

# Intrathecal Drug Delivery for the Management of Cancer Pain

## A Multidisciplinary Consensus of Best Clinical Practices

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**D**espite increasing awareness and education, cancer pain remains undertreated.<sup>1-5</sup> To address this problem, a multidisciplinary panel of experts gathered in October 2003 to develop consensus recommendations for the management of intractable pain in patients with cancer. The need was conceived by a multidisciplinary group of physicians subsequent to the completion of a prospective, multicenter, randomized trial comparing an implantable drug delivery system with comprehensive medical management. Oncologists in this group noted that despite the expansion of knowledge about the benefits of intraspinal analgesia, there was a lack of guidelines for the adoption of advanced pain management techniques in appropriate clinical circumstances, and most specifically for the use of intraspinal drugs in cancer pain.

The author (L. Stearns) participated in the Polyanalgesic Consensus Conference in 2003 and proposed a similar meeting for cancer pain. Recognizing that a multidisciplinary approach would ensure the highest level of patient care, panel

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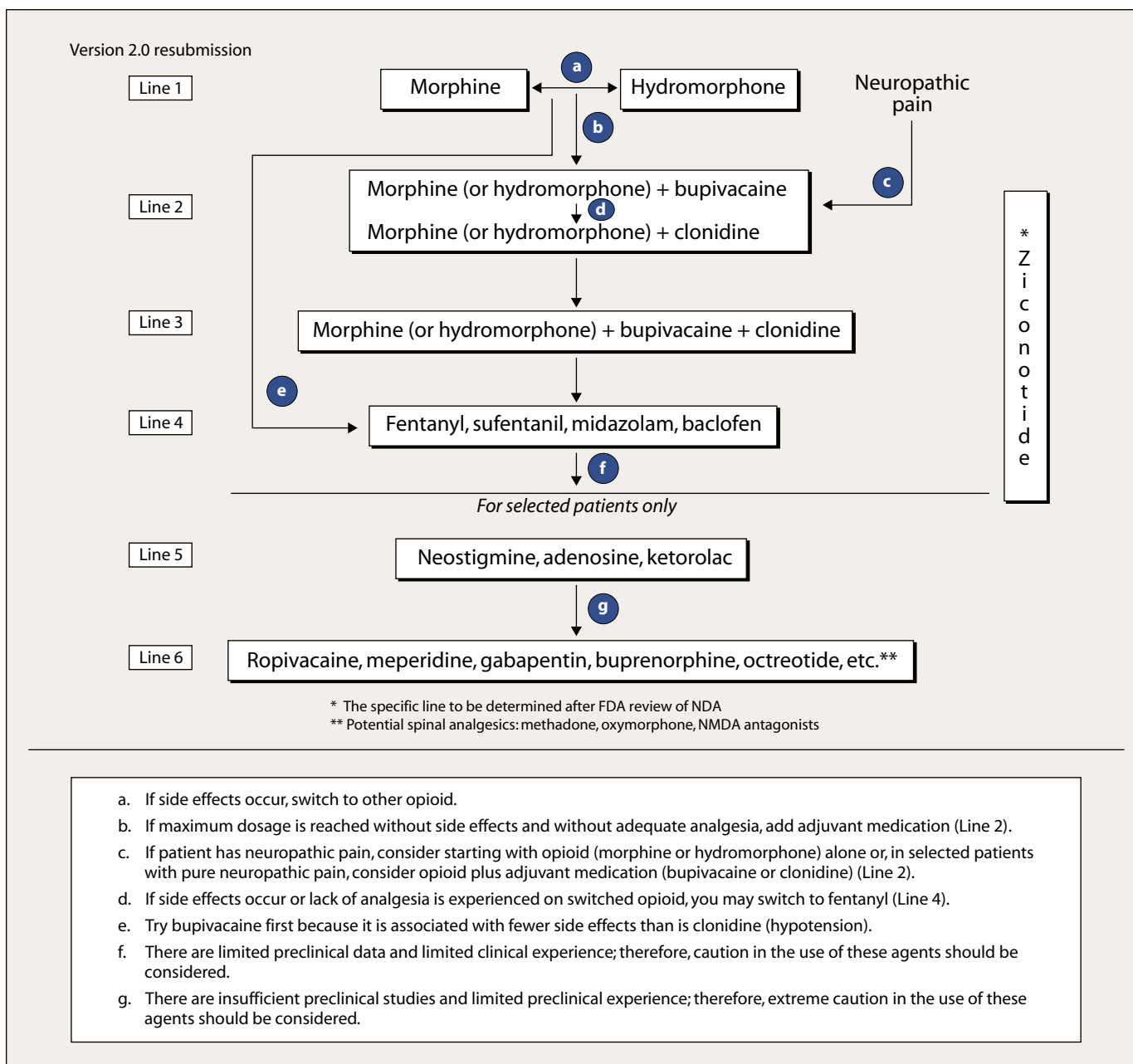
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**Abstract** A substantial number of patients with cancer suffer considerable pain at some point during their disease, and approximately 25% of cancer patients die in pain. Providing effective pain management for patients with severe pain that impacts quality of life can present the oncologist or palliative care specialist with complex clinical challenges that often require multifaceted therapeutic measures. This paper presents multidisciplinary consensus-based recommendations for the treatment of intractable cancer pain using intrathecal drug delivery systems, which offer rapid and effective pain relief with less toxicity relative to oral or parenteral administration. Intrathecal drug delivery systems can be highly effective in a variety of patient settings, including cases of refractory pain, diminished performance status, poor tolerability of oral medications, polyanalgesia for complex pain, and inadequate dosing due to addiction concerns. The use of implantable or external systems is discussed, as well as implantation procedures, drug titration recommendations, and management of potential side effects. The authors offer a newly developed algorithm for delivering intraspinal analgesia in patients with cancer. The intent is that increased understanding of available options for truly effective pain management in the oncology and palliative care arena and the benefits of multidisciplinary cooperation will translate into genuine improvements in patient quality of life and a measurable decrease in the number of patients who suffer needlessly in their final days.

