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Polyanalgesic Consensus Conference 2012: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel

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Introduction: The use of intrathecal (IT) infusion of analgesic medications to treat patients with chronic refractory pain has increased since its inception in the 1980s, and the need for clinical research in IT therapy is ongoing. The Polyanalgesic Consensus Conference (PACC) panel of experts convened in 2000, 2003, and 2007 to make recommendations on the rational use of IT analgesics based on preclinical and clinical literature and clinical experiences.

Methods: The PACC panel convened again in 2011 to update the standard of care for IT therapies to reflect current knowledge gleaned from literature and clinical experience. A thorough literature search was performed, and information from this search was provided to panel members. Analysis of published literature was coupled with the clinical experience of panel members to form recommendations regarding the use of IT analgesics to treat chronic pain.

Results: After a review of literature published from 2007 to 2011 and discussions of clinical experience, the panel created updated algorithms for the rational use of IT medications for the treatment of neuropathic pain and nociceptive pain.

Conclusions: The advent of new algorithmic tracks for neuropathic and nociceptive pain is an important step in improving patient care. The panel encourages continued research and development, including the development of new drugs, devices, and safety recommendations to improve the care of patients with chronic pain.

Keywords: Chronic pain, consensus, intrathecal

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INTRODUCTION

The use of intraspinal (intrathecal [IT]) infusion of analgesic medications to treat patients with chronic refractory pain has increased since its inception in the 1980s, and the need for clinical research in IT therapy is ongoing. Thus far, research has not kept pace with the growing need for innovative pain management; therefore, a consensus opinion is needed to clarify the current research and address deficiencies in the data.

The Polyanalgesic Consensus Conference (PACC) panel first convened in 2000 to address the research gaps and review the existing data (1). This expert panel is composed of physicians and other clinicians in the field of IT therapy. The panel developed an IT drug selection algorithm on the basis of best evidence and expert opinion and prepared supplemental reports that included a literature review, documentation of results from a survey of peers regarding IT therapy, and projections for future directions in the field of IT therapy. The PACC panel reconvened in 2003 (2) and 2007 (3) to evaluate the most recent literature and to update the algorithm for intraspinal drug selection. In 2011, to formulate consensus opinions on critical issues involving IT therapy and identify areas for future research in the field, the PACC panel again convened, with objectives of modifying and updating the IT drug selection algorithm by reviewing previous PACC guidelines including literature published before January 14, 2007; preclinical and clinical data on IT therapy published from January 15, 2007, through March 1, 2011; and results of a peer survey.

METHODS

A broad literature search was conducted to identify preclinical and clinical data on IT therapy published from January 15, 2007, through March 1, 2011. MEDLINE®, BioMed Central®, Current Contents Connect®, Embase, International Pharmaceutical Abstracts®, and Web of Science® data bases were searched for publications on a range of medications that are either currently in use or potentially useful for the IT treatment of chronic pain. Search terms included *intrathecal*, *intraspinal*, *morphine*, *fentanyl*, *sufentanil*, *methadone*, *adenosine*, *hydromorphone*, *meperidine*, *gabapentin*, *baclofen*, *ketorolac*, *midazolam*, *neostigmine*, *octreotide*, *ziconotide*, *ropivacaine*, *dexmedetomidine*, *clonidine*, *bupivacaine*, and *lidocaine*. These searches yielded 391 articles, which were examined for relevance to the IT treatment of chronic pain. Google was also used to search for recent relevant

information regarding IT therapy for chronic pain, and additional literature considered by panel members to be relevant to this new consensus paper was reviewed. Wherever pertinent, proposed mechanisms of action for the particular class are provided, along with a summary of preclinical studies, followed by clinical review. Literature published before the dates stated above is cited when relevant. After reviewing the literature, the PACC panel convened to develop recommendations for IT analgesia. Supporting literature is included following these recommendations and discussions of the panel.

RECOMMENDATIONS OF PACC 2012 FOR IT THERAPY

Since the publication of the third PACC report in 2007 (3), the published literature on IT therapy has expanded, and the 2012 updated version of the PACC treatment algorithm is based on the best available evidence from published reports and on panel discussions. The current algorithm for drug selection provides clinical practice guidelines for the optimization of IT therapy with single-drug treatments and drug combinations in a rational and prioritized order. Unlike the previous PACC algorithms, the current algorithm contains separate arms for neuropathic, nociceptive, and mixed pain states. In each arm of the algorithm, the medications are arranged in a hierarchy on the basis of evidence of efficacy and safety. First-line medications/combinations are supported by extensive clinical experience and published clinical and preclinical literature and are typically used to initiate IT therapy. Notably, morphine and ziconotide are the only two agents approved by the US Food and Drug Administration (FDA) for IT analgesia, while in Europe morphine and ziconotide are approved for use in Europe, the Middle East, and Africa. The use of other agents is common among pain practitioners who manage IT pumps, and discussions of such agents are included to give guidance on safe practice and patient safety. These algorithms were created to help guide clinicians in the safe and effective use of IT therapy; however, physicians should use their own best clinical judgment in making treatment decisions for their patients.

Neuropathic Pain (Table 1)

Line 1 Approach

For neuropathic pain, line 1 contains morphine (the only opioid approved by the US FDA for IT analgesia), alone or in combination with the local anesthetic bupivacaine. Consistent with the recommendations from the 2007 PACC, ziconotide, a nonopioid that is approved by the US FDA for IT analgesia, is also recommended as a first-line drug for both nociceptive and neuropathic pain.

Line 2 Approach

For neuropathic pain, line 2 contains hydromorphone, either as monotherapy or in combination with bupivacaine or in combination with clonidine, and the combination of morphine and clonidine.

Line 3 Approach

Fentanyl, either alone or in combination with bupivacaine or in combination with clonidine, is considered a third-line approach to neuropathic pain. Additionally, clonidine and the combination of ziconotide and an opioid are third-line therapies.

Line 4 Approach

As fourth-line treatment of neuropathic pain, the combination of bupivacaine and clonidine, with or without an opioid, is recommended.

Line 5 Approach

As fifth-line treatment of neuropathic pain, the panel recommends the use of baclofen.

Nociceptive Pain (Table 2)

Line 1 Approach

For nociceptive pain, line 1 contains morphine, hydromorphone, and ziconotide. Fentanyl has been upgraded to a first-line drug in this population because of a long-term positive safety profile, the most compelling reason being a lack of granuloma formation with long-term use (4,5). The lipophilic nature of fentanyl makes it ideal for treatment of focal pain issues, where the catheter tip is in the area of the pain generator cephalad to the conus.

Line 2 Approach

For nociceptive pain, bupivacaine, in combination with morphine, hydromorphone, or fentanyl, is recommended as second-line therapy. The combination of ziconotide and an opioid drug may also be used as a second-line treatment approach.

Line 3 Approach

Third-line approaches to nociceptive pain include sufentanil monotherapy and the combination of an opioid (i.e., morphine, hydromorphone, or fentanyl) and clonidine.

Table 1. 2012 Polyanalgesic Algorithm for Intrathecal (IT) Therapies in Neuropathic Pain.

