he wasn't moving at all.*

Mobility was also substantially affected by pain, with all patients being unable or finding it difficult to carry out simple movements such as sitting, walking, or moving around. One patient was unable to move at all without being in pain. Pain caused some patients to need to use mobility-assistance devices such as wheelchairs, crutches, or walkers.

> *I went from riding my bike to work and working out at the gym to being in a wheelchair. So that was quite devastating.*

> *I use a walker right now, but I expect to get better.*

> *When he was at his worst, he couldn't even move a centimetre, and he was just stuck to the bed. The burden of living with pain affected almost every aspect of patients' lives. Participants reported that pain contributed to a loss of patients' independence, particularly when pain affected mobility. Pain severely limited patients' ability to participated in basic activities of daily living such as personal care, cleaning, transportation, cooking, and child care, as well as hobbies and socializing. Younger patients spoke about having to stop working because of their pain.*

I'm a very active person …. I did rock climbing. I never owned a car, so I rode my bike everywhere, and that was my only form of transportation. So, to go from that to Wheel-Trans [a paratransit system] was devastating to me.

I had to leave work as well due to the pain…. So, it has impacted me financially, mentally, emotionally. It has limited my ability to form relationships or attend festivals or entertainment and hugely impacted my ability to travel. All of that.

She had 3 small children at home [and] was trying to manage. She was unable to sit up or feed herself.

The loss of independence meant a substantial increase in reliance on caregivers and community care providers for assistance with activities of daily living. Caregivers spoke of the burden posed by the increased responsibilities placed on them, which took a physical toll. Physical demands on caregivers included assisting with personal care activities such as toileting and bathing. Caregivers also reported taking on additional duties such as daily household chores as well as scheduling and arranging medical appointments. Patients also acknowledged the burden their care placed on caregivers.

Transferring was just a total nightmare. And I'm not even exaggerating when I say it would take 25 minutes each way to the commode…. I would be trying to help him to get onto the commode … my back hurts so bad.

I've seen him [the caregiver] become exhausted when I'm lying in the bed, and I'm talking about the days that are really bad. He'll run around. He'll bathe me; he'll put me back in bed. He'll clean the house. He'll go get groceries; he'll cook some dinner. He'll try to see some friends or check his email, and that seems like an extra or business [task]…. It was a major influencing factor in him leaving work.

Caring for a person with cancer pain takes not only a physical but also a mental toll. Caregivers spoke about the effect on their mental health and the trauma of feeling helpless as they watched their loved ones experience pain and distress. Patients also reflected on the impact on their caregivers of witnessing their pain.

He would be screaming and crying that he wanted to die every 10 minutes. "Just kill me. Just kill me," he would say …. He just couldn't put up with it no more. So that's really hard on me and everyone watching that, as well – that we're just watching this go on, and there's nothing we could do about it.

He [the caregiver] can't stand it [seeing the patient in pain]. It drives him crazy, and I worry about his own mental health, right? Because he's watching. He's basically watching me die.

Mental Health

Patients reported on the overwhelming toll that living with cancer pain had on their mental health. Some reported being depressed, which often led to social isolation. Some mentioned having anxiety, especially with regard to the inability to predict the severity of their pain given its episodic nature. They also spoke about the how the limitations imposed by their pain on everyday life caused them frustration and distress.

It was frustrating. It was upsetting. I couldn't even sit.

I certainly wanted to stay in bed a lot because of the pain. I was very depressed, crying a lot because it's so exhausting to be in pain.

It can play on my mood, obviously. I can get depressed because I can only do so much in a day, and I want to do it all, and I can't. It creates anxiety.

One patient who is a visible minority and gay spoke about the lack of specialized mental health support for people with cancer pain in general but also for people of diverse cultural backgrounds and those who identify as 2SLGBTQIA+.

To find [a] counsellor who was familiar with especially the pain related to cancer, there are very few and far in between. And then if you want anything else, like in my case being brown, being gay, all of that kind of stuff … it would be nice to have someone to chat with who was both culturally aware and queer or trans positive.

Pain Management Journey

Patients had a great deal of experience with various treatments for cancer pain. Patients spoke about their lengthy journey to find pain management solutions, which included both over-the-counter and prescription medications, as well as nonpharmacological treatments such as massage, chiropractic care, reflexology, and meditation. Patients felt that they had exhausted all options but still not achieved adequate pain relief. In all cases, patients were willing to try anything to manage their pain.

[I tried] meditation, breath work, imagery, relaxation, yoga, deep breathing …
We were trying so many different types of pain [management options] … then we had to fiddle around with the dose for a while.

Most participants reported that the treatments offered by patients' care teams were ineffective and reported frustration as a result of trying various options but not finding an effective one. Some patients spoke about their care teams not providing them with adequate pain management solutions and experiencing stigma with regard to taking pain medication. Most also noted their extended health benefits were insufficient to cover the cost of the extensive and complex pain management strategies required.

Nothing was really touching his pain. Like, no pharmaceuticals [were] touching his pain whatsoever.

[My doctor] acted like I was a drug addict …. That created a lot of mental anguish for me because I'm thinking … "Am I using too much medicine?"

I don't have benefits to cover me to do a massage once a week [or] a chiropractor [or] reflexology [or] acupuncture. So, when I've exhausted all my benefits, I'm sort of, like, out of luck.

Patients spoke about the side effects of their pain medications such as drowsiness, nausea, and hallucinations. The side effects also had a negative impact on their daily lives, especially when their dose was increased, which led to increased fatigue and subsequently spending a lot of time in bed.

My family was worried that [the pain medication] was too much because I was hallucinating.

When I would take medication, it would make me sleepy. So, I would be sleeping a lot.

They're [the side effects are] horrible. It was more the shakiness or instability from the medication … And then the fatigue.

Patients also reported concerns over the amount of pain medication they were taking and the risk of addiction.

I'm also concerned about potentially becoming addicted to it [pain medication], but when you're in pain, that's not the priority in terms of what you're thinking.

I'm always worried. Oh my God, am I taking too much? Am I addicted?

Awareness of IDDSs

The only patients with awareness of an IDDS as a pain management option before these interviews were those who had been offered one by their care team. However, all participants viewed IDDSs favourably and perceived them as an additional pain management option that should be available to patients with cancer pain.

I didn't know that it [an IDDS] existed because I hadn't been around anyone who had had it.

There should be more solutions available to me to help with my pain.

Decision to Undergo IDDS Implantation

Patients with experience of an IDDS reported that the progression and intensity of their pain were the main factors in their decision to receive an IDDS. These patients looked to their care team for guidance on pain management options. Given that they had exhausted all other previously recommended treatments and that the implantation procedure is invasive, they saw an IDDS as their last resort.

I was really willing to try anything because we did try everything, but nothing worked.

It was first presented to me by the nurses in the hospital … They wanted me to have consistent pain control and be able to go home.

Another decision-making factor was the risk associated with taking a high dose of pain medication for an extended period of time.

Taking the pills does damage to other parts of my body. So, this way it's an advantage.

Both patients and caregivers reported on their state of mind at the time an IDDS was offered, remarking on the distress of not having their pain or the pain of the person they were caring for well managed.

But to me, the pros of it out outweighed those negatives because I was up and down so much, and I just wanted to be somewhat stable.

They did give me a lot of information up front, but during that time I was going through so much trying to deal with his pain that I really didn't care about anything that they were telling me except I just needed the pain to be taken care of.

One caregiver stated that it was the patient's preference to try other pain management options before an IDDS because of the invasiveness of the device.

He was very worried about it because he's never had anything like that … That's why he opted for the nerve blocker first. That's one of the reasons: because it was less invasive.

Those without experience of an IDDS reported being open to trying it if they were to meet the eligibility criteria but also noted that they would consider it a last resort because of the invasiveness of the device.

Because I've tried everything else, and I'm willing to try anything.

If it can be managed without something being implanted in me, I think I would probably lean in that direction. Whereas anything that's implanted in me becomes a different commitment. But when I'm in that severe pain, I may say yes to it.

IDDS Implantation and Follow-Up Care

Patients who had undergone IDDS implantation stated that the procedure was fairly simple and not overly burdensome. However, all patients noted that it took longer for the incision to heal than expected.

It took a long time for his incision to heal, and at one point it even split right back open, so he had to go back and get more stitches put in. So, like, this skin integrity was another problem.

Patients also spoke about the ease and simplicity of the pump refill procedure.

It [the refill procedure] hasn't bothered me. And it's not a very big deal having it refilled.

I went in early in the morning, and … we were home the same day. I think by 2 o'clock I was in the car to go home.

We just go into a room, and they get everything all set up, and then they inject. They take out whatever medicine was left over, which is hardly anything, and then put the new stuff in, and then off we go. It's very quick.

One patient reported having their intrathecal medication modified because of side effects but noted that this was done promptly.

The first time that they filled the pump, it was a mixture of the morphine and anaesthetic …. For some reason I found that I was getting numbness in my foot … so, the next time they took the anaesthetic out.

Impact of IDDS Pain Management

Participants reported that having an IDDS had a substantial impact on patients' quality of life, for example by increasing their mobility and their ability to engage in health-promoting activities such as sleeping and eating.

> *I can do a lot more. I have more stamina. I can now stand longer [and] walk a little bit farther.*
>
> *He got his appetite back … and I just couldn't believe it. It was so great to see him eating again.*
>
> *And then when we got home … he was up and walking around the house again with crutches.*
>
> *He's pretty good now. He's independent, and he's enjoying his life again. He can smile and actually have his friends over.*

The patient interviewed in the 2003 Global News segment described the impact of their IDDS on their life as follows:

> *I can do things. I can be a mom; I can be a wife. I have a life.*

One patient who had been restricted to their bed was able to get up and move around again. It had also been expected that they would regain the ability to sit for longer periods, but this was not the case. Regardless, this patient's caregiver reported that the IDDS had an immensely positive impact on their quality of life.

> *The doctor that put it in, he was very hopeful that he [the patient] would be able to sit in a chair … but he still can't stay in a seated position for very long.*
>
> *And he's happier because he can do it [personal care] now, and he goes for little walks throughout the house.*

Another noted benefit was an increase in independence. Patients regained the ability to manage their personal care and other day-to-day activities without assistance, which in turn led to a decrease in caregiver burden.

> *I'm able to cook a meal. I'm able to do things around the house, so that's a plus for me.*
>
> *He can do all of his personal care pretty much by himself with supervision, and he feels so much better about it because he doesn't want his mom to be doing everything for him.*

Access Barriers

One key barrier to accessing an IDDS is lack of awareness. As mentioned, the only patients who knew of an IDDS as a pain management option before these interviews were those who had been offered one by their care team.

Geography poses another important barrier for many patients, with IDDS implantation and follow-up care currently available only at 1 centre in Ontario. One caregiver reported substantial transportation and financial challenges to receiving IDDS care. Because the patient lives far from the centre and is

unable to be in a seated position for very long, a private ambulance is required for transportation to and from the hospital every 6 weeks.

> *We have to get an ambulance to go every time … because he still can't stay in a seated position for very long.*
>
> *Another thing is not just about the money; it's about him being strapped to a hard stretcher for close to 4 hours. Being transported, getting hot. What if he had to go to the bathroom or something? It's … really not an ideal situation for him to be in every 6 weeks as well.*
>
> *Because he still can't stay in a seated position for very long, we are now having to find different charities. I'm exhausting every single charity that there is trying to come up with $1,000 each time because that's what it's costing for an ambulance ride every 6 weeks.*

Discussion

All participants had lived experience with cancer pain, either as a patient or as a family member or caregiver of a person with cancer pain. All participants reported that cancer pain had a substantial negative impact on patients' quality of life and mental health.

All participants reported a lengthy pain management journey, which involved trying many pharmacological and nonpharmacological treatments and often did not result in effective pain management. Unwanted side effects were experienced with pharmacological options, and being on a high dose of pain medication created concern around addiction.

Those with experience of an IDDS reported favourably on its impact on patients' pain, quality of life, and mental health.

There are some limitations to this work. Our recruitment rate was low, which could be attributed to the frailty of our population in terms of disease severity and the pain they were experiencing. Further, few participants had experience with an IDDS, which could be attributed to the limited access to and availability of IDDSs across Ontario. There was also a lack of geographic representation among participants, all of whom lived in southern Ontario. However, we did speak with people living in both urban and rural areas.

Conclusions

Participants spoke about the debilitating nature of cancer pain and the impact it had on patients' quality of life and mental health. All spoke of the frustration of having to try many options to find effective pain management, with an IDDS often considered a last resort given its invasiveness. However, those with experience of an IDDS emphasized the tremendous positive impact it had on patients' pain, quality of life, and mental health. Importantly, lack of awareness and geography pose substantial access barriers for people with cancer pain in Ontario.

Preferences and Values Evidence Discussion

Although we identified no quantitative evidence on the preferences and values of patients and caregivers regarding IDDSs that was applicable to the Ontario context, direct engagement with patients and caregivers provided in-depth insights into these important areas.

Preferences and Values Evidence Conclusions

We identified no studies on the quantitative preferences and values of patients and caregivers regarding IDDSs compared with other routes of medication delivery for the management of cancer pain that were applicable to Ontario context. Through direct engagement with patients and caregivers, we learned of the positive impact IDDSs had on patients' pain, quality of life, and mental health. However, lack of awareness and geography pose substantial access barriers for people with cancer pain in Ontario.

Ethics Evidence

Objective

This ethics evidence review identifies and describes ethical considerations that arise in the context of implementing intrathecal drug delivery systems (IDDSs) for the management of cancer pain in adults and children in Ontario, paying particular attention to equity and access considerations.

Research Questions

Two questions guided our exploration of the ethical considerations related to the use of IDDSs for the management of cancer pain in adults and children in Ontario:

- What ethical considerations arise in the context of IDDSs for the management of cancer pain in adults and children in Ontario?
- What are the implications of these considerations for implementing IDDSs for the management of cancer pain in adults and children in Ontario?

These research questions are explored across 4 domains of inquiry:

- Ethical considerations in the management of cancer pain (e.g., disparities in care, challenges related to clinical care, factors that might prevent patients from gaining access to available therapies)
- The evidence used to evaluate IDDSs (e.g., ethical considerations in relevant clinical studies and economic models, including their design, representativeness, and interpretation)
- The use of IDDSs in the management of cancer pain in practice, including considerations related to benefits and harms to patients, family members, caregivers, clinicians, and society and considerations related to access
- The implementation of IDDSs in health systems, including considerations related to the distribution of health care resources

Methods

Approach

To identify ethical considerations relevant to the context and implementation of IDDSs in Ontario, this ethics review was driven by relevant questions identified in the EUnetHTA Core Model 3.0, Ethics Analysis Domain,[114] and supplemented by relevant questions from the Equity Checklist for HTA.[115] We organized these guiding questions to respond to the research questions across the 4 domains of inquiry identified.

We drew the data to inform this ethics review from 2 categories of inputs:

- A review of the normative and empirical ethics literature relevant to IDDSs in the management of cancer pain in adults and children
- Engagement with the other evidence sections of this health technology assessment and with the clinical experts who advised on those sections. This work served to identify and further expand upon the ethical considerations that arose in those reviews, as well as to situate findings within the context of Ontario

We synthesized the findings and results of these analyses to identify and discuss ethical considerations related to the use of IDDSs for the management of cancer pain in adults and children and to raise potential implications relevant to the context of the Ontario health system.

Ethics Literature Search

An information specialist conducted a literature search of key resources including MEDLINE and Philosopher's Index, accessed through the Ovid interface, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), accessed through the EBSCOhost interface. The search strategy comprised controlled vocabulary (e.g., Medical Subject Headings) and keywords. We applied search filters developed by the Canadian Agency for Drugs and Technologies in Health[116] to limit retrieval to citations related to ethical concepts or considerations.

A preliminary search for "cancer pain" and "intrathecal drug delivery systems" did not yield relevant results, so "cancer pain" was broadened to "pain" to expand indexing and article retrieval. The final strategy encompassed the search terms "pain" and "intrathecal drug delivery systems." Duplicates were removed by manual deduplication in EndNote.[117] Retrieval was limited to the English language. The search was completed on March 1, 2023. The search strategy is available on request. We also performed targeted Google searches beginning on March 1, 2023, and ending on March 22, 2023, to supplement the initial search. These iterative searches were enhanced by reviewing bibliographies of key papers and through contact with the authors of the other sections of this health technology assessment.

Literature Screening and Selection

A single reviewer conducted an initial screening of titles and abstracts and then obtained the full texts of studies if their titles or abstracts provided a normative analysis (i.e., focusing on "what ought to be" through argumentation) or presented empirical research (i.e., focusing on "what is" through observation) of ethical considerations related to the use of IDDSs in the context of cancer pain. The reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined grey literature and reference lists and consulted with content experts and other members of the project team for any additional studies not identified through the search.