members who treated large numbers of cancer patients or were experienced in intraspinal drug delivery were invited from a range of disciplines. These specialists included pain management physicians, neurosurgeons, medical oncologists, radiation oncologists, and palliative care physicians. This article represents the panel's consensus statement, and is designed to raise awareness among oncologists and palliative care physicians of the benefits and practical management considerations of intraspinal analgesia.

The consensus was that the oncologist or palliative care physician can incorporate intrathecal drug delivery into clinical practice provided he or



**Figure 1** Update of Clinical Guidelines for the Use of Intraspinal Drug Infusion in Pain Management

Recommendations for intraspinal polyanalgesia in patients with chronic pain and cancer patients who are considered long-term survivors. Reprinted with permission from Hassenbusch et al.<sup>22</sup> Abbreviations: NDA = new drug application; NMDA = N-methyl-D-aspartate

she gains a basic understanding of the technology, medication dosages, and titration regimens used for delivering drugs in the intrathecal space (Figure 1).<sup>6</sup>

Comprehensive medical management (CMM) of pain includes the use of analgesics as well as adjuvant medications. Although these medications can effectively control pain in most patients with cancer, side effects such as fatigue, anorexia, loss of short-term memory, sedation, delirium, constipation, and nausea can adversely affect performance status and diminish function and quality of life to the extent that

anticancer therapies may not be tolerated. Compounding this problem is the titration of adjuvant medications for pain control, which can take days to weeks, resulting in patient frustrations associated with poorly controlled pain, worsening side effects, and reduced performance scores.

**Role of Intrathecal Drug Delivery**

Intrathecal drug delivery offers an effective pain-control approach for the small percentage of cancer patients whose pain is not otherwise controlled or who develop analgesic-related

toxicities. A 2002 randomized multicenter clinical trial investigated the safety and efficacy of an intrathecal drug delivery system (IDDS) plus CMM versus CMM alone in patients with refractory cancer pain.<sup>7</sup> The authors concluded that patients receiving IDDS plus CMM had reduced pain, fewer common drug toxicities, and improved survival compared with patients receiving CMM alone. Although the IDDS and CMM group achieved better outcomes than the control group, results from the trial also demonstrated that algorithm use by pain specialists in the control group receiving CMM alone also reduced cancer pain by 39% and pain medication toxicity by 17%. Improvement in pain reduction with use of algorithms was similarly observed by Du Pen and colleagues<sup>8</sup> in a randomized trial of routine oncology care versus algorithms. The panel thus recommended use of algorithms for the management of cancer pain.

Administration of intrathecal opioids and adjuvant medications also allows reductions of up to 200% in the amount of administered oral or parenteral medication.<sup>9-11</sup> In addition to reduced dosages, intrathecal opiate and adjuvant medications enhance pain control with minimal side effects. The receptors targeted are virtually the same as those targeted with oral, parenteral, and transdermal medications. However, because side effect profiles are dramatically improved with intrathecal delivery, drug titration requires hours instead of days, and pain can be aggressively treated with less risk of life-threatening toxicities. Rapid pain relief also results in fewer hospitalizations for pain control and thus saves healthcare dollars.<sup>12</sup>

### Targeted Receptors

Like oral, parenteral, and transdermal medication regimens, IDDS targets specific receptors to relieve pain, as shown in Table 1. Most physicians are familiar with the simultaneous use of these medications in patients with complex pain syndromes. However, the polyanalgesic approach may increase symptom side effects when delivered by the intravascular or oral route, especially when high doses are required. Polyanalgesia administered in the intrathecal space provides aggressive pain control by direct distribution of the drug to areas of the nervous system generating the discomfort, with minimal drug concentrations and less toxicity. Furthermore, toxicities associated with shortened survival (eg, anorexia, decreased gut motility, and pseudo-obstructions) may be minimized or eliminated, and other serious side effects that diminish quality of life may be significantly reduced.<sup>7</sup> Ambulatory patients are also less likely to develop thromboses, pulmonary emboli, atelectasis, pneumonia, or osteoporosis, which contribute to morbidity and mortality in debilitated cancer patients.

Although intraspinal drug delivery may enhance the ability of oncologists and palliative care physicians to treat complicated pain syndromes in cancer patients, a number of factors have hampered its widespread use. These factors include a lack of understanding of the relevant indications for this mode of analgesia and of the types of patients who may benefit. Furthermore, at centers where expertise with intraspinal analge-

**Table 1**

### Receptor Targets for Pain Medications

RECEPTORS TARGETED	ORAL MEDICATION	IDDS MEDICATION
<b>Nociceptive pain</b>		
Mu	Opioids (morphine, hydromorphone, fentanyl, methadone, meperidine)	Same
<b>Neuropathic pain</b>		
GABA	Anticonvulsants, benzodiazepine, tizanidine	Baclofen, midazolam
Alpha-2 receptors	Clonidine	Same
Dopaminergic receptors	None	Droperidol
NMDA	Methadone, ketamine	Same
Sodium channel receptors	Anti-arrhythmic (mexiletine)	Local anesthetics
<b>Sympathetic and visceral pain</b>		
Alpha-2 receptors	Clonidine	Same
Sodium channel receptors	Anti-arrhythmic (mexiletine)	Local anesthetics

Abbreviations: IDDS = intrathecal drug delivery system; GABA = gamma-amino-butyric acid; NMDA = N-methyl-D-aspartate

sia as a pain management tool is limited, oncologists are not likely to refer patients for implantation of IDDS.