Line 1	Morphine	Ziconotide		Morphine + bupivacaine
Line 2	Hydromorphone	Hydromorphone + bupivacaine or Hydromorphone + clonidine		Morphine + clonidine
Line 3	Clonidine	Ziconotide + opioid	Fentanyl	Fentanyl + bupivacaine or Fentanyl + clonidine
Line 4	Opioid + clonidine + bupivacaine		Bupivacaine + clonidine	
Line 5	Baclofen			

Line 1: Morphine and ziconotide are approved by the US Food and Drug Administration for IT therapy and are recommended as first-line therapy for neuropathic pain. The combination of morphine and bupivacaine is recommended for neuropathic pain on the basis of clinical use and apparent safety. **Line 2:** Hydromorphone, alone or in combination with bupivacaine or clonidine, is recommended. Alternatively, the combination of morphine and clonidine may be used. **Line 3:** Third-line recommendations for neuropathic pain include clonidine, ziconotide plus an opioid, and fentanyl alone or in combination with bupivacaine or clonidine. **Line 4:** The combination of bupivacaine and clonidine (with or without an opioid drug) is recommended. **Line 5:** Baclofen is recommended on the basis of safety, although reports of efficacy are limited.

Table 2. 2012 Polyanalgesic Algorithm for Intrathecal (IT) Therapies in Nociceptive Pain.

Line 1	Morphine	Hydromorphone	Ziconotide	Fentanyl
Line 2	Morphine + bupivacaine	Ziconotide + opioid	Hydromorphone + bupivacaine	Fentanyl + bupivacaine
Line 3	Opioid (morphine, hydromorphone, or fentanyl) + clonidine			Sufentanil
Line 4	Opioid + clonidine + bupivacaine		Sufentanil + bupivacaine or clonidine	
Line 5	Sufentanil + bupivacaine + clonidine			

Line 1: Morphine and ziconotide are approved by the US Food and Drug Administration for IT therapy and are recommended as first-line therapy for nociceptive pain. Hydromorphone is recommended on the basis of widespread clinical use and apparent safety. Fentanyl has been upgraded to first-line use by the consensus conference. **Line 2:** Bupivacaine in combination with morphine, hydromorphone, or fentanyl is recommended. Alternatively, the combination of ziconotide and an opioid drug can be employed. **Line 3:** Recommendations include clonidine plus an opioid (i.e., morphine, hydromorphone, or fentanyl) or sufentanil monotherapy. **Line 4:** The triple combination of an opioid, clonidine, and bupivacaine is recommended. An alternate recommendation is sufentanil in combination with either bupivacaine or clonidine. **Line 5:** The triple combination of sufentanil, bupivacaine, and clonidine is suggested.

Table 3. Recommended Starting Dosage Ranges of Intrathecal Medications.

Drug	Recommended starting dosage
Morphine	0.1–0.5 mg/day
Hydromorphone	0.02–0.5 mg/day
Ziconotide	0.5–2.4 mcg/day
Fentanyl	25–75 mcg/day
Bupivacaine	1–4 mg/day
Clonidine	40–100 mcg/day
Sufentanil	10–20 mcg/day

Line 4 Approach

Recommendations for fourth-line treatment for nociceptive pain include the combination of an opioid, clonidine, and bupivacaine or the combination of sufentanil and either bupivacaine or clonidine.

Line 5 Approach

The triple combination of sufentanil, bupivacaine, and clonidine is the recommended fifth-line treatment for nociceptive pain. This should be reserved for patients with the most refractory pain.

Mixed Pain

The recommended use of IT therapies for pain that is primarily neuropathic or primarily nociceptive in character has been discussed above. In some cases, the managing physician or team member will have trouble identifying the pain type. In these cases, the clinical scenario should drive the decision-making process in choosing the appropriate treatment algorithm. In some cases, this pathway may change after reevaluation of the patient.

Recommended Starting Dosages

Starting dosage ranges of IT medications recommended by the PACC panel are shown in Table 3. Appropriate starting opioid dosages may vary on the basis of a patient's baseline oral intake at the time IT therapy is initiated.

ANALYSIS OF THE CONSENSUS PANEL

The 2012 PACC panelists closely examined the published literature, their own clinical experiences, and other anecdotal reports from colleagues regarding the use of IT analgesic drugs and formulated several consensus opinions and recommendations regarding key issues of IT therapy. These opinions are offered to lend guidance and to improve patient safety and are not intended to promote or recommend off-label use of medications. Physicians should consult their national approval processes when making decisions.

Cerebrospinal Fluid Flow/Dynamics

Most of the current knowledge on IT drug distribution is derived from literature on spinal anesthesia and factors that presumably increase drug spread, including morphological and technical factors (6). However, because of the difference in the order of magnitude between the volume and flow rate (1 mL/30 sec and 40 mcL/day, respectively), most spinal anesthesia data are not applicable in the context of chronic long-term IT drug administration. It was previously assumed that, upon administration of the drug in the cerebrospinal fluid (CSF), the drug would be transported by the flow of CSF and diffuse throughout the subarachnoid space to reach specific receptors in the spinal cord or the brain. However, this concept is outdated and simplistic, as evidence against the existence of a net CSF flow includes biochemical, radiological, and experimental data. Biochemical studies have shown a consistent and marked rostrocaudal concentration gradient for normal CSF constituents, whether small (7) or large (8) molecules. Early radiological findings from gated magnetic resonance imaging (MRI) have demonstrated that CSF moves in a to-and-fro oscillation (9) that is more marked in the cervical than in the lumbar region but have not indicated the existence of a CSF bulk flow (10,11). Additionally, the motion of CSF varies in velocity and amplitude, depending on which part of the spinal cord is considered (12). Direct evidence that CSF does not circulate has been shown in a pig model (13). Continuous IT low-flow-rate injection results show that drug distribution in the CSF and uptake in the spinal cord are limited to a few centimeters around the tip of the catheter (14–16) and that drug does not seem to disperse around the spinal cord (17).

From a fluid dynamics perspective, the main "engine" responsible for the dispersion of IT drugs is the heart, which generates CSF pulsations. These oscillations produce two diffusion-enhancing phenomena: 1) steady streaming, which is related to the perturbations created by obstacles, such as ligaments and nerve roots, present in an oscillatory flow; and 2) enhanced diffusion, which is caused by shear forces at the liquid/solid interface and is enhanced by geometric changes, whether cross-sectional or due to an intrinsic object such as a catheter (18). Anatomical, functional, and fluid dynamic factors interact in a complex way whereby drug movements across and within nonhomogenous spaces (IT and epidural) are difficult to predict and require different pharmacokinetic

Table 4. Octanol-Water Partition Coefficient of Commonly Used Drugs.

