Evidence-Based Series 18-1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Intraspinal Techniques for Pain Management in Cancer Patients

J. Myers, V. Chan, V. Jarvis, C. Walker-Dilks, and the Palliative Care Clinical Program

Report Date: May 5, 2009

An assessment conducted in November 2013 deferred the review of Evidence based Series (EBS) 18-1, which means that the document remains current until it is assessed again next year.

EBS 18-1 is comprised of 3 sections and is available on the CCO website (http://www.cancercare.on.ca)

PEBC Palliative Care page at: http://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=44668

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Phone: 905-527-4322 ext. 42822    Fax: 905-526-6775    E-mail: ccopgi@mcmaster.ca


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Intraspinal Techniques for Pain Management in Cancer Patients: Guideline Recommendations

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QUESTIONS
1. In patients with cancer-related pain, what is the effectiveness of intraspinal pain management techniques?
2. What are the indications for use of intraspinal analgesia?
3. What are the key implementation considerations that should be considered when offering intraspinal analgesia to cancer patients? In particular, what aspects of the practice setting, practice team, and education and training of health professionals, patients, and family need to be addressed?

TARGET POPULATION
Patients with cancer with disease-related pain. Procedure-related pain was not of interest.

INTENDED USERS
This guideline is targeted for:
2. Clinicians involved in the care of cancer patients who are eligible for intraspinal analgesic intervention and who would make referrals to the appropriate care team.

RECOMMENDATIONS AND KEY EVIDENCE
Recommendations
I. Clinical Effectiveness
1. Evidence supports the use of intraspinal analgesia for certain patients in the management of their cancer pain.
2. Intraspinal analgesia with an opioid alone, local anesthetic alone, or opioid and local anesthetic combined is each a reasonable option.
II. **Indications for Use of Intraspinal Analgesia**

Patient selection and eligibility
1. Intractable severe pain despite aggressive pharmacologic interventions by conventional administration routes (oral, rectal, transdermal, subcutaneous, and intravenous)
2. Dose-limiting side effects experienced from conventional administration routes

Contraindications
1. Active systemic or local infection at the site of catheter insertion or pump implantation
2. Bleeding diathesis at the time of procedure
3. Increased intracranial pressure
4. Spinal pathology that may prevent successful placement (e.g., hardware) or lead to adverse effects (i.e., severe spinal stenosis)

Additional Considerations
1. Careful consideration must be given to patient selection
2. The availability of appropriate equipment, supplies, expertise, and 24-hour coverage for clinical support
3. The expectation that intraspinal analgesia would improve a patient’s quality of life and level of function
4. Informed consent has been given by patient or substitute decision maker
5. Availability of home care nursing and medical support for intraspinal catheter care
6. Patient general medical condition is amenable to intraspinal analgesia
7. For a fully implanted system, a screening trial is recommended; for intraspinal analgesia using an external pump, a trial is not necessary

III. **Key Implementation Considerations**

1. Long-term intraspinal analgesic treatment can be provided by epidural analgesia or intrathecal (subarachnoid) analgesia. For both routes of administration, there are basically three types of intraspinal delivery systems: externalized system, partially externalized system, and totally internalized implanted system.
2. Planned length of use should be a determining factor for choosing which pump to use.
3. Medication must be preservative free.
4. Straight alcohol or acetone should never be used for site preparation or cleansing. Disinfectants containing alcohol may be used, but must be allowed to dry prior to use.
5. Patients require admission for intraspinal placement, and the facility must have health personnel who are competent in the care of patients with intraspinal analgesia and policy and procedures that are available and approved.
6. While in hospital post-procedure, routine monitoring of patients is required for all key clinical indicators including vital signs, pain, sensory and motor functioning, and complications and side effects. Routine monitoring of insertion site is also required.
7. A clear discharge plan is required as defined by protocols, that includes roles and responsibilities of care providers to ensure timely response should complications arise and appropriate patient follow-up by members of the team.
8. The care team should consist of interventional pain physicians, nurses, palliative care physicians, pharmacists, and primary care providers.
9. All members of the team should have appropriate and specialized training in accordance with professional college/association standards and certification.
10. Patients and family members should be fully informed in all aspects of intrathecal pain management care. This includes knowing whom and when to call for support, should complications arise.

11. Strict aseptic conditions must be maintained in all aspects of intraspinal analgesia administration.

12. All equipment should be compatible with epidural and intrathecal use (pump, tubing, catheter, solution bag, dressing, etc), must be appropriately labelled (different colours for epidural and intrathecal), and should be dated at time of equipment change.

13. Patients should have a MedicAlert emblem that alerts healthcare professionals to the presence of an intraspinal device in emergency situations.

For the complete summary of implementation issues and considerations, readers are referred to Appendices B through M in Section 2: Evidentiary Base of this document.

**Key Evidence**

The database literature search yielded two systematic reviews, one consensus document, and 12 randomized controlled trials (RCTs) that addressed the questions of clinical effectiveness and clinical indications. The use of intraspinal techniques was effective in controlling pain in patients with cancer and noncancer pain who no longer achieve adequate pain control by other routes. For pain control, intraspinal analgesia was as effective as or better than conventional medical management and was generally associated with fewer side effects. Furthermore, the addition of a local anesthetic to an opioid improved analgesic efficacy and reduced the dose requirements for either drug alone. However, there is insufficient evidence to recommend one drug option or regimen over another.

The systematic review and RCT evidence varied in terms of interventions tested and methodological quality. Insufficient evidence existed to recommend one particular intraspinal technique over another or to identify the optimal intraspinal medication. However, the evidence showed that intraspinal analgesia was effective in controlling pain in patients with cancer who could no longer achieve pain relief by other methods.

The environmental scan yielded eight practice guidelines, four local practice algorithms, and one practice standard that addressed the implementation issues related to patient selection, contraindications, monitoring, aftercare, follow-up, hospital discharge, equipment, practice team, professional competencies, patient education, and/or patient safety.

**RELATED GUIDELINES**

- EBS 16-2 *Cancer-Related Pain Management*
- EBS 19-1 *Advance Care Planning with Cancer Patients*
- EBS 19-2 *Provider-patient Communication*
- EBS 16-1 *Managing Central Venous Access Devices in Cancer Patients*
- EBS 13-8 *The Use of Gabapentin and Tricyclic Antidepressants in the Treatment of Neuropathic Pain in Cancer Patients*

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Phone: 905-527-4322 ext. 42822  Fax: 905 526-6775
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INTRODUCTION
Through advances in knowledge and use of disease-modifying therapies, patients with cancer are living longer. Cancer-related pain, however, remains poorly managed (1). In an effort to standardize and improve cancer pain management, the World Health Organization (WHO) endorsed a three-step approach outlining the use of opioids and adjuvant medications (2). Because many of the cancer-related pain syndromes are complex, a significant number of patients continue to experience refractory pain despite adherence to the WHO guidelines (3). In response to this, a revised approach was released by the WHO in 1996 identifying the fourth step, known as “invasive therapy” (4). Intraspinal (epidural or intrathecal) analgesia is an example of such a therapy.

Intraspinal catheters have been in routine use for decades in various surgical and anesthesia settings. In an effort to more specifically target pain pathways via the spinal cord, clinicians in the mid 1970s successfully introduced intraspinal catheter insertion and subsequent analgesic infusion as an effective intervention in the setting of refractory cancer pain.

The delivery of intraspinal pain control is currently dependent on local policies and procedures and the interest and competence of interventional pain physicians, palliative care physicians, nurses, and family physicians in this field of care.
This review is intended to examine the clinical evidence related to intraspinal analgesia as well as outline the resources required to support patient care before, during, and after intraspinal analgesia administration in the setting of cancer-related pain.

METHODS

Evidence was selected and reviewed by a three-member working group derived from the CCO Palliative Care Clinical Program that included a palliative care physician, a palliative care nurse, and an interventional pain physician.

This systematic review is a convenient and up-to-date source of the best available evidence on intraspinal pain management for cancer-related pain. The body of evidence in this review is primarily comprised of RCT and systematic review data to answer the question of effectiveness, and guidelines on intraspinal pain management techniques from regional, national, and international agencies to answer questions pertaining to physical and human resource requirements. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

To inform the evidence base supporting the clinical effectiveness of intraspinal pain techniques, MEDLINE (1950 to May, week 2, 2008), EMBASE (1980 to week 20, 2008), CINAHL (1982 to week 3, 2008), and the Cochrane Library were searched using the search terms shown in Table 1. The search strategies are shown in Appendix A.

Table 1. Literature search strategy for clinical effectiveness.

<table>
<thead>
<tr>
<th>Search date</th>
<th>Database</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 May 2008</td>
<td>MEDLINE</td>
<td>Spinal injections; intrathecal, intraspinal, epidural textwords; pain; neoplasms; carcinoma; neoplasm, carcinoma, oncology textwords; randomized controlled trials, clinical trials; systematic reviews, meta-analysis; practice guidelines.</td>
</tr>
<tr>
<td>22 May 2008</td>
<td>EMBASE</td>
<td></td>
</tr>
<tr>
<td>23 May 2008</td>
<td>CINAHL</td>
<td></td>
</tr>
<tr>
<td>23 May 2008</td>
<td>Cochrane Library</td>
<td>Intraspinal; pain; intrathecal; epidural; cancer</td>
</tr>
</tbody>
</table>

In addition, an environmental scan was undertaken to search for clinical practice guidelines and resource documents (non-indexed) using the Google™ search engine on the Internet. This scan was targeted at a list of organizations known to develop evidence-based practice guidelines of good quality or of relevance to the Ontario context.

Table 2. Guideline and Resource documents - targeted environmental scan.

| NHS national Institute for Health and clinical Excellence (NICE) |
| Scottish Intercollegiate Guidelines Network (SIGN) |
| American Society of Clinical Oncology (ASCO) |
| National Comprehensive Cancer Network (NCCN) |
| National Health and Medical Research Council Australia |
| New Zealand Guidelines Group |
| BC Cancer Agency |
| Alberta Cancer Board |
| Saskatchewan Cancer Agency |
| Cancer Care Manitoba |
| Cancer Care Nova Scotia |
Finally, to inform some of the organizational and implementation considerations, an untargeted search to find resource documents of relevant oncology, pain management, and anesthesiology professional organizations was undertaken.

The reference lists of all retrieved documents were scanned for additional relevant articles and working group members were asked about local guidelines, standards, and procedure manuals of which they were aware.

**Selection Criteria**

The following selection criteria were used to evaluate the clinical effectiveness literature:

1. study design: clinical practice guidelines, systematic reviews of RCTs, and RCTs
2. patient population: cancer patients (any age, any diagnosis) with cancer-related pain
3. intervention and comparisons:
   - intraspinal techniques alone or in combination versus (vs.) other interventions (e.g., medical management) alone or in combination
   - different intraspinal techniques
   - external pumps vs. internal pumps
   - timing of intraspinal techniques
4. outcomes: pain measured using a validated scale

Studies or reviews on the use of intraspinal techniques for procedure-related pain or techniques other than epidural or intrathecal analgesia (e.g., intracerebroventricular) were not included. Comments, letters, editorials, case reports, news, and non-English language articles were excluded.