To facilitate education and dispel misperceptions, the expert panel developed an algorithm to assist the incorporation of IDDS into oncology clinical practice. The panel agreed that the algorithm should include the following topics: 1) patient selection, 2) screening trials and pump implantation considerations, 3) long-term management issues, and 4) drug utilization.

### Patient Selection

IDDS is an attractive option for pain management in patients with refractory cancer pain as well as analgesic-related toxicities. The panel agreed that it should be recommended as an option for patients in a variety of situations. Characteristics of patients who might benefit from IDDS are shown in Table 2. Patients who are intolerant of oral opioids or concerned about dependence or addiction may be receptive to intraspinal therapy. Use of local anesthetics to block both nociceptive and neuropathic pain reduces the amount of pain medication needed. Another scenario in which toxicity concerns may prompt a physician to consider IDDS is in cancer patients receiving highly toxic chemotherapy regimens. In this case, the use of IDDS for pain control has a lower risk of additive adverse effects compared with conventional pain treatments, and therefore patients are more likely to maintain performance scores and are able to tolerate aggressive anticancer therapies.<sup>7</sup>

Patients with pain refractory to high-dose opioids also benefit from intraspinal, targeted receptor therapy. Further, the addition of gamma-amino-butyric acid agonists and alpha-2 agonists to an opioid/local anesthetic regimen allows for control of severe neuropathic pain that may be refractory

**Table 2**  
Patient Selection for Intrathecal Drug Delivery System

UNDERLYING CONCERN	GOAL	CLINICAL SCENARIOS SUGGESTING NEED TO EXPLORE INTRASPINAL THERAPY
Toxicity or dependency	Reduce dose	<ul style="list-style-type: none"> <li>• Inability to tolerate adequate oral medications</li> <li>• Fear of side effects or addiction</li> <li>• Receiving aggressive chemotherapy regimens with high toxicity profile</li> </ul>
Disease or treatment-related refractory, worsening, or severe pain	Provide more effective pain treatment options	<ul style="list-style-type: none"> <li>• Pain refractory to oral regimens</li> <li>• Presence of visceral tumors of autonomic dysfunction that results in anorexia, gut dysmotility, and pseudo-obstructions or bowel obstructions</li> <li>• Severe neuropathic pain (plexopathies)</li> <li>• Impending spinal cord paralysis</li> <li>• Acute, unstable pathologic fractures</li> <li>• Complex regional pain syndromes secondary to surgery, chemotherapy, or radiation treatment</li> </ul>

to oral adjuvant regimens. In patients with visceral tumors or autonomic dysfunction that results in gut dysmotility, anorexia, early satiety, and nausea, IDDS improves gut function through chemical sympathectomy. Chemical sympathectomy is achieved by administration of local anesthetics and clonidine (Duraclon) to the upper thoracic nerve roots, which blocks pain generating from visceral afferent fibers and reduces efferent fiber signals that influence visceral dysmotility. Following intrathecal therapy, this panel noted that patients have increased appetite, less constipation, fewer pseudo-obstructions, and augmented weight gain. Intraspinal therapy is also beneficial in patients with severe neuropathic pain from tumor invasion of neural plexuses or with painful impending spinal cord paralysis. A polyanalgesic approach directed at the nerve roots above the pain generator lesion allows chemical blockage of pain signals. This approach is used in cases in which neurolysis (both surgical and chemical) had been used in the past. By avoiding permanent nerve destruction, the psychological consequences of irreversible nerve lesioning are avoided.

Finally, in cancer survivors who develop complex regional pain syndrome secondary to cancer treatment, intraspinal therapy may offer an effective long-term treatment option.

### Drug Delivery Systems

Implantable devices used to deliver intrathecal therapy include a disposable short-term intrathecal catheter, a long-term tunneled intrathecal catheter, and an implantable infusion pump and catheter system, with both programmable and nonprogrammable options.

Delivery systems for the therapy are selected based on patient categories (according to expected survival) and cost efficiency. For the terminal patient, a short-term intrathecal catheter can be implanted at the patient's home, hospice, or palliative-care unit at minimal cost. The procedure takes approximately 10 minutes and causes minimal discomfort. The other systems are usually placed in sterile conditions under fluoroscopic guidance. The long-term systems can generally be implanted in less than 1 hour. Risks of the procedure are similar to those associated with implanting central venous ac-

cess systems; however, the possibility of nerve injury secondary to needle or catheter placement also exists with implantation of a drug delivery system.

Specifically, an externalized system is used for patients with a life expectancy of less than 3 months. These systems require constant home health monitoring and are therefore more expensive than indwelling systems after 2–3 months.<sup>13</sup> When life expectancy is greater than 3 months, an implantable infusion pump and catheter system are recommended. Due to the complexity and dynamic state of cancer pain, the use of a programmable pump may be preferred in this population.