Drug	Partition coefficient	Reference information
Morphine sulfate	(Octanol/water) 1.42 at pH 7.4	• Infumorph200 and Infumorph500 Package Insert, Baxter International, Inc.
Hydromorphone hydrochloride	(Octanol/water) 1.23 at pH 7.4 buffer	• Neural Blockade in Clinical Anesthesia and Management of Pain, Issue 494, by Michael J. Cousins, Phillip O. Bindenbaugh. Lippincott Williams & Wilkins, 1998
Clonidine	7.1	• Hayek et al., Seminars in Pain Medicine, Vol. 1 (4) Dec 2003: 238–253
Ziconotide	XLogP −10.3	• Rogawski MA et al., Neurotherapeutics, 2009 April 6 (2): 344–351
Bupivacaine hydrochloride	n-Heptane/water 27.5 at pH 7.4 buffer	• Neural Blockade in Clinical Anesthesia and Management of Pain, Issue 494, by Michael J. Cousins, Phillip O. Bindenbaugh. Lippincott Williams & Wilkins, 1998
Baclofen	0.1	• Hayek et al., Seminars in Pain Medicine, Vol 1 (4) Dec 2003: 238–253
Sufentanil citrate	1788 at pH 7.4 buffer	• Neural Blockade in Clinical Anesthesia and Management of Pain, Issue 494, by Michael J. Cousins, Phillip O. Bindenbaugh. Lippincott Williams & Wilkins, 1998
Fentanyl citrate	813 at pH 7.4 buffer	• Neural Blockade in Clinical Anesthesia and Management of Pain, Issue 494, by Michael J. Cousins, Phillip O. Bindenbaugh. Lippincott Williams & Wilkins, 1998

models (14,19). The CSF renewal throughout the day also has an unknown impact on these pharmacokinetics. The clinical implications of wide variability in response to IT injections may account for a substantial portion of the discrepancies observed between single injections and continuous infusions (20). A common assumption is that, for a given daily dose, the therapeutic effect is diminished with lower flow rate of higher drug concentrations. This intuitive belief is based on a number of anecdotal and mostly unpublished observations that are contradicted by two recently published randomized controlled studies. In patients with complex regional pain syndrome (CRPS)-related dystonia, van der Plas et al. (21) showed that, when the daily dose of baclofen was maintained, a fourfold increase in flow rate had no effect on dystonia or pain, but adverse event (AE) rates increased. Similar results were obtained in patients with chronic pain: a fourfold increase in flow rate at a constant daily dose did not result in improved pain scores but was associated with a significant decrease in EQ-5D quality-of-life scores (22). Finally, the link between the cardiovascular system, CSF oscillation, and drug spread is emphasized by data from a study in laboring women who received IT fentanyl. In this study, the duration of analgesia correlated with blood pressure, not with CSF fentanyl concentration (23).

Effects of Drug Injection Rate and Mode of IT Delivery on Analgesia

Continuous Infusion

The use of continuous IT delivery to treat chronic pain has become the standard mechanism to deliver drugs to the neural structures. No prospective studies exist to define the best rate to deliver the drug. Some have theorized that the use of lower flow rates may result in higher concentrations of the drug at the catheter tip and may result in higher risk of granuloma formation, but this has not been proven clinically.

Lipid Solubility of Commonly Used Agents

The lipid solubility of an agent has an impact on the action it has on the spinal structures. The lipophilicity impacts the spread of the drug in the CSF and may impact the location and planning of the catheter tip if the physician has a treatment algorithm that includes the use of lipid soluble drugs. Morphine sulfate has a more hydrophilic character than some other commonly used drugs, and spreads widely in the CSF. Fentanyl and sufentanil, for example, have a very lipophilic characteristic that gives an impact much more focused on the area near the catheter tip. Table 4 shows the octanol–water partition coefficient of commonly used drugs that are in the PACC algorithm.

Drug Flow Rates (22) and Intermittent Bolus Dosing

In addition to drug flow rates, the mechanism of continuous flow vs. intermittent bolus dosing has been discussed in relation to clinical outcomes and granuloma formation. Constant-flow pumps cannot be used to change flow rates or administer boluses. Programmable pumps allow for changes in flow. Bolus doses can be given by programming the pump to give doses at set times and, when available, by giving the patient the option of delivering boluses as needed, a concept known as patient-controlled analgesia (PCA), which may be achieved with a personal therapy manager (PTM). In most cases, the PTM is set to give 5% to 20% of the daily dose that is administered at the continuous rate. Caution must be used since doses are additive to baseline infusion and particularly when clonidine or bupivacaine are involved due to cumulative side-effects. Generally, to avoid hypotension or motor block, the dose of clonidine given as bolus should not exceed 20 mcg, and the dose of bupivacaine should not exceed 3 mg.

Trialing

Trialing may be considered in patients with existing implanted pumps for whom a change in IT medication is being considered, or trialing may be performed before a patient undergoes pump implantation. The concept of trialing before the implantation of an IT drug delivery device is based on the assumption that it will provide information on the efficacy of the therapy, certainly in the short term but also, hopefully, the long term. Trialing was previously thought to be critical but has now become somewhat debatable. Issues of opioid-induced hyperalgesia (OIH) or disease progression cannot be addressed during a single-shot trial or even a brief 72- to 96-hour infusion. Therefore, a trial may lead to underestimation of the failure rate with long-term infusion. Another issue to consider is the need for trialing in cancer or end-of-life patients. Many panel members felt that trialing is not needed in these groups if patients have previously tolerated the same drug by another route. Trialing can be performed by IT or epidural injection or infusion for most drugs; however, some authors feel that epidural trials are slightly less helpful due to different drug kinetics in the IT space. No prospective studies have shown a clear advantage for predictability of success in IT vs. epidural trialing.

Table 5. Recommended Doses for Intrathecal (IT) Bolus Trialing.

Drug	Recommended IT bolus dose
Morphine	0.2–1.0 mg
Hydromorphone	0.04–0.2 mg
Ziconotide	1–5 mcg
Fentanyl	25–75 mcg
Bupivacaine	0.5–2.5 mg
Clonidine	5–20 mcg
Sufentanil	5–20 mcg

Commonly Used Drugs

Opioids To date there has been considerable controversy and little consistency in the trialing of opioids, although trialing with morphine or hydromorphone is common. Current knowledge regarding OIH suggests that an opioid-naive brain would be ideal for trialing. In such cases, opioids are more potent at lower dosages (i.e., microdosages) and are preferable to higher dosages. The proper use of pretrialing systemic opioid dose conversions to derive an appropriate dose for IT opioid trialing is debatable because of pretrial weaning of systemic opioids and differences in pharmacology between systemic and IT opioids. In many situations, the patient's disease process and pain severity will not allow for tapering before the trial, and the trialing process can be used, in part, to determine whether systemic opioid doses can be reduced while neuraxial medications are infused.

Ziconotide In patients with neuropathic pain who are not responsive to pretrialing systemic opioid therapy, a trial of ziconotide should be considered. Trialing with ziconotide can be challenging because the drug's side-effect profile is more closely related to the rate of dosage increase than to the absolute dosage. Thus, trialing with an externalized catheter may be impractical and hazardous because of the slow titration required with ziconotide (e.g., dosage increases of 0.5–1.0 mcg every several days). Although trialing with bolus dosing can be useful to identify some appropriate candidates, side-effects associated with bolus dosing may eliminate many patients who might otherwise have benefited from IT ziconotide therapy. Thus, the use of alternate trialing methods in order to avoid a trial failure because of intolerable side-effects would be advantageous in this regard. Although meclizine treatment is sometimes used before IT ziconotide trials in clinical practice, there is insufficient evidence to support this approach. Proper hydration via intravenous (IV) infusion before trialing may limit the side-effect of hypotension.