To inform recommendations on clinical indications and organizational and implementation issues, clinical practice guidelines and resources documents (policy statements, position papers, practice parameters, care pathways, and manuals) were considered if they commented on at least one of: patient selection, contraindications, monitoring, aftercare, follow-up, hospital discharge, equipment, practice team, professional competencies, patient education and patient safety.

**Synthesizing the Evidence**

Meta-analysis of the included studies was considered where clinically homogenous studies reported comparable outcomes. However, the identified studies were not homogeneous due to dissimilar administration routes, comparison groups, and outcome measures, so no meta-analysis was performed.

**RESULTS**

**Literature Search Results**

Three systematic reviews (6-8) and three consensus conferences (one an update of a previous) (9,10,37), and 12 RCTs (11-22), met the selection criteria of studies examining clinical effectiveness. Although the systematic reviews and consensus conferences included some relevant RCTs, no single systematic review or consensus conference included all relevant RCTs or sufficiently discussed the effectiveness of intraspinal analgesia for cancer-related pain to support recommendations. Further, while all included cancer patients, only two (7,8) systematic reviews and one (10) consensus conference commented specifically on or presented separate data specifically relevant to this population. The remainder combined studies across all patient populations and will, therefore, not be discussed further.

Of the 12 RCTs, six compared intraspinal techniques alone or in combination with other interventions alone or in combination, four compared different intraspinal medications, and two compared different intraspinal techniques. Indicators of quality extracted from each
study were publication status (full publication or meeting abstract), allocation concealment, blinding, statement of statistical power or sample size calculation, intention-to-treat analysis, and statement of sponsorship or funding.

Characteristics of the included systematic reviews, consensus conferences, and RCTs, including quality features, are in Tables 3 to 5.

The environmental scan yielded 13 documents that were summarized and reviewed for quality and their utility in informing recommendations on the delivery of intraspinal pain management: eight documents were practice guidelines (Oncology Nursing Society [ONS], British Pain Society [BPS], Cancer Care Nova Scotia [CCNS], Scottish Intercollegiate Guidelines Network [SIGN], Singapore, American Pain Society [APS], National Comprehensive Cancer Network [NCCN], and American Society of Anesthesiologists [ASA] [23-30]), four were local internal-use clinical care algorithms or policy and procedure documents (Calgary, Cornwall, Ottawa, and St Wilfrid’s [31-34]), and one was a practice standard (Infusion Nursing Standards [INS] [35]). The eight practice guidelines were evaluated independently by two reviewers using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument (36) (Table 6). As can be seen, the guidelines varied in quality; however, the majority were either recommended or strongly recommended. Further, the rigour of development score (domain considered most important by the PEBC) exceed 90% for two of the groups. The remaining five reports were not evaluated for quality, as there is not an agreed-upon standard for these types of resources.
Table 3. Characteristics of systematic reviews and consensus conferences.

<table>
<thead>
<tr>
<th>Review</th>
<th>Question</th>
<th>Data sources</th>
<th>Study selection</th>
<th>Outcomes</th>
<th># relevant RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carr (2004)</td>
<td>Among several questions, are different analgesic drug formulations and routes of administration associated with different patient preferences or different efficacy rates?</td>
<td>Update of the 2001 AHRQ report on management of cancer pain and 2002 conference on symptom management in cancer. Searched MEDLINE, Cochrane, CancerLit, and references of reviews.</td>
<td>RCTs evaluating the efficacy of treatments for cancer-related pain.</td>
<td>Pain.</td>
<td>3</td>
</tr>
<tr>
<td>Study</td>
<td>Publication status</td>
<td>Allocation concealment</td>
<td>Blinding</td>
<td>Statistical power</td>
<td>Intention-to-treat analysis</td>
</tr>
<tr>
<td>---------------</td>
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<td>-------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Vainio (1988) (11)</td>
<td>Full publication</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Smith (2002) (12)</td>
<td>Full publication</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Kalso (1996) (13)</td>
<td>Full publication</td>
<td>NR</td>
<td>Double</td>
<td>NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Staats (2004) (14)</td>
<td>Full publication</td>
<td>Yes</td>
<td>Double</td>
<td>96% to detect &gt;30% change in VAS between groups (70 ziconotide and 35 placebo)</td>
<td>Yes</td>
</tr>
<tr>
<td>Eisenach (1995) (15)</td>
<td>Full publication</td>
<td>NR</td>
<td>Double</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pasqualucci (1987) (16)</td>
<td>Full publication</td>
<td>NR</td>
<td>Double</td>
<td>NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Dahm (2000) (17)</td>
<td>Full publication</td>
<td>NR</td>
<td>Double</td>
<td>NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>van Dongen (1999) (18)</td>
<td>Full publication</td>
<td>NR</td>
<td>Double</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Lauretti (1999) (19)</td>
<td>Full publication</td>
<td>Unclear</td>
<td>Double</td>
<td>Sample size calculation done - details not given</td>
<td>NR</td>
</tr>
<tr>
<td>Yang (1996) (20)</td>
<td>Full publication</td>
<td>NR</td>
<td>Double</td>
<td>NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Gourlay (1991) (21)</td>
<td>Full publication</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Georgiou (2000) (22)</td>
<td>Full publication</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported.
Table 5. Characteristics and results of included RCTs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Characteristics</th>
<th>Length Follow-up</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vainio (1988) (11)</td>
<td>30 patients with severe cancer (mean age 52 y, range 23 to 86) FU: 30/30</td>
<td>To end of treatment (usually death of patient)</td>
<td>Epidural opiate using a conventional tunneled catheter (n=10), implanted catheter and injection port (n=10), or systemic per oral opiate (n=10).</td>
<td>Pain intensity (10-cm VAS), performance status (100-point Karnofsky scale), side effects, and complications.</td>
<td>Groups did not differ for VAS scores, which were &lt;5 in all 3 groups. The oral group had more side effects than the epidural groups. Karnofsky scores were nonstatistically significantly better in the epidural groups than the oral group. 12 incidences of complications occurred in the epidural groups compared with no complications in the oral group.</td>
</tr>
<tr>
<td>Smith (2002) (12) [ITT]</td>
<td>202 patients ≥18 y (mean age 57 y, 55% men) with advanced cancer and mean 10-point VAS (10 = worst) score ≥5 FU: 143/202 (71%)</td>
<td>6 mo</td>
<td>Intrathecal morphine delivered through an implantable drug delivery system (IDDS) plus comprehensive medical management (CMM) (n=101) vs. CMM alone (n=99)</td>
<td>Clinical success: ≥20% reduction in VAS or equal VAS with ≥20% reduction in drug toxicity at 4 wk</td>
<td>VAS pain score reduction 52% with IDDS vs. 39% CMM (p=0.055). Clinical success 85% with IDDS vs. 71% with CMM (p=0.05). 30 patients in whom CMM failed crossed over to IDDS and had significantly reduced VAS (27% reduction) and drug toxicity (51% reduction) scores within 4 weeks (Smith2005a). The as-treated analysis showed greater clinical success with IDDS than non-IDDS (89% vs. 71%, p=0.02) (Smith2005b).</td>
</tr>
<tr>
<td>Kalso (1996) (13)</td>
<td>10 hospitalized patients (age range 22 to 75 y, 60% women) with severe cancer-related pain requiring opioids FU: 9/10</td>
<td>Two 48-h periods</td>
<td>Crossover design: Epidural or subcutaneous continuous infusion of morphine</td>
<td>100-mm VAS score (100=worst) and adverse effects</td>
<td>Pain at rest was less during subcutaneous morphine than oral morphine (prettrial) and pain while moving was less during subcutaneous and during epidural morphine than prettrial oral morphine; subcutaneous and epidural did not differ for either measurement. Prettrial oral morphine had more adverse effects than subcutaneous (P&lt;0.05). Epidural did not differ from either oral or subcutaneous for adverse effects.</td>
</tr>
</tbody>
</table>

**Comparisons of different intraspinal administration techniques.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Characteristics</th>
<th>Length Follow-up</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staats (2004) (14)</td>
<td>111 patients 24 to 85 y (mean age 56 y, 50% men) with cancer (n=95) or AIDS (n=13) and mean 100-mm VAS (100=worst) score ≥50 FU: 108/111 (97%)</td>
<td>Initial titration period 5 to 6 d plus 5-d maintenance phase</td>
<td>Ziconotide (n=71) or placebo (n=40) by already implanted pump or by intrathecal catheter with external infusion. At end of titration, responders received 5 d of maintenance and nonresponders crossed over to alternate treatment.</td>
<td>Mean percentage change in VAS to end of titration phase</td>
<td>53% improvement with ziconotide vs. 18% with placebo (p&lt;0.001)</td>
</tr>
<tr>
<td>Eisenach (1995) (15)</td>
<td>85 patients (age range 31 to 83 y, mean 56 y, 60% men) with severe cancer-related pain despite systemic or epidural morphine or morphine equivalents FU: 56/85 (66%)</td>
<td>15 d</td>
<td>Continuous epidural infusion of clonidine, 30 μg/h (n=38) or placebo (n=47) by patient-controlled analgesia pump for 14 d. All patients had rescue epidural morphine.</td>
<td>Treatment success: any reduction in morphine use or VAS, or either variable decreasing with the other remaining constant</td>
<td>Treatment success was achieved by more clonidine patients than placebo patients (45% vs. 21%, p=0.016). Greatest success was seen in neuropathic pain control (50% vs. 11%). Groups did not differ for adverse events (33% vs. 33%).</td>
</tr>
</tbody>
</table>