Infusion costs are generally comparable for externalized intraspinal and parenteral drug delivery because similar equipment is used. Patients unable to tolerate oral or transdermal medications who require parenteral pain medication have decreased drug utilization with the intraspinal approach, which may provide significant cost savings to payors. Like intravenous and subcutaneous patient-controlled analgesia systems, externalized IDDS may be programmed with both a continuous rate and patient-controlled bolus options.

### Screening Trials and Implantation Considerations

The panel recommends a screening trial before proceeding with pump implantation. A trial provides patients with rapid pain relief and offers a general sense of the therapy. It also gives physicians the opportunity to evaluate patient responses and potential side effects (eg, nausea, pruritus) to specific medications, which aids in selecting appropriate agents. A trial is not necessary for patients receiving externalized intrathecal systems. Screening trials are performed by physicians knowledgeable in intraspinal catheter insertion and initiation of intrathecal drug delivery therapy (eg, neurosurgeons, pain physicians).

The trial should employ a continuous infusion catheter (the short-term catheter described earlier) to provide intrathecal or epidural drug delivery. Use of fluoroscopy is recommended to confirm catheter placement and to expedite the procedure. Sedation is given upon request but often is not necessary. Following implantation of the trial catheter, the patient is observed overnight in the hospital or hospice unit to

monitor pain medication titration and side effects. Some centers, however, have effectively utilized a single-dose trial.<sup>11</sup>

Patients can proceed to implantation 1 day following a successful trial so that cancer chemotherapy regimens are not delayed. In these situations, patients receive antibiotic prophylaxis covering skin flora 1 hour prior to the procedure and the trial catheter is removed immediately before the surgery.<sup>14</sup>

### CONTRAINDICATIONS AND SURGICAL RISKS

Several factors should be considered before proceeding with a trial catheter and/or pump implantation. Absolute contraindications include unstable vital signs, anticoagulant therapy, and ongoing infection or sepsis. Other factors that may affect surgical risk include hematologic abnormalities, wound infections, emaciation, and the presence of tumors in the spinal canal.

**Anticoagulant therapy.** In patients receiving anticoagulants, risk stratification for development of blood clots and pulmonary emboli dictates treatment. Patients considered at low risk can have anticoagulants stopped and proceed with trial and implantation when international normalized ratio value normalizes. Oral anticoagulants may be resumed the night of surgery. In the moderate-risk group, low molecular weight heparin (LMWH) may be administered to protect against thrombosis until international normalized ratio decreases to 1.5. LMWH should be discontinued 24 hours prior to the trial and pump implantation scheduled for the following day. If the trial extends beyond 24 hours, the patient should resume LMWH. LMWH is discontinued 24 hours before the implantation procedure and is resumed 12 hours postoperatively along with oral anticoagulants.<sup>15</sup>

In high-risk patients, a heparin drip may be used to maintain anticoagulation until 4–6 hours before surgery. A thromboelastograph is useful in guiding therapy and in determining when it is safe to proceed with spinal access. Once the catheter is placed, risk of spinal bleeding is low. Postoperatively, the heparin drip can be resumed or LMWH started along with oral anticoagulants. If risk of pulmonary emboli is high, placement of an inferior vena cava filter prior to surgery should be considered.

**Hematologic factors.** The panel consensus is that a white blood cell (WBC) count of  $\leq 2 \times 10^9/L$  and/or an absolute neutrophil count of  $\leq 1,000/\mu L$  may be a contraindication for surgical placement of an IDDS pump, depending on the patient's condition. Patients with a lower WBC count (eg,  $\leq 1.5 \times 10^9/L$ ) may undergo the procedure if growth factor treatment has been started. For patients undergoing aggressive chemotherapy associated with low WBC nadirs, coordination of schedules with the oncologist is recommended to minimize surgical infection risk and to avoid significant delays in cancer treatment.

Thrombocytopenia risk also needs to be addressed in this patient population. If the platelet count is  $\leq 20 \times 10^3/\mu L$ , the risks versus benefits of implantation should be carefully considered. Platelet transfusion may be an option for these pa-

tients; however, risk of antiplatelet antibody formation should be considered prior to transfusion. Normal clot formation and retraction may be demonstrated with a thromboelastograph to determine need for additional platelets.

**Infection and wounds.** Although sepsis is a contraindication to implantation, gross wound infections, if properly managed with aggressive wound care and antibiotics, do not preclude surgery. Antibiotic therapy for appropriate bacterial coverage should be instituted perioperatively and continued for 3 to 4 days postoperatively; if wound cultures are positive, antibiotic therapy should be continued beyond this point until the surgical wound is completely healed.<sup>14</sup> Consultation with an infectious disease physician is recommended in complicated cases. In the immunocompromised patient (eg, human immunodeficiency virus-positive), intrathecal therapy can be safely utilized.

**Emaciation.** Emaciation is not a contraindication to pump implantation, although poor nutritional status may interfere with wound healing. Improving nutritional status prior to implantation is preferable but often not possible because of opioid-induced anorexia and disease-induced cachexia. In patients with low performance scores, a trial of intrathecal therapy may increase appetite, gut motility, and caloric intake. Supplementation with a multivitamin, zinc, and vitamin C may improve wound healing.

**Spinal lesions.** For patients with spinal column instability (eg, bilateral pedicle fracture) surgical stabilization prior to a trial or intrathecal catheter placement is advised, when practical. If the patient is not a surgical candidate, proceeding with a trial and initiation of therapy is recommended. Compression fractures are not a contraindication to a therapeutic trial or pump placement. This technique may be used in combination with vertebroplasty if pain control is ineffective or by itself. In cases of spinal lesions, the trial catheter and the long-term catheter tip should be placed above the lesion.