Recommended Doses for Trialing

Recommended doses for IT trialing are shown in Table 5. The doses of trialing medications are often determined by the patients' preoperative medications; therefore, the recommended doses may not be applicable, depending on the clinical setting. Fluoroscopic guidance should be used in the bolus dosing of any drug, and dosing should be followed by a period of observation. The use of constant infusion requires careful titration and hospital admission unless used as a palliative approach at the end of life. Infusion doses are based on preexisting opioid doses and observations.

Trialing Methods

Several possible methods for trialing exist. These include epidural bolus, IT bolus, continuous epidural infusion, and continuous IT infusion. Current US Medicare requirements dictate that trials must be performed using an IT catheter; however, the panelists felt that such trialing methods are inappropriate for some patients (e.g., end-of-life patients, immunocompromised patients, patients to receive trials with IT ziconotide) and that such restrictions would limit access to care.

Advantages and Disadvantages of Various Trialing Methods Disagreement exists regarding many aspects of trialing. First, there is no consensus on the outcome (e.g., extent of pain alleviation, improved function, side-effect tolerance) that should be used to judge the efficacy of a trial. Consensus is that trialing should be performed following the principles of the consensus algorithm for drug selection based on the type of pain. To date, no studies have been conducted to evaluate patients who have "failed" trialing but are nevertheless implanted with IT delivery devices. Thus, the fate of the "screened out" patients (i.e., those with unsuccessful trials) is unknown, and consequently, the sensitivity and specificity of trialing is unclear.

Currently, no consensus exists regarding the most appropriate techniques for trialing. Acute tests with single epidural or subarachnoid injections or the placement of percutaneous catheters for "long-term" (days to weeks) trials (both either IT or epidural), have all been used. Trial catheter tip position and permanent implant position may be important in the long-term outcome, although this point has not been studied.

The intuitive rationale for trialing with IT catheters is that it best mimics the system that would eventually be implanted. However, there are no data from controlled studies to support this assumption, and the (limited) literature on the topic does not support this hypothesis. Although a trial itself may not be predictive of long-term response to IT therapy, some evidence suggests that the long-term (two-year) opioid responsiveness correlates loosely with the initial dose that is needed to control pain (24), the morphine dose escalation being an order of magnitude higher in patients requiring high doses in a trial than for those requiring low doses.

There is currently no solid base to either refute or adopt preimplantation trials, although these are generally recommended. The trialing technique and the definition of a positive trial remain largely controversial and may depend on the clinical context. The British Pain Society has published well-documented recommendations for the best clinical practice in IT drug delivery for pain and spasticity (25). The panel concluded that trials should always be performed before the implantation of a drug delivery system, which can be done either by single bolus or continuous injections, the former considered less informative. The panel recommended that each practitioner develop a trialing protocol for his or her practice that is based on safety, adherence to safe algorithmic principles, and proper patient monitoring.

Considerations for Trialing

Patients for Whom Trialing May Be Unnecessary Trialing may not be appropriate for all patients. In some cases, socioeconomic factors may be involved in the decision of whether to forgo trialing. Furthermore, time constraints associated with terminal illnesses, such as cancer, can make trialing counterproductive and unnecessary. Trialing may also be unnecessary and/or detrimental in some nonmalignant conditions, such as cerebral palsy, or in patients who have had a stroke. Further details regarding patients for whom trialing may be unnecessary are provided in the brief report "Polyanalgesic Consensus Conference—2012: Consensus on Trialing for Intrathecal Drug Delivery."

Trial Setting Panel members strongly agreed that most patients who undergo trialing should be monitored for at least 24 hours.

Such monitoring may occur in an inpatient setting or another appropriate environment. An inpatient setting is appropriate for patients with cancer-related pain who have high life expectancies and for patients with noncancer-related pain who receive opioid trials. An inpatient setting is also recommended for bolus trialing of short-acting IT opioids. Patients who have normal neurological function after 12 hours of inpatient monitoring following a ziconotide bolus trial may be discharged unless they have unacceptable reactions. Further details regarding appropriate trial settings are provided in the brief report "Polyanalgesic Consensus Conference—2012: Consensus on Trialing for Intrathecal Drug Delivery."

Comorbid Conditions and Concomitant Medications In order to optimize peri-trialing medical care, comorbid conditions should be well controlled and certain treatments must be discontinued. Patients with diabetes, sleep apnea, a history of infections, or immunosuppression should receive appropriate therapy throughout the duration of IT trialing (26). In patients with conditions that are associated with immunosuppression, different antibiotics (e.g., vancomycin) than those used in non-immunocompromised patients (e.g., cephalosporin) may be recommended (27). Although bleeding disorders must be managed appropriately, anticoagulant treatments must be discontinued before trialing (28). Additionally, because benzodiazepines and opioids have synergistic effects, if trialing is to be performed with an opioid, reduction of the benzodiazepine dose, when possible, before trialing and vigilant monitoring during the trial are required (29). In cases where the benzodiazepine dose cannot be reduced or eliminated, the rate of opioid dose increase during trialing should be tempered.

For patients who are receiving systemic opioid medications, three pretrialing options exist: 1) wean the patient off all systemic opioid medications and conduct the trial; 2) reduce the systemic opioid dose as much as possible and conduct the trial; and 3) keep the systemic opioid dose stable and conduct the trial. Doses of all other concomitant medications should be kept constant during trialing so that the infusate is the only variable, helping clinicians to avoid drawing unwarranted conclusions from the results of the trial. In option 1, complete tapering of pretrialing systemic opioids six weeks before opioid trialing may reduce the risk of hyperalgesia in patients with nociceptive pain and result in sustained analgesia during IT therapy. This approach may also help to reveal whether OIH was responsible for a patient's continued pain (30). Thus, if weaning of systemic opioids results in elimination of hyperalgesia and resolution of pain, pump implantation may not be needed. Alternatively, in patients who are still responsive to systemic opioids, partial or no tapering of opioid doses before trialing may be warranted.

Additional optimal medical care during IT therapy trialing involves the establishment of IV access, and the optimization of fluid status. Ideally, endocrine status should also be tested; however, the procedure is expensive and may not be feasible in all patients. Further details regarding optimization of peri-trialing medical care are provided in the brief report "Polyanalgesic Consensus Conference—2012: Consensus on Trialing for Intrathecal Drug Delivery."

Psychological Aspects of Trialing A patient's psychological readiness for and response to trialing should be evaluated. It is important that the patient's expectations regarding trialing and IT therapy are realistic. Additionally, the patient should have a stable mental status and an adequate social support network (31). Further information regarding psychological aspects of trialing is provided in the brief report "Polyanalgesic Consensus Conference—2012: Consensus on Trialing for Intrathecal Drug Delivery."

Complications Meningitis is a rare complication of trialing that can be managed (with consultation with an infectious disease specialist) via bolus of IV gentamicin or other antibiotic. Post-dural puncture headache, another possible complication of trialing, can be managed with fluid loading, caffeine, theophylline, and/or blood patch. In cases of urinary retention, the patient may require catheterization. If orthostatic hypotension develops during trialing, proper hydration and monitoring are appropriate.