Data Analysis

Data analysis included the collection, coding, and thematic analysis of data, driven by the research questions and organized by the 4 domains of inquiry identified. The reviewer conducted 3 iterative cycles of coding and analysis to abstract, identify, and synthesize relevant ethical considerations in the literature and from the other sections of this health technology assessment.

In the initial coding phase, publications were reviewed for ethical content (e.g., claims related to potential harms, benefits, equity, justice, resource allocation, or ethical issues in the evidence). Once identified, claims related to ethical content were coded using methods of qualitative description.[118] In the next coding phase, themes and subcodes were identified through repeated readings of the data[118] and comparisons with initial themes. These themes and subcodes were then summarized into thematic categories within each domain of inquiry. Where ethical content did not fit into any categories, this was noted, as were discrepancies or conflicts between ethical considerations or values identified between sources or within thematic categories. Data analysis was iterative, and themes identified in the literature and in the other sections of this health technology assessment were used to further refine and reinterpret the ethical considerations identified.

Results and Analysis

Overview

A total of 27 papers from the published literature were used to inform this ethics review. Eleven were derived from the formal literature review, and 16 were derived from other sources, including targeted Google searches and relevant sources cited in the other sections of this health technology assessment. In addition, the other sections of this health technology assessment identified both explicit and implicit ethical and equity considerations related to access barriers in Ontario, as well as disparities in allocation and clinical acceptance of IDDSs for the management of cancer pain.

We organized the results according to ethical considerations arising in the context of IDDS use across 4 domains:

- The management of cancer pain, including challenges in clinical management and in equitable and culturally safe access to pain management modalities
- The evidence used to evaluate IDDSs for the management of cancer pain, including ethical barriers to evidence generation and the limitations of the current evidence base
- The use of IDDSs for patients, caregivers, and health care providers, including equity and access challenges in the process of determining eligibility, patients' and clinicians' experiences with IDDSs, considerations for informed consent, and considerations related to equity of access
- The implementation of IDDSs in health systems, including considerations related to resource constraints, inequities, and supplier challenges

Ethical Considerations in the Management of Cancer Pain

Cancer pain, which results from either the disease itself or as a side effect of treatment, raises many ethical considerations related to patient vulnerability, the role of clinical knowledge and judgment, access, and structural inequities that may arise in the prescription and uptake of cancer pain management therapies, including IDDSs. This ethics review did not aim to address the totality of ethical challenges associated with the experiences and management of cancer pain but rather focused on highlighting relevant findings that arose in the review of the IDDS literature.

The World Health Organization cancer pain management guidelines have identified inadequate cancer pain management as a global health concern, and access to pain management has been positioned as a fundamental human right.[119] Indeed, severe, chronic, and refractory cancer pain represents an area of unmet need where additional management options may be welcome.[120] The clinical evidence and preferences and values evidence sections of this health technology assessment discuss how pain is a very distressing symptom for adults and children with cancer, as well as the negative effects of cancer pain on quality of life and mental health and the overall undertreatment of pain among patients with cancer. In addition, the clinical evidence review notes that as more patients are receiving life-prolonging or even curative cancer treatments, more patients are living longer, and many of these patients are living with chronic pain. For many patients, poor pain control is often not only physical but can also be associated with psychological distress and a decrease in social activities and social support.[121]

In pediatric populations, assessing and managing pain can be particularly challenging because of variations in children's abilities to comprehend and communicate their symptoms.[42] Authors have argued that, overall, children's cancer pain has been treated ineffectively and that children have not been included in advances made in pain management.[15] Further, there tends to be a lack of awareness of IDDSs as a pain modulation modality in pediatric settings.[42]

The management of cancer pain has been positioned as a duty or ethical responsibility of health care providers.[122,123] However, medical and nursing education tends to underemphasize pain management, and providers tend to lack training in pain management therapies in the oncology context.[122,124,125] Indeed, inadequate provider knowledge regarding cancer pain management has been described as the most pervasive barrier to pain management in patients with cancer,[125] and providers may underestimate the impact of cancer pain on patients' activities of daily living and quality of life.[126] Further, providers' perceptions of and fears related to addiction to or tolerance of pain medications, as well as uncertainties about their side effects, have driven both patients' and physicians' reluctance to use novel modalities of pain management in patients with cancer.[122] Limitations in provider knowledge of and attention to cancer pain management may cause undue harm to patients who face ongoing, intractable cancer pain.

Equity Considerations in the Management of Cancer Pain

Several disparities exist in the assessment and management of cancer pain. Data from the United States have demonstrated that biases associated with the use of opioids in cancer pain management have led to implicit or explicit biases among clinicians in their prescribing of pain medications.[125] Providers have been observed to be more likely to underestimate pain in Black and Hispanic patients and less likely to prescribe opioids adequately in these populations.[125,127] These disparities and inequities in the practice of pain medicine tend to disadvantage underserved and equity-deserving populations, and they tend to be compounded by socioeconomic disparities.[127] Implicit biases can arise in pain management care, as can cultural differences in communication about pain between patients and providers.[127] Further, culturally safe and attentive practices of pain management have been described as inadequately attended to in medical school curricula.[128]

In Canada, Indigenous peoples face several inequities and disparities in health care and research, including in the context of cancer care. In the context of survivorship and palliative care, Indigenous peoples often lack access to health services to alleviate the physical and psychosocial symptoms associated with cancer and cancer treatment, particularly those living on reserve.[129] Supportive care in the context of cancer symptom management tends not to be available in or near these communities,

and information can be difficult to access or inadequately provided upon discharge from tertiary care centres.[129] Few to no palliative care services are available to most First Nations communities, and when are they are available, they are generally not designed to address Indigenous practices around pain, death, and dying and tend not to be experienced as culturally safe.[129]

Ethical Considerations in the Evidence Used to Evaluate Intrathecal Drug Delivery Systems

In general, the clinical evidence to support the use of IDDSs as a cancer pain management strategy has been sparse and often deemed to be of low quality. In part, this is because of research ethics challenges, such as the unethical nature of using placebos and the lack of randomization in studies of the refractory cancer pain population, as well as the general overall low uptake of IDDSs for pain management. The clinical evidence review rated systematic review evidence for the use of IDDSs for cancer pain management as moderate or low, with noted uncertainties in the evidence. Methodological weaknesses noted include lack of randomization, lack of blinding, small sample sizes, short follow-up duration, and limitations in self-reported pain measurements. In children, the data are similarly or more sparse than in adults and have been restricted to anecdotal evidence from case studies or case series.[42]

Further, research with patients experiencing cancer pain in general tends to be limited, and the few randomized controlled trials of cancer pain management tend to enrol few subjects and involve heterogeneous interventions and outcome measures.[130] Patients with advanced-stage cancer who are experiencing severe pain often have multiple comorbidities, which can make data collection and interpretation challenging. This issue is further complicated by differences across cancer types and the wide range of adverse effects associated with various cancer therapies.[131] Additionally, long-term follow-up can be difficult in this population because many patients become too unwell to continue participating in research or have a limited life expectancy.[131] Research into IDDSs in the context of cancer pain has been further challenged by ethical concerns in the conduct of placebo-controlled trials and in direct comparisons between IDDSs and conventional medical management in patients likely to benefit from an IDDS.[131] However, it has been suggested that alternative comparators such as epidural, external pump, or neurolysis could be used to assess the comparative effectiveness of IDDSs.[119]

As a result of the limited clinical evidence, economic evaluations of IDDSs in practice have also been limited. Consistent with previous evaluations, the economic evidence review reported serious or very serious limitations with existing economic analyses of IDDSs. As reported, these analyses have relied on small sample sizes; have tended to underestimate certain costs, such as those associated with conventional medical management or with intrathecal pump placement; and may have excluded cases of more severe cancer pain. The noted limitations in the clinical data may thus limit the accuracy of economic assessments of cost-effectiveness, especially where long-term data and evidence of comparative effectiveness are lacking.

Because of the purported scarcity of rigorous evidence available in the IDDS space and the overall positioning of the evidence as inconclusive with respect to comparative effectiveness, only weak recommendations have been made with regard to the use of IDDSs,[132] and IDDSs have seldom been integrated into clinical practice.[119] To augment the available evidence, registries of patients using IDDSs have been suggested, and one has been implemented in the United Kingdom to facilitate a longer-term observation and audit of outcomes.[120] In the Canadian context, such a registry could augment currently available evidence and inform clinical management and resource allocation decisions. Subsequent sections address further implications of the limitations in the evidence base for IDDSs at the level of

clinical decision-making for individual patients and health system decision-making regarding the costs and benefits of IDDSs for the management of cancer pain.

Ethical Considerations in the Use of Intrathecal Drug Delivery Systems

Despite the challenges in identifying and treating cancer pain and the uncertainties in the evidence used to evaluate IDDSs for the management of cancer pain, several published analyses have examined considerations in the use of IDDSs, including those related to patients, caregivers, and health care providers in terms of determining eligibility for and providing IDDS care. As IDDS pain management requires a multidisciplinary team to determine eligibility and to initiate and maintain care, it is often restricted to well-resourced treatment centres typically located in large urban settings, leading to potential access challenges for many patients.

Assessing Eligibility for an Intrathecal Drug Delivery System

Several ethical considerations arise in the processes of determining a patient's eligibility for an IDDS, including challenges of equity of opportunity and equity of access for patients who may benefit from an IDDS but do not meet eligibility criteria. Further, uncertainties exist in the validity of current selection and eligibility criteria, and authors have argued that these criteria may not be supported by high-quality evidence.[119] Additionally, these assessment processes can cause patients to experience feelings of powerlessness and a lack of agency.[133]

The United Kingdom's National Health Service has determined that IDDSs play an important role in the management of intractable cancer pain in appropriately selected patients who have faced a reduction in quality of life and have no other pain management options.[120] Additionally, studies have shown that there is only a limited time frame within which patients can benefit from IDDS implantation: prognosis must be long to enough to justify an implanted device, yet many patients who might benefit from an IDDS may be relatively close to end of life because they are in a state of multiple-refractory cancer and associated pain.[134] IDDSs have thus been positioned as a therapy for late-stage pain management in patients who are not good candidates for the continuation of oral or transdermal pain medications because of the severity of side effects or lack of efficacy.[43]

Despite the positioning of IDDSs as a therapy of last resort, the primary economic evaluation in this health technology assessment identified a growing shift in the medical community to offer IDDSs to patients with cancer before their pain progresses to the point of being considered severe. Clinical experts engaged in this health technology assessment indicated that it would be unethical to wait for potentially eligible patients to experience an acute pain crisis before offering an IDDS (E. Baig, MD, telephone communication, October 27, 2023; J. Osborn, MD, telephone communication, April 12, 2023; V. Varshney, MD, telephone communication, April 25, 2023) and that patient characteristics including age, comorbidities, and overall health should be assessed by clinicians to inform eligibility (P. Hawley, MD, telephone communication, May 8, 2023).

In addition, the experts noted that patients who may be candidates for an IDDS tend not to be referred or are referred too late to be eligible, thus potentially limiting access and causing undue harm.

In international settings, it has been recommended that assessment for IDDS eligibility include an evaluation of patient expectations, goals of care, relationship with the treatment team, ability to adhere to recommendations, and ability to cope with side effects, and that family members and caregivers be part of the assessment process.[119] Patient selection for an IDDS can thus be a resource-intensive

process, requiring multidisciplinary care and collaboration across a number of specialties including anaesthesiology, neurology, nursing, oncology, pain management, palliative care, physiotherapy, psychiatry, and social work.[135] Access to assessment for IDDS eligibility can thus be limited by the ability of patients to access specialized care for referral, as multidisciplinary teams and well-resourced treatment centres are typically located in large urban settings.

Current eligibility criteria in Ontario also indicate that patients must have caregiver support to assist with the management of the IDDS device at home. Patients who lack access to familial or informal caregivers and lack the resources to employ a formal caregiver may therefore face access inequities in accessing an IDDS if they are disproportionately deemed ineligible for IDDS owing to lack of caregiver support.

Assessing Psychological Fitness

In addition to an assessment of physical eligibility, an assessment of psychological fitness is often required to determine eligibility for an IDDS, which may pose unique ethical considerations. For example, depression, anxiety, substance use, cognitive dysfunction, and other psychosocial stressors are currently listed as relative contraindications for IDDS implantation in Ontario (E. Baig, MD, virtual communication, October 27, 2022). Clinical experts stated that a patient's psychological comorbidities must be assessed because of the need for the patient to be involved in managing the device once implanted and because of the need to manage their expectations of the device within their overall treatment plan (E. Baig, MD, email communication, May 30, 2023).

Psychological evaluations can be complex in the area of refractory cancer pain, where distress, depression, and anxiety are common[136] and where many patients present in pain crisis with cognitive impairments as a result of the severity of the pain or medication side effects.[134] Indeed, cancer pain itself can cause psychological symptoms and complications and decrease patients' quality of life.[137] While some early research indicated that patients who face psychological distress may experience less benefit from an IDDS, many of these studies took place in the noncancer space.[136] However, it has also been suggested that, rather than denying them access to an IDDS, patients with cancer and more severe psychological symptoms could be offered greater levels of comprehensive care before and after IDDS implantation.[30,136] Clinical experts noted that these patients could be provided with psychological therapy concurrently with moving forward with IDDS implantation rather than be excluded from access unless any untreated psychologic comorbidities would pose a risk of harm to the patient (E. Baig, MD, email communication, May 30, 2023). However, some questions remain for those patients who cannot access appropriate psychological care as a potential limitation to IDDS access.

Patients' and Caregivers' Experiences With Intrathecal Drug Delivery Systems

Despite the limitations of clinical evidence in this space, the use of IDDSs for cancer pain has been associated with higher rates of satisfactory pain relief and lower rates of treatment failure, especially when compared with epidural pain management.[43] In the pediatric context, patients have also reported satisfactory analgesia with an IDDS.[42] The clinical evidence review found that in adults with cancer pain, intrathecal drug delivery likely reduces pain intensity and decreases the use of systemic opioids and may improve health-related quality of life, functional outcomes, and survival. Similarly, the primary economic evaluation stated that IDDS use could result in a reduction in the use of systemic opioids, thereby reducing some risks associated with prescription opioid misuse and poisoning for both patients and those who may have access to patients' oral or transdermal opioid medications.

Quality-of-life benefits associated with the use of IDDSs have been described using qualitative data. In a qualitative study of IDDS users in Canada, patients reported reductions in pain scores after starting IDDS pain management and reported valuing pain relief achieved with an IDDS, as it allowed for improvements in independence and an increased sense of control, allowing them to "carry on more of a regular life."[134] Other qualitative studies have similarly shown that patients value the increased socialization and participation in everyday activities they experienced after receiving an IDDS.[133] In a qualitative study conducted in the United Kingdom, caregivers described the profound effects of IDDS pain management on patients' experiences of daily living and reflected on how the IDDS removed some of the side effects of other pain medications, which enabled patients to communicate more lucidly, to participate in activities with friends and family, and "to be themselves."[138] Similarly, in Switzerland, IDDS pain management was found to enable patients to engage more fully in personal endeavours, including mobilization.[126] The limited systemic side effects of IDDS use have also been described as allowing children to return to activities such as attending school, playing sports, and spending time with friends.[15,42] The preferences and values evidence section of this health technology assessment further describes the impact of IDDS use on mobility, independence, and resuming day-to-day activities based on interviews with patients and caregivers.

As discussed in the clinical evidence review, there are certain direct harms related to IDDS device implantation and side effects associated with the drugs used in these devices. Technical challenges associated with device implantation in children have also been described, including pumps often being too large for pediatric implantation and the potential for pumps to migrate as children grow.[42] Device malfunction, with the associated potential to cause substantial patient harm, has also been described.[15,42] Though the likelihood of malfunction is rare, especially with newer models of IDDSs, patients may need to be sufficiently informed of the risk of malfunction and educated on how to recognize signs of device failure.