**Intraspinal techniques alone or in combination vs. other interventions alone or in combination.**
<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (age range)</th>
<th>Conditions (15 cancer)</th>
<th>FU:</th>
<th>Administration of opioids</th>
<th>Pain control</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasqualucci (1987) (16)</td>
<td>12 patients (age range 45 to 75 y, 75% men) with severe, continuous cancer-related pain (VAS 5/10) not responding to common analgesics (NSAIDs)</td>
<td>FU: 12/12</td>
<td>18 h</td>
<td>Single dose via epidural of morphine, 3 mg (n=6) or buprenorphine, 0.3 mg (n=6).</td>
<td>Pain (10-cm VAS) and ventilatory function (breathing control and gas exchange).</td>
<td>Pain control improved in both groups through the first 6 h. Buprenorphine had significantly better pain control compared with baseline than morphine compared with baseline at 18 h.</td>
</tr>
<tr>
<td>Dahm (2000) (17)</td>
<td>21 patients 26 to 76 y (median age 63 y) with refractory pain conditions (15 cancer)</td>
<td>FU: 12/12</td>
<td>Two 7-d periods</td>
<td>Crossover design: continuous intrathecal infusion of ropivacaine or bupivacaine</td>
<td>Need for local anesthetics, mean 10-point VAS score (10=worst), side effects</td>
<td>Need for local anesthetics higher with ropivacaine (62 vs. 58 mg/d, p&lt;0.02), VAS scores no difference (p&gt;0.3), no difference in side effects</td>
</tr>
<tr>
<td>van Dongen (1999) (18)</td>
<td>20 patients (age range 35 to 82 y) with refractory cancer pain.</td>
<td>FU: 20/20</td>
<td></td>
<td>Intrathecal administration of morphine + bupivacaine (n=11) or morphine alone (n=9).</td>
<td>Progression of morphine dose and side effects.</td>
<td>Adequate pain relief was achieved in both groups. The rate of dose progression of morphine was less in the morphine + bupivacaine group than the morphine alone group (0.0003 vs.0.005 mg/h, p=0.0001).</td>
</tr>
<tr>
<td>Lauretti (1999) (19)</td>
<td>48 patients (mean age range 50 to 56 y, 63% men) with refractory cancer pain.</td>
<td>FU: 48/48</td>
<td>25 d</td>
<td>Epidural administration of morphine + ketamine, neostigmine, midazolam, or placebo (12 patients per group) whenever VAS score was ≥4/10.</td>
<td>10-cm VAS (10=worst), time to complaint of pain (VAS ≥4/10) and adverse effects.</td>
<td>VAS scores 60 min after drug admin were lower with ketamine than midazolam (p=0.018). Patients in the ketamine and neostigmine groups had a longer time to pain complaint than placebo patients. Groups did not differ for adverse events.</td>
</tr>
<tr>
<td>Yang (1996) (20)</td>
<td>20 hospitalized patients 22 to 69 y (50% men) with cancer using opioid analgesics for pain control.</td>
<td>FU: 20/20</td>
<td>Two 48-h periods</td>
<td>Crossover design: intrathecal morphine + ketamine or morphine alone twice daily</td>
<td>Intrathecal morphine and rescue morphine requirements; pain intensity on 10-point VAS score (10=worst); pain frequency on 4-point verbal ordinal scale (3=constant)</td>
<td>The required dose of intrathecal morphine to be effective was less in the morphine+ketamine group (0.17 vs.0.38 mg, p&lt;0.05); pain intensity and pain frequency were both decreased after either intervention compared with pretrial.</td>
</tr>
</tbody>
</table>

**Comparisons of different intraspinal medications.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients (75% men) with severe cancer-related pain refractory to oral therapy with opioids</th>
<th>FU: 28/29</th>
<th>Patients were followed until death (mean 140 to 169 d)</th>
<th>Epidural morphine administered as continuous infusion via pump (n=15) or intermittent bolus via catheter (n=14)</th>
<th>VAS and problems encountered with the devices (0 to 4 [very troublesome])</th>
<th>VAS scores were low (good) in both infusion and bolus groups and did not differ, 1.48 vs.1.23) and very few problems occurred with the devices (0.52 vs. 0.49).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gourlay (1991) (21)</td>
<td>29 patients (mean age 68 y, 97% men) with terminal head or neck cancer with pain not controlled by oral morphine.</td>
<td>FU: 29/29</td>
<td>Patients were followed until death; pain was measured up to 10 d.</td>
<td>Morphine administered epidurally in the thoracic (n=16) or cervical region (n=13).</td>
<td>100-mm VAS score (100=worst), morphine use, and complications.</td>
<td>Groups did not differ in pain scores. The bolus dose and daily dose of morphine were lower in the cervical group (p&lt;0.05) and the duration of analgesia after each bolus dose was longer in the cervical group (p&lt;0.05). Nausea/vomiting and pruritus were mild or moderate and more common in thoracic patients, as was constipation.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ITT: Intention to treat analysis; CO: cross over from CMM; ATA: as-treated analysis.
Table 6. Quality of clinical practice guidelines, using the AGREE instrument. Number of reviewers: 2.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Scope &amp; purpose</th>
<th>Stakeholder involvement</th>
<th>Rigor of development</th>
<th>Clarity &amp; presentation</th>
<th>Applicability</th>
<th>Editorial independence</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONS (23)</td>
<td>55.6%</td>
<td>16.7%</td>
<td>45.2%</td>
<td>45.8%</td>
<td>0%</td>
<td>16.7%</td>
<td>Would not recommend</td>
</tr>
<tr>
<td>BPS (24)</td>
<td>83.3%</td>
<td>58.3%</td>
<td>61.9%</td>
<td>91.7%</td>
<td>27.8%</td>
<td>16.7%</td>
<td>Recommend</td>
</tr>
<tr>
<td>CCNS (25)</td>
<td>83.3%</td>
<td>70.8%</td>
<td>90.5%</td>
<td>95.8%</td>
<td>38.9%</td>
<td>8.3%</td>
<td>Strongly recommend</td>
</tr>
<tr>
<td>SIGN (26)</td>
<td>83.3%</td>
<td>45.8%</td>
<td>90.5%</td>
<td>95.8%</td>
<td>27.8%</td>
<td>58.3%</td>
<td>Strongly recommend</td>
</tr>
<tr>
<td>Singapore (27)</td>
<td>83.3%</td>
<td>37.5%</td>
<td>45.2%</td>
<td>95.8%</td>
<td>22.2%</td>
<td>0%</td>
<td>Recommend</td>
</tr>
<tr>
<td>APS (28)</td>
<td>94.4%</td>
<td>50.0%</td>
<td>78.6%</td>
<td>83.3%</td>
<td>66.7%</td>
<td>100%</td>
<td>Strongly recommend</td>
</tr>
<tr>
<td>NCCN (29)</td>
<td>61.1%</td>
<td>25.0%</td>
<td>19.0%</td>
<td>75.0%</td>
<td>5.6%</td>
<td>75.0%</td>
<td>Recommend</td>
</tr>
<tr>
<td>ASA (30)</td>
<td>88.9%</td>
<td>37.5%</td>
<td>59.5%</td>
<td>50.0%</td>
<td>38.9%</td>
<td>0%</td>
<td>Recommend</td>
</tr>
</tbody>
</table>

Table 7. Organizational guidance: summary of evidence.

<table>
<thead>
<tr>
<th>Section</th>
<th>Practice Guidelines</th>
<th>Resource Standards</th>
<th>Papers: Policy and Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ONS 2004 (23)</td>
<td>BPS 2006 (24)</td>
<td>CCNS 2005 (25)</td>
</tr>
<tr>
<td>Indications for use</td>
<td></td>
<td>CCNS 2005 (25)</td>
<td>SIGN 2000 (26)</td>
</tr>
<tr>
<td></td>
<td>Patient selection</td>
<td></td>
<td>Sing 2003 (27)</td>
</tr>
<tr>
<td></td>
<td>Contraindications</td>
<td></td>
<td>APS 2005 (28)</td>
</tr>
<tr>
<td>Practice setting</td>
<td>Monitoring, aftercare, follow-up</td>
<td></td>
<td>NCCN 2007 (29)</td>
</tr>
<tr>
<td></td>
<td>Hospital discharge</td>
<td></td>
<td>ASA 1996 (30)</td>
</tr>
<tr>
<td></td>
<td>Equipment</td>
<td></td>
<td>St Wilf 2001 (34)</td>
</tr>
<tr>
<td></td>
<td>Practice team</td>
<td></td>
<td>Cal 2004 (31)</td>
</tr>
<tr>
<td></td>
<td>Professional competencies</td>
<td></td>
<td>Corn 2001 (32)</td>
</tr>
<tr>
<td></td>
<td>Patient education</td>
<td></td>
<td>Ott 2007 (33)</td>
</tr>
<tr>
<td></td>
<td>Patient safety</td>
<td></td>
<td>INS 2006 (35)</td>
</tr>
</tbody>
</table>

Clinical Effectiveness - Evidence

Systematic reviews

Two systematic reviews met inclusion criteria (7,8). Raffaeli (7) reviewed the literature on intraspinal medication for chronic pain between 1990 and 2005. Of the 34 studies identified, 19 were on cancer pain, and two of these were RCTs (12,18). Overall, the review demonstrated that intraspinal administration of opioids was effective in attenuating pain in patients with cancer pain and noncancer pain. A 2002 Agency for Healthcare Research and Quality (AHRQ) evidence report (8) focused on the prevalence, assessment, and treatment of cancer-related pain, depression, and fatigue. RCT evidence was used to assess the efficacy of interventions. Intraspinal analgesia as an intervention was addressed in a summary of RCTs evaluating adjuvant analgesics. Three of the six RCTs were relevant (17-19). The review concluded insufficient RCT evidence was available to determine the relative efficacy of the spinal versus systemic route of drug administration.
**Expert consensus conferences**

Informed by a polyanalgesic consensus conference on the management of pain by intraspinal drug delivery across patient types (37), a similar multidisciplinary meeting was held to arrive at consensus-based recommendations for the use of intrathecal drug delivery for intractable cancer pain (10). Based on consensus, and citing the Smith 2002 RCT (12), the panel supported the use of intrathecal drug delivery in the management of cancer pain, but noted that few RCTs have been conducted on the optimal medication for cancer pain, prompting reluctance among the medical community to accept intraspinal analgesia for widespread clinical use.

**Randomized controlled trials**

The quality, characteristics, and results of the 12 eligible RCTs are in Tables 4 and 5 and are briefly summarized below. While most of the studies were double blinded, the reporting of the quality features was typically incomplete. Further, sample sizes varied widely, but most studies were small and likely underpowered.

**Intraspinal techniques alone or in combination vs. other interventions alone or in combination**

Three RCTs compared an intraspinal technique alone or in combination with another pain intervention alone or in combination. In a three-arm trial, Vainio (11) (n=30) compared morphine given orally, by conventional tunnelled catheter, or by implanted catheter. All three groups achieved marked pain relief and did not differ statistically from one another, but a higher rate of side effects was observed in the oral morphine group (16 occurrences) compared with seven occurrences in the conventional epidural group and three occurrences in the port group. Technical complications were more common in the epidural groups and included dislocation in the epidural space (three times in the conventional catheter group), disconnection of the port (three times in the port group), and local infection of the skin (once in the conventional catheter group and twice in the port group).

Smith (12) (n=202) compared intrathecal delivery of morphine through a programmable infusion system plus comprehensive medical management with medical management alone in 202 patients with refractory cancer pain. Clinical success was defined as ≥20% reduction in visual analogue pain scale (VAS) and ≥20% reduction in drug toxicity at four weeks. The difference between the two groups met borderline statistical significance (P=0.05). The reduction in pain scores was greater in the intrathecal group, but the difference was just short of statistical significance (P=0.055). Significant reductions in fatigue and depressed level of consciousness occurred in the intrathecal delivery group (p<0.05). In two separately published reports, preplanned analyses of crossovers (38) and as-treated patients (39) showed statistically significantly greater clinical success with combined therapy.

Kalso (13) (n=10) compared epidural with subcutaneous continuous infusion of morphine in a crossover trial. Both groups improved in pain control over that of oral morphine at baseline. The groups did not differ for adverse effects.

**Comparisons of different intraspinal medications**

Seven RCTs compared different types of drugs or compared drug with placebo in patients receiving an intraspinal drug delivery system. Staats (14) (n=111) compared ziconotide with placebo by implanted pump or intrathecal catheter with external infusion. Patients who received ziconotide showed an improvement of 53% at the initial titration phase (five to six days) compared with 18% improvement with placebo. Adverse effects such as somnolence, confusion, urinary incontinence, and fever were more common with ziconotide than placebo but were easily recognized and decreased when the dose of ziconotide was...
Evidentiary Base – page 11

decreased. A long-term follow-up of open-label ziconotide (40) showed significant improvement in pain intensity scores from baseline at all time points and past 12 months.