In our experience, catheter dislodgment during trialing is rare; efforts to prevent or manage this complication are important. Catheter dislodgment is unlikely after catheter placement at a low entry site in the lumbar region (positioning at the anchor of the sacrum) because there is minimal movement of the spine at this level. Such placement may prevent dislodgment by minimizing applied force. Catheter dislodgment is unfortunate, but should that occur, the panel recommends repeating the trial either immediately or at another time. In some cases, the catheter can be tunneled the length of a 3.5-inch Tuohy needle and secured with a suture. This can be very helpful in patients with abnormal movement, body habitus, or tape allergy. One consensus member indicated that he tunnels all catheters in this manner, since catheter migration during a trial necessitates another procedure and can compromise patient safety (T. Deer, unpublished data, August 2011).

Safety Issues/Complications

Patient Risk Factors and Comorbidities

Several patient characteristics, including comorbidities and concomitant medications, may increase a patient's risk of complications during IT therapy. Sleep apnea, other respiratory conditions (e.g., chronic obstructive pulmonary disease, emphysema), smoking, and the use of certain drugs (e.g., systemic opioids, benzodiazepines, psychotropics, antihistamines) or supplements (e.g., melatonin, valerian) are associated with an increased risk of complications, particularly respiratory depression (29,32). In addition to its association with sleep apnea and decreased functional residual capacity, obesity may increase a patient's risk of catheter complications, such as catheter migration. Smoking presents a risk factor for pulmonary issues, increased infection, and diminished blood flow. Additional factors that increase patients' risk of complications during IT therapy are discussed in greater detail in the brief report, "Polyanalgesic Consensus Conference—2012: Consensus on Reducing Morbidity and Mortality in Intrathecal Drug Delivery."

Drug-Related AEs

Peripheral Edema Peripheral edema is sometimes associated with the use of IT opioid therapy with a mechanism related to an effect of these agents on the levels of antidiuretic hormone (33). In patients who have existing peripheral edema or a history of peripheral edema, IT therapy must be used with caution, and such patients should be closely monitored during each clinic visit. If peripheral edema develops, it is important to first rule out other potential causes (renal or cardiovascular) that may explain the effect on the venous system. In the event of drug-induced peripheral edema that fails initial treatment, switching patients to IT ziconotide therapy or other nonopioids may be considered. Diuretic medications and compression stockings may be used to alleviate the symptoms. Nighttime use of sequential compression (venodynes) may also be beneficial. Additional information, including an algorithm for the treatment of peripheral edema, is included in the brief report, "Consensus on Reducing Morbidity and Mortality in Intrathecal Drug Delivery."

Hormonal Changes Several hormonal changes may be associated with IT therapy, including alterations in levels of growth hormone, follicle-stimulating hormone, luteinizing hormone, and testosterone. If hormonal changes occur, weaning from IT opioids should be considered, but often, this is not in the patient's best interest. In many patients, hormone replacement therapy may be appropriate, but clinicians should carefully consider the risks and benefits of such therapy and collaborate with primary care specialists or other specialists in the area of the hormonal imbalance (34). These changes, their effects, and recommendations for monitoring such changes in patients with IT therapy are discussed in the brief report, "Polyanalgesic Consensus Conference—2012: Consensus on Reducing Morbidity and Mortality in Intrathecal Drug Delivery."

Respiratory Depression Respiratory depression is a potential but rare complication of opioid use. Patients with sleep apnea and those on certain adjuvant medications (e.g., benzodiazepines, systemic opioids) or supplements (e.g., melatonin) are at greater risk for respiratory depression. Smoking also increases a patient's risk of respiratory depression and infection; thus, cessation of smoking should be encouraged in patients on IT therapy (32). Other comorbidities that increase the risk of respiratory depression include chronic obstructive pulmonary disease, obesity, and emphysema.

Patients in whom IT therapy is initiated should be monitored for adequate ventilation, oxygenation, and level of consciousness at least every 1 to 2 hours during the first 12 hours and every 2 hours for the next 12 hours. The frequency of monitoring should be increased in high-risk patients. If frequent monitoring is not possible, administration of very low starting doses of morphine is recommended.

Granuloma Formation The formulation of granulomas has been associated with the use of several IT medications, including morphine, hydromorphone, sufentanil, and tramadol (35). Baclofen has been associated with some form of foreign body reaction at the catheter tip, but this process appears to be different from that involving opioids (36,37). The risk for granuloma formation as a consequence of IT therapy can be minimized in a number of ways. Use of the lowest effective dose and concentration of IT opioids, using intermittent bolus dosing, and adjuvant therapy with nonopioid analgesic medications may all prevent granuloma formation. Additionally, the use of IT agents that have not been associated with granuloma formation (i.e., ziconotide or fentanyl) may help minimize a patient's risk. US FDA reporting has shown no cases of granuloma in patients receiving fentanyl as a monotherapy agent (Medtronic physician communication, 2008) (38). Further measures for minimizing risk of granulomas, as well as an algorithm for the treatment of IT granulomas are described in detail in the brief report, "Polyanalgesic Consensus Conference—2012: Consensus on Diagnosis, Detection, and Treatment of Inflammatory Masses and Granulomas." The panel urges all physicians and members of the care team to read this important document to improve patient safety.

Post–dural Puncture Headaches/CSF Leak Most post-dural puncture headaches resolve with oral hydration, caffeine, and bed rest. In some cases, the headaches are associated with visual disturbances, tinnitus, nausea, and vomiting. In the event of continued post-dural puncture headache despite conservative care, the patient should be admitted, positioned in a supine posture, and treated with adequate hydration, IV dexamethasone, and analgesics. In some cases, use of an epidural blood patch is useful but must be carefully considered because of the increased risk of infection, particularly in patients with newly implanted pumps (39). If headache persists, reanchoring of the catheter may be considered. If persistent headache is accompanied by unrelenting nausea and vomiting, the panel recommended that a computed tomography (CT) scan be performed to check for the presence of bleeding.

In some cases, placement of fibrin glue at the catheter insertion site can alleviate post-dural puncture headache. In severe cases that cause severe CSF hypotension, a subdural hematoma can occur and can result in significant morbidity or mortality. With this consideration, conservative measures should be used, but symptoms of neurologic demise should be closely monitored and addressed if present (17). Further guidelines for treating post-dural puncture headache are provided in the brief report, "Polyanalgesic Consensus Conference—2012: Consensus on Reducing Morbidity and Mortality in Intrathecal Drug Delivery."

IT Catheter and Pump Complications With IT therapy, there is an associated risk of complications related to the pump and/or catheter. Catheter complications are the most common mechanical problem with these devices. Catheters can become dislodged or develop tears or kinks. Pumps may corrode or malfunction. Guidelines for pump implantation, catheter placement, and pump refill, which may help clinicians avoid catheter- and pump-related complications, are included in the brief report, "Polyanalgesic Consensus Conference—2012: Consensus on Reducing Morbidity and Mortality in Intrathecal Drug Delivery." Appropriate training for health-care professionals who are involved in implanting, managing, and refilling pumps is also provided in the brief report.