Some have argued that pain management modalities should also be evaluated for their impact on family caregivers. IDDS pain management may ease caregiver burden, as described in the preferences and values evidence section; alternatively, it may increase burden if the device requires frequent caregiver manipulation or generates anxiety in caregivers related to their role in monitoring patients.[124]

Intrathecal Drug Delivery Systems and Clinical Practice

Introducing IDDSs into clinical practice can also pose challenges for clinicians, as many are unlikely to be trained in or familiar with the use of IDDSs, and some may experience dissonances between IDDSs and noninterventional forms of cancer pain management in the palliative setting. Clinicians who have not been exposed to or do not have experience with IDDSs may also be concerned about risks associated with device implantation and management; it has been noted that such concerns have limited the clinical uptake of this therapy.[139] Indeed, a lack of clinical training in and awareness of IDDS pain management and the potential inclination for palliative care physicians to avoid invasive treatments can lead to access barriers for patients.[124] Variations in clinical practice, as well as unfamiliarity with the intervention among both patients and clinicians, have meant that IDDSs are rarely available in Canada.[140]

IDDS management often requires multidisciplinary care, which may pose challenges in clinical management and care for providers who do not typically collaborate across specialties.[131,137] For example, outside large tertiary care centres, interactions between oncologists and pain physicians are typically limited, and provider experience with IDDSs tends to be limited and heterogeneous.[131] In

addition, much of the literature in support of IDDS pain management has been published outside the oncology space, meaning that many oncologists have not been exposed to this option,[131] and the IDDS expertise that is available tends to be clustered in well-resourced specialized pain centres.[120]

Treating physicians may also experience a "reinforcement paradigm," meaning they may become more inclined to provide IDDS pain management once they have seen positive results in their patients.[141] However, because IDDS use is increasingly restricted by reimbursement criteria, practice and access complexities, and uncertainties in the evidence, few clinicians in Ontario have had experience with these devices and their effects, thus limiting the ability of the reinforcement paradigm to encourage greater use of IDDS pain management. Further, clinicians may be less willing to implement interventions with which they are less familiar or that appear discordant with current clinical practice, thereby limiting access to and acceptance of this therapy.

Implications for Informed Consent

Several of the issues and uncertainties discussed in the preceding sections have implications for how information on IDDSs is shared with patients and for the process of obtaining informed consent. The absence of robust clinical data means that clinical teams and patients may be unaware of the comparative effectiveness or expectations of benefit from IDDSs, or indeed about IDDSs as an option for refractory cancer pain, which can lead to uncertainties in clinical decision-making and communication regarding the risk–benefit ratio for individual patients. To facilitate balanced and open communication in the processes of informed consent, clinicians should disclose these uncertainties and the potential risks of IDDS use,[142] and they should engage patients and family members in a process of shared decision-making.[135] In addition, the general lack of awareness of IDDSs as a pain management option, as well as the complexity of IDDS use, may result in its mechanism of action being more difficult for some patients to understand,[143] thus requiring a more detailed discussion with patients and caregivers to ensure an accurate understanding of how the device works and to set appropriate expectations.[135]

Given that many patients with cancer are not offered an IDDS until late in their disease trajectory, when their pain is severe, providing access to information about the device (i.e., mechanism of action, what it will be like to live with an IDDS implant) early in their cancer pain journey would likely be beneficial.[133] A qualitative study in the United Kingdom found that caregivers tend to rely on physicians to determine the "correct" time for IDDS implantation.[138] Yet, where physicians consider an IDDS to be a therapy of last resort, it is often introduced at a time when informed consent may be challenging, that is, when patients may be in an acute pain crisis.[138] Accordingly, it has been suggested that care teams discuss pain management earlier in the disease trajectory and in the context of patients' priorities and goals.[138] Caregivers may also need to be involved in ongoing education about the implantation procedure, the drugs used, and potential device-related harms.[142] In pediatric populations, family-centred care, including effective communication and shared decision-making, can enhance well-being and facilitate access to appropriate pain management therapies, including IDDSs.[42]

Equity of Geographic Access

In Ontario, across Canada, and internationally, access to IDDSs is often limited by geography in terms of the ability of patients to travel to a treatment centre for both implantation and follow-up care. Currently in Ontario, there is only 1 treatment centre (encompassing 2 hospitals) with capacity to provide IDDSs using implantable pumps in Ontario. A clinical expert stated that if IDDSs for the management of cancer pain are publicly funded in Ontario, all IDDS implants would initially be delivered at 1 of the 2 sites, given established expertise and care processes, and that patients would be required to return to one of these

sites for intrathecal opioid refills and device programming about once every 3 months once they are stable, though potentially more frequently (E. Baig, MD, telephone communication, October 27, 2022). IDDSs may become more widely available over time, but new sites will need to have established pain centres and multidisciplinary clinical expertise. These resourcing requirements may make establishing new sites difficult and delay more widespread access, especially given the limited capacity of experienced clinicians to transfer and spread the required skills across the province. Those patients who live far from a centre and are unable or lack the resources to travel (e.g., those with limited financial resources, those physically unable to travel, those without caregiver support) may be disadvantaged in their ability to access to an IDDS despite otherwise meeting the eligibility criteria.

As identified in the primary economic evaluation, a shift from inpatient to outpatient implantation may yield some improvement in access, as well as a reduction in the use of health care resources. While IDDS implantation at the 1 centre in Ontario was first performed as an inpatient procedure, it is now done as an outpatient procedure, given the experience and expertise clinicians have gained over time. It may also be possible for IDDS programming and refills to be performed at satellite centres by appropriately trained clinicians, potentially reducing some travel and associated burdens for patients and caregivers. However, there are capacity-related challenges associated with training such clinicians, as well as challenges for patients physically unable or without caregiver support to access such centres.

In jurisdictions where IDDSs are available, patients are often transferred from distant locations to centres with expertise in IDDS implantation.[119] Clinical experts stated that while assessment and implantation should occur at a tertiary care centre, virtual care visits could be used for some follow-up, though in-person care is required to check the implant site and adjust medications (E. Baig, MD, virtual communication, October 27, 2022). Ongoing IDDS management thus requires frequent interactions with a multidisciplinary care team, including for follow-up and pump refills,[142] and requires this team to work with the patient's primary care provider or team.[120] Despite the access challenges associated with the need for care by highly trained, multidisciplinary medical teams, there may also be access benefits with regard to IDDSs relative to other pain management modalities. As an IDDS typically requires a pump refill only every 3 months, patients are able to avoid the repeated administration of oral medication throughout the day, thus experiencing less invasive care and a reduction in the need to access health care resources.[119]

Although the 1 IDDS pump available in Ontario can be used in children with its smaller reservoir size, it is not specified as a pediatric pump. As noted, the limited evidence in the pediatric population tends to be restricted to older adolescents. It is therefore unclear whether and how younger children will be considered for IDDS implantation with regard to access, clinical appropriateness, and safety.

The clinical evidence review used the PROGRESS+ health equity framework to identify inequities relevant to this health technology's population and intervention of interest. The clinical evidence search retrieved no evidence on equity issues relevant to how PROGRESS+ factors might affect inequity in IDDS implantation across various populations. However, by examining barriers to accessing IDDSs (e.g., eligibility criteria, capacity for implantation, geographic access barriers), we have identified several inequities in access and delivery in this ethics review. Attending to these inequities will have implications for who does and does not have access to IDDS pain management and for the equitable allocation of clinical and infrastructural resources across populations.

Health System Considerations

IDDSs tend to have high upfront costs (i.e., cost of device, implantation, hospitalization for implantation) but are associated with decreased health care use following implantation and therefore lower costs of health care use over time if patients are selected using appropriate criteria.[120,135] This decrease in health care use over time can be attributed to fewer inpatient hospitalizations and outpatient visits, a reduction in the use of lab services and other drugs (e.g., corticosteroids, appetite stimulants), and a reduction in the use of opioid medications, as well as the costs associated with opioid misuse.[140,144] While the primary economic evaluation indicated only small incremental gains in quality-adjusted life-years (QALYs) for IDDS use as compared with standard care, the analysis also highlighted some debate about the valuation of QALYs in the palliative setting where willingness to pay may be higher.

As identified throughout this ethics review, the implementation of IDDSs for the management of cancer pain in Ontario faces several health system capacity challenges, especially given that infrastructure and expertise are currently limited to 1 treatment centre. While it is currently estimated that about 60 patients with cancer pain in Ontario will be eligible for IDDS annually, any increase in the number of eligible patients or in patient and clinician awareness of this therapy may result in increased demand. In turn, an increase in demand will require the establishment and implementation of highly resourced multidisciplinary treatment centres, as well as education and training for clinicians and multidisciplinary care teams on the implantation and use of IDDSs. Equitable selection criteria and geographic access pathways that enable greater access may increase the number of eligible patients, thus increasing the responsibilities to provide these patients with access to an IDDS. Yet, expanding access criteria will also increase the resource, clinical, and infrastructural requirements needed to support this therapy, thus increasing the budget impact.

Another important consideration is that access to IDDSs may become limited by supply chain challenges. Currently, 3 IDDSs are licensed by Health Canada, while only 1 system is available in Canada. Disruptions in supply chain or other manufacturing processes may disrupt access to the technology.

Because of the many issues identified related to the resource-intensive and multidisciplinary nature of IDDS referral and management, as well as the potential for IDDSs to provide benefits for patients, demand for IDDSs may exceed the supply or health system capacity to fund and support IDDSs for all patients who meet the eligibility criteria. If such a situation occurs, some form of rationing or priority setting will be needed for the allocation of IDDSs; accordingly, fair, transparent, and equitable criteria for priority setting and resource allocation will need to be developed.

Finally, given the issues of the lower quality of clinical evidence to support IDDSs and the resource-intensive nature of implementing IDDSs, health system decision-making may require ongoing assessments of the costs and benefits of IDDS implementation. This could be facilitated by ongoing real-world assessments of the evidence, feasibility, and implementation of IDDSs in Ontario. However, uncertainties in the evidence may complicate health system decision-making and the evaluation of opportunity costs.

Limitations

Many of the limitations facing clinical and economic evaluations of IDDSs for the management of cancer pain affected this ethics review. Specifically, the paucity of research on and evidence for the use of IDDSs in the context of cancer pain has meant that little published literature has examined ethical

considerations related to the implementation, use, and outcomes of this pain management system. This highlights the need for an analysis of equity considerations and access disparities in the context of IDDSs for the management of cancer pain, especially as these disparities may lie along geographic, socioeconomic, racialized, and gender lines.

Nonetheless, several ethical considerations related to the cancer pain population, the evidence used to evaluate IDDSs, the use of IDDSs, and health system implications were gleaned from a review of the published literature in conjunction with a review of the other sections of this health technology assessment. By bringing together these literatures to examine both gaps and opportunities, as applied to the Ontario context, this ethics review was able to identify relevant ethical considerations for the use of IDDSs to manage cancer pain.

Conclusions

Considerations related to the funding and implementation of IDDSs for the management of cancer pain in Ontario require explicit and focused attention to issues of equity and access that arise in the identification and management of cancer pain, how clinical research is designed, how clinical evidence is perceived and used, how IDDSs are introduced and assessed in clinical practice, and where and how IDDSs are made available to patients. Because of the uncertain clinical evidence and the resource-intensive nature of IDDS implementation, IDDSs for the management of cancer pain are currently provided and managed only at large, well-resourced tertiary centres, which limits access for many patients. Mechanisms to address the equity implications of geographic and resource-based access limitations should be considered in order to attempt to reduce disparities in delivery.

Uncertainties in the evidence and challenges in introducing IDDSs into clinical practice have limited access to IDDSs in Ontario and across Canada. This has meant that many clinicians may lack the "reinforcement paradigm" that could normalize the use of IDDSs for the management of cancer pain, and that many clinicians may remain unaware or unfamiliar with this pain management modality, thereby further limiting access. Whether to publicly fund IDDSs for the management of cancer pain in Ontario is a complex decision requiring attention to multifactorial barriers to implementation and many points of potential inequity that may arise in the processes of providing pain management for patients with cancer, the selection of appropriate candidates for an IDDS, clinical capacity and uptake of this technology, and infrastructure and resource constraints.

Conclusions of the Health Technology Assessment

Based on evidence of moderate to low quality from systematic reviews of clinical studies, intrathecal drug delivery likely reduces pain intensity and decreases the use of systemic opioids in adults who have a life expectancy greater than 6 months. It may also improve health-related quality of life, functional outcomes, and survival, although the evidence for survival is very uncertain. The clinical evidence in children is very uncertain. Considering the inherent limitations in conducting research on this topic, the likelihood of any high-quality evidence more robust than the current state emerging in the next few years is low. IDDS implantation carries certain rare risks related to mechanical errors, drug-related side effects, and surgical complications.

Our primary economic evaluation found that compared with standard care, care with an IDDS generated 0.08 additional QALYs and cost an additional $4,482, resulting in an ICER of $57,314 per QALY over a 1-year time horizon. The likelihood of IDDSs being cost-effective compared with standard care is uncertain at $50,000 per quality-adjusted life-year (QALY) and moderately likely at $100,000 per QALY. We estimate that publicly funding IDDSs in Ontario would cost an additional $1.34 million over the next 5 years.

We did not identify any studies on the quantitative preferences and values of patients, caregivers, or health care providers regarding IDDSs for the management of cancer pain that were applicable to Ontario context.

Patients with cancer pain and caregivers with whom we spoke described the debilitating nature of cancer pain and its severely detrimental effects on their quality of life and mental health. All reported a lengthy and difficult journey to find effective pain management. Those with experience of an IDDS spoke of its effectiveness in managing pain and its positive impact on patients' quality of life and mental health.

Considerations related to the funding and implementation of IDDSs in Ontario require explicit and focused attention to equity and access issues that arise in the identification and management of cancer pain; how clinical evidence is designed, perceived, and used; how IDDSs are introduced and assessed in clinical practice; and where and how IDDSs are made available to patients. Owing to the uncertain clinical evidence and the resource-intensive nature of IDDSs, this pain management strategy is currently delivered only in large, well-resourced tertiary care centres, which can limit access for many patients. Mechanisms to address geographic and resource-based access limitations should be considered during implementation.

Abbreviations

CADD: continuous ambulatory delivery device

CADTH: Canadian Agency for Drugs and Technologies in Health

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CI: confidence interval

DAD: Discharge Abstract Database

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICER: incremental cost-effectiveness ratio

IDDS: intrathecal drug delivery system

MOED: morphine oral equivalent dose

NACRS: National Ambulatory Care Reporting System

NICE: National Institute for Health and Care Excellence

ODB: Ontario Drug Benefit

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

RCT: randomized controlled trial

SD: standard deviation

WTP: willingness-to-pay

Glossary

Adverse event: Any noxious, pathological, or unintended change in a physical or metabolic function, revealed by signs or symptoms or a change in the results of laboratory tests, in any phase of a clinical study, whether or not the change is considered treatment related. Note: It may involve the exacerbation of a preexisting condition, intercurrent diseases, an accident, a drug interaction, or a significant worsening of the disease.[145]

Budget impact analysis: An evaluation of the financial impact of the introduction of a technology or service on the capital and operating budgets of a government or agency.[145]

Case report: In clinical research, an uncontrolled observational study of an intervention or of exposure to a given factor and of its outcome in a single individual.[145]

Case series: An uncontrolled observational study of an intervention or of exposure to a given factor and of its outcome in a series of subjects.[145]

Cohort model: In economic evaluations, a cohort model is used to simulate what happens to a homogeneous cohort (group) of patients after receiving a specific health care intervention. The proportion of the cohort who experiences certain health outcomes or events is estimated, along with the relevant costs and benefits. In contrast, a microsimulation model follows the course of individual patients.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: A curve illustrating the probability that a given option is efficient on the basis of the value assigned to an additional quality-adjusted life year.[145]

Cost-effectiveness analysis: An economic evaluation consisting of comparing various options, in which costs are measured in monetary units, then aggregated, and outcomes are expressed in natural (non-monetary) units.[145]

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost–utility analysis: An economic evaluation consisting of comparing various options, in which costs are measured in monetary units and outcomes are measured in utility units, usually in terms of utility to the patient (using quality-adjusted life years, for example). Note: This is a form of cost-effectiveness analysis in which the effectiveness of an option is adjusted on the basis of quality of life.[145]

Discounting: A mathematical process used to bring future costs and benefits to their present value. Note: These adjustments imply that future costs and benefits have less value than the same costs and

benefits in the present.[145] The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of 5 questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are 3 response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes 5 response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[146] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Equity-deserving populations: Those who exhibit the socially stratifying characteristics identified in the PROGRESS-Plus framework.[147] These characteristics involve:

- Place of residence (e.g., rural and remote populations)
- Race/ethnicity/culture (e.g., First Nations, Métis, and Inuit populations, immigrant populations, and linguistic minority populations)
- Occupation or labour-market experiences more generally (e.g., those in "precarious work" arrangements like minimum-wage, seasonal, or part-time work)
- Gender
- Religion
- Educational level (e.g., health literacy)
- Socioeconomic status (e.g., economically disadvantaged populations)
- Social capital/social exclusion (e.g., citizenship/residence)
- Personal characteristics associated with discrimination (e.g.., age, disability, sexual orientation)
- Time-dependent relationships (e.g., leaving the hospital, in respite care)

Health inequity: Health inequities are avoidable inequalities in health between groups of people within countries and between countries.[148] These inequities arise from inequalities within and between societies. Social and economic conditions and their effects on people's lives determine their risk of illness and the actions taken to prevent them becoming ill or treat illness when it occurs.