Eisenach (15) (n=85) compared a continuous epidural infusion of clonidine with placebo, both administered by patient-controlled pump. Significantly greater treatment success (defined as a decrease in morphine use or decrease in pain) was seen with clonidine than placebo (45% vs. 21%). Adverse events occurred in 33% of patients in both groups. Groups did not differ for sedation or decreased respiratory function, but clonidine decreased blood pressure by about 10 mm Hg.

Pasqualucci (16) (n=12) compared epidural administration of morphine with buprenorphine, and showed significant reduction in pain in both groups at six hours. At 18 hours better pain control (compared with baseline) was seen with buprenorphine in three pain indices compared with morphine in one pain index. Adverse reactions occurred in four of six buprenorphine patients and in two of six morphine patients.

In a crossover RCT comparing intrathecal bupivacaine with ropivacaine (n=21), Dahm (17) showed no significant difference in pain scores, but higher daily doses of local anesthetic to achieve a similar degree of pain relief were used with ropivacaine. Groups did not differ for side effects or complications.

van Dongen (18) (n=20) compared intrathecal delivery of morphine plus bupivacaine with morphine alone. Both groups had adequate pain relief, but the rate of morphine alone dose progression from day 10 to day 30 was greater in the morphine group than in the combined group (p<0.001). No severe bupivacaine-related neurological deficits were observed.

Lauretti (19) (n=48) evaluated patients allocated to epidural administration of morphine plus ketamine, neostigmine, midazolam, or placebo. Patients receiving ketamine had lower pain scores than those receiving midazolam at 60 minutes after administration. Pain relief lasted longer in the ketamine and neostigmine groups than the placebo group. Morphine consumption up to day 25 was lower in the ketamine group than the placebo group (p=0.003). There were no differences among the groups for adverse effects, the most common being somnolence, constipation, diminished appetite, and skin redness around the epidural catheter, and one patient experienced hallucinations.

In a crossover trial, Yang (20) (n=20) compared intrathecal morphine plus ketamine with intrathecal morphine alone. Pain intensity and pain frequency were both decreased from baseline. The addition of ketamine resulted in a lower dose of morphine being required. Side effects did not differ between groups and were not serious. No cases of respiratory depression occurred.

Comparisons of different intraspinal administration techniques

Two small RCTs (each n=29) compared different intraspinal techniques. Gourlay (21) evaluated epidural morphine administered as a continuous infusion by Infusaid pump or intermittent bolus by Port-a-Cath. Pain scores were low in both groups and did not significantly differ. Mean scores for problems associated with the devices were also low in both groups.

Giorgiou (22) evaluated epidural administration of morphine in the thoracic compared with the cervical region and showed no difference in pain scores. The cervical route required smaller bolus doses and gained longer lasting analgesia than the thoracic route. The thoracic route led to a greater rate of adverse effects (constipation, nausea and vomiting, and pruritus).

Summary of Clinical Effectiveness Evidence
Two systematic reviews, one consensus conference, and 12 RCTs evaluated the effectiveness of intraspinal medication for cancer-related pain. Overall, the quality and quantity of evidence was poor. None of the systematic reviews specifically addressed the topic of effectiveness of intraspinal analgesia for cancer pain, but only as one aspect of the review. The systematic review by Walker (6) provided good evidence for the effectiveness of combination drug therapy administered intraspinally, including the use of local anesthetics. One consensus conference (10) directly addressed intraspinal drug delivery for cancer pain, but its focus was on best practices rather than effectiveness. The conclusions of the reviews and consensus conference favoured the use of intraspinal medication for cancer and noncancer pain.

Of the 12 RCTs meeting the selection criteria, none were found that compared epidural with intrathecal administration, compared external with internal pumps, or evaluated the timing of intraspinal analgesia. Five of the studies had ≤20 patients, and three were crossover trials. Serious study follow-up limitations were noted in three trials, and one trial included nonrandomized patients (Table 5). Two trials included a comparison with conventional medical management: Vainio (11) showed no difference between groups for VAS scores, but side effects were more common in the oral opioid group than in the epidural group. Smith (12), a large trial of >200 patients, showed a borderline improvement in VAS score with intrathecal morphine, compared with comprehensive medical management, and a reduction in toxicity. Furthermore, preplanned secondary analyses of crossovers (38) and as-treated patients (39) showed continued clinical success with intrathecal therapy. The trials of Van Dongen (18), Lauretti (19), and Yang (20) showed the addition of another agent such as a local anesthetic enhanced the benefit of an opioid alone and required less escalation in morphine dose.

In general, the use of intraspinal techniques was effective in controlling pain in patients with cancer and noncancer pain who no longer achieve adequate pain control by other routes. For pain control, intraspinal analgesia was as effective as or better than conventional medical management and was generally associated with fewer side effects. Furthermore, the addition of a local anesthetic to an opioid improved analgesic efficacy and reduced the dose requirements for either drug alone. A recent polyanalgesic consensus conference (41) provided an updated review of intrathecal drugs, although this includes nonmalignant pain. However, there is insufficient evidence to recommend one drug option or regimen over another. As a result, recommendations cannot be made regarding appropriate and effective medication regimens, and collaborative clinical decisions should be made based on the expertise of each institution’s relevant healthcare providers. There is no evidence to guide the choice of intrathecal or epidural routes or implanted or external systems. Such decisions should be made by the insertion team.

Clinical Effectiveness - Recommendations
- Evidence supports the use of intraspinal analgesia for certain patients in the management of their cancer pain
- Intraspinal analgesia with an opioid alone, local anesthetic alone, or opioid and local anesthetic combined are all reasonable options

Indications for Use - Evidence
Ten guidelines and resource documents and one consensus conference were found that provided guidance regarding patient indications and contraindications for the use of intraspinal analgesia (ONS, BPS, CCNS, SIGN, Singapore, APS, NCCN, ASA, Calgary, and Cornwall [23-32] and Stearns [10]). As described above, the reports varied in their use of evidence. Among those that did include evidence, it is important to note that the quality and
quantity of evidence available was weak; this area has been studied very little. Table 8 outlines all the indications that were identified and the documents that supported those indications.

There were two indications that received support by all groups:
1. Intractable pain that could not be controlled by other conventional medical routes
2. Side effects from conventional medical routes that prevented dose escalation

**Contraindications**

Five documents (Stearns, ONS, BPS, Calgary, and Cornwall [10,23,24,31,32]) addressed contraindications for the administration of intraspinal analgesia. Active systemic or local infection and anticoagulation were the most commonly reported contraindications. The working group members felt that special consideration should be given to patients with active spinal cord compression issues. They also felt that anticoagulation was considered a contraindication to intraspinal analgesia at the time of catheter insertion, but not if the patient was anticoagulated after intraspinal analgesia was administered.

**Infectious Considerations**

Septicemia is an absolute contraindication because of the high risk of catheter infection after implantation. This can lead to epidural abscess formation and the possibility of spinal cord compression resulting from a space-occupying abscess. This can also result in a CNS infection (e.g., meningitis and encephalitis).

- Sepsis or any systemic infection **controlled** after institution of antibiotic treatment is not a contraindication.
- Any local superficial infection after successful treatment is not a contraindication. An epidural/spinal catheter or an internalized pump may be implanted at a site or segmental level that is distant from the infected area.
- Patients with immunosuppression or insulin dependent diabetes have a higher risk of infection.

**Hemorrhagic Considerations**

Bleeding diathesis or any hemorrhagic conditions that can increase the risk of an epidural or spinal hematoma formation and long term neurologic deficit is a contraindication.

- Patients on therapeutic or prophylactic anticoagulation treatment can receive intraspinal catheter treatment provided that anticoagulation is reversed prior to procedure.
- Patients with significant thrombocytopenia can receive intraspinal catheter treatment after adequate platelet transfusion.
- Patients with other coagulation disorders (e.g., von Willebrand disease, hemophilia) should be treated prior to procedure.
- Patients with known epidural metastases have a higher risk of spinal bleeding and hematoma if the catheter passes through the tumour mass. It is advisable to insert the catheter cephalad to the level of known or suspected spinal metastases.

**Neurologic Considerations**

- Unmotivated, non compliant patients
- Pre-existing uncontrolled or unstable CNS disorders (e.g., raised intracranial pressure)
- Spinal canal pathology (e.g., spinal stenosis) that may predispose the patient to development of neurologic symptoms as a result of long term spinal infusion and increased spinal canal pressure
- Spine pathology (e.g., previous fusion or laminectomy) that may impair successful catheter placement
Seven documents (ONS, BPS, CCNS, APS ASA, Calgary, and Cornwall [23-25,28,30-32]) recommended a trial of intraspinal analgesia using a temporary epidural or spinal catheter to determine efficacy and appropriate dose range. One document (Calgary [31]) cautioned that limiting intraspinal analgesia to patients whose pain has failed to be controlled by other methods causes unnecessary waiting resulting in unacceptable suffering that leads to an even more complex pain management problem. Earlier consideration of intraspinal analgesia may lead to more rapid pain control and less patient suffering. The Polyanalgesic Consensus Conference recommended a screening trial before proceeding with pump implantation to evaluate patient response and potential side effects but indicated a trial was not necessary for patients receiving external intraspinal systems (Stearns [10]).

Table 8. Indications and contraindications for use of intraspinal analgesia for cancer pain.

<table>
<thead>
<tr>
<th>Category</th>
<th>ONS</th>
<th>BPS</th>
<th>CCNS</th>
<th>SIGN</th>
<th>Sing</th>
<th>APS</th>
<th>NCCN</th>
<th>ASA</th>
<th>Cal</th>
<th>Corn</th>
<th>Stearns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications for use of intraspinal analgesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intractable pain control</td>
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<tr>
<td>Appropriate equipment and expertise available</td>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>Expectation that intraspinal analgesia would improve patient’s quality of life</td>
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<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<tr>
<td>Life expectancy of weeks or months</td>
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<tr>
<td>Informed consent</td>
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<tr>
<td>Contraindications</td>
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<tr>
<td>Bleeding diathesis</td>
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<tr>
<td>Active or local infection</td>
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<tr>
<td>Psychosocial distress</td>
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<tr>
<td>Unstable angina, severe left ventricular dysfunction, critical aortic stenosis, prohibitive spinal abnormality, previous spinal fusion</td>
<td>✓</td>
<td>✓</td>
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<td></td>
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<td></td>
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<tr>
<td>Unfit for surgery or anesthesia</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>Disseminated disease contraindicated for regional therapy</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>Unstable vital signs, hematologic abnormalities, wound infections, emaciation, spinal lesions</td>
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<tr>
<td>Requirement for large volume infusions</td>
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<tr>
<td>Presence of another implanted device</td>
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</tbody>
</table>

While the evidentiary base in this area is incomplete, at least two of the guidelines (SIGN and CCNC [26,29]) were extremely explicit with respect to the methods used to select, assemble, and synthesize what evidence does exist. The working group members agreed with the conclusions made in the practice guidelines described above regarding indications for
intraspinal analgesia use. Thus, the following recommendations are based on a consensus of the expert clinical opinion of the working group informed by these sources.