Hyperalgesia

In 1915, Pohl (40) studied *N*-allylnorcodeine and discovered that it not only antagonized the respiratory depressant effects of morphine and heroin but that it also stimulated respiration in its own right. This observation was largely overlooked until it was suggested by Isbell and Fraser in 1950 (41) that nalorphine might be useful as an analgesic. This suggestion was confirmed by the work of Lasagna and Beecher in 1954 (42).

Martin demonstrated the existence of an endogenous kappa-opioid peptide in the pontine-medullary region of the brainstem, wherein the administration of low doses of naloxone produced analgesia; furthermore, although low doses produced analgesia, higher doses produced hyperalgesia. Finally, he demonstrated that this center is activated by exposure of higher brain centers to exogenous opioids. In 1983, Wu et al. (43) suggested that opioid peptides may play a dual role in modulating pain perception, not only lessening the sensation of pain, but also facilitating its recognition.

Multiple authors have described potential cellular mechanisms for OIH. This phenomenon, although distinct from pharmacologic tolerance, appears closely linked thereto, most likely by multiple mechanisms.

The rostral ventromedial medulla may be important in the induction of hyperalgesia. This hyperalgesic effect is possibly induced by cholecystokinin-mediated descending upregulation at the level of the rostral ventromedial medulla. In a critical experiment, Gardell et al. (44) produced bilateral lesions of the dorsolateral funiculus and thereby eliminated the release of spinal excitatory peptides in response to opioid administration, supporting the importance of a descending mechanism.

Patients who have had inadequate pain control with multiple opioids and have nociceptive pain could be experiencing a hyperalgesic effect, which can be confirmed or refuted by opioid weaning. If a patient's pain is refractory because it is neuropathic in nature, opioids may have a reduced role in treatment. These theo-

Figure 1. Algorithm for behavioral evaluation of patients considered for intrathecal therapy for management of pain. (Prepared by Marilyn S. Jacobs, PhD).

ries have led to the concept of microdosing with doses as low as 12.5 mcg/day. More prospective studies are needed to evaluate the role of weaning oral opioids before implantation and the role of microdosing in patient care.

Patient Monitoring After Initiation of Therapy

Routine inpatient monitoring after initiation of IT therapy, catheter revision, or reinitiation of IT therapy is recommended, and guidelines are provided in the brief report "Polyanalgesic Consensus Conference—2012: Consensus on Reducing Morbidity and Mortality in Intrathecal Drug Delivery." Literature review suggests that there is a markedly increased risk of mortality in the immediate period after reinitiating IT opioids or performing a revision (45). Vigilance is critical and can lead to improved safety if these guidelines are adhered to during patient care. Notably, patients with sleep apnea or psychiatric conditions, patients taking certain concomitant medications or supplements, and other high-risk patients may require more frequent and vigilant monitoring.

For patients in whom ziconotide therapy is initiated, monitoring of serum creatine kinase levels does not appear to be necessary in cases where there is no evidence of muscle weakness, wasting, or myalgia.

Switching or Discontinuing IT Therapy

Rotation or change in the infused drug should be considered when pain scores, function, and quality of life are unacceptable despite the administration of dosages that are considered to be in the acceptable range. AEs should also be considered in the decision to change medications. Adding an adjuvant drug rather than executing a drug rotation should be considered when AEs are acceptable but efficacy is suboptimal.

In some clinical settings, the outcome of the physician's attempt to manage the patient's pain by completing the algorithm of care may be unsatisfactory, despite best efforts. This may necessitate the weaning of the IT drug(s) and eventual explantation of the IT infusion system. When considering this course, the physician should complete the following steps:

- Evaluate catheter function
- Evaluate pump function
- Consider the possibility of concomitant therapies, such as physical medicine, injections, radiofrequency ablation, spinal cord stimulation (SCS), or change in oral medications
- Consider the possibility of disease progression, and treat as appropriate
- Consider the possibility of new disease processes causing worsening of pain

Psychological Aspects of IT Therapy

Many patients with chronic pain disorders have comorbid psychological disorders, such as mood, anxiety, eating, substance dependence, sleep, personality, and factitious disorders. Assessment of these conditions in the context of medical decision making for IT therapies is essential to determine whether they have the potential to interfere with the outcome of IT therapy (Fig. 1). Psychological evaluation may be necessary for insurance coverage of the procedure. Ideally, a clinical psychologist trained in health psychology should perform evaluations for IT therapy suitability. However, if a

clinical psychologist is not available, a mid-level health practitioner or physician can perform a basic evaluation. For some selected groups of patients (intractable cancer pain), the authors suggest that psychological evaluation might not be necessary if the patient's quality for end of life might be drastically improved by IT therapy and other conservative treatments have failed. Further information regarding psychological aspects of IT therapy is included in the brief report titled, "Polyanalgesic Consensus Conference—2012: Consensus on Trialing for Intrathecal Drug Delivery."

Psychiatric Considerations With Ziconotide Therapy

Ziconotide has been shown to be an efficacious drug in properly selected patients. The therapeutic window can be narrow with rapid titration; therefore, slow and monitored drug dose increases are recommended. One concern with rapid ziconotide titration is the psychological side-effects that may impact the use of the drug. Although these AEs typically resolve on discontinuation of the drug, they can be troubling to patients and caregivers. During the titration phase the panel recommends that patients be monitored by a caregiver or someone who can do frequent home visits for those who reside alone. Patients being considered for IT ziconotide therapy should be assessed by a careful psychological evaluation, with special attention to their premorbid psychological state and functioning. The patient's stress management and coping skills as the pain disorder has progressed over time offer valuable information for medical decision making about the use of ziconotide. It has been theorized that prior mental disorders may predispose the patient to have significantly increased risk of adverse psychiatric events with the use of this agent, but that has not been shown in a prospective fashion. With the use of new, slow-titration protocols, the risks of psychological side-effects have dissipated, but have not been eliminated. Given recent reports of increased suicidality associated with ziconotide, worsening of mood disorders and increased suicidal ideation are possible sequelae of ziconotide therapy (46). Cognitive impairment, new onset of psychosis, and changes in consciousness are other possible AEs (15,47). Considering these risks, patients with a history of psychosis are not candidates for ziconotide therapy (46–48). Even when an IT trial with ziconotide is successful, patients undergoing this therapy require continual review of their psychological functioning and a thorough mental status examination by the pain practitioner (see Appendix 1) (49).

Future Direction

Several future technologies and methodologies that may improve the safety of IT therapy are reservoir indicators, needle placement indicators, pump volume indicators, and the use of ultrasound to ensure that drug is not delivered to the pump pocket. Recent work by Gofeld (50) has shown the value of ultrasound that uses color Doppler to show proper filling of the device. The advent of reservoir indicators that give a discrete signal when the needle is in proper position should dramatically improve safety. The "gas gauge," a mechanism of measuring exact volume in the pump on the basis of actual content will be invaluable for troubleshooting. Other features that will be potentially approved for clinical use include pressure monitors to establish catheter occlusion, new materials to enhance catheter durability, and new conopeptides to improve patient outcomes in those who have had inadequate results with the current algorithm.