Health-related quality of life: The measures of the impact of an intervention on patients' health status, extending beyond the traditional measures of mortality and morbidity to include dimensions such as physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception and general life satisfaction. Note: Some of these elements are also called health status, functional status or quality-of-life measures.[145]

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Incremental cost: The difference between the cost of an option and the cost of another option with which it is compared.[145]

Incremental cost-effectiveness ratio (ICER): he additional cost of the more expensive intervention compared with the less expensive intervention, divided by the difference between the effects of the interventions on the patients (the additional cost per QALY, for example).

Intrathecal drug delivery system (IDDS): An IDDS consists of a drug infusion device (a pump) and a catheter (a thin tube). The drug infusion device is implanted subcutaneously (under the skin) in the abdominal wall or the gluteal area (the buttocks). The device stores pain medication and delivers it through the catheter to the fluid-filled space around the spinal cord known as the intrathecal space. A drug reservoir in the drug infusion device is accessed percutaneously (through the skin) through a port to change or refill the medication.[18] The drug infusion device can be programmed to release medication at a fixed rate, thus delivering a constant flow of medication over a defined period, or at a variable rate, delivering different amounts of medication at different times of day. The drug infusion device also allows patients to administer boluses (additional doses) via patient-controlled programming.[19]

Markov model: A type of quantitative modelling that involves a specified set of mutually exclusive and exhaustive health states for which there are transitional probabilities of moving from one state to another, including the probability of remaining in the same state. Note: Typically, states have a uniform time period, and transitional probabilities remain constant over time.[145]

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): A unit of outcome of an intervention where gains (or losses) of years of life subsequent to this intervention are adjusted on the basis of the quality of life during those years. Note: This parameter can provide a common unit for comparing cost-utility across different interventions and health problems. Disability-adjusted life year (DALY) and healthy-years equivalent (HYE) are QALY-analogous units.[145]

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Refractory cancer pain: cancer pain no longer responding to conventional pain management.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity analysis: A means for evaluating the robustness of a mathematical model by testing a plausible range of estimates of key independent variables to determine whether such variations result in meaningful changes in the model's results. Note: Sensitivity analysis can also be used for other study types, such as clinical trials analysis, to determine whether inclusion or exclusion of certain data changes the results, and meta-analysis, to determine whether inclusion or exclusion of certain studies changes the results.[145]

Systematic review: A synthesis that collates all empirical evidence fitting pre-specified eligibility criteria in order to answer a specific research question. Note 1: Systematic reviews are conducted according to a pre-specified protocol. The methods used are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made. Note 2: Many systematic reviews contain meta-analyses. A meta-analysis is the use of statistical methods to summarize the results of independent studies.[145]

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where 2 technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: (1) In economic and decision analysis, the desirability of a specific health status or health outcome, usually expressed as being on a continuum from 0 to 1 (death having a utility value of 0, and a full healthy life having a utility value of 1). Note: This term is often used as a synonym for *preference*. (2) The relative desirability of, or preference for, a specific health outcome or health status (usually from the perspective of the patient).[145]

Visual analogue scale (VAS): The visual analogue scale (VAS) is a direct method of measuring people's preferences for various health states. Respondents are first asked to rank a series of health states from least to most preferable. Then, they are asked to place the health states on a scale with intervals reflecting the differences in preference among the given health states. The scale ranges from 0 (worst imaginable health) to 100 (best imaginable health). The value of a respondent's preference for each health state is given by their placement of each health state on the scale.

Willingness to pay: The maximum amount that a person is willing to pay: (a) to achieve a good health state or particular outcome, or to increase its probability of occurrence; or (b) to avoid a bad health state or outcome, or to decrease its probability of occurrence.[145]

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search for Systematic Reviews

Search date: December 19, 2022

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 14, 2022>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 50>, Ovid MEDLINE(R) ALL <1946 to December 16, 2022>

Search strategy:

---

1 Cancer Pain/ (25095)
2 ((adenocarcinoma* or cancer* or carcinoma* or neoplasm* or oncolog* or tumor* or tumour* or malignan* or metasta*) adj10 (pain or pains or painful*)).ti,ab,kf. (101335)
3 or/1-2 (110080)
4 Infusion Pumps, Implantable/ (3944)
5 *Infusion Pumps/ (4913)
6 *Injections, Spinal/ (1277)
7 (intrathecal or intra-thecal).ti. (20681)
8 (((intrathecal* or intra-thecal* or implantabl*) adj3 (deliver* or device* or drug administrat* or infus* or pump* or system* or therap* or analgesi* or baclofen* or morphine* or ziconotide*)) or IDD or IDDS or ITDD or IADP).ti,ab,kf. (56750)
9 (target* drug deliver* or TDD).ti,ab,kf. (19920)
10 (subarachnoid adj4 (deliver* or drug* or infusion* or pump*)).ti,ab,kf. (687)
11 (synchromed* or isomed* or infusaid* or constant flow infusion*).ti,ab,kf. (737)
12 or/4-11 (96168)
13 3 and 12 (2183)
14 exp Animals/ not Humans/ (16112591)
15 13 not 14 (1690)
16 15 use coch,cleed (5)
17 (Systematic Reviews or Meta Analysis).pt. (172604)
18 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (906264)
19 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (658461)
20 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (614800)
21 (evidence adj2 (review* or overview* or synthes#s)).ti,ab,kf. (96967)
22 (review of reviews or overview of reviews).ti,ab,kf. (2337)
23 umbrella review*.ti,ab,kf. (2506)

24 GRADE Approach/ (2416)
25 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).ti,ab,kf. (601433)
26 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (696823)
27 cochrane.ti,ab,kf. (294490)
28 (meta regress* or metaregress*).ti,ab,kf. (30246)
29 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (37022)
30 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (73823)
31 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (55749)
32 or/17-31 (1725675)
33 15 and 32 (87)
34 limit 33 to english language [Limit not valid in CDSR; records were retained] (87)
35 34 use medall (38)
36 cancer pain/ (25095)
37 ((adenocarcinoma* or cancer* or carcinoma* or neoplasm* or oncolog* or tumor* or tumour* or malignan* or metasta*) adj10 (pain or pains or painful*)).tw,kw,kf. (102243)
38 or/36-37 (110925)
39 exp intrathecal pump/ (963)
40 implantable drug delivery system/ (156)
41 *drug delivery device/ (1624)
42 *intraspinal drug administration/ (238)
43 (intrathecal or intra-thecal).ti,dv. (20683)
44 (((intrathecal* or intra-thecal* or implantabl*) adj3 (deliver* or device* or drug administrat* or infus* or pump* or system* or therap* or analgesi* or baclofen* or morphine* or ziconotide*)) or IDD or IDDS or ITDD or IADP).tw,kw,kf,dv. (57357)
45 (target* drug deliver* or TDD).tw,kw,kf,dv. (19979)
46 (subarachnoid adj4 (deliver* or drug* or infusion* or pump*)).tw,kw,kf,dv. (704)
47 (synchromed* or isomed* or infusaid* or constant flow infusion*).tw,kw,kf,dv. (1106)
48 or/39-47 (91107)
49 38 and 48 (2133)
50 (exp animal/ or nonhuman/) not exp human/ (11631176)
51 49 not 50 (1951)
52 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (880224)
Annotation: Added Systematic review/ or "systematic review (topic)"/ for thoroughness, but these may add many results. Will monitor
53 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (881548)
54 ((systematic* or methodologic*) adj3 (review* or overview*)).tw,kw,kf. (668962)
55 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw,kw,kf. (622705)
56 (evidence adj2 (review* or overview* or synthes#s)).tw,kw,kf. (99220)
57 (review of reviews or overview of reviews).tw,kw,kf. (2546)

58 umbrella review*.tw,kw,kf. (2535)
59 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).tw,kw,kf. (610894)
60 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (696823)
61 cochrane.tw,kw,kf. (297913)
62 (meta regress* or metaregress*).tw,kw,kf. (31194)
63 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).tw,kw,kf. (38067)
64 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (73823)
65 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).tw,kw,kf. (57058)
66 or/52-65 (1729878)
67 51 and 66 (131)
68 limit 67 to english language [Limit not valid in CDSR; records were retained] (131)
69 68 use emez (80)
70 16 or 35 or 69 (123)
71 70 use medall (38)
72 70 use coch (3)
73 70 use cleed (2)
74 70 use emez (80)
75 remove duplicates from 70 (86)

Clinical Evidence Search for Primary Studies

Search date: January 26, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2022>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 03>, Ovid MEDLINE(R) ALL <1946 to January 25, 2023>

Search strategy:

---

1 Cancer Pain/ (25416)
2 ((adenocarcinoma* or cancer* or carcinoma* or neoplasm* or oncolog* or tumor* or tumour* or malignan* or metasta*) adj10 (pain or pains or painful*)).ti,ab,kf. (109300)
3 or/1-2 (118003)
4 Infusion Pumps, Implantable/ (4091)
5 *Infusion Pumps/ (4922)
6 *Injections, Spinal/ (1277)
7 (intrathecal or intra-thecal).ti. (23458)

8 (((intrathecal* or intra-thecal* or implantabl*) adj3 (deliver* or device* or drug administrat* or infus* or pump* or system* or therap* or analgesi* or baclofen* or morphine* or ziconotide*)) or IDD or IDDS or ITDD or IADP).ti,ab,kf. (60456)
9 (target* drug deliver* or TDD).ti,ab,kf. (20650)
10 (subarachnoid adj4 (deliver* or drug* or infusion* or pump*)).ti,ab,kf. (781)
11 (synchromed* or isomed* or infusaid* or constant flow infusion*).ti,ab,kf. (793)
12 or/4-11 (102279)
13 3 and 12 (2302)
14 exp Animals/ not Humans/ (16206139)
15 13 not 14 (1802)
16 15 use cctr (101)
17 ((Letter not (Letter and Randomized Controlled Trial)) or Conference Proceeding or Editorial or Comment).pt. (4340041)
18 16 not 17 (90)
19 15 use medall,cleed (751)
20 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6277420)
21 19 not 20 (572)
22 18 or 21 (662)
23 limit 22 to english language (581)
24 limit 23 to yr="2021 -Current" (68)
25 cancer pain/ (25416)
26 ((adenocarcinoma* or cancer* or carcinoma* or neoplasm* or oncolog* or tumor* or tumour* or malignan* or metasta*) adj10 (pain or pains or painful*)).tw,kw,kf. (112463)
27 or/25-26 (121098)
28 exp intrathecal pump/ (986)
29 implantable drug delivery system/ (159)
30 *drug delivery device/ (1648)
31 *intraspinal drug administration/ (238)
32 (intrathecal or intra-thecal).ti,dv. (23460)
33 (((intrathecal* or intra-thecal* or implantabl*) adj3 (deliver* or device* or drug administrat* or infus* or pump* or system* or therap* or analgesi* or baclofen* or morphine* or ziconotide*)) or IDD or IDDS or ITDD or IADP).tw,kw,kf,dv. (61444)
34 (target* drug deliver* or TDD).tw,kw,kf,dv. (20710)
35 (subarachnoid adj4 (deliver* or drug* or infusion* or pump*)).tw,kw,kf,dv. (871)
36 (synchromed* or isomed* or infusaid* or constant flow infusion*).tw,kw,kf,dv. (1151)
37 or/28-36 (97527)
38 27 and 37 (2254)
39 (exp animal/ or nonhuman/) not exp human/ (11709839)
40 38 not 39 (2067)
41 40 use emez (1269)
42 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (13039109)
43 41 not 42 (727)
44 limit 43 to english language (624)
45 limit 44 to yr="2021 -Current" (65)
46 24 or 45 (133)
47 remove duplicates from 46 (86)

Economic Evidence Search

Search date: December 20, 2022

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 14, 2022>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 50>, Ovid MEDLINE(R) ALL <1946 to December 19, 2022>

Search strategy:

---

1 Cancer Pain/ (25327)
2 ((adenocarcinoma* or cancer* or carcinoma* or neoplasm* or oncolog* or tumor* or tumour* or malignan* or metasta*) adj10 (pain or pains or painful*)).ti,ab,kf. (108314)
3 or/1-2 (117085)
4 Infusion Pumps, Implantable/ (4093)
5 *Infusion Pumps/ (4913)
6 *Injections, Spinal/ (1277)
7 (intrathecal or intra-thecal).ti. (23264)
8 (((intrathecal* or intra-thecal* or implantabl*) adj3 (deliver* or device* or drug administrat* or infus* or pump* or system* or therap* or analgesi* or baclofen* or morphine* or ziconotide*)) or IDD or IDDS or ITDD or IADP).ti,ab,kf. (59597)
9 (target* drug deliver* or TDD).ti,ab,kf. (20135)
10 (subarachnoid adj4 (deliver* or drug* or infusion* or pump*)).ti,ab,kf. (772)
11 (synchromed* or isomed* or infusaid* or constant flow infusion*).ti,ab,kf. (788)
12 or/4-11 (100803)
13 3 and 12 (2282)
14 exp Animals/ not Humans/ (16113207)
15 13 not 14 (1789)
16 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6228339)
17 15 not 16 (1577)
18 17 use coch,cleed (5)
19 economics/ (264087)
20 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1014692)
21 economics.fs. (467196)
22 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1212422)
23 exp "costs and cost analysis"/ (669973)
24 (cost or costs or costing or costly).ti. (321514)
25 cost effective*.ti,ab,kf. (430417)
26 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kf. (297887)
27 models, economic/ (15548)

28 markov chains/ or monte carlo method/ (103442)
29 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (62895)
30 (markov or markow or monte carlo).ti,ab,kf. (171682)
31 quality-adjusted life years/ (52949)
32 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (105666)
33 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (180551)
34 or/19-33 (3241089)
35 17 and 34 (154)
36 35 use medall,cctr (59)
37 18 or 36 (64)
38 cancer pain/ (25327)
39 ((adenocarcinoma* or cancer* or carcinoma* or neoplasm* or oncolog* or tumor* or tumour* or malignan* or metasta*) adj10 (pain or pains or painful*)).tw,kw,kf. (111829)
40 or/38-39 (120531)
41 exp intrathecal pump/ (963)
42 implantable drug delivery system/ (156)
43 *drug delivery device/ (1624)
44 *intraspinal drug administration/ (238)
45 (intrathecal or intra-thecal).ti,dv. (23266)
46 (((intrathecal* or intra-thecal* or implantabl*) adj3 (deliver* or device* or drug administrat* or infus* or pump* or system* or therap* or analgesi* or baclofen* or morphine* or ziconotide*)) or IDD or IDDS or ITDD or IADP).tw,kw,kf,dv. (60661)
47 (target* drug deliver* or TDD).tw,kw,kf,dv. (20194)
48 (subarachnoid adj4 (deliver* or drug* or infusion* or pump*)).tw,kw,kf,dv. (874)
49 (synchromed* or isomed* or infusaid* or constant flow infusion*).tw,kw,kf,dv. (1157)
50 or/41-49 (96126)
51 40 and 50 (2244)
52 (exp animal/ or nonhuman/) not exp human/ (11631798)
53 51 not 52 (2062)
54 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12936038)
55 53 not 54 (1367)
56 Economics/ (264087)
57 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (144705)
58 Economic Aspect/ or exp Economic Evaluation/ (536249)
59 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1232662)
60 exp "Cost"/ (669973)
61 (cost or costs or costing or costly).ti. (321514)
62 cost effective*.tw,kw,kf. (439184)
63 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kw,kf. (307205)
64 Monte Carlo Method/ (80463)
65 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (66279)
66 (markov or markow or monte carlo).tw,kw,kf. (175146)
67 Quality-Adjusted Life Years/ (52949)
68 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (108992)
69 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (201120)

70 or/56-69 (2778655)
71 55 and 70 (166)
72 71 use emez (96)
73 37 or 72 (160)
74 73 use medall (53)
75 73 use emez (96)
76 73 use cctr (6)
77 73 use coch (3)
78 73 use cleed (2)
79 remove duplicates from 73 (109)
80 limit 79 to english language [Limit not valid in CDSR; records were retained] (104)

Quantitative Evidence of Preferences and Values Search

Search date: January 4, 2023

Databases searched: Ovid MEDLINE and CINAHL

Database segment: Ovid MEDLINE(R) ALL <1946 to December 30, 2022>

Search strategy:

---

1 Cancer Pain/ (2202)
2 ((adenocarcinoma* or cancer* or carcinoma* or neoplasm* or oncolog* or tumor* or tumour* or malignan* or metasta*) adj10 (pain or pains or painful*)).ti,ab,kf. (39498)
3 or/1-2 (39847)
4 Infusion Pumps, Implantable/ (3822)
5 *Infusion Pumps/ (2321)
6 *Injections, Spinal/ (1067)
7 (intrathecal or intra-thecal).ti. (9020)
8 (((intrathecal* or intra-thecal* or implantabl*) adj3 (deliver* or device* or drug administrat* or infus* or pump* or system* or therap* or analgesi* or baclofen* or morphine* or ziconotide*)) or IDD or IDDS or ITDD or IADP).ti,ab,kf. (23570)
9 (target* drug deliver* or TDD).ti,ab,kf. (8670)
10 (subarachnoid adj4 (deliver* or drug* or infusion* or pump*)).ti,ab,kf. (313)
11 (synchromed* or isomed* or infusaid* or constant flow infusion*).ti,ab,kf. (271)
12 or/4-11 (42834)
13 3 and 12 (813)
14 Attitude to Health/ (85492)
15 Health Knowledge, Attitudes, Practice/ (125319)
16 Patient Participation/ (29013)
17 Patient Preference/ (10560)
18 Attitude of Health Personnel/ (130503)
19 *Professional-Patient Relations/ (12468)
20 *Physician-Patient Relations/ (37246)
21 Choice Behavior/ (34770)
22 (choice or choices or value* or valuation* or knowledg*).ti. (309803)

23 (preference* or expectation* or attitude* or acceptab* or point of view).ti,ab,kf. (709705)
24 ((clinician* or doctor* or (health* adj2 worker*) or oncologist* or nurse*1 or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or surgeon* or user*1 or women or men) adj2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value*1 or knowledg*)).ti,ab,kf. (195212)
25 health perception*.ti,ab,kf. (3228)
26 *Decision Making/ (46288)
27 (clinician* or doctor* or (health* adj2 worker*) or oncologist* or nurse*1 or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or surgeon* or user*1 or women or men).ti. (3008484)
28 26 and 27 (9199)
29 (decision* and mak*).ti. (35906)
30 (decision mak* or decisions mak*).ti,ab,kf. (198163)
31 29 or 30 (199794)
32 (clinician* or doctor* or (health* adj2 worker*) or oncologist* or nurse*1 or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or surgeon* or user*1 or women or men).ti,ab,kf. (9753068)
33 31 and 32 (127567)
34 (discrete choice* or decision board* or decision analy* or decision-support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*).ti,ab,kf. (48106)
35 Decision Support Techniques/ (22522)
36 (health and utilit*).ti. (1881)
37 (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best-worst scaling or time trade-off or TTO or probability trade-off).ti,ab,kf. (16328)
38 (preference based or preference score* or preference elicitation or multiattribute or multi attribute).ti,ab,kf. (3647)
39 or/14-25,28,33-38 (1537266)
40 13 and 39 (55)
41 limit 40 to english language (50)

CINAHL

#	Query	Results
S1	(MH "Cancer Pain")	6,112
S2	((adenocarcinoma* or cancer* or carcinoma* or neoplasm* or oncolog* or tumor* or tumour* or malignan* or metasta*) N10 (pain or pains or painful*))	18,139
S3	S1 OR S2	18,139
S4	(MH "Infusion Pumps, Implantable")	939
S5	(MM "Infusion Pumps")	1,187
S6	(MM "Injections, Intraspinal")	560
S7	TI (intrathecal or intra-thecal)	2,349

CINAHL

#	Query	Results
S8	(((intrathecal* or intra-thecal* or implantabl*) N3 (deliver* or device* or drug administrat* or infus* or pump* or system* or therap* or analgesi* or baclofen* or morphine* or ziconotide*)) or IDD or IDDS or ITDD or IADP)	8,338
S9	(target* drug deliver* or TDD)	423
S10	(subarachnoid N4 (deliver* or drug* or infusion* or pump*))	421
S11	(synchromed* or isomed* or infusaid* or constant flow infusion*)	73
S12	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	11,523
S13	S3 AND S12	315
S14	(MH "Attitude to Health")	48,736
S15	(MH "Health Knowledge")	36,024
S16	(MH "Consumer Participation")	23,653
S17	(MH "Patient Preference")	2,206
S18	(MH "Attitude of Health Personnel")	52,509
S19	(MM "Professional-Patient Relations")	14,597
S20	(MM "Physician-Patient Relations")	17,420
S21	(MM "Nurse-Patient Relations")	14,940
S22	TI (choice or choices or value* or valuation* or knowledg*)	114,453
S23	(preference* or expectation* or attitude* or acceptab* or point of view)	536,513
S24	((clinician* or doctor* or (health* N2 worker*) or nurse or nurses or oncologist* or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or surgeon* or user or users or women or men) N2 (knowledg* or misperception* or misunderstand* or participation or perceiv* or perception* or perspective* or understand* or value or values or view*))	178,364
S25	health perception*	5,225
S26	(MH "Decision Making, Shared")	3,048
S27	(MH "Decision Making, Patient")	15,890
S28	(MH "Decision Making, Family")	4,243
S29	(MM "Decision Making")	25,606
S30	TI (clinician* or doctor* or (health* N2 worker*) or nurse or nurses or oncologist* or patient or patients or personal or physician* or practitioner* or	1,386,096

CINAHL #	Query	Results
	professional or professionals or provider* or surgeon* or user or users or women or men)	
S31	S29 AND S30	5,494
S32	TI (decision* and mak*)	21,103
S33	(decision mak* or decisions mak*)	178,980
S34	S32 OR S33	179,212
S35	(clinician* or doctor* or (health* N2 worker*) or nurse or nurses or oncologist* or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or surgeon* or user or users or women or men)	3,856,421
S36	S34 AND S35	128,051
S37	(discrete choice* or decision board* or decision analy* or decision support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*)	35,825
S38	(MH "Decision Support Techniques")	7,694
S39	TI (health and utilit*)	1,129
S40	(gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best worst scaling or time trade off or TTO or probability trade off)	20,871
S41	(preference based or preference score* or preference elicitation or multiattribute or multi attribute)	1,801
S42	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S31 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41	903,476
S43	S13 AND S42	33
S44	S13 AND S42 Limiters - English Language	33

Grey Literature Search

Performed: December 21–22, 2022; January 27, 2023

Websites searched:
Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services, Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Cancer Care Ontario Guidelines and Advice, Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force, Sick Kids Paediatric Economic Database Evaluation (PEDE), Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used:
cancer pain, intrathecal, drug delivery system, intrathecal drug administration, implantable, IDDS, targeted drug delivery, analgesic delivery pumps, synchromed, isomed, douleur du cancer, intrathécale

Clinical results (included in PRISMA): 5

Economic results (included in PRISMA): 3

Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 5

Ongoing clinical trials: 8

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

	Phase 2				Phase 3
Author, year	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review
Hayek et al, 2011[43]	Low[b]	High[c]	Low	Low	High
Belgian Health Care Knowledge Centre, 2012[45]	Low	Low	Low	Low	Low
Health Quality Ontario, 2016[23]	Low[b]	High[c]	Low	Low	High
Kenfield et al, 2021[42]	Low[b]	High[c,d,e]	High[f]	Low	High
Duarte et al, 2022[39]	Low	Low	Low	Low	Low
Perruchoud et al, 2022[44]	Low[b]	High[c]	High[g,h]	High[i]	High

[a]Possible risk of bias levels: low, high, unclear.

[b]No information about whether study protocol was registered a priori or predefined.

[c]References of excluded full-text articles not provided.

[d]Single reviewer for study selection.

[e]Limited search terms in literature search.

[f]Single reviewer for data extraction.

[g]No risk-of-bias assessment.

[h]No information about whether data extraction was conducted by 1 or 2 reviewers.

[i]This review defined safety as an outcome but only data on infection were extracted and synthesized.

Table A2: GRADE Evidence Profile for Comparison of Pain Management With vs. Without Intrathecal Drug Delivery Systems in Adults With Cancer

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Pain intensity							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	Other considerations (+1)[c]	⨁⨁⨁ Moderate
16 (observational studies)	No serious limitations[d]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	Other considerations (+1)[c]	⨁⨁ Low
Use of systemic opioids							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate
11 (observational studies)	No serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Health-related quality of life							
1 (observational study)	No serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Functional outcomes							
4 (observational studies)	No serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Survival							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⨁⨁ Low
10 (observational studies)	No serious limitations[d]	No serious limitations	No serious limitations	Serious limitations (−1)[e]	Undetected	None	⨁ Very Low
Complications and side effects							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
16 (observational studies)	No serious limitations[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

[a]Duarte et al[39] considered the RCT included in their systematic review to have high risk of bias.

[b]The meta-analysis on pain intensity (including RCT and observational studies) by Duarte et al[39] showed high degree of unexplained heterogeneity between studies.

[c]Upgraded because of large magnitude of effect (30-50% pain reduction). Intrathecal drug delivery systems represent the only treatment option to provide pain relief for patients with refractory cancer pain.

[d]Observational studies started with a low GRADE level because of inherent limitations in study design (e.g., lack of randomization, lack of blinding, loss to follow-up). We did not lower the GRADE level further unless there were more substantial study limitations.

[e]Heterogeneity of cancer diagnosis and differing prognosis at baseline had an impact on survival other than intrathecal drug delivery.

Table A3: GRADE Evidence Profile for Comparison of Pain Management With vs. Without Intrathecal Drug Delivery Systems in Children With Cancer

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Pain intensity							
6 (case study/case series)	Very serious limitations (−2)[a]	No serious limitations	No serious limitations	Very serious limitations (−2)[b]	Potential[c]	None	⨁ Very Low
Survival							
6 (case study/case series)	Very serious limitations (−2)[a]	No serious limitations	No serious limitations	Very serious limitations (−2)[b]	Potential[c]	None	⨁ Very Low
Functional outcomes							
6 (case study/case series)	Very serious limitations (−2)[a]	No serious limitations	No serious limitations	Very serious limitations (−2)[b]	Potential[c]	None	⨁ Very Low
Complications and side effects							
6 (case study/case series)	Very serious limitations (−2)[a]	No serious limitations	No serious limitations	Very serious limitations (−2)[b]	Potential[c]	None	⨁ Very Low

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]In addition to the inherent limitations of observational studies (e.g., lack of randomization, lack of blinding, risk of selection bias, loss to follow-up), the use of case studies and case series posed further limitations in terms of study design (e.g., lack of control group, risk of reporting bias).

[b]Outcomes were presented in narrative with no control group, which prevented us from being able to compare or gauge the range of difference in effect between intervention and controls.

[c]Potential publication bias because case studies and case series are considered to provide low-tier evidence, are less likely to be published, and when published tend to have positive findings.

Appendix 3: Selected Excluded Studies – Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Table A4: Selected Excluded Systematic Reviews – Clinical Evidence

Citation	Primary reason for exclusion
Brogan S, Perruchoud C, Papi B, et al. Intrathecal drug delivery for cancer pain management: a systematic review and meta-analysis. Neuromodulation. 2021;24(4):e26.	An abstract
Canadian Agency for Drugs and Technologies in Health. Rapid response report: intrathecal bupivacaine via infusion pump for the management of pain: clinical evidence, safety, and guidelines. Ottawa (ON): The Agency; 2012.	Not a systematic review
Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC): recommendations for intrathecal drug delivery: guidelines for improving safety and mitigating risks. Neuromodulation. 2017;20(2):155-76.	Not a systematic review
University of Calgary Health Technology Assessment Unit. Neuromodulation for cancer and non-cancer pain. Vancouver (BC): Health Technology Assessment Office, Province of British Columbia; 2018.	Mixed populations (patients with cancer and noncancer pain) with results not presented separately
Kurita GP, Kaasa S, Sjogren P, European Palliative Care Research Collaborative (EPCRC). Spinal opioids in adult patients with cancer pain: a systematic review: a European Palliative Care Research Collaborative (EPCRC) opioid guidelines project. Palliat Med. 2011;25(5):560-77.	Mixed interventions of spinal opioids (epidural, intrathecal, and intracerebroventricular) with results not presented separately
Sawhney M, Fletcher GG, Rice J, Watt-Watson J, Rawn T. Evidence summary 18-4: guidelines on management of pain in cancer and/or palliative care. Toronto (ON): Cancer Care Ontario; 2017.	Not a systematic review
Williams J, Louw G, Towlerton G. Intrathecal pump systems for giving opioids in chronic pain: a systematic review. Health Technol Assess. 2000;4(32):1-71.	Mixed populations (patients with cancer and noncancer pain) with results not presented separately

Table A5: Selected Excluded Primary Studies – Clinical Evidence

Citation	Primary reason for exclusion
Giglio M, Preziosa A, Mele R, et al. Effects of an intrathecal drug delivery system connected to a subcutaneous port on pain, mood and quality of life in end-stage cancer patients: an observational study. Cancer Control. 2022; 29:10732748221133752.	Not timing of interest
Qin W, Zhao L, Liu B, et al. Comparison of external system and implanted system in intrathecal therapy for refractory cancer pain in China: a retrospective study. Brain Behav. 2023;13(1):e2851.	Not comparator of interest[a]

[a]This evidence review was predefined to exclude external intrathecal drug delivery systems. The study by Qin et al was designed to compare external with implanted intrathecal drug delivery systems for refractory cancer pain. Although it did report scores on numerical pain rating scales and the Karnofsky Performance Status Scale for activities of daily living before and after the implantation of an intrathecal drug delivery system in a part of a figure in the article, the inclusion of these data would not have made any material difference to the analysis or results of the clinical evidence review.

Table A6: Selected Excluded Primary Studies – Quantitative Evidence of Preferences and Values

Citation	Primary reason for exclusion
Cahana A, Arigoni F, Robert, L. Attitudes and beliefs regarding the role of interventional pain management at the end-of-life among caregivers: a 4-year perspective. Pain Practice. 2007;7(2):103-109.	Mixed interventions (epidural and intrathecal drug delivery systems) with results not presented separately
Hawley P, Beddard-Huber E, Gross C, et al. Intrathecal infusions for intractable cancer pain: a qualitative study of the impact on a case series of patients and caregivers. Pain Res Manag. 2009;14(5):371-79.	Qualitative evidence
Patel N, Huddart M, Makins H, et al. "Was it worth it?" Intrathecal analgesia for cancer pain: a qualitative study exploring the views of family carers. Palliat Med. 2018;32(1):287-93.	Qualitative evidence
Warner LL, Moeshler SS, Pittelknow TP, Strand JJ. Attitudes of hospice providers regarding intrathecal targeted drug delivery for patients with cancer. Am J Hosp Palliat Care. 2019;36(11):955-58.	Not timing of interest

Appendix 4: Summary of Identified Systematic Reviews That Were Excluded

Table A7: Characteristics of Systematic Reviews Considered for Inclusion but Excluded

Author, year, literature search end date	Population	Intervention(s)	Comparator(s)	Outcome(s)
Belgian Health Care Knowledge Centre, 2012,[45] January–February 2012	Adults with intractable pain not satisfactorily responding to optimal medical and paramedical treatment	Neuromodulation, either implanted medullar electrical stimulation or an implanted intrathecal analgesic delivery pump as with or without optimal medical treatment	Placebo only or any other type of nonactive comparator (e.g., no treatment, waiting list) without any other type of pain medication or specific drug treatment, as applicable	Satisfactory pain relief Health-related quality of life Physical and functional abilities (e.g., activities of daily living, medication intake) Anxiety Depression Adverse events
Hayek et al, 2011,[43] October 2010	Subjects with chronic pain including patients with cancer and noncancer pain with or without history of previous spine surgery	IDDS implanted and followed for at least 3 mo for cancer pain and 12 mo for noncancer pain (results on cancer pain and noncancer pain reported separately)	All	Pain relief Functional status Psychological status Return to work Reduction in opioid intake
Health Quality Ontario, 2016,[23] April 2014	Adults with chronic malignant pain	IDDS, either fixed-rate or programmable	Standard pharmacologic (oral or parenteral analgesics) or nonpharmacologic pain management	Pain intensity or relief Total analgesic/opioid consumption Rescue analgesia (or changes in the use of concomitant pain treatments) Physical function Emotional function Drug-related harms Procedure-related harms Equipment-related harms All serious events Aggregate outcomes Economic outcomes

Author, year, literature search end date	Population	Intervention(s)	Comparator(s)	Outcome(s)
Perruchoud et al, 2022,[44] January 2019	Patients with chronic, intractable or refractory cancer-related pain	Intrathecal infusion with implanted or external pump (subgroup analyses of implantable IDDS were performed)	All	Pain intensity Safety

Abbreviation: IDDS, intrathecal drug delivery system.