### POSTOPERATIVE MANAGEMENT CONSIDERATIONS

In the postoperative period, patients may experience spinal headaches, acute increases in pain, infections, pump pocket seromas and hematomas, or pulmonary emboli. Investigators from the Cancer Pain Trial<sup>7</sup> reported a 1% infection rate and seroma/hematoma rate. There is little documentation in the literature regarding other complications. In patients with indwelling systems and an unexplained increase in pain, spinal magnetic resonance imaging (MRI) is recommended to assess the possibility of an inflammatory mass.<sup>16</sup> Other issues to address in the immediate postoperative period include nutritional and biopsychosocial needs, functional assessment for activities of daily living, and rehabilitation services.

**Spinal headaches.** Patients who develop post-dural puncture headaches are initially treated conservatively with fluids, antiemetics, opioids, and caffeine. Persistent spinal headaches may be treated with an epidural blood patch directed near the catheter entry site under fluoroscopic imaging if WBC counts are stable and anticoagulants are not being administered.

**Acute increases in pain.** Increased pain in the immediate postoperative period should be evaluated aggressively. Concerns for epidural bleeding should be evaluated with an MRI. Possible catheter occlusion or leakage should be investigated under fluoroscopy with a catheter dye study. Occasionally, post-dural puncture headaches present with increased low back or neck pain but lessen in intensity in the supine position. Pain should be treated with additional oral or intravenous medication until resolved. Intrathecal dose rate adjustments should be made daily for unresolved cancer pain.

**Infections.** The rate of device-related infections after implantation is low. They usually occur early after implantation and primarily involve the abdominal pocket site. The most common causative organism is *Staphylococcus epidermidis*. Antibiotic therapy should be started at the first sign of device-related infection. Explantation of the device may be necessary but is not common. Conditions that may increase infection risk (diabetes, debilitation, malnutrition, extremes in body habitus, autoimmune disorders, poor hygiene, and fecal incontinence) should be identified and, if possible, managed preoperatively. Chronically infected patients with *Staphylococcus aureus* nasal colonization should receive mupirocin (Bactroban) preoperatively and postoperatively, in addition to the perioperative antibiotics all patients receive 1 hour before incision. Guidelines for the prevention and management of infections related to intrathecal therapy have been published.<sup>14</sup>

**Seromas.** Wound seromas may develop in patients with implanted or externalized systems. Back wound seromas are likely to be secondary to cerebral spinal leaks around the catheter insertion site. If fluid is draining through the wound or around the externalized catheter, the implanting physician should re-evaluate. Persistent leakage does not necessitate catheter removal but should be addressed on an individual basis. Pump pocket seromas are more likely to occur in patients with low protein levels and in the presence of lymphedema or obstructed venous drainage from the area. Infection and spinal fluid leak should be ruled out as causes of excess pump pocket fluid. Repeated drainage of the seroma is not recommended secondary to infection because many seromas self-resolve over time and with use of an abdominal binder. In problematic and painful seromas, placement of a drain and use of an abdominal binder should be considered. Tetracycline or doxycycline 1.0–2.0 g diluted in 20 cc of saline may be injected into the pocket after seroma drainage to seal persistent fluid accumulation (as in pleurodesis). Even with gross ascites and aberrant venous drainage, seromas frequently resolve spontaneously. In the absence of resolution, movement of the pump should be considered.

**Pump pocket hematomas.** Hematomas that develop in the pump pocket of anticoagulated patients are best treated conservatively with an abdominal binder and external pressure.

**Pulmonary emboli.** In patients who are bedridden due to pain, options to prevent pulmonary emboli should be considered. LMWH may be administered to decrease the risk of thrombotic events. Doppler studies of lower extremities to evaluate the pres-

ence of deep venous thromboses may be considered. Any symptom suggestive of a pulmonary embolus in the first postoperative week should elicit an immediate and thorough evaluation.

**Other considerations.** Functional capacity should be reassessed postoperatively. Results regarding activities of daily living, in particular, and related recommendations should be discussed with patients prior to discharge. Consultation of the cancer care team is recommended, when possible, to address the patient's psychological and social needs. In some cases, consultation for rehabilitation services may also be beneficial. Nutritional guidance should be offered when concerns of cachexia, anorexia, and impaired wound healing exist.

## IDDS Management Considerations

### MENINGITIS

The diagnosis of aseptic or viral meningitis in the cancer patient with an intrathecal catheter and/or pump should not cause alarm. Supportive care and neurologic monitoring should be provided until symptoms resolve, but the pump and catheter do not need to be removed. In cases of bacterial meningitis, risk stratification, pain assessment, and life expectancy need to be considered. Removal of the pump and catheter is recommended<sup>14</sup> but may be undesirable because of potential uncontrolled pain. Intravenous antibiotics should be initiated immediately, with more specific treatment prescribed after obtaining spinal bacterial cultures and susceptibilities. If the infection is sensitive to vancomycin and the patient refuses pump removal, intrathecal vancomycin may be administered at 10 mg/d. Based on individual case reports from the authors, this treatment has been used successfully for 6 months in such patients. Other published data demonstrate that intravenous vancomycin combined with epidural vancomycin (150 mg/d for 3 weeks) resolved infection.<sup>14</sup>

### CONCURRENT CHEMOTHERAPY

The initiation or continuation of intrathecal therapy should not interfere with chemotherapeutic regimens. The trial and implantation procedures are coordinated with the oncologist to avoid delays in cancer treatment and to minimize infection risk.