IT Microdosing

The analgesia produced by IT delivery of morphine is well established, but equally well known is the complicating factor of decreasing efficacy with increasing duration of therapy. In the absence of disease progression, this decreasing efficacy is now widely believed to be caused by the development of OIH. As the duration of therapy increases, continuous dosage escalation can be a substantial barrier to effective treatment. IT microdosing is an approach that produces intense and durable analgesia at dosages as low as 25 to 50 mcg/day and, in so doing, may reduce the development of OIH. The validity of this approach is controversial and has not been proven in prospective blinded fashion but may have great promise.

The theory of this approach is founded on the complex neurophysiology of spinal flow dynamics. Spinal fluid produced in the choroid plexi of the ventricular system travels through the third ventricle, the aqueduct of sylvius, and the fourth ventricle overlying the medulla, and it then exits through the foraminae of Luschka and Magendie. In the absence of pathology, CSF flow is rather consistent at this level. Once CSF exits the foraminae to flow over the surface of the brain and spinal cord, the rate and direction of flow are far less consistent. The total CSF volume in an adult ranges from 140 to 270 mL and is produced at a rate of about 600 to 700 mL/day. Magnetic resonance phase imaging and other techniques have been used to show a bulk flow of 0 to 3 cm/sec (51,52). The flow pattern is highly variable between individuals and in different states of hydration, with changes in cardiac output or posture, and with many other variables. The CSF is absorbed by the arachnoid villi and by extracranial lymphatics, both of which serve as one-way paths to the venous circulation (53). Because of this one-way circulation, a very low dose of IT hydrophilic opioid delivered low in the spinal canal would be diluted substantially before reaching the brainstem and, therefore, may not provide a sufficient amount of drug to induce the descending system.

Table 6. Concentrations and Doses of Intrathecal Agents by the Polyanalgesic Consensus Panelists, 2012.

Drug	Maximum concentration	Maximum dose per day
Morphine	20 mg/mL	15 mg
Hydromorphone	15 mg/mL	10 mg
Fentanyl	10 mg/mL	No known upper limit
Sufentanil	5 mg/mL	No known upper limit
Bupivacaine	30 mg/mL	10 mg
Clonidine	1000 mcg/mL	40–600 mcg/day
Ziconotide	100 mcg/mL	19.2 mcg/day

Maximum Concentrations and Dosages

To reduce the risk of granuloma formation and minimize complications, the panel recommended maintaining the concentration of opioids at the least concentrated value. This goal must be weighed against the need for frequent refills, and the decision should be based on clinical necessity. Table 6 lists the maximum concentrations and dosages of IT drugs recommended by the PACC panel.

Other Drugs and Combinations in IT Therapy

Table 7 lists drugs that have been shown to be neurotoxic and are not recommended for routine use in IT therapy. However, the panel recognizes that, in some cases, clinicians may operate outside of these guidelines in order to offer their patients the best possible care, which may be acceptable at the end of life when the patient has given proper informed consent. With the approval of ziconotide and the widespread experience with bupivacaine and clonidine, it is

Table 7. Drugs That Have Demonstrated Neurotoxicity and Are Not Recommended for Intrathecal Use (Except in Special Cases).

Opioids
- Meperidine
- Methadone
- Tramadol

Local anesthetic
- Tetracaine

Adrenergic agonist
- Dexmedetomidine

NMDA antagonists
- All agents in this group

Other nonopioids
- Droperidol
- Midazolam
- Methylprednisolone
- Ondansetron

NMDA, *N*-methyl-D-aspartate.

Table 8. Drugs That Appear to Be Safe but for Which Efficacy in the Intrathecal Treatment of Chronic Pain Has Not Been Demonstrated.

GABA analogs
- Gabapentin
- Baclofen

Peptidomimetic
- Octreotide

Local anesthetic
- Ropivacaine

unlikely that a physician would need to deviate from the main treatment algorithm, and the panel recommended extreme caution. Additionally, drugs that appear to be safe but for which efficacy has not been demonstrated for the IT treatment of chronic pain are presented in Table 8.

Special Considerations

Cancer Pain

Cancer-related pain is often more successfully controlled with IT therapy than with systemic therapy. Cancer pain may also be responsive to local anesthetics that can only be given intrathecally or to neurotoxic analgesics that could be used to treat pain at the end of life. Additionally, because time is a critical issue for terminally ill patients, preimplantation trialing may be unnecessary and counterproductive. However, previous recommendations for the placement of pumps only in patients with >3 months of life expectancy are based on antiquated data (54). Landmark work by Deer et al. (55) showed that life expectancy may be improved with IT therapies because of diminished side-effects, which suggests that, in the absence of impending death, IT pump therapy should be considered. Patients at the end of life should be treated to reduce systemic side-effects, improve quality of life particularly cognition and awareness, and possibly improve survival times. Such treatment may require higher doses, higher concentrations, and combinations of drugs that are outside of standard recommendations. This approach may also necessitate the use of agents that are normally felt to be unacceptable. The PACC panel recommended consultation with a tertiary center, when possible, regarding the treatment of such complex patients. IT therapy for patients at the end of life should be weighed against the risk of surgery, infection, and IT drug management compared with other options, such as hospice and palliative care.

SUPPORTING LITERATURE REVIEW

Opioids

Preclinical data on IT opioids published between January 15, 2007, and March 1, 2011, are summarized in Table 9 (14,15,56–80).

Results from a preliminary study of the effects of IT opioids on pain control and cytokine levels suggest that an inverse correlation exists between pain intensity and plasma concentrations of interleukin (IL)-10 and IL-6 in patients with chronic pain who are receiving IT opioid therapy ($p \leq 0.05$) (81). Thus, these cytokines could be biomarkers of persistent pain. Additionally, the CSF concentrations of IL-6 were approximately fivefold higher in patients who were treated with IT opioids for approximately five years than in patients who received IT opioids for three months. These results could suggest that CSF IL-6 contributes to the development of opioid analgesic tolerance.

Animal Studies: Neurotoxicity

Standardized assessments of preclinical safety of IT opioids in chronically catheterized large animal models have suggested that continuous infusions of morphine, hydromorphone, methadone, or fentanyl for at least 28 days resulted in no evident change in parenchymal morphology at the highest doses and concentrations examined. However, all these agents, with the exception of fentanyl, were observed to produce IT granulomas in dogs at the highest concentrations employed (morphine, 12 mg/mL; hydromorphone, 3 mg/mL; methadone, 3 mg/mL) (4,82). In sheep, morphine produced similar results, with no direct effect on the parenchyma but with an associated space-occupying mass (83). Unlike in the dog, hydromorphone was observed to have no evident granuloma-producing effect at the maximum concentration and dose employed (6 mg/day at a fixed infusion rate of 1.92 mL/day for 28–31 days) (84).