Appendix 5: Selected Excluded Studies – Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Table A8: Selected Excluded Systematic Reviews – Economic Evidence

Citation	Primary reason for exclusion
Bedder MD, Burchiel K, Larson A. Cost analysis of two implantable narcotic delivery systems. J Pain Symptom Manage. 1991;6(6):368-73.	Comparator (a second implantable IDDS)
Camberlin CS, San Miguel L, Smit Y, Post P, Gerkens S, De Laet C. Neuromodulation for the management of chronic pain: implanted spinal cord stimulators and intrathecal analgesic delivery pumps. Brussels: Belgian Health Care Knowledge Centre; 2012.	Population (non-malignant cancer)
Duarte RV, Sale A, Desai P, Marshall T, Eldabe S. The unmet need for intrathecal drug delivery pumps for the treatment of cancer pain in England: an assessment of the hospital episode statistics database. Neuromodulation. 2020;23(7):1029-33.	Does not assess cost-effectiveness
Dupoiron D, Duarte R, Carvajal G, Aubrun F, Eldabe S. Rationale and recent advances in targeted drug delivery for cancer pain: is it time to change the paradigm? Pain Physician. 2022;25(3):E414-25.	Does not assess cost-effectiveness
Gilmer-Hill HS, Boggan JE, Smith KA, Frey CF, Wagner Jr FC, Hein LJ. Intrathecal morphine delivered via subcutaneous pump for intractable pain in pancreatic cancer. Surg Neurol. 1999;51(1):6-11.	Does not assess cost-effectiveness
Hassenbusch SJ. Cost modeling for alternate routes of administration of opioids for cancer pain. Oncology. 1999;13(5 Suppl 2):63-67.	Comparator (external/epidural pump)
Hassenbusch SJ, Paice JA, Patt RB, Bedder MD, Bell GK. Clinical realities and economic considerations: economics of intrathecal therapy. J Pain Symptom Manage. 1997;14(3):S36-48.	Population (non-malignant pain)
Health Quality Ontario. Intrathecal drug delivery systems for cancer pain: a health technology assessment. Ontario Health Technol Assess Ser. 2016;16(1):1-51.	Does not assess cost-effectiveness
Kumar K, Rizvi S, Bishop S, Tang W. Cost impact of intrathecal polyanalgesia. Pain Med. 2013;14(10):1569-84.	Population (non-malignant pain)
Lambe T, Duarte R, Eldabe R, Copley S, Kansal A, Black S, Dupoiron D, Eldabe S. Ziconotide for the management of cancer pain: a budget impact analysis. Neuromodulation. 2023;26(6):1226-32.	Comparator (IDDS with morphine monotherapy)
Miles J. Intrathecal therapy for chronic pain. Stereotact Funct Neurosurg. 2002;77(1-4):156-58.	Population (non-malignant pain)
Mueller-Schwefe G, Hassenbusch SJ, Reig E. Cost effectiveness of intrathecal therapy for pain. Neuromodulation. 1999;2(2):77-84.	Does not assess cost-effectiveness
Nguyen H, Hassenbusch SJ. Cost-effectiveness of intraspinal drug delivery for chronic pain. Seminars in Pain Medicine. 2004;2(1):43-45.	Population (non-malignant pain)

Citation	Primary reason for exclusion
Ohlsson LJ, Rydberg TS, Edén T, Glimhall BA, Thulin LA. Microbiologic and economic evaluation of multiday infusion pumps for control of cancer pain. Ann Pharmacother. 1995;29(10):972-76.	Intervention (external pump)
Qin W, Li Y, Liu B, Liu Y, Zhang Y, Zhang X, Li P, Fan B. Intrathecal morphine infusion therapy via a percutaneous port for refractory cancer pain in China: an efficacy, safety and cost utilization analysis. J Pain Re. 2020;23:231-37.	Intervention (intrathecal morphine infusion via percutaneous port)
Simpson KH, Jones I. Intrathecal drug delivery for management of cancer and noncancer pain. J Opioid Manag. 2008;4(5):293-304.	Does not assess cost-effectiveness
Textor LH. Intrathecal pumps for managing cancer pain. Am J Nurs. 2016;116(5):36-44.	Does not assess cost-effectiveness
Williams JE, Louw G, Towlerton G. Intrathecal pumps for giving opioids in chronic pain: a systematic review. Database of Abstracts of Reviews of Effects (DARE): Quality-Assessed Reviews. 2000. York (UK): Centre for Reviews and Dissemination.	Does not assess cost-effectiveness

Appendix 6: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A9: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Intrathecal Drug Delivery Systems Compared With Nonintrathecal Methods of Pain Management

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment[a]
Stearn et al, 2019, United States[80]	Yes	Yes	No	Yes, payer perspective	No	NA	No	No	Partially applicable
University of Calgary, 2018, Canada[26]	Yes	Yes	Yes	Yes, Canadian public health care system	Partially, health-related quality-of-life measures not included	Yes, 1.5%	No	No	Partially applicable
Stearns et al, 2016, United States[79]	Yes	Yes	No	Yes, payer perspective	No	No	No	No	Partially applicable
Brogan et al, 2013, United States[81]	Yes	Yes	No	Partially, US hospital	No	NA	No	No	Partially applicable

Abbreviation: NA, not applicable.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A10: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Intrathecal Drug Delivery Systems Compared With Nonintrathecal Methods of Pain Management

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[b]
Stearns et al, 2019, United States[80]	NA	Yes	No	NA	NA	Yes	Yes	NA	Yes	No	Yes, manufacturer was involved in design and conduct of study; most authors associated with manufacturer either as employee or paid consultant	Potentially serious limitations
University of Calgary, 2018, Canada[26]	Yes	Yes	No, health-related quality-of-life measures not included	Yes	Yes	No	No	No	Yes	Yes	No	Potentially serious limitations
Stearns et al, 2016, United States[79]	NA	Yes	No	NA	NA	Yes	Yes	NA	Yes	No	Yes, most authors associated with manufacturer as employee, paid consultant, or stockowner	Potentially serious limitations
Brogan et al, 2013, United States[81]	NA	Yes	No	Yes	Yes	No	No	Yes	No	No	No	Very serious limitations

Abbreviation: NA, not applicable.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Appendix 7: Supplementary Economic Tables

Table A11: Utilities Used in the Economic Model With Parameter Distributions

Health State	Utility (95% CI)	Distribution	Reference
IDDS			
Alive with reduced pain	0.56 (0.48 to 0.63)	Beta	Stearns et al, 2020[65]
Standard care			
Alive with refractory cancer pain	0.39 (0.31 to 0.46)	Beta	Stearns et al, 2020[65]

Abbreviations: CI, confidence interval; IDDS, intrathecal drug delivery system.

Table A12: Costs Used in the Economic Model With Parameter Distributions

Variable	Mean (95% CI)	Distribution	Reference
IDDS			
Device cost (programmable drug infusion device plus intrathecal catheter)	$10,350 ($9,371 to $11,367)[a]	Gamma	Medtronic Canada Inc., email communication, November 15, 2022
Implantation procedure cost (physician billing)	$1,019	Fixed	Schedule of Benefits[87]
Hospital cost for IDDS implantation	$12,335 ($9,009 to $16,181)[b]	Gamma	NACRS
Post-procedure follow-up cost: follow-up visits plus infusion pump programming (physician billing)	$407	Fixed	Schedule of Benefits[87]
Long-term (1-year) follow-up cost (physician billing)	$693	Fixed	Schedule of Benefits[87]
Refill kit cost	$31	Fixed	Medtronic Canada Inc., email communication, November 15, 2022
Monthly cost of intrathecal opioids	$111.15 ($81 to $147)[b]	Gamma	Calculated
Standard care			
Monthly cost of systemic opioids	$342 ($248 to $449)[b]	Gamma	Calculated
Number of additional yearly hospitalizations for poorly managed pain or severe side effects of systemic opioids	2.3 (1.31 to 3.51)[b]	Gamma	Stearns et al, 2019[80]

Variable	Mean (95% CI)	Distribution	Reference
Average cost per hospitalization due to poorly managed pain in Ontario	7,483 (7,302 to 7,656)	Gamma	CIHI Patient Cost Estimator, 2015/16 to 2019/20[93]

Abbreviations: CI, confidence interval; CIHI, Canadian Institute for Health Information; IDDS, intrathecal drug delivery system; NA, not applicable; NACRS, National Ambulatory Care Reporting System.
[a]Standard error assumed to be 5% of mean.
[b]Standard error assumed to be 15% of mean.

Table A13: Physician Billing Codes Used for Costing Parameters

		Surgeon	Anaesthesiologist[a]				
Billing code	Description	Total fees, $	Unit fee, $	Basic units	Time units	Total fees, $	Total, $
N555	Insertion/revision of implantable infusion pump	590.40	15.49	8	20	433.72	1,024.12
A013	Specific assessment	64.65	NA	NA	NA	NA	64.65
Z943	Programming infusion pump or dorsal column simulator	142.20	NA	NA	NA	NA	142.20

[a]Amount payable for anaesthesia services are calculated by adding the number of basic and time units, then multiplying the total by the anaesthesiologist unit fee ($15.49). Basic units are the number of basic units listed for the corresponding procedure code. Time units are calculated based on time spent by the anaesthesiologist during the procedure. Time units are calculated for each 15 minutes or part thereof. The unit value of each 15-minute period of part thereof is (1) during the first hour, 1 unit; (2) after the first hour, up to and including the first 1.5 hours, 2 units; and (3) after 1.5 hours, 3 units. The time units for this procedure was calculated based on the assumption that the average procedure time is 2.5 hours (E. Baig, MD, email communication, January 8, 2023).
Source: Schedule of Benefits.[87]

Table A14: Canadian Classification of Heath Interventions Code for the Intrathecal Drug Delivery System Implantation Procedure

Description	Code
Implantation of internal device, spinal canal, and meninges	1.AX.53.LA.QK

Source: Canadian Institute for Health Information, 2022.[149]

Table A15: Prescription Opioid Costing

Active ingredient	Brand name (DIN)	Strength	Unit price	Conversion factor[a]	Daily quantity[b]	Daily cost	Monthly cost	Pharmacy mark-up	Pharmacy dispensing fee	Total cost
Standard care										
Oral opioids										
Morphine sulfate (sustained release)	TEVA-Morphine SR (02302799)	100 mg	$1.54	1.0	3 tablets	$4.62 ($1.54 x 3)	$140.57 ($4.62 x 30.437)	$11.25	$8.83	$160.65
Morphine sulfate (immediate release)	Morphine Sulfate-Immediate Release (0214254)	30 mg	$0.55	1.0	10 tablets	$5.47 ($0.55 x 10)	$166.49 ($5.47 x 30.437)	$13.32	$8.83	$188.64
Oxycodone (immediate release)	PMS-Oxycodone (0231993	20 mg	$0.60	0.667	10 tablets	$6.00 ($0.60 x 10)	$182.74 ($6.00 x 30.437)	$14.62	$8.83	$206.19
Hydromorphone HCL (controlled release)	Hydromorph Contin (02125390)	30 mg	$4.54	0.2	2 tablets	$9.08 ($4.54 x 2)	$276.49 ($9.08 x 30.437)	$22.12	$8.83	$307.44
Hydromorphone (immediate release)	PMS-Hydromorphone (02364158)	8 mg	$0.35	0.2	7.5 tablets	$2.65 ($0.35 x 7.5)	$80.54 ($32.65 x 30.437)	$6.44	$8.83	$95.81
Methodone (long-acting)	Metadol-D (02244290)	10 mg	$0.15	0.2	6 tablets	$0.90 ($0.15 x 6)	$27.39 ($0.90 x 30.437)	$2.19	$8.83	$38.41
Average total cost										$166.19
Proportion of systemic opioids administered orally in standard care										0.6

Active ingredient	Brand name (DIN)	Strength	Unit price	Conversion factor[a]	Daily quantity[b]	Daily cost	Monthly cost	Pharmacy mark-up	Pharmacy dispensing fee	Total cost
Transdermal opioids										
Fentanyl patch	Co Fentanyl Matrix Patch (02386887)	75 mcg/h	$9.68	NA	0.33 of a patch	$3.23 ($9.68 x 0.33)	$98.23 ($3.23 x 30.437)	$7.86	$8.83	$114.92
Average total cost										$114.92
Proportion of systemic opioids administered transdermally in standard care										0.1
Subcutaneous opioids										
Morphine sulfate	Morphine HP-50 (0617288)	50 mg/ mL	$6.18	0.50	3 mL	$18.55 ($6.18 x 3)	$564.48 ($18.55 x 30.437)	$45.16	$8.83	$618.47
Hydromorphone HCL	Hydromorphone HP-10 (02145928)	10 mg/ mL	$4.35	0.50	3 mL	$13.04 ($4.35 x 3)	$396.84 ($13.04 x 30.437)	$31.75	$8.83	$437.41
Average total cost										$527.94
Proportion of systemic opioids administered subcutaneously in standard care										0.3
IDDS										
Intrathecal opioids										
Morphine sulfate	Morphine HP-50 (0617288)	50 mg/ mL	$6.18	0.01	0.05 mL	$2.50 ($6.18 x 0.05)	$76.09 ($2.50 x 30.437)	NA	NA	$76.09
Average total cost										$76.09

Active ingredient	Brand name (DIN)	Strength	Unit price	Conversion factor[a,b,c]	Daily quantity[d]	Daily cost	Monthly cost	Pharmacy mark-up	Pharmacy dispensing fee	Total cost
Systemic opioids (oral)										
Morphine sulfate (sustained release)	TEVA-Morphine SR (02302799)	100 mg	$1.54	1.0	0.5 tablets	$0.77 ($1.54 x 0.5)	$23.43 ($0.77 x 30.437)	$1.87	$8.83	$34.13
Morphine sulfate (immediate release)	Morphine Sulfate-Immediate Release (0214254)	30 mg	$0.55	1.0	1.67 tablets	$0.91 ($0.55 x 1.67)	$27.75 (0.91 x 30.437)	$2.22	$8.83	$38.80
Oxycodone (immediate release)	PMS-Oxycodone (0231993	20 mg	$0.60	0.667	1.67 tablets	$1.00 ($0.60 x 0.667)	$30.46 ($1.00 x 30.437)	$2.44	$8.83	$41.72
Hydromorphone HCL (controlled release)	Hydromorph Contin (02125390)	30 mg	$4.54	0.2	0.33 tablets	$1.51 ($4.54 x 0.33)	$46.08 ($1.51 x 30.437)	$3.69	$8.83	$58.60
Hydromorphone (immediate release)	PMS-Hydromorphone (02364158)	8 mg	$0.35	0.2	1.25 tablets	$0.44 ($0.35 x 1.25)	$13.42 ($0.44 x 30.437)	$1.07	$8.83	$23.33
Methodone (long-acting)	Metadol-D (02244290)	10 mg	$0.15	0.2	1 tablet	$0.15 ($0.15 x 1)	$4.57 ($0.15 x 30.437)	$0.37	$8.83	$13.76
Average total cost										$35.06

Abbreviations: DIN, drug identification number; HCL, hydrochloride; IDDS, intrathecal drug delivery system.

[a]As recommended by conversion guidelines.[89,150-152]

[b]Refers to the daily quantify of tablets required to achieve 300 mg of the morphine equivalent of opioids.

Source: Ontario Drug Benefit Formulary.[153]

Appendix 8: Methods for Simulating Survival Data for Probabilistic Analysis

For our probabilistic analysis, we generated nested binomial distribution data using the digitized survival curve (see Figure 3) we derived from Stearns et al.[65] Specifically, we calculated the risk of mortality in each month over 1 year, conditional on having survived the previous months. For example, the probabilities of survival were 0.83 and 0.68 in month 1 and month 2, respectively. The conditional probability of mortality in month 2 for individuals who are still alive (i.e., who have survived month 1) can be calculated as (0.83 − 0.68)/0.83 = 0.18. Using this approach, we calculated the conditional probability of mortality for each month. Next, we simulated binomial data for month 1 and obtained the number of people who survived and died by the end of that month. Based on the number of people who survived month 1 and the conditional probability of mortality in month 2, we then simulated binomial distribution data for survival and mortality outcomes in month 2, month 3, and so forth. Based on the simulated survival data in each month, we calculate the probability of survival by the end of each month over 1 year. We repeated these steps 5,000 times for our probabilistic analysis. This approach kept the logic consistency of the survival curve (i.e., the probability of survival decreases over time).