### RADIATION THERAPY

**Programmable pumps.** Radiation therapy has a prominent role in palliation of cancer pain; however, in treated patients, pain improvement may not be evident for up to 10 days or longer. By combining IDDS with palliative radiation therapy, pain can be rapidly controlled until radiation effects are realized. Once pain is diminished, temporary catheters may be removed or programmable pumps decreased to prevent overmedication.

The limits of exposure to radiation therapy have not been defined for current implantable programmable intrathecal drug delivery pumps, but the American Society for Therapeutic Radiology and Oncology is assessing the possibility for guidelines. Battery life of the implant system may be decreased if the pump is near the radiation field, and battery drain or electric fail-

ure may occur if the pump is directly in the field.<sup>17</sup> Moving the radiation source as much as possible, shielding the implant with lead, and minimizing exposure are prudent management recommendations. In patients with pelvic tumors, pump placement location should be planned to avoid future radiation fields. If an indwelling device is expected to be directly in the radiation field, pump relocation should be considered.

### DIAGNOSTIC ASSESSMENTS

Cancer patients undergo continuous assessments and procedures, none of which is contraindicated with intrathecal therapy. The programmable pump is affected by a magnetic field and will turn off while exposed to the magnet. Once the patient leaves the magnetic field, the pump will automatically resume at its preprogrammed settings. For patients undergoing lengthy MRI scanning, additional oral or intravenous medication is recommended to provide adequate breakthrough pain relief during the procedure. Externalized pump systems are not compatible with the MRI; the system should be disconnected from the patient and the intrathecal catheter capped off during the evaluation.

### HYPERBARIC THERAPY

For patients whose wounds necessitate hyperbaric therapy and who have indwelling programmable pumps, additional pain medication may be needed during treatment. The pump turns off under hyperbaric conditions and resumes when exposed to ambient pressures. Patients with externalized systems may continue therapy during hyperbaric treatment if the hyperbaric chamber is large enough to accommodate the external pump.

### Intrathecal Medication Utilization and Titration

#### ALGORITHMS FOR LONG-TERM AND SHORT-TERM SURVIVORS

The panel recommends different treatment approaches for patients categorized as short-term or long-term survivors. The Polyanalgesic Consensus Conference in 2003 developed updated recommendations for patients with chronic pain.<sup>6</sup> Long-term survivors should be treated according to this updated algorithm, which is shown in Figure 1. Maximal dosing and concentration recommendations for intrathecal medications for long-term survivors are shown in Table 3. These recommendations were based on available research regarding drug safety and stability, toxicity, clinical experience, and best practices.

The panel agreed that a separate algorithm was needed for short-term cancer survivors, characterized as having a high disease stage or grade, incapacitation due to pain, and/or life expectancy  $\leq 1$  year. Because end-of-life issues include escalating pain that may require more rapid dose escalation and more complex polyanalgesia, as well as the need to maintain quality of life, the panel agreed that the revised management algorithm needed to allow more flexibility and more aggressive therapy for such patients. The cancer pain algorithm devel-

**Table 3**

#### Recommended Dosages and Concentrations for Medications Used in the Intrathecal Cancer Pain Algorithm for Long-term Survivors

DRUG	DOSAGE (mg/day)	MAX CONCENTRATION (mg/mL)
Morphine	15	30
Hydromorphone	5–10	30
Bupivacaine	2–30	38
Clonidine	0.01–1.0	2

**Table 4**

#### Recommended Dosages and Concentrations for Medications Utilized in the Intrathecal Cancer Pain Algorithm for Short-term Survivors