**Indications for Use of Intraspinal Analgesia - Recommendations**

**Patient selection and eligibility**
- Intractable severe pain despite aggressive pharmacologic interventions by conventional administration routes (oral, rectal, transdermal, subcutaneous, and intravenous)
- Dose-limiting side effects experienced from conventional administration routes

**Contraindications**
- Active systemic or local infection at the site of catheter insertion or pump implantation
- Bleeding diathesis at the time of procedure
- Increased intracranial pressure
- Spinal pathology that may prevent successful placement (e.g., hardware) or lead to adverse effects (e.g., severe spinal stenosis)

**Additional considerations**
- Careful consideration must be given to patient selection
- The availability of appropriate equipment, supplies, expertise, and 24-hour nursing and medical coverage that would include interventional pain physician
- The expectation that intraspinal analgesia would improve a patient’s quality of life and level of function
- Informed consent has been given by patient or substitute decision maker
- Availability of home care nursing and medical support for intraspinal catheter care
- Patient general medical condition is amenable to intraspinal analgesia
- For an fully implanted system, a screening trial is recommended; for intraspinal analgesia using an external pump, a trial is not necessary

**Implementation Issues for Safe Delivery of Intraspinal Analgesia**

Several issues related to the safe delivery of intraspinal analgesia as it relates to equipment, aftercare, monitoring, hospital discharge, follow-up, practice team, professional education and competency, patient and family education, and patient safety (See Table 7) were identified through the environmental scan. A summary of some the key issues are presented below, with greater detail found in appendices B to L. What is presented below and in the appendices is informed by resources found in the environmental scan and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the issues discussed below (nor was the intent of the source documents to provide that), the working group decided to discuss them in this report because they provide good advice related to implementation. Thus, users of this guideline should consider this information as a resource to think through some of the practical, technical and organizational issues related to ensuring high-quality and safe delivery of intraspinal analgesia.

**Equipment (Appendices B and C)**

Specific equipment requirements for delivering intraspinal analgesia were included in six documents (Stearns, ONS, BPS, Calgary, Ottawa, and INS [10,23,24,31,33,35]). None of the documents contained evidence comparing different types of delivery systems, but various options and the technical considerations in their use were presented. It is recommended that the choice of delivery system (e.g., epidural vs. intrathecal or implanted vs. external) be
based on the HCP expertise at each institution factoring in any relevant practical considerations. Guidance covers general equipment requirements as well as details concerning different kinds of intraspinal delivery systems: external, partially external, and fully implanted. Two issues concerning equipment that were considered particularly important in the administration of intraspinal analgesia were the use of preservative-free medication and the appropriate cleansing of the catheter site. The working group agrees with the INS (35) recommendations that straight alcohol or acetone should never be used for site preparation or cleansing but supports the use of staining disinfectants that contain alcohol, because several studies comparing providione-iodine, chlorhexidine, and chlorhexidine with alcohol have found reduced epidural infection rates using chlorhexidine with alcohol as the skin disinfectant (42-46).

Aftercare (Appendix D)
Four documents (ONS, BPS, Calgary, and Ottawa [23,24,31,33]) provided advice concerning care to be given immediately after intraspinal analgesia insertion. These activities included the application of generic postoperative principles delivered by nurses trained in intraspinal drug delivery techniques, with appropriate protocols in place, availability of medical support and equipment, and protection of patients from any infectious environment (such as not being cared for on a ward where there are Methicillin-resistant Staphylococcus aureus (MRSA) patients). Immediate concerns after the procedure also included monitoring patients’ vital signs and pain levels; assessing the insertion site for such complications as leakage, bleeding, and infection; checking and changing the dressing; and assessing the proper functioning of the equipment.

Monitoring (Appendices E and F)
Nine documents (Stearns, ONS, BPS, CCNS, APS, Calgary, Cornwall, Ottawa, and INS [10,23-25,28,31-33,35]) provided guidance regarding monitoring of patients receiving intraspinal pain management. The careful assessment of pain control and monitoring for complications and side effects were emphasized. Many monitoring issues surrounding intraspinal patients pertain to the management of cancer-related pain in general. Tools and instruments for monitoring pain and detecting complications and adverse effects were found in the CCNS (25), Calgary (31), and Ottawa (33) documents.

The inspection of intraspinal drug delivery devices was also emphasized as an important aspect of monitoring. Seven documents (Stearns, ONS, BPS, APS, Calgary, Cornwall, and INS [10,23,24,28,31,32,35]) warned of problems that could be encountered, including catheter malposition or migration, catheter disconnection, catheter occlusion (dislodgement, kinking, and erosion), and device failure or malfunction.

Hospital discharge (Appendix G)
Four documents (BPS, ASA, Calgary, and Cornwall [24,30-32]) provided advice regarding the hospital discharge of intraspinal patients. These documents stressed the importance of having a discharge plan in place before the initiation of the intraspinal analgesia procedure. The plans should ensure that properly trained professionals and an adequately equipped care setting are ready to receive the patient. In addition, the plans should include details about ordering equipment, drugs, and refills; the contact details of health professionals who will be involved in the patient’s care; and provision for the education of the patients, families, and home-care staff.
**Follow-up (Appendix H)**

Six documents (ONS, BPS, Calgary, Cornwall, and Ottawa, INS [23,24,31-33,35]) provided advice for the follow-up of patients with intraspinal pain medication in the community. The interprofessional nature of follow-up care was emphasized, as was the importance of establishing protocols so that all healthcare personnel are aware of the procedures to be followed in the intraspinal care of a patient, particularly in dealing with complications. Important elements for patient follow-up included ensuring the availability of pain management physicians outside of working hours to resolve problems that cannot be managed by nursing staff or local on-call medical staff. Such complications included increased sedation score, respiratory depression, signs of infection, persistent pain, and equipment malfunction. Provision should also be in place should patients require referral to hospital or hospice if their needs can no longer be met in the community. Similarly, if a patient moves away from the centre where intraspinal analgesia was initiated, a plan should be in place to allow for the smooth transfer of care.

**Practice team: interprofessional roles (Appendices I and J)**

Six documents (ONS, BPS, ASA, Calgary, St Wilfrid’s, and INS [23,24,30,31,34,35]) provided guidance on the roles of healthcare professionals involved in cancer pain management. The interprofessional nature of intraspinal care, the need for accurate communication among all persons involved, and the importance of working as a team that includes all healthcare professionals and patients and their families were emphasized. Responsibilities should be in keeping with quality standards of relevant professional college or association certification. A list of possible participants in intraspinal care includes:

1. Referring healthcare professional (palliative care physician, advanced practice/Specialist nurse, nurse practitioner, oncologist, or primary physician)
2. Interventional pain physician (interventional pain physician, neurosurgeon) Note that one targeted reviewer suggested including neurosurgeon under interventional pain physician. Another targeted reviewer suggested adding surgeon/neurosurgeon as a separate practice team member.
3. Registered nurse (palliative care unit, community, and inpatient)
4. Pharmacist (inpatient and community)
5. Patient and family members

Suggested responsibilities for key members of an intraspinal care team are in Appendix J.

**Professional education and competencies (Appendix K)**

Six documents (ONS, BPS, SIGN, Calgary, St Wilfrid’s, and INS [23,24,26,31,34,35]) provided advice with respect to the necessary training and competencies for healthcare professionals involved in intraspinal care. Specific education training is required for healthcare professionals caring for patients receiving intraspinal analgesia. For example, the BPS (24) recommended a mentoring system among healthcare professionals and the establishment of a network of trained clinicians in order to provide coverage. Practitioners who do the implanting must have appropriate training and a caseload sufficient to maintain expertise. At this time, the ideal caseload is not known.

Four documents (ONS, Calgary, St Wilfrid’s, and INS [23,31,34,35]) provided guidance on training and education specifically for nurses involved in intraspinal care. Nursing care of intraspinal patients is an advanced nursing competency requiring certification. Educational activities for nurses should cover the operation of intraspinal drug delivery systems, insertion and access procedures, care and maintenance (assessment of site, dressing change, and flushing and aspiration procedures), potential complications and interventions, and patient
and family education. Routine continuing education opportunities to maintain knowledge and clinical competency are recommended.

**Patient and family education (Appendix L)**

Eight documents (ONS, BPS, CCNS, APS, ASA, Calgary, Cornwall, and Ottawa [23-25,28,30-33]) included advice on patient and family education. The use of intraspinal analgesia in the community setting requires that patients and family are frequently educated about and highly motivated and competent in the use of the drug delivery system. Documentation of what has been taught should be part of the patient record so that all healthcare providers can reinforce the teaching points. Several guidelines stressed that patients must understand the importance of communicating worsening or unrelieved pain and reporting adverse effects. Four documents (ONS, BPS, Calgary, and Cornwall [23,24,31,32]) contained patient-specific information on intraspinal drug delivery systems.

**Patient safety (Appendix M)**

Six documents (ONS, BPS, Calgary, Cornwall, Ottawa, and INS [23,24,31-33,35]) provided advice on patient safety. Two safety measures were emphasized across all documents:

1. The maintenance of strict aseptic conditions in all aspects of intraspinal analgesia administration. This includes wearing a mask and gloves when accessing an intraspinal device.
2. The clear labelling of all equipment. All intraspinal drug delivery equipment must be appropriately labelled (yellow for epidural and blue for intrathecal) as to its purpose and the date and time of initiation of infusion.

The use of intraspinal analgesia can confer increased mobility for patients, thus raising special safety concerns that patients should be aware of such as avoiding scanners in airports and shops, saunas and sunbeds, and sports or activities that may cause injury or dislodgement of the pump. Some intraspinal drug delivery systems are at risk for significant damage and malfunction from magnetic resonance imaging (MRI) scanners, and advice on how to proceed will be required from individual scanning departments and the specific drug delivery system manufacturers. It was advised that patients have a MedicAlert emblem that alerts healthcare professionals to the presence of an intraspinal device in emergency situations or carry an identification card indicating the make and model of any intraspinal device, the drugs within the pump, and the current or last prescribed dose.

**DISCUSSION**

In the setting of cancer care, pain control in general tends to be poorly understood and managed. Common barriers to adequate pain control include the belief that patients are not good judges of the severity of their pain; the inability to distinguish between tolerance, physical dependence, and addiction; fear of opioid side effects or addiction; and lack of knowledge about the multiple approaches to managing pain (28). Because few cancer patients will require intraspinal analgesia, such barriers are magnified with respect to the use of intraspinal analgesia. According to Stearns (10), a general lack of understanding exists about the relevant indications for intraspinal analgesia and the types of patients who would benefit from it. Furthermore, at centres where expertise in intraspinal analgesia is limited, oncologists are unlikely to be familiar with its use and unlikely to refer patients for this type of pain control.