Appendix 9: Letter of Information

LETTER OF INFORMATION

Ontario Health

Ontario Health is conducting a review of **Intrathecal Drug Delivery Systems (Pain Pumps) for people with cancer related pain**. The purpose is to understand whether this technology should be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers of those who have been diagnosed with cancer related pain and who may or may not have experience with intrathecal drug delivery systems (Pain Pumps).

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30-40 minutes of your time for a phone
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 30-40 minutes. It will be held over the telephone and with your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives on screening options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

Please ensure to avoid providing any identifiable information throughout the interview as there may be opportunity for inadvertent collection personal health information via our auto-recording and transcription process.

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however, no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project's completion, the records will be destroyed.

If you are sending us personal information by email, please be aware that electronic communication is not always secure and can be vulnerable to interception.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experiences.

FOR MORE INFORMATION, PLEASE CONTACT:

Appendix 10: Interview Guide

IDDS Patient Interview Guide

Care and Treatment Journey
History of cancer – type, diagnosis and background (general only)
Feelings when diagnosed?
Post-diagnosis journey (Impact)
Wait times
Impact on family

Decision-Making
What pain management options were offered?
Enough information going on pain management solutions? Risks vs benefits?
Mental health impacts

Pain Pump Experience
Information given about pain pump
How was the pain pump presented to you
Decision-making surrounding using the main pump
Maintenance of the pain pump
Access/barriers? Wait times, travel, out of pocket costs
Impact of pain pump

Pain Pump General Questions
Awareness of pain pump
Comfort level
Preference (pills vs pump)
Impact on qualify of life
Any equity/ethical concerns? (theoretically)
Anything else you want to add?

References

(1) Caraceni A, Portenoy RK, working group of the IASP Task Force on Cancer Pain. An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. Pain. 1999;82(3):263-74.

(2) Kroenke K, Theobald D, Wu J, Loza JK, Carpenter JS, Tu W. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. J Pain Symptom Manage. 2010;40(3):327-41.

(3) Bruera E, Kim HN. Cancer pain. JAMA. 2003;290(18):2476-9.

(4) van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage. 2016;51(6):1070-90.e9.

(5) Roberto A, Greco MT, Uggeri S, Cavuto S, Deandrea S, Corli O, et al. Living systematic review to assess the analgesic undertreatment in cancer patients. Pain Pract. 2022;22(4):487-96.

(6) Henley SJ, Singh SD, King J, Wilson RJ, O'Neil ME, Ryerson AB. Invasive cancer incidence and survival--United States, 2012. MMWR Morb Mortal Wkly Rep. 2015;64(49):1353-8.

(7) Glare PA, Davies PS, Finlay E, Gulati A, Lemanne D, Moryl N, et al. Pain in cancer survivors. J Clin Oncol. 2014;32(16):1739-47.

(8) World Health Organization. Cancer pain relief [Internet]. Geneva: The Organization; 1986 [cited 2022 Nov 7]. Available from: https://apps.who.int/iris/bitstream/handle/10665/43944/9241561009_eng.pdf?sequence=1&isAllowed=y

(9) Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012;13(2):e58-68.

(10) Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2017;7:CD012592.

(11) Miguel R. Interventional treatment of cancer pain: the fourth step in the World Health Organization analgesic ladder? Cancer Control. 2000;7(2):149-56.

(12) Burton AW, Hamid B. Current challenges in cancer pain management: does the WHO ladder approach still have relevance? Expert Rev Anticancer Ther. 2007;7(11):1501-2.

(13) Portenoy RK. Treatment of cancer pain. Lancet. 2011;377(9784):2236-47.

(14) Rizvi S, Kumar K. History and present state of targeted intrathecal drug delivery. Curr Pain Headache Rep. 2015;19(2):474.

(15) Galloway K, Staats PS, Bowers DC. Intrathecal analgesia for children with cancer via implanted infusion pumps. Med Pediatr Oncol. 2000;34(4):265-7.

(16) Mele C. Intrathecal pain pump for pediatric perverse oncological pain. J Pediatr Nurs. 2021;56:99-100.

(17) Lau J, Flamer D, Murphy-Kane P. Interventional anesthesia and palliative care collaboration to manage cancer pain: a narrative review. Can J Anaesth. 2020;67(2):235-46.

(18) Smith HS, Deer TR, Staats PS, Singh V, Sehgal N, Cordner H. Intrathecal drug delivery. Pain Physician. 2008;11(2 Suppl):S89-S104.

(19) Cohen SP, Dragovich A. Intrathecal analgesia. Anesthesiol Clin. 2007;25(4):863-82, viii.

(20) Bruel BM, Burton AW. Intrathecal therapy for cancer-related pain. Pain Med. 2016;17(12):2404-21.

(21) Bottros MM, Christo PJ. Current perspectives on intrathecal drug delivery. J Pain Res. 2014;7:615-26.
(22) Flowonix Medical Inc. About Prometra [Internet]. Mt. Olive (NJ): Flowonix Medical Inc.; 2022 [cited 2022 Nov 15]. Available from: https://flowonix.com/patientcare-giver/about-prometra
(23) Health Quality Ontario. Intrathecal drug delivery systems for cancer pain: a health technology assessment. Ont Health Technol Assess Ser. 2016;16(1):1-51.
(24) Health Quality Ontario. Intrathecal drug delivery systems for cancer pain and noncancer pain: OHTAC recommendation [Internet]. Toronto (ON): Queen's Printer for Ontario; 2016 [cited 2023 May]. Available from: http://www.hqontario.ca/evidence/publications-and-ohtacrecommendations/ontario-health-technology-assessment-series/cancer-noncancer-pain
(25) Smith TJ, Coyne PJ, Staats PS, Deer T, Stearns LJ, Rauck RL, et al. An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug-related toxicity, and possibly better survival compared with comprehensive medical management (CMM). Ann Oncol. 2005;16(5):825-33.
(26) University of Calgary Health Technology Assessment Unit. Neuromodulation for cancer and non-cancer pain [Internet]. Vancouver (BC): Health Technology Assessment Office, Province of British Columbia; 2018 [cited 2022 Oct 20]. Available from: https://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/heath-care-partners/health-authorities/bc-health-technology-assessments/neuromodulation-for-cancer-and-non-cancer-pain.pdf
(27) Deer TR, Hayek SM, Pope JE, Lamer TJ, Hamza M, Grider JS, et al. The Polyanalgesic Consensus Conference (PACC): recommendations for trialing of intrathecal drug delivery infusion therapy. Neuromodulation. 2017;20(2):133-54.
(28) Deer TR, Pope JE, Hayek SM, Lamer TJ, Veizi IE, Erdek M, et al. The Polyanalgesic Consensus Conference (PACC): recommendations for intrathecal drug delivery: guidance for improving safety and mitigating risks. Neuromodulation. 2017;20(2):155-76.
(29) Aman MM, Mahmoud A, Deer T, Sayed D, Hagedorn JM, Brogan SE, et al. The American Society of Pain and Neuroscience (ASPN) best practices and guidelines for the interventional management of cancer-associated pain. J Pain Res. 2021;14:2139-64.
(30) Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S, et al. The Polyanalgesic Consensus Conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. Neuromodulation. 2017;20(2):96-132.
(31) Specialised Commissioning Team, NHS England. Clinical comissioning policy: intrathecal pumps for treatment of severe cancer pain [Internet]. London: NHS England; 2015 [cited 2023 Feb 27]. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/07/Intrathecal-pumps-for-treatment-of-severe-cancer-pain.pdf
(32) Duarte R, Raphael J, Eldabe S. Intrathecal drug delivery for the management of pain and spasticity in adults: an executive summary of the British Pain Society's recommendations for best clinical practice. Br J Pain. 2016;10(2):67-9.
(33) McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40-6.
(34) Covidence (systematic review software) [Computer program]. Veritas Health Innovation. Melbourne (Australia). Available at: https://www.covidence.org/home.
(35) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol [Internet]. 2021 [cited 2021 May 27]; 134: 178-89. Available from: https://www.sciencedirect.com/science/article/pii/S0895435621000731

(36) Campbell and Cochrane Equity Methods Group. PROGRESS-Plus [Internet]. London: Cochrane; 2022 [cited 2023 Feb 28]. Available from: https://methods.cochrane.org/equity/projects/evidence-equity/progress-plus
(37) O'Neill J, Tabish H, Welch V, Petticrew M, Pottie K, Clarke M, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. J Clin Epidemiol. 2014;67(1):56-64.
(38) Spiegel MA, Chen GH, Solla AC, Hingula LP, Legler A, Gulati A. Evaluation of an intrathecal drug delivery protocol leads to rapid reduction of systemic opioids in the oncological population. J Palliat Med. 2021;24(3):418-22.
(39) Duarte R, Copley S, Nevitt S, Maden M, Al-Ali AM, Dupoiron D, et al. Effectiveness and safety of intrathecal drug delivery systems for the management of cancer pain: a systematic review and meta-analysis. Neuromodulation. 2023;26(6):1126-41.
(40) Whiting P, Savovic J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.
(41) Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook [Internet]. Hamilton (ON): Grade Working Group; 2013 [cited 2017 Dec]. Available from http://gdt.guidelinedevelopment.org/app/handbook/handbook.html.
(42) Kenfield M, Zacharias N, Abd-Elsayed A. Intrathecal drug delivery for the treatment of cancer-associated chronic pain in children. Neuromodulation. 2023;26(6):1153-63.
(43) Hayek SM, Deer TR, Pope JE, Panchal SJ, Patel VB. Intrathecal therapy for cancer and non-cancer pain. Pain Physician. 2011;14(3):219-48.
(44) Perruchoud C, Dupoiron D, Papi B, Calabrese A, Brogan SE. Management of cancer-related pain with intrathecal drug delivery: a systematic review and meta-analysis of clinical studies. Neuromodulation. 2023;26(6):1142-52.
(45) Camberlin C, San Miguel L, Smit Y, Post P, Gerkens S, De Laet C. Neuromodulation for the management of chronic pain: implanted spinal cord stimulators and intrathecal analgesic delivery pumps [Internet]. Brussels: Belgian Health Care Knowledge Centre; 2012 [cited 2023 Jan 3]. Available from: https://kce.fgov.be/sites/default/files/2021-11/KCE_189C_neuromodulation_chronic_pain_0.pdf
(46) Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boortz-Marx RL, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. J Clin Oncol. 2002;20(19):4040-9.
(47) Smith TJ, Coyne PJ. Implantable drug delivery systems (IDDS) after failure of comprehensive medical management (CMM) can palliate symptoms in the most refractory cancer pain patients. J Palliat Med. 2005;8(4):736-42.
(48) Becker R, Jakob D, Uhle EI, Riegel T, Bertalanffy H. The significance of intrathecal opioid therapy for the treatment of neuropathic cancer pain conditions. Stereotact Funct Neurosurg. 2000;75(1):16-26.
(49) Brogan SE, Winter NB. Patient-controlled intrathecal analgesia for the management of breakthrough cancer pain: a retrospective review and commentary. Pain Med. 2011;12(12):1758-68.
(50) Chen GH, Spiegel MA, Magram YC, Baig E, Clement K, Laufer I, et al. Evaluation of fixed intrathecal bupivacaine infusion doses in the oncologic population. Neuromodulation. 2020;23(7):984-90.
(51) Dupoiron D, Leblanc D, Demelliez-Merceron S, Bore F, Seegers V, Dubois PY, et al. Optimizing initial intrathecal drug ratio for refractory cancer-related pain for early pain relief. A retrospective monocentric study. Pain Med. 2019;20(10):2033-42.

(52) Erdine S, Oaeztakcin S, Yücel A. Intrathecal morphine delivered by implanted manual pump for cancer pain. Pain Digest. 1996;6:161-5.
(53) Onofrio BM, Yaksh TL. Long-term pain relief produced by intrathecal morphine infusion in 53 patients. J Neurosurg. 1990;72(2):200-9.
(54) Reig E, Abejon D. Continuous morphine infusion: a retrospective study of efficacy, safety, and demographic variables. Neuromodulation. 2009;12(2):122-9.
(55) Sayed D, Monroe F, Orr WN, Phadnis M, Khan TW, Braun E, et al. Retrospective analysis of intrathecal drug delivery: outcomes, efficacy, and risk for cancer-related pain at a high volume academic medical center. Neuromodulation. 2018;21(7):660-3.
(56) Scanlon MM, Gazelka HM, Moeschler SM, Hoelzer BC, Hooten WM, Bendel MA, et al. Surgical site infections in cancer patients with intrathecal drug delivery devices. Pain Med. 2017;18(3):520-5.
(57) Sindt JE, Odell DW, Dalley AP, Brogan SE. Initiation of intrathecal drug delivery dramatically reduces systemic opioid use in patients with advanced cancer. Neuromodulation. 2020;23(7):978-83.
(58) Yegul I, Uyar M, Erhan E. Implanted drug delivery systems for spinal administration of morphine in cancer pain relief. Agri-Istanbul. 1999;11:13-21.
(59) Brogan SE, Winter NB, Okifuji A. Prospective observational study of patient-controlled intrathecal analgesia: impact on cancer-associated symptoms, breakthrough pain control, and patient satisfaction. Reg Anesth Pain Med. 2015;40(4):369-75.
(60) Brogan SE, Sindt JE, Jackman CM, White J, Wilding V, Okifuji A. Prospective association of serum opioid levels and clinical outcomes in patients with cancer pain treated with intrathecal opioid therapy. Anesth Analg. 2020;130(4):1035-44.
(61) Carvajal G, Dupoiron D, Seegers V, Lebrec N, Bore F, Dubois PY, et al. Intrathecal drug delivery systems for refractory pancreatic cancer pain: observational follow-up study over an 11-year period in a comprehensive cancer center. Anesth Analg. 2018;126(6):2038-46.
(62) Cheng Y, Wang L, Zha Z, Zhao X. Effects of family integrated care on refractory cancer-related pain receiving intrathecal morphine pump therapy: a cohort study. Ann Palliat Med. 2020;9(4):2163-70.
(63) Dupoiron D, Lefebvre-Kuntz D, Brenet O, de Bourmont S, Grelon F, Dixmeria F, et al. Refractory cancer pain and intrathecal infusion: experience of three cancer management centers. Douleurs : Evaluation - Diagnostic - Traitement. 2011;12(3):140-6.
(64) Rauck RL, Cherry D, Boyer MF, Kosek P, Dunn J, Alo K. Long-term intrathecal opioid therapy with a patient-activated, implanted delivery system for the treatment of refractory cancer pain. J Pain. 2003;4(8):441-7.
(65) Stearns LM, Abd-Elsayed A, Perruchoud C, Spencer R, Hammond K, Stromberg K, et al. Intrathecal drug delivery systems for cancer pain: an analysis of a prospective, multicenter product surveillance registry. Anesth Analg. 2020;130(2):289-97.
(66) Tobias JD. Applications of intrathecal catheters in children. Paediatr Anaesth. 2000;10(4):367-75.
(67) Saroyan JM, Schechter WS, Tresgallo ME, Granowetter L. Role of intraspinal analgesia in terminal pediatric malignancy. J Clin Oncol. 2005;23(6):1318-21.
(68) Bengali R, Huang MS, Gulur P. The use of an intrathecal pump to manage intractable cancer pain in a pediatric patient: a case report. J Pediatr Hematol Oncol. 2014;36(3):e162-4.
(69) Kim E, Gamble S, Schwartz A, Cucchiaro G. Neuromodulation in pediatrics: case series. Clin J Pain. 2018;34(11):983-90.
(70) Smith SM, Dworkin RH, Turk DC, McDermott MP, Eccleston C, Farrar JT, et al. Interpretation of chronic pain clinical trial outcomes: IMMPACT recommended considerations. Pain. 2020;161(11):2446-61.