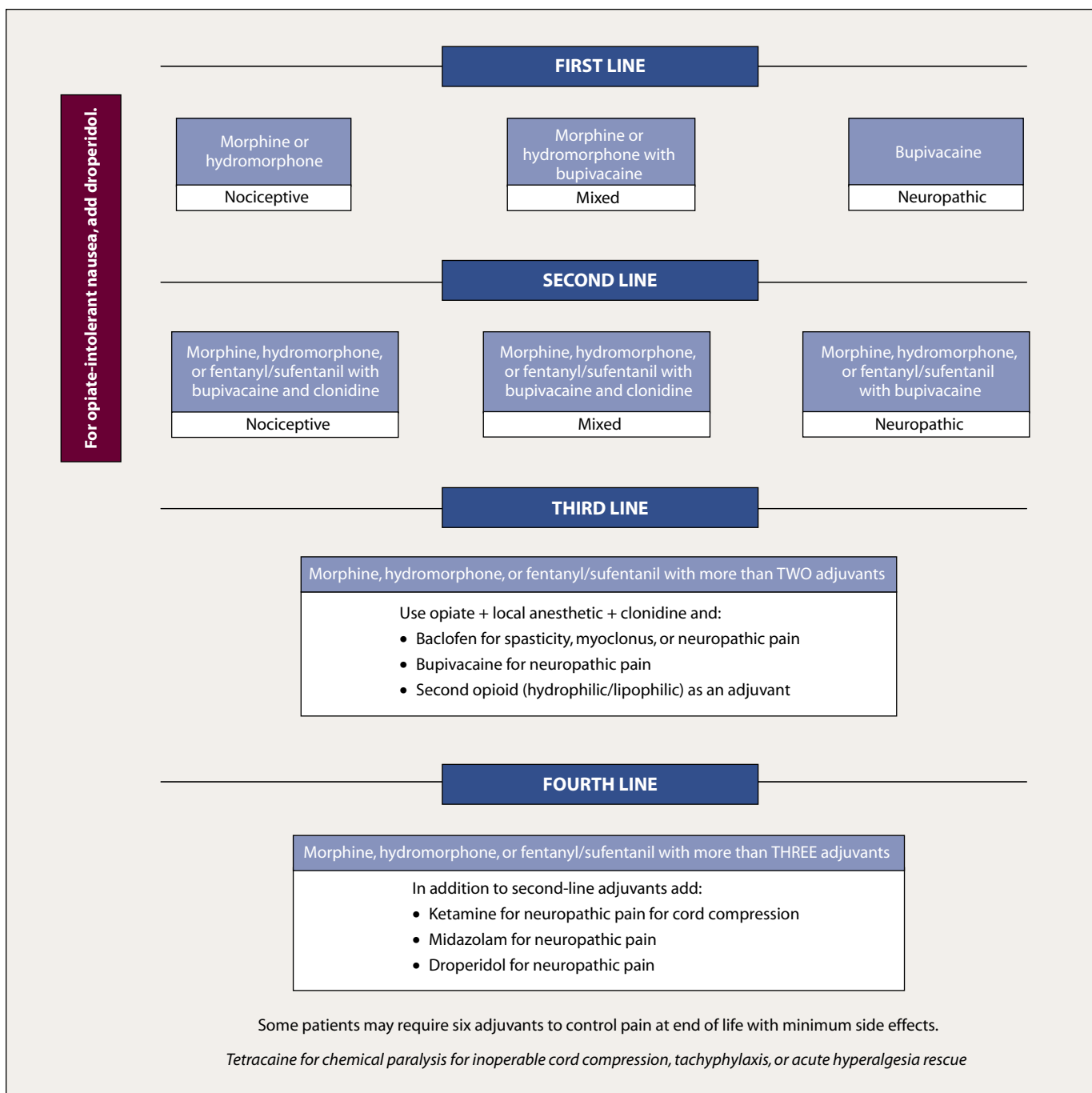
DRUG	DOSAGE (mg/day)	MAX CONCENTRATION (mg/mL)
<b>First-line medications (1–3 medications in mixture)</b>		
Morphine	0.1–50	50
Hydromorphone	0.1–100	100
Bupivacaine	3–50	38
Droperidol (nausea indication)	0.025–0.15	0.5
<b>Second-line medications (2–4 medications in mixture) Above medications and/or:</b>		
Fentanyl	0.01–5	20
Sufentanil	0.001–0.5	2
Clonidine	0.025–0.8	2
<b>Third-line medications (4–6 medications in mixture) Above medications and/or:</b>		
Baclofen	10–1,000	2
<b>Second opioid:</b>		
Morphine	0.1–15	30
Hydromorphone	0.1–10	30
Fentanyl	0.01–0.15	1
<b>Fourth-line medications (more than 3 medications) Possibly neurotoxic; use for rescue only Above medications and/or:</b>		
Tetracaine	30–85	100
Ketamine	0.025–1.0	2
Midazolam (HCL form only)	0.025–1.0	2
Droperidol (pain indication)	0.025–0.25	1

Abbreviation: HCL = hydrochloride

oped by the authors is shown in Figure 2 and the maximal dosage and concentration recommendations for short-term survivors are shown in Table 4.

### MEDICATION TITRATION

Titration of multiple medications in an intrathecal infusion is usually based on one of the component drugs. For simplicity, this drug is usually the opioid or local anesthetic in the solution, as these medications tend to have the greatest side effects when titrated too aggressively. Other component medications



**Figure 2** Cancer Pain Best Practices Algorithm

Recommendations for intraspinal polyanalgesia in cancer patients with pain.

are compounded with dosage safety margins and target effect in mind. Individual responses to each medication should be anticipated and often take precedence in titration tolerance. As in oral titration regimens, some patients need slow titration, as tolerance develops to side effects. Infusion titration recommendations for implantable and external methods are shown in Table 5.

Titration should be guided according to a patient’s pain level as determined by the visual analog scale (VAS) and accord-

ing to functional status. If VAS scores are 2–4, the dose of an implanted device may be increased by 10%–25% over 3 to 4 days. With externalized systems, dose rate may be increased 10%–25% per hour per day until pain relief is satisfactory.

If VAS scores are 5–6, dose rates of implanted devices can be increased by 25%–50% daily, and a therapeutic bolus dose should be considered. If local anesthetic is present in the solution, multiple small boluses should be utilized until pain relief is achieved to avoid motor blockade. With external systems,

**Table 5**  
Best Practice Titration Recommendations

OPIOID TITRATION DIRECTED BY PAIN LEVEL	IMPLANTABLE		EXTERNAL	
VAS 2–4 (if patient desired reduction and has unacceptable function)	Increase dose 10%–25% over 3–4 days		Increase 10%–25% per hour per day	
VAS 5–6	Increase 25%–50% daily (consider therapeutic bolus carefully)		Increase 35%–50% per hour twice daily	
VAS 7–10 <sup>a</sup>	Increase rate 50%–100% per day		Titrate to efficacy	

<sup>a</sup>Patients may require inpatient/hospice or equivalent care (to treat pain crisis); therapeutic bolus should also be considered for immediate comfort in either system.

Abbreviation: VAS = visual analog scale

hourly rates should be adjusted 35%–50% twice daily until pain relief is achieved.