The main advantages of intraspinal analgesia for cancer pain are the delivery of adequate pain control and fewer side effects than with conventional analgesia routes.
Disadvantages of intraspinal analgesia include the technically demanding insertion procedure and close patient follow-up required by skilled healthcare personnel. Because intraspinal techniques are an infrequently used, intervention for treating cancer pain, high-quality evidence evaluating their effectiveness, and the provision of practical guidance for their delivery is sparse. Some of the most methodologically rigorous documents identified had very little information specifically on intraspinal techniques, while relevant guidance was more often obtained from internal use care pathways or non-evidence-based procedure manuals. The evidence for this organizational guideline was based on two systematic reviews, one consensus conferences, 12 RCTs, and 13 advice documents (practice guidelines, standards, and local policies and procedures). The clinical evidence confirmed the effectiveness of intraspinal analgesia in carefully selected patients with intractable cancer pain. Among the RCTs, some limitations with respect to the small numbers of patients both entered and followed-up were apparent. Given the small proportion of patients with cancer pain for whom intraspinal analgesia is the appropriate intervention, it is unlikely accrual for well-designed randomized trials intending to clarify effectiveness could reach statistical significance. As a result, clinical decisions regarding the use of intraspinal analgesia tend to be based on local experience and anecdote. Advice pertaining to organizational guidance was obtained from practice guidelines, standards, and local policy and procedures manuals. With these documents plus the clinical expertise of the working group, we were able to make recommendations regarding specific indications for use of intraspinal analgesia, practice setting requirements for caring for a cancer patient receiving intraspinal analgesia, the roles and responsibilities of the healthcare professionals involved in providing intraspinal care, the training and education required for healthcare professionals and patients and families, and the elements of patient safety.

CONCLUSIONS
As part of a comprehensive cancer pain management strategy, intraspinal catheter insertion should be a consideration for appropriately selected patients. For institutions that have the resources available to safely insert and subsequently manage intraspinal infusions, it is essential that the institution develop the necessary policies, procedures, and competencies to support the healthcare professionals involved in the care of these patients.

CONFLICT OF INTEREST
The authors declared no actual or potential conflicts of interest in relation to this report.

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Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775
REFERENCES


APPENDICES

Appendix A. Literature search strategies.

Database: Ovid MEDLINE(R) <1950 to May Week 2 2008>
Search Strategy:

1. exp injections, spinal/ (10709)
2. (intrathecal: or intraspinal: or epidural:).mp. (45447)
3. exp pain/ (226898)
4. exp neoplasms/ or exp carcinoma/ (1951483)
5. (cancer: or carcinoma or neoplas: or oncol:).mp. (1763326)
6. 1 or 2 (47850)
7. 4 or 5 (2090036)
8. 3 and 6 and 7 (1347)
9. limit 8 to (english language and humans) (958)
10. 9 to "therapy (sensitivity)" (713)
11. exp meta-analysis/ (18398)
12. (meta-anal: or overview or systematic review).mp. (88252)
13. practice guideline.pt. (12227)
14. 11 or 12 or 13 (100135)
15. 9 and 14 (19)
16. 10 or 15 (715)

Database: EMBASE <1980 to 2008 Week 20>
Search Strategy:

1. exp Intraspinal Drug Administration/ (14744)
2. (intrathecal: or intraspinal: or epidural:).mp. (47507)
3. exp pain/ (343810)
4. exp NEOPLASM/ (1419457)
5. exp carcinoma/ (333886)
6. (cancer: or carcinoma or neoplas: or oncol:).mp. (1106836)
7. 1 or 2 (47742)
8. 4 or 5 or 6 (1551107)
9. 3 and 7 and 8 (2142)
10. limit 9 to (human and english language) (1603)
11. limit 10 to "treatment (2 or more terms high sensitivity)" (541)
12. Meta Analysis/ (33329)
13. (meta-anal: or overview or systematic review).mp. (97579)
14. guideline.mp. or exp practice guideline/ (139917)
15. 12 or 13 or 14 (231286)
16. 10 and 15 (96)
17. 11 or 16 (551)
18. from 17 keep 1-551 (551)
Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to May Week 3 2008>
Search Strategy:

1 exp INJECTIONS, EPIDURAL/ or exp INJECTIONS, INTRASPINAL/ (621)
2 (intrathecal: or intraspinal: or epidural:).mp. (3451)
3 1 or 2 (3451)
4 exp CANCER PAIN/ or exp PAIN/ (51404)
5 cancer.mp. or exp Neoplasms/ (104861)
6 carcinoma.mp. or exp CARCINOMA/ (9809)
7 oncol:.mp. (18220)
8 5 or 6 or 7 (110468)
9 3 and 4 and 8 (229)
10 limit 9 to english (226)
11 from 10 keep 1-226 (226)
Appendix B. Catheters and pumps.
The implementation advice provided below is informed by resources found in the environmental scan (referenced where appropriate) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high quality and safe intraspinal analgesia.

Long-term intraspinal analgesic treatment can be provided by:
1) epidural analgesia
2) intrathecal or subarachnoid analgesia

For both routes of administration, there are basically three types of intraspinal delivery systems. They are 1) externalized system; 2) partially externalized system; and 3) totally internalized implanted system.

Externalized System
The external end of the catheter is percutaneous. The catheter may or may not be tunneled subcutaneously.

It is usually indicated for short-term use (hours to days) because of risk for infection and often for epidural use only.

The types of catheter are
- silicone catheter with a closed tip and lateral orifices (e.g., Algoline Intraspinal cath by Medtronic Inc.)
- DuPen epidural catheter with a Dacron cuff for antimicrobial protection
- polyamide nylon epidural catheter for operative use

Injection is through a continuous infusion and less commonly by intermittent injections.

The catheter is connected to an externalized electronic infusion pump.

Partially Externalized System
The external end of the catheter is connected to a subcutaneous access port implanted through a small skin incision. The port is secured by suture loops, and the incision is then closed. Injection is made by placing a needle through the skin into the access port.

It is usually indicated for a longer term use (weeks to years).

The types of access port include the Port-a-Cath epidural port system (Pharmacia Deltec) with a silicone open-tip catheter and an implanted subcutaneous port.

Injection is through a continuous infusion and less commonly by intermittent injections.

The catheter is connected to an externalized electronic infusion pump.

Totally Implanted System
The catheter and the delivery system are completely implanted, thus having a lower risk for infection. A surgical procedure is required.
It is usually indicated for long-term use (life expectancy > 6 to 12 months).

The pumps are made of titanium or stainless steel.

There are several types of implanted systems (e.g., SynchroMed Infusion pump [Medtronic Inc.] and CODMAN® 3000 Drug Pump).

These systems are accessed percutaneously for pump refills into the pump reservoir. The pump is programmable externally through a radio-telemetry link.
Appendix C. Equipment.
The implementation advice provided below is informed by resources found in the environmental scan (Stearns, ONS, BPS, Calgary, Ottawa, and INS [10,23,24,31,33,35]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia. It is important to recognize that each type of catheter system requires its own specific process of care. Some catheters, such as the subcutaneous port system will require flushing to check for correct placement of the gripper needle, while percutaneous catheters will not require flushing.

Access to equipment and its appropriate application is essential to intraspinal analgesia delivery.

General:
- Epidural devices should be aspirated to ascertain the absence of spinal fluid and blood before medication administration (INS)
- Intrathecal devices should be aspirated to ascertain the presence of spinal fluid and the absence of blood before medication administration (INS)
- A 0.2-micron surfactant-free, particulate-retentive, and air-eliminating filter should be used for intraspinal medication administration (INS)
- Medication must be preservative-free (INS)

Straight alcohol or acetone should never be used for site preparation or cleansing due to potential effects as a neurotoxin (INS) However, reduced epidural infection rates were found using chlorhexidine with alcohol as the skin disinfectant (42-46). It is important to allow the disinfectant to dry.

- Continuous intraspinal infusions should be administered by an electronic infusion device with anti-free-flow protection (INS).

Tunneled or untunneled catheters, attached to an external pump:
- Percutaneous catheters or those that can be implanted in home, hospice, or palliative care unit quickly and with minimal discomfort (Calgary, ONS, BPS, Ottawa, and Stearns)
- Require frequent monitoring for infection and migration and restrict a patient’s mobility (BPS)

Implantable drug delivery systems:
- Fully implanted fixed-rate or programmable drug delivery system (ONS, BPS, Ottawa, and Stearns)
- Pump is composed of a pump body, septum, reservoir, and intrinsic power source (ONS)
- Mobility and functional activity are not adversely affected (BPS)
- Can be used for continuous infusion as well as intermittent bolus therapy (ONS)
- Surgery, sterile conditions required to do implantation (takes about 1 hour) and removal (ONS, BPS, and Stearns)
- Interprofessional infrastructure must be in place (BPS)
- Programmable devices provide flexibility of prescription administration allowing for dose alteration without invasive intervention and in case of malfunction or suspected overdose; the pump can be deactivated without emptying the drug reservoir (BPS)
- An implantable pump must be refilled on a schedule with the interval dependent on drug concentration, drug stability, pump reservoir volume, daily dose, and other treatment
considerations. The pump should never be allowed to become completely empty. Care must be taken not to overfill the pump reservoir, as this will result in over pressurization and over infusion of medication (ONS)

- Accessing, filling, and refilling of implantable delivery devices should be done in accordance with the manufacturer’s directions (INS)

- Links with implant manufacturers and distributors are important for ongoing support and education (Cornwall)
Appendix D: Aftercare.
The implementation advice provided below is informed by resources found in the environmental scan (ONS, BPS, Calgary, and Ottawa [23,24,31,33]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

The following issues should be considered in the aftercare of patients:

- Patients must be cared for in a facility that has staff who are competent in the care of a patient with intraspinal analgesia and where policy and procedures are available and approved.
- Appropriate 24-hour nursing and medical support must be available.
- Patients must be protected from any infectious environment.
Appendix E. Monitoring.
The implementation advice provided below is informed by resources found in the environmental scan (Stearns, ONS, BPS, CCNS, APS, Calgary, Cornwall, Ottawa, and INS [10,23-25,28,31-33,35]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

The following issues should be considered in the monitoring of patients:

- Patients with intraspinal analgesia must be closely and frequently monitored for all vital signs and level of consciousness, using a validated sedation scale.
- Changes in vital signs and level of consciousness must be reported to the appropriate medical staff.
- Regular monitoring of pain using a validated pain assessment tool.
- Regular and documented sensory and motor testing. Changes in sensory and motor block must be reported to the appropriate medical staff.
- Regular assessment of insertion site and documentation and reporting of bleeding, erythema, epidural catheter fibrosis (pain on injection, decreased therapeutic effectiveness), drainage, leakage, displacement, blockade, catheter migration (epidural to intrathecal [subarachnoid]), and tubing attachment.
- Assessment for urinary retention and/or constipation/diarrhea.
Appendix F. Complications and side effects of intraspinal analgesia.
The implementation advice provided below is informed by resources found in the environmental scan (Stearns, ONS, BPS, APS, Calgary, Cornwall, Ottawa, and INS [10,23,24,28,31-33,35]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

The following complications and side effects should be routinely monitored.