(71) Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.
(72) Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018;23(2):60-3.
(73) International Association for the Study of Pain. Access to pain managment: declaration of Montreal [Internet]. Washington (DC): The Association; 2010 [cited 2023 Mar 9]. Available from: https://www.iasp-pain.org/advocacy/iasp-statements/access-to-pain-management-declaration-of-montreal/
(74) National Institute for Health and Care Excellence. Process and methods guides. Appendix I: Quality appraisal checklist–economic evaluations [Internet]. London: The Institute; 2012 [cited 2016 Jan]. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-i-quality-appraisal-checklist-economic-evaluations
(75) University of Calgary. Neuromodulation for Cancer and Non-Cancer Pain. 2018 July.
(76) Stearns LJ, Hinnenthal JA, Hammond K, Berryman E, Janjan NA. Health services utilization and payments in patients with cancer pain: a comparison of intrathecal drug delivery vs. conventional medical management. Neuromodulation: Technology at the Neural Interface. 2016;19(2):196-205.
(77) Stearns LJ, Narang S, Albright RE, Hammond K, Xia Y, Richter HB, et al. Assessment of health care utilization and cost of targeted drug delivery and conventional medical management vs conventional medical management alone for patients with cancer-related pain. JAMA Network Open. 2019;2(4):e191549-e.
(78) Brogan SE, Winter NB, Abiodun A, Safarpour R. A cost utilization analysis of intrathecal therapy for refractory cancer pain: identifying factors associated with cost benefit. Pain Medicine. 2013;14(4):478-86.
(79) Stearns LJ, Hinnenthal JA, Hammond K, Berryman E, Janjan NA. Health services utilization and payments in patients with cancer pain: a comparison of intrathecal drug delivery vs. conventional medical management. Neuromodulation. 2016;19(2):196-205.
(80) Stearns LJ, Narang S, Albright RE Jr, Hammond K, Xia Y, Richter HB, et al. Assessment of health care utilization and cost of targeted drug delivery and conventional medical management vs conventional medical management alone for patients with cancer-related pain. JAMA Network Open. 2019;2(4):e191549.
(81) Brogan SE, Winter NB, Abiodun A, Safarpour R. A cost utilization analysis of intrathecal therapy for refractory cancer pain: identifying factors associated with cost benefit. Pain Med. 2013;14(4):478-86.
(82) King G, Nielsen R. Why propensity scores should not be used for matching. Political Analysis. 2019;27(4):435-54.
(83) Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.
(84) Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): The Agency; 2017. p. 76.
(85) Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2015.
(86) WebPlotDigitizer [Internet]. Oakland (CA): Ankit Rohatgi; c2010-2022 [cited 2023 Jun]. Available from: https://automeris.io/WebPlotDigitizer/
(87) Ministry of Health. Schedule of benefits: physician services under the Health Insurance Act (effective April 1, 2023) [Internet]. Toronto (ON): Queen's Printer for Ontario; 2023 Mar [cited

2023 Jun]. Available from: https://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20210314.pdf
(88) Scottish Intercollegiate Guidelines Network. Control of pain in adults with cancer: a national clinical guideline. Edinburgh: The Network; 2008.
(89) Alberta Health Services. Cancer pain: clinical practice guideline supp-012 [Internet]. Edmonton (AB): Alberta Health Services; 2018 Sep [cited 2023 Jun]. Available from: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-supp012-cancer-pain.pdf
(90) Canadian Institute for Health Information. National Prescription Drug Utilization Information System: plan information: sumary of changes [Internet]. Ottawa (ON): The Institute; 2020 Jul 31 [cited 2023 Jun]. Available from: https://secure.cihi.ca/free_products/npduis-plan-information-summary-of-changes-2020-en.pdf
(91) Ministry of Health. Ontario Drug Benefit Program: dispensing fees [Internet]. Toronto (ON): Queen's Printer for Ontario 2014 Apr 7 [cited 2023 May 8]. Available from: https://www.health.gov.on.ca/en/public/programs/drugs/programs/odb/opdp_dispensing_fees.aspx
(92) Thunder Bay Regional Health Sciences Foundation. Equipment funded [Internet]. Thunder Bay (ON): The Foundation; 2022 [cited 2023 Jun 2]. Available from: https://www.healthsciencesfoundation.ca/equipment-funded#impact2022
(93) Patient cost estimator [Internet]. Ottawa (ON): Canadian Institute for Health Information; c1996-2023 [cited 2023 Apr 20]. Available from: https://www.cihi.ca/en/patient-cost-estimator
(94) Krahn M, Miller F, Bayoumi A, Brooker AS, Wagner F, Winsor S, et al. Development of the Ontario decision framework: a values based framework for health technology assessment. Int J Technol Assess Health Care. 2018;34(3):290-9.
(95) Interactive opioid tool: opioid-related mobidity and mortality in Ontario [Internet]. Toronto (ON) Public Health Ontario; c2023 [updated 2023 Mar 31; cited 2023 May 5]. Available from: https://www.publichealthontario.ca/en/data-and-analysis/substance-use/interactive-opioid-tool#/drug
(96) Grywacheski V, O'Connor S, Louie K. Opioid-related harms in Canada. Healthc Q. 2018;20(4):10-2.
(97) Fischer B, Bibby M, Bouchard M. Non-medical use and diversion of psychotropic prescription drugs in North America: a review of sourcing routes and control measures. Addiction. 2010;105(12):2062-70.
(98) Wichmann AB, Adang EM, Stalmeier PF, Kristanti S, Van den Block L, Vernooij-Dassen MJ, et al. The use of quality-adjusted life years in cost-effectiveness analyses in palliative care: mapping the debate through an integrative review. Palliat Med. 2017;31(4):306-22.
(99) Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S, et al. The Polyanalgesic Consensus Conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. Neuromodulation: Technology at the Neural Interface. 2017;20(2):96-132.
(100) Prager J, Deer T, Levy R, Bruel B, Buchser E, Caraway D, et al. Best practices for intrathecal drug delivery for pain. Neuromodulation: Technology at the Neural Interface. 2014;17(4):354-72.
(101) Barham L. Public and patient involvement at the UK National Institute for Health and Clinical Excellence. Patient. 2011;4(1):1-10.
(102) Messina J, Grainger DL. A pilot study to identify areas for further improvements in patient and public involvement in health technology assessments for medicines. Patient. 2012;5(3):199-211.
(103) Ontario Health Technology Advisory Committee Public Engagement Subcommittee. Public engagement for health technology assessment at Health Quality Ontario—final report from the Ontario Health Technology Advisory Committee Public Engagement Subcommittee [Internet].

Toronto (ON): Queen's Printer for Ontario; 2015 Apr [cited 2018 Apr 30]. Available from: http://www.hqontario.ca/Portals/0/documents/evidence/special-reports/report-subcommittee-20150407-en.pdf
(104) Selva A, Sola I, Zhang Y, Pardo-Hernandez H, Haynes RB, Martinez Garcia L, et al. Development and use of a content search strategy for retrieving studies on patients' views and preferences. Health Qual Life Outcomes. 2017;15(1):126.
(105) Kvale S. Interviews: an introduction to qualitative research interviewing. Thousand Oaks (CA): Sage; 1996.
(106) Kuzel AJ. Sampling in qualitative inquiry. In: Miller WL, Crabtree BF, editors. Doing qualitative research. Thousand Oaks (CA): Sage; 1999. p. 33–45.
(107) Morse J. Emerging from the data: cognitive processes of analysis in qualitative research. In: Morse J, editor. Critical issues in qualitative research methods. Thousand Oaks (CA): Sage; 1994. p. 23-41.
(108) Patton MQ. Qualitative research and evaluation methods. 3rd ed. Thousand Oaks (CA): Sage; 2002.
(109) Strauss AL, Corbin JM. Basics of qualitative research: techniques and procedures of developing a grounded theory. 2nd ed. Thousand Oaks (CA): Sage; 1998.
(110) Health Technology Assessment International. Introduction to health technology assessment [Internet]. Edmonton (AB): Health Technology Assessment International; 2015 [cited 2018 Apr 30]. Available from: http://www.htai.org/fileadmin/HTAi_Files/ISG/PatientInvolvement/v2_files/Resource/PCISG-Resource-Intro_to_HTA__KFacey__Jun13.pdf
(111) Strauss AL, Corbin JM. Grounded theory research: procedures, canons, and evaluative criteria. Qual Sociol. 1990;13(1):3-21.
(112) Strauss AL, Corbin JM. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. Thousand Oaks (CA): Sage; 1994. p. 273-85.
(113) NVivo qualitative data analysis software. QSR International. Doncaster, Victoria (Australia). Available at: https://www.qsrinternational.com/nvivo/home.
(114) EUnetHTA Joint Action 2 Work Package 8, HTA Core Model, version 3.0 [Internet]. European Network for Health Technology Assessment; c2016 [cited 2023 Jan 13]. Available from: http://www.htacoremodel.info/BrowseModel.aspx
(115) Benkhalti M, Espinoza M, Cookson R, Welch V, Tugwell P, Dagenais P. Development of a checklist to guide equity considerations in health technology assessment. Int J Technol Assess Health Care. 2021;37(1).
(116) CADTH search filters database [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; c2023 [cited 2023 Mar]. Available from: https://searchfilters.cadth.ca/
(117) EndNote [Computer program]. London: Clarivate; 2020.
(118) Sandelowski M. Whatever happened to qualitative description? Res Nurs Health. 2000;23(4):334-40.
(119) Smyth C, Ahmadzai N, Wentzell J, Pardoe A, Tse A, Nguyen T, et al. Intrathecal Analgesia for Chronic Refractory Pain: Current and Future Prospects. Drugs. 2015;75(17):1957-80.
(120) NHS England. Clinical commissioning policy: intrathecal pumps for treatment of severe chronic pain [Internet]. London: NHS England; 2015 [cited 2023 Jan 13]. Available from: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/d08pa-intrathecal-pumps-oct15.pdf
(121) Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. CA Cancer J Clin. 2018;68(3):182-96.
(122) Rattani SA. Ethical perspective of cancer pain management. Int J Nurs Ed. 2015;7(3):91.

(123) Brennan F, Lohman D, Gwyther L. Access to pain management as a human right. Am J Public Health. 2019;109(1):61-5.
(124) Whedon M, Ferrell BR. Professional and ethical considerations in the use of high-tech pain management. Oncol Nurs Forum. 1991;18(7):1135-43.
(125) Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. CA: a Cancer Journal for Clinicians. 2018;68(3):182-96.
(126) Cahana A, Arigoni F, Robert L. Attitudes and beliefs regarding the role of interventional pain management at the end-of-life among caregivers: a 4-year perspective. Pain Pract. 2007;7(2):103-9.
(127) Telusca N, Gaisey JN, Woods C, Khan JS, Mackey S. Strategies to promote racial healthcare equity in pain medicine: a call to action. Pain Med. 2022;23(7):1225-30.
(128) Brennan PM, Whittle IR. Intrathecal baclofen therapy for neurological disorders: a sound knowledge base but many challenges remain. Br J Neurosurg. 2008;22(4):508-19.
(129) Horrill T, Lavoie J, Martin D, Schultz A. Places and spaces: a critical analysis of cancer disparities and access to cancer care among First Nations Peoples in Canada. Witness. 2020;2(2):104-23.
(130) Kongsgaard U, Kaasa S, Dale O, Ottesen S, Nordoy T, Hessling SE, et al. Palliative treatment of cancer-related pain: report from Norwegian Knowledge Centre for the Health Services (NOKC) No. 09-2005 [Internet]. Oslo: Norwegian Institute of Public Health; 2005 [cited 2023 Jan 20]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK464794/
(131) Brogan SE, Sindt JE, Odell DW, Gulati A, Dupoiron D. Controversies in intrathecal drug delivery for cancer pain. Reg Anesth Pain Med. 2022;48(6):319-25.
(132) Mastenbroek TC, Kramp-Hendriks BJ, Kallewaard JW, Vonk JM. Multimodal intrathecal analgesia in refractory cancer pain. Scand J Pain. 2017;14:39-43.
(133) McCarron TL, MacKean G, Dowsett LE, Saini M, Clement F. Patients' experience with and perspectives on neuromodulation for pain: a systematic review of the qualitative research literature. Pain. 2020;161(8):1708-15.
(134) Hawley P, Beddard-Huber E, Grose C, McDonald W, Lobb D, Malysh L. Intrathecal infusions for intractable cancer pain: a qualitative study of the impact on a case series of patients and caregivers. Pain Res Manag. 2009;14(5):371-9.
(135) Xing F, Yong RJ, Kaye AD, Urman RD. Intrathecal drug delivery and spinal cord stimulation for the treatment of cancer pain. Curr Pain Headache Rep. 2018;22(2):11.
(136) Aigner CJ, Hernandez M, Koyyalagunta L, Novy D. The association of presurgery psychological symptoms with postsurgery pain among cancer patients receiving implantable devices for pain management. Support Care Cancer. 2014;22(9):2323-8.
(137) Allano G, George B, Minello C, Burnod A, Maindet C, Lemaire A. Strategies for interventional therapies in cancer-related pain—a crossroad in cancer pain management. Support Care Cancer. 2019;27:3133-45.
(138) Patel N, Huddart M, Makins H, Mitchell T, Gibbins JL, Graterol J, et al. "Was it worth it?" Intrathecal analgesia for cancer pain: a qualitative study exploring the views of family carers. Palliat Med. 2018;32(1):287-93.
(139) Galica R, Hayek SM, Veizi IE, Lawrence MM, Khalil AA, McEwan MT. Sudden intrathecal drug delivery device motor stalls: a case series. Reg Anesth Pain Med. 2016;41(2):135-9.
(140) Stearns LM, Abd-Elsayed A, Perruchoud C, Spencer R, Hammond K, Stromberg K, et al. Intrathecal Drug Delivery Systems for Cancer Pain: An Analysis of a Prospective, Multicenter Product Surveillance Registry. Anesth Analg. 2020;130(2):289-97.
(141) Loeser JD. Response to letter by Verdolin...Verdolin MH. Response to ethics forum: low dose targeted drug approaches need highlighting and consideration. Pain Medicine. 2015;16:19–20. Pain Med. 2015;16(1):21.

(142) Smyth C, Ahmadzai N, Wentzell J, Pardoe A, Tse A, Nguyen T, et al. Intrathecal analgesia for chronic refractory pain: current and future prospects. Drugs. 2015;75(17):1957-80.
(143) Stoltzfus DP, Stamatos JM. An appraisal of the ethical issues involved in high-technology cancer pain relief. J Clin Ethics. 1991;2(2):113-5.
(144) Xing F, Yong RJ, Kaye AD, Urman RD. Intrathecal drug delivery and spinal cord stimulation for the treatment of cancer pain. Curr Pain Headache Rep. 2018;22:1-7.
(145) International Network of Agencies for Health Technology Assessment. HTA glossary [Internet]. Edmonton (AB): The Network; 20XX [cited 20XX Mon XX]. Available from: http://htaglossary.net/HomePage.
(146) Ontario Health. Ontario Health's equity, inclusion, diversity and anti-racism framework [Internet]. Toronto (ON): Queen's Printer for Ontario; 2022 [cited 2023 Mar 22]. Available from: https://www.ontariohealth.ca/sites/ontariohealth/files/2020-12/Equity%20Framework.pdf
(147) Cochrane Equity Methods Group. Evidence for equity: PROGRESS-Plus [Internet]. London: The Group; 2020 [cited 2023 Jun]. Available from: https://methods.cochrane.org/equity/projects/evidence-equity/progress-plus
(148) World Health Organization. Social determinants of health: key concepts [Internet]. Geneva: The Organization; 2013 May 7 [cited 2022 Mar 22]. Available from: https://www.who.int/news-room/questions-and-answers/item/social-determinants-of-health-key-concepts
(149) Canadian Institute for Health Information. Canadian Classification of Health Interventions (CCI): alphabetical index and tabular list. Ottawa (ON): The Institute; 2022.
(150) Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. CMAJ. 2017;189(18):E659-E66.
(151) College of Physicians and Surgeons of British Columbia. Guidelines: methadone for analgesia [Internet]. Vancouver (BC): The College; 2022 Aug 15 [cited 2023 Jun]. Available from: https://www.cpsbc.ca/files/pdf/DP-Methadone-for-Analgesia-Guidelines.pdf
(152) Government of Canada. Fentanyl transdermal systems - new changes to the dose conversion guidelines - for health care professionals [Internet]. Ottawa (ON): Government of Canada; 2010 Mar 10 [cited 2023 May 5]. Available from: https://recalls-rappels.canada.ca/en/alert-recall/fentanyl-transdermal-systems-new-changes-dose-conversion-guidelines-health-care
(153) Ministry of Health, Ministry of Long-Term Care. Ontario drug benefit formulary/comparative drug index [Internet]. Toronto (ON): Queen's Printer for Ontario. 2023 [cited 2023 Aug 1]. Available from: https://www.formulary.health.gov.on.ca/formulary

About Us

We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

For more information about Ontario Health, visit OntarioHealth.ca.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

ontariohealth.ca/equity-inclusion-diversity-and-anti-racism

About the Ontario Health Technology Advisory Committee

How to Obtain Reports From the Ontario Health Technology Assessment Series

Disclaimer

Ontario Health
500–525 University Avenue
Toronto, Ontario
M5G 2L3
Toll Free: 1-877-280-8538
TTY: 1-800-855-0511
Email: OH-HQO_HTA@OntarioHealth.ca
hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4868-7654-9 (PDF)