Patients with VAS scores of 7–10 may require inpatient/hospice or equivalent care for treatment of the pain crisis. The panel recognizes that many patients desire to remain in the home environment. These patients may require a 50%–100% rate increase in the external or implanted system. Therapeutic boluses should be administered until pain relief is achieved, with subsequent daily medication adjustments until pain relief is sustained. These significant rate increases may result in problematic drug toxicities in the initial 12 hours following the adjustment, and clinicians should be available to manage acute effects.

In patients whose pain is stable, intrathecal medication combinations are limited to first- and second-line therapy. As the complexity of pain progresses, movement through the algorithm results in more complex combinations to achieve pain relief. Rotation between opiates alone may improve pain or the combination of a lipophilic opioid (fentanyl) to a hydrophilic opioid (morphine or hydromorphone [Dilaudid]) may be necessary to control some painful syndromes. Adjuvant medications are added according to minimal dosage guidelines to prevent toxicities and are titrated to effect. Baclofen and clonidine are typically started at a dose of 25 mg/d. Initial dose should be reduced to 10 mg/d in the hemodynamically fragile patient. Concentrations of all medications in the polyanalgesic mix are altered to provide maximal time between pump refills, with safe pump rate increases for uncontrolled pain.

Rate-limiting side effects for pain medications are summarized in Table 6. If a medication is not beneficial or causes adverse effects in a particular patient, it should be weaned appropriately or the caregiver should inform the patient of likely withdrawal symptoms and arrange for outpatient interventions. Acute discontinuation of baclofen or clonidine may result in hemodynamic instability, seizures, or death. To avoid these complications, physicians should institute oral replacement therapy on discontinuation of intrathecal medications and provide an appropriate weaning schedule.

**Table 6**  
Side Effects Associated With  
Intrathecal Pain Medications

MEDICATION	SIDE EFFECTS
Opioids	Nausea, urinary retention, sedation, edema, constipation
Bupivacaine	Weakness, hypotension, urinary retention
Baclofen	Loss of balance, auditory disturbances
Clonidine	Orthostatic hypotension, edema, sedation, worsening of depression
Droperidol	Extrapyramidal effects
Ketamine	Increased anxiety and agitation, facial flushing, delusional thoughts
Midazolam	Sedation

Cancer patients with complex pain may require several polyanalgesic combinations until satisfactory relief is achieved with minimal side effects. Medication regimens may be reformulated after two unsuccessful attempts to improve response with aggressive dosage adjustments. Tables 3 and 4 review recommended medication concentrations and dosing ranges. Medications should be selected to target specific receptor responses and pain syndromes. Local anesthetics are important in initial therapy until adjuvant medications reach therapeutic levels with minimal side effects, after which local anesthetic doses may be reduced to limit effects such as weakness, urinary retention, and hypotension.

#### SIDE EFFECT MANAGEMENT

Management of potential side effects of intrathecal therapy is similar to that of oral therapies. Opioid-induced nausea is managed with traditional antiemetics, opioid rotation, and/or administration of droperidol intrathecally at 0.5–1.0  $\mu\text{g}/\text{kg}/\text{d}$ . Constipation is typically managed with stimulant or bulk laxatives, stool softeners, and oral naloxone 1,000  $\mu\text{g}$  twice daily. Urinary retention is treated with 10–50 mg of oral urecholine four times daily. Medication doses may need to be modified in cases of persistent urinary retention not responsive to urecholine. In cases in which edema develops or escalates after initiation of intrathecal therapy, opioids can be rotated or doses reduced and adjuvant medications adjusted to achieve pain control. Initiation of loop or potassium-sparing diuretics may be helpful. In most cases, edema secondary to opioid therapy resolves on its own with conservative treatment. Patients with lymphedema may benefit from fluid mobilization therapy.

#### BREAKTHROUGH PAIN

Breakthrough pain may originate from a source different from that of background pain and requires immediate assessment. Oral immediate-release opiate agents should be provided for rescue; patients should also have a small amount of benzodiazepine on hand for treatment of acute anxiety related to severe pain onset until an intrathecal dose titration can be provided.

Treatment should be tailored to the individual's needs and altered according to treatment algorithms if pain persists.

## Conclusion

The adoption of intrathecal therapy by oncologists and palliative care physicians broadens their ability to control pain and limit medication side effects. The goals of intrathecal therapy are to preserve patient quality of life, function, and independence, regardless of prognosis. Furthermore, the availability of intrathecal therapy as a management option for uncontrolled pain or intolerable side effects offers significant reassurance to cancer patients.

This paper, as a consensus statement, has supported the use of intrathecal therapy for cancer pain management. Based on a lack of adequate data from randomized controlled trials, however, the medical community has been reluctant to accept this therapy for widespread clinical use. It should be noted

that few randomized trials have been conducted regarding optimal medication for cancer pain. Therefore, clinical care should be guided by the best current evidence, with application of data from randomized trials when available, such as that from Smith and colleagues who compared CMM with implantable drug delivery.<sup>7,18,19</sup>

Additional randomized controlled trials evaluating polyanalgesia and efficacy and safety of various agents in the spinal space are necessary to increase acceptance of intrathecal therapy in cancer pain management. Comparative studies of conventional medical management versus intrathecal drug delivery in cancer patients, with a focus on performance scores and survivorship as end points, would also be of interest. Finally, studies comparing cost-effectiveness of conventional medical management and intrathecal therapy, including hospital and nursing staff utilization costs, may provide insights regarding cases where financial considerations may otherwise limit access to therapy.

*A peer viewpoint on this article by Dr. Richard Penn appears on page 411.*

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