- Respiratory depression (Calgary, ONS, INS, and Ottawa)
- Headache (Calgary, BPS, and INS)
- Infection (including abscess, inflammation, tenderness, edema, and swelling) (Calgary, INS, BPS, Cornwall, and Stearns)
- Altered sensation, motor function, or mobility (Calgary, BPS, Cornwall, and Ottawa)
- Neurological damage or change in neurological or mental status (including CSF leak, CSF hygroma, post-dural puncture headache, spinal hematoma, spinal granuloma [due to long-term catheter and high-dose opioid]) (Calgary, ONS, and BPS)
- Change in level of consciousness or sedation (Calgary, INS, and Ottawa)
- Development of tolerance (APS)
- Central nervous system depression (Calgary and ONS)
- Urinary retention (Calgary, ONS, INS, Cornwall, APS, and Stearns)
- Leakage around the catheter insertion/exit site (BPS, INS, Cornwall, and ONS)
- Bleeding (ONS)
- Nausea or vomiting (Calgary, ONS, and INS)
- Constipation (Calgary, APS, and Stearns)
- Pruritus (ONS, INS, Cornwall, and APS)
- Hematoma or tissue trauma (Calgary)
- Back pain (Cornwall)
- Paresthesia (ONS and INS)
- Myoclonus (Calgary)
- Hypotension (Calgary, INS, and Ottawa)
- Cardiovascular toxicity (Calgary)
- Poor pain control
Appendix G: Hospital discharge.
The implementation advice provided below is informed by resources found in the environmental scan (BPS, ASA, Calgary, and Cornwall [24,30-32]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

A comprehensive discharge strategy is a necessary component of the overall patient care plan. Issues that should be considered:

- A clear discharge plan should be initiated prior to insertion of intraspinal catheter.
- Patients’ pain must be stabilized prior to discharge.
- Communication with community nurses and homecare personnel for availability of equipment, including tubing, filters, labels, and drugs are essential prior to discharge.
- Healthcare professionals in the community should receive relevant education.
- Protocols for the care of a patient with intraspinal analgesia that includes troubleshooting should be available to the community staff.
- Patients and family members should be educated with regard to equipment, drug supply arrangements, side effects, complications, and when and who to call when problems are encountered.
- Clear directions for who are the primary and secondary persons most responsible should complications occur following discharge.
Appendix H. Follow-up.
The implementation advice provided below is informed by resources found in the environmental scan (ONS, BPS, Calgary, Cornwall, Ottawa, and INS [23,24,31-33,35]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

A clear follow-up strategy with well-articulated roles and responsibilities for the different members of the care team should be established. Issues for consideration include:

- A primary interventional pain physician must be identified for follow-up guidance.
- A palliative care physician and or family physician and or advanced practice nurse must be identified and regular appointment/visiting plan be in place.
- A primary community nurse should be identified.
- A protocol to support timely admission to hospital or hospice in the event of problems that cannot be resolved locally.
- Should the patient move away from the centre where intraspinal analgesia was initiated, a plan should be in place to allow for a smooth and timely transfer of care.
- Monitoring of the patient should continue in the community as stated above and changes reported to the personnel identified.
Appendix I. Key Clinical Activities.
The implementation advice provided below is informed by resources found in the environmental scan and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

There are a range of key clinical activities in the administration of intraspinal analgesia. Outside of “catheter insertion” (interventional pain physician) and “medication preparation” (pharmacist), the individual roles/responsibilities of each team member will be site specific. These must be clarified and agreed upon, preferably *before* catheter insertion. The roles and responsibilities include but are not limited to:

- patient selection
- inpatient admission and discharge planning
- ongoing assessment and medication management
- monitoring for side effects and complications
- care of the catheter site
- equipment maintenance
- patient/family education
Appendix J: Suggested health professional responsibilities regarding intraspinal care. The implementation advice provided below is informed by resources found in the environmental scan (ONS, ASA, Calgary, St Wilfrid’s, and INS [23,30,31,34,35]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

An interprofessional team is required to ensure safe planning, administration, aftercare, discharge and follow-up of the patient. The recommended members of the team and the responsibilities of each participant are identified below.

Responsibilities of interventional pain physicians:
- Intraspinal analgesia insertion (Calgary and St Wilfrid’s)
- Documentation of catheter position (St Wilfrid’s)
- Instruction and training on catheter management to medical and nursing staff in hospital (St Wilfrid’s)
- Medication orders (Calgary and St Wilfrid’s)
- Management of patient, medication, analgesia-related complications (Calgary)
- Collaborating with other healthcare providers in pain management coordination (ASA)

Responsibilities of palliative care physicians:
- Medication orders (Calgary)
- Management of patient, medication, analgesia-related complications (Calgary)

Responsibilities of pharmacists:
- Dosages (Calgary)
- Side effects (Calgary)
- Issues around discharge planning and continuity of care (Calgary)
- Patient and family teaching (Calgary)

Responsibilities of nurses:
- Demonstrate competency in the use of intraspinal analgesia, including knowledge of anatomy and physiology, neuropharmacology, assessment of placement and function of the access devices, care and maintenance practices, and documentation (INS, Calgary, St Wilfrid’s)
- Patient assessment (Calgary and St Wilfrid’s)
- Care of catheter site. Visually inspect the site and palpate for tenderness. Any evidence of infection should be documented and reported to the physician (INS and St Wilfrid’s)
- Dressing changes - the optimal time is dependent on the dressing material, age and condition of the patient, infection rate reported by the organization, environmental conditions, and manufacturer’s directions (INS)
- Inspecting the condition and length of the intraspinal access device upon removal, implementing nursing interventions as required, and documenting observations and actions (INS)
- Equipment maintenance (St Wilfrid’s)
- Troubleshooting, problem solving (Calgary)
- Report any intraspinal access device defect to the risk management department, the manufacturer, and regulatory agencies (INS)
• Nursing management of complications (Calgary and INS)
• Patient and family teaching (Calgary and INS)
• Coordination of medication and supply orders and prescription changes in the community (Calgary)
• Topping up, recharging of continuous infusion if qualified and with appropriate training (St Wilfrid’s)
• After access device removal, the site should have an occlusive sterile dressing applied. The access site should be inspected every 24 hours until the site is epithelialized (INS)
• Specially trained nurses may administer intraspinal medications and perform access device repair or removal on the order of the prescribing physician authorized by their local nursing practice regulations (INS and ONS)
Appendix K: Professional education and competencies.
The implementation advice provided below is informed by resources found in the environmental scan (ONS, BPS, SIGN, Calgary, St Wilfrid’s, and INS [23,24,26,31,34,35]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

The members of the team must be qualified in the administration of intraspinal analgesia. Issues for consideration include:

- The physician implanting the catheter must have appropriate training
- Nurses must be knowledgeable about the principles of intraspinal drug administration
- Educational activities for nurses should cover specific intraspinal drug delivery systems, insertion and access procedures, care and maintenance (assessment of site, dressing change, and flushing and aspiration procedures), potential complications and interventions, patient and family education
- The physician or advanced practice nurse responsible for communication with nursing staff and subsequent medication changes should have knowledge and competency in managing patients with intraspinal analgesia
- The pharmacist should have knowledge and competency in preparing medication concentrations and delivery methods
Appendix L: Patient and family education.
The implementation advice provided below is informed by resources found in the environmental scan (ONS, BPS, CCNS, APS, ASA, Calgary, Cornwall, and Ottawa [23-25,28,30-33]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

As with any care option, patient and family education is essential. As it relates to this clinical situation, patient information guides should include but are not limited to information addressing:

- What is epidural or intrathecal pain management?
- Why I need epidural or intrathecal pain management?
- Description of the catheter insertion process.
- Description of postoperative in hospital monitoring and preparing for discharge.
- Description of the follow up care required.
- Description of the equipment the patient will have.
- Description of the risks and complications.
- When and who to contact if problems arise.
Appendix M: Patient safety.
The implementation advice provided below is informed by resources found in the environmental scan (ONS, BPS, Calgary, Cornwall, Ottawa, and INS [23,24,31-33,35]) and the deliberations among the working group members. While acknowledging there is typically little explicit direct evidence supporting the statements, the working group believes they provide practical advice that can facilitate the delivery of high-quality and safe intraspinal analgesia.

There are specific considerations related to the safety of intraspinal analgesia administration. These include:

- Strict aseptic conditions must be maintained in all aspects of intraspinal analgesia administration.
- All equipment must be intended specifically for epidural or intrathecal use only and each piece (pump, tubing, catheter, solution bag, dressing, etc) must be appropriately labelled (different colors for epidural and intrathecal) denoting purpose and date and time of initiation of infusion.
- Some intraspinal drug delivery systems are at risk for significant damage and malfunction from MRI scanners and advice on how to proceed will be required from individual scanning departments and the specific drug delivery system manufacturers.
- Scanners in airports and shops must be avoided. Patients should carry cards indicating that special accommodation is required.
- Patients should carry an identification card with them at all times indicating the make and model of any intraspinal device, the drugs within the pump, and the current or last prescribed dose.
- Patients should have a MedicAlert emblem that alerts healthcare professionals to the presence of an intraspinal device in emergency situations.
- Patients should avoid sports or activities that may cause injury or dislodgement of the pump.
Evidence-Based Series #18-1: Section 3

Intraspinal Techniques for Pain Management in Cancer Patients: EBS Development Methods and External Review Process

J. Myers, V. Chan, V. Jarvis, C. Walker-Dilks, and the Palliative Care Clinical Program

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: May 5, 2009

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province to whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

• **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review

This EBS was developed by a working group of healthcare professionals identified by the Palliative Care Clinical Program of the CCO PEBC. The working group members included a palliative care physician, an anaesthesiologist, and an advanced practice nurse. The series is a convenient and up-to-date source of the best available evidence on intraspinal pain techniques in cancer patients developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Both reviewers agreed that the document was comprehensive and adequately covered the components of clinical effectiveness and implementation of intraspinal analgesia in cancer patients. One reviewer observed that the evidence supporting the clinical effectiveness had substantial limitations that did not stand out in the guideline. The working group addressed this by adding more explanation of supporting evidence in the Key Evidence section of the guideline.

External Review by Ontario Clinicians

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, Sections 1 and 2 of this guideline were circulated to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence.

BOX 1:

QUESTIONS
1. In patients with cancer-related pain, what is the effectiveness of intraspinal pain management techniques?
2. What are the indications for use of intraspinal analgesia?
3. What are the key implementation considerations that should be considered when offering intraspinal analgesia to cancer patients? In particular, what aspects of the practice setting, practice team, and education and training of health professionals, patients, and family need to be addressed?

TARGET POPULATION
Patients with cancer with disease-related pain. Procedure-related pain was
not of interest.

INTENDED USERS
This guideline is targeted for:
Clinicians involved in the delivery of intraspinal analgesia for cancer patients.
Clinicians involved in the care of cancer patients who are eligible of intraspinal analgesic intervention and who would make referrals to the appropriate care team.

RECOMMENDATIONS AND KEY EVIDENCE
Recommendations
I. Clinical Effectiveness
   1. Evidence supports the use of intraspinal analgesia for certain patients in the management of their cancer pain.
   2. Intraspinal analgesia with an opioid alone, local anesthetic alone, or opioid and local anesthetic combined is each a reasonable option.

II. Indications for Use of Intraspinal Analgesia
   Patient selection and eligibility
   1. Intractable pain control despite aggressive pharmacologic interventions by conventional administration routes (oral, rectal, transdermal, subcutaneous, and intravenous)
   2. Dose-limiting side effects experienced from conventional administration routes

Contraindications
   1. Active or local infection at the site of catheter insertion or pump implantation
   2. Anticoagulation required at the time of insertion
   3. Raised intracranial pressure
   4. Spinal pathology that may lead to spinal hematoma

Additional considerations
   1. Careful consideration must be given to patient selection
   2. The availability of appropriate equipment, supplies, expertise, and around-the-clock clinical support
   3. The expectation that intraspinal analgesia would improve a patient's quality of life and level of function
   4. Informed consent has been given by patient or substitute decision maker
   5. Availability of home care nursing and medical support for intraspinal catheter care
   6. Patient general medical condition is amenable to intraspinal analgesia
   7. For an fully implanted system, a screening trial is recommended; for intraspinal analgesia using an external pump, a trial is not necessary

III. Key Implementation Considerations
   1. Long-term intraspinal analgesic treatment can be provided by epidural analgesia or intrathecal (subarachnoid) analgesia. For both routes of administration, there are basically three types of intraspinal delivery systems: externalized system, partially externalized system, and totally
internalized implanted system.

2. Planned length of use should be a determining factor for choosing which pump to use.

3. Medication must be preservative free.

4. Straight alcohol or acetone should never be used for site preparation or cleansing. Disinfectants containing alcohol may be used, but must be allowed to dry prior to use.

5. Patients require admission for intraspinal placement, and the facility must have health personnel who are competent in the care of patients with intraspinal analgesia and policy and procedures that are available and approved.

6. While in hospital post-procedure, routine monitoring of patients is required for all key clinical indicators including vital signs, pain, sensory and motor functioning, and complications and side effects. Routine monitoring of insertion site is also required.

7. A clear discharge plan is required as defined by protocols, that includes roles and responsibilities of care providers to ensure timely response should complications arise and appropriate patient follow-up by members of the team.

8. The care team should consist of anesthesiologists, nurses, palliative care physicians, pharmacists, and primary care providers.

9. All members of the team should have appropriate and specialized training in accordance with professional college/association standards and certification.

10. Patients and family members should be fully informed in all aspects of intrathecal pain management care. This includes knowing whom and when to call for support, should complications arise.

11. Strict aseptic conditions must be maintained in all aspects of intraspinal analgesia administration.

12. All equipment should be compatible with epidural and intrathecal use (pump, tubing, catheter, solution bag, dressing, etc), must be appropriately labelled (different colours for epidural and intrathecal), and should be dated at time of equipment change.

Patients should have a MedicAlert emblem that alerts healthcare professionals to the presence of an intraspinal device in emergency situations.

For the complete summary of implementation issues and considerations, readers are referred to Appendices B through M in Section 2: Evidentiary Base of this document.

**Key Evidence**

The database literature search yielded two systematic reviews, one consensus document, and 12 randomized controlled trials (RCTs) that addressed the questions of clinical effectiveness and clinical indications. The use of intraspinal techniques was effective in controlling pain in patients with cancer and noncancer pain who no longer achieve adequate pain control by other routes. For pain control, intraspinal analgesia was as effective as or better than conventional medical management and was generally associated with fewer side effects. Furthermore, the addition of a local anesthetic to an opioid improved analgesic efficacy and reduced the dose requirements for either drug alone. However, there is insufficient evidence to recommend one drug option or regimen over another.
The systematic review and RCT evidence varied in terms of interventions tested and methodological quality. Insufficient evidence existed to recommend one particular intraspinal technique over another or to identify the optimal intraspinal medication. However, the evidence showed that intraspinal analgesia was effective in controlling pain in patients with cancer who could no longer achieve pain relief by other methods.

The environmental scan yielded eight practice guidelines, four local practice algorithms, and one practice standard that addressed the implementation issues related to patient selection, contraindications, monitoring, aftercare, follow-up, hospital discharge, equipment, practice team, professional competencies, patient education, and/or patient safety.

**Methods**

**Targeted Peer Review:** During the guideline development process, four targeted peer reviewers from Ontario considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report, and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on October 3, 2008. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The working group reviewed the results of the survey.

**Professional Consultation:** Feedback was obtained through a brief online survey of healthcare professionals who are the intended users of the guideline. Healthcare professionals in the fields of palliative care and nursing were identified from the PEBC database and were contacted by email to inform them of the survey. Furthermore, lists of healthcare professionals from relevant Canadian organizations (e.g., palliative care, advance practice nursing, interventional pain physicians) were identified from the Internet. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on December 16, 2008. The consultation period ended on February 2, 2009. The working group reviewed the results of the survey.

**Results**

**Targeted Peer Review:** Three responses were received. Key results of the feedback survey are summarized in Table 9.
Table 9. Responses to nine items on the targeted peer reviewer questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Lowest Quality (1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
<th>(6)</th>
<th>Highest Quality (7)</th>
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<tbody>
<tr>
<td>1. Rate the guideline development methods.</td>
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<tr>
<td>(Consider: The appropriate stakeholders were involved in the development of the guideline. The evidentiary base was developed systematically. Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs were made.)</td>
<td></td>
<td>2</td>
<td>1</td>
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<td>2. Rate the guideline presentation.</td>
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<td>(Consider: The guideline is well organized. The recommendations were easy to find.)</td>
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<td>3. Rate the guideline recommendations.</td>
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<td>(Consider: The recommendations are clinically sound. The recommendations are appropriate for the intended patients.)</td>
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<td>4. Rate the completeness of reporting.</td>
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<td>2</td>
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<tr>
<td>(Consider: The guideline development process was transparent and reproducible. How complete was the information to inform decision making?)</td>
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<tr>
<td>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
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<td>1</td>
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<td>6. What are the barriers or enablers to the implementation of this guideline report? Responses are compiled in the comments section below.</td>
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General Questions: Overall Guideline Assessment

<table>
<thead>
<tr>
<th>Overall Quality of the Guideline Report</th>
<th>Lowest Quality (1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
<th>(6)</th>
<th>Highest Quality (7)</th>
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<td></td>
<td>Strongly Disagree (1)</td>
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<tr>
<td></td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6)</td>
<td>Strongly Agree (7)</td>
<td></td>
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<td>8. I would make use of this guideline in my professional decisions.</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>9. I would recommend this guideline for use in practice.</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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Summary of Written Comments

The targeted reviewers agreed that the methods used to formulate the guideline and the literature review were sound and that the recommendations were consistent with the evidence. The main criticisms contained in the written comments were that the document did not provide enough detailed guidance and the recommendations were too generic. Specific observations and suggestions were:

- Broaden/strengthen the evidence base by including non-malignant pain literature, particularly in presenting pharmacotherapeutic options.
- Include discussion on choice of epidural vs. intrathecal administration route.
- Elaborate on harms and complications associated with intraspinal analgesia.
- Clarify recommendations regarding anticoagulation.
- Provide specific drug options.
- Define “around the clock clinical support.”
Some of the barriers to implementation of the guideline indicated by the targeted reviewers included the intensive care of the patients required (e.g., frequent vital sign monitoring or around the clock support) and lack of familiarity with the procedure in the community (community hospital and home care) to whom the majority of patient care will fall after catheter insertion.

It was indicated that implementation of the guideline would be enabled through emphasis on staff education and skill development to increase knowledge and familiarity with intraspinal techniques. Patient and family education was also noted to be important in contributing to implementation.

Professional Consultation: Twenty responses were received. Key results of the feedback survey are summarized in Table 10.

Table 10. Responses to four items on the professional consultation survey.

<table>
<thead>
<tr>
<th>General Questions: Overall Guideline Assessment</th>
<th>Lowest Quality (1) (2) (3) (4) (5) (6)</th>
<th>Highest Quality (7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rate the overall quality of the guideline report.</td>
<td>2 2 8 7</td>
<td></td>
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<tr>
<td>2. I would make use of this guideline in my professional decisions.</td>
<td>1 4 2 6 5</td>
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<tr>
<td>3. I would recommend this guideline for use in practice.</td>
<td>1 4 1 5 8</td>
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<tr>
<td>4. What are the barriers or enablers to the implementation of this guideline report? Responses are compiled in the comments section below.</td>
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</table>

Summary of Written Comments

Several reviewers surveyed in the professional consultation reiterated the barriers to implementation noted by the targeted reviewers. These observations included a lack of expertise and familiarity with intraspinal pain control techniques both in the hospital and in the community, the high levels of coordination required among various healthcare professionals and sites to administer intraspinal pain control, a lack of resources in the community, and specifically a lack of anesthesia resources.

Some reviewers urged that the use of intraspinal pain control not be viewed as the last option. One reviewer observed that the guideline should form one part of a province-wide plan for offering intraspinal pain control which would also include a policy and procedure manual, training video, and supporting resources.
**Modifications**

**Including non-malignant pain literature**

The selection criteria for the evidence base restricted the patient population to cancer patients with cancer-related pain. Efforts were made in the discussion of clinical effectiveness to include guidelines, systematic reviews, and RCTs that concerned cancer pain. Documents that addressed non-malignant pain as well as cancer pain were included in both the systematic review and environmental scan but the emphasis for this guideline was on cancer pain.

One reviewer cited a 2007 update of the polyanalgesic consensus conference (3), which we had not identified in our literature search. This consensus conference included a literature update to January 2007 presenting preclinical and clinical data on intrathecal agents and discussion of the consensus panelists. Citing the 2004 Staats RCT (4) and recent approval by the U.S. Food and Drug Administration, the panelists recommended the addition of ziconotide to the options for first-line intrathecal therapy. Reference to this updated consensus conference was added.

**Epidural vs. intrathecal administration route**

This was a comparison the working group was interested in addressing, but no studies were identified that compared epidural with intrathecal administration. Discussion of different devices and systems was added to the evidentiary base.

**Elaborate on harms and complications**

Several reviewers requested additional detail on harms and complications associated with the use of intraspinal analgesia. Clarification on the management of anticoagulation was requested. Further information on contraindications was added to the evidentiary base.

**Provide specific drug options**

The working group refrained from becoming prescriptive in the advice provided in this guideline, particularly concerning drug options. The choices of intraspinal routes and agents must be made by the interventional pain physician and may be influenced by several different factors.

**Define “around the clock clinical support”**

This pertains to the close attention that must be given to patients receiving intraspinal analgesia, particularly immediately after insertion. The BPS indicates that “as complications are potentially life threatening, arrangements must be in place for 24-hour medical and nursing coverage.”

**Other modifications**

A number of errors and inconsistencies were identified that have been corrected in the manuscript. It was suggested the term “anesthetist” be replaced with “interventional pain physician,” and this has been done throughout the manuscript.

**Conclusion**

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.
Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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REFERENCES