Morphine

Monotherapy Efficacy Clinical data on IT morphine continue to support its use as a first-line therapy. Results from several long-term studies support the efficacy of IT morphine in treating patients with chronic pain, including both cancer and noncancer pain types. In a retrospective study, medical records from 57 patients with chronic malignant pain on long-term IT opioid therapy (morphine, hydromorphone, or sufentanil) were reviewed (85). Visual analog scale (VAS) scores for pain significantly decreased from baseline to time of first refill ($p \leq 0.001$); VAS scores then remained stable and significantly lower than baseline scores ($p \leq 0.001$) through Year 3. Oral opioid use decreased significantly in the first year of IT therapy ($p \leq 0.001$) and increased slightly but insignificantly between Years 1 and 3. In a prospective, open-label study of IT morphine infusion in which a new type of pump was used, 110 patients with chronic pain were treated and followed up for approximately one year (86). Pain relief was noted within one month and was sustained during the following six months; trends indicated consistent pain relief through 12 months. In an open-label study, 13 patients with intractable pain from chronic pancreatitis who had undergone a successful trial of IT opioids received IT opioid infusions for a mean duration of 29 months (87). The intention-to-treat analysis revealed an overall success rate of IT opioid therapy of 76.9% of patients. In another open-label study, IT morphine was infused in 24 patients with vertebral fractures due to osteoporosis who had not responded to

Table 9. Summary of Preclinical Literature on Intrathecal Opioids.

Reference	Drug(s)	Model(s)	Main findings
Mechanistic/effectiveness studies			
Fukazawa et al. 2007 (56)	IT morphine	Rat	• CCK-mediated neural systems in the spinal cord appear to be involved in attenuation of IT morphine analgesia following electroacupuncture stimulation. • Activation of NK1 receptors by substance P may be an important mechanism for the antiopioid effects of CCK in the spinal cord
Kolesnikov et al. 2007 (57)	IT morphine	Rat model of neuropathic pain (CCI of sciatic nerve)	• The analgesic potency of IT morphine was significantly diminished in CCI mice (compared with sham-operated control mice).
Liu et al. 2007 (58)	IT morphine	Rat model of nociception (tail-flick test)	• Recruitment of spinal opioid analgesic receptor populations differs between male and female rats, which highlights the need for inclusion of both sexes in studies of antinociceptive mechanisms.
Shui et al. 2007 (59)	IT morphine	Rat	• Eight different proteins (including some involved in targeting and trafficking of glutamate and opioid receptors, some involved in oxidative stress, and cytoskeletal proteins) were found to be upregulated or downregulated in the spinal cords of rats that had developed tolerance to IT morphine.
Satarian et al. 2008 (60)	IT morphine and epinephrine	Rat model of nociception (tail-flick test) *CaMKIIa* gene expression	• Epinephrine in combination with IT morphine inhibited and reversed tolerance to the analgesic effects of morphine. • Expression of *CaMKIIa* (a molecular indicator of morphine tolerance) increased in animals treated with the epinephrine/morphine combination.
Fisher and Dickenson 2009 (61)	IT morphine	MIA rat model of OA pain	• OA rats were more resistant than their naïve counterparts to the analgesic effects of IT morphine.
Chen et al. 2010 (62)	IT morphine	Rat	• SNSR may modulate tolerance to IT morphine by inhibition of the PKC pathway, resulting in decreased enhancement of neuronal NOS and CGRP. • Intermittent use of SNSR agonists and IT opioids could hold promise for sustained use of opioids without the development of tolerance.
Gonzalez-Rodriguez et al. 2010 (63)	IT morphine	Mouse model of inflammation	• Enhancement of the effects of IT morphine by inflammation does not appear to be attributable to upregulation of the m-opioid receptor population and is independent of augmented NOS. • This enhancement may involve increased activation of postsynaptic opioid mechanisms mediated through GIRK channels
Hajializadeh et al. 2010 (64)	IT morphine	Rat model (streptozotocin-induced diabetes)	• Antinociceptive effects of IT morphine were significantly decreased in diabetic rats, but this state was reversible with insulin replacement. • Changes in expression patters of G_{ai}, G_{as}, G_b mRNAs and proteins (i.e., cellular components of morphine analgesia) were seen in diabetic rats without insulin replacement.
Hutchinson et al. 2010 (65)	IT morphine	Rat	• Blockade of TLR4 potentiated acute morphine analgesia.
Hutchinson et al. 2010 (66)	IT morphine (+) isomers	Rat	• IT administration of the (+)-isomers of morphine was found to induce the enhancement of pain responsivity dependent on microglial, interleukin-1, and TLR-4/myeloid differentiation factor-2.
Holtman et al. 2010 (67)	IT morphine-6-*O*-sulfate	Rat model of nociception (tail-flick test)	• IT administration of the morphine derivative morphine-6-*O*-sulfate produced dose-dependent antinociceptive effects and was tenfold more potent than was morphine.
Nielsen et al. 2007 (68)	IT norBNI, oxycodone, and morphine	Rat model of neuropathic pain (CCI of sciatic nerve)	• Pretreatment with the k-selective opioid antagonist norBNI abolished the antinociceptive effects of IT oxycodone but not IT morphine. • Pretreatment with the nonselective opioid antagonist naloxone abolished the antinociceptive effects of IT morphine, but antinociceptive effects of IT oxycodone were maintained at decreased potency.
Holtman et al. 2008 (69)	IT morphine, IT S(+)norketamine	Rat model of nociception (tail-flick test)	• Antinociceptive effects of IT morphine were significantly enhanced by S(+)norketamine in a dose-related manner
Kosson et al. 2008 (70)	IT ketamine, morphine, and biphalin	Rat model of nociception (tail-flick test)	• Infusion of IT ketamine and IT administration of either morphine or the opioid peptide analog biphalin resulted in greater antinociception than either morphine or biphalin alone; thus, lower doses of morphine or biphalin may be required if ketamine is coadministered.
Makuch et al. 2009 (72)	IT morphine and endomorphin-1	Rat models of acute and neuropathic pain	• Nitric oxide pathways may underlie the weaker efficacy of morphine in treating neuropathic pain. • Nitric oxide may also contribute to the differences in analgesic efficacy of various m-opioid receptor ligands.
Nishiyama 2009 (73)	IT morphine and epibatidine	Rat models thermal and inflammatory of acute pain	• Coadministration of IT morphine and IT epibatidine resulted in synergistic antinociceptive effects, with ED_{50} of the drug combination being significantly lower than the ED_{50} of either drug alone.
Pettersen et al. 2009 (74)	IT morphine, amitriptyline, maprotiline, and citalopram	Rat model of acute thermal pain	• The intensity and duration of antinociceptive effects of IT morphine increased when used in combination with IT amitriptyline or IT maprotiline but not citalopram. • The nociceptive effects of IT morphine and maprotiline appear to be synergistic, with involvement of a_2-adrenergic and opioid receptors.
Tai et al. 2009 (75)	IT morphine and amitriptyline	Rat	• Amitriptyline may restore the antinociceptive effects of IT morphine in morphine-tolerant rats via upregulation of the anti-inflammatory cytokine IL-10. • This effect appears to be mediated by the p38 MAP kinase and heme oxygenase-1 signal transduction cascade, which leads to decreased expression of several proinflammatory cytokines.
Lin et al. 2010 (76)	IT morphine and naloxone	Rat model of nociception (tail-flick test)	• Administration of ultra-low-dose naloxone preserved the antinociceptive effects of chronic IT morphine.
Shen et al. 2011 (77)	IT morphine and etanercept	Rat model of nociception (tail-flick test)	• IT etanercept restored antinociceptive effects in IT morphine-tolerant rats. • Effects appeared to be attributable to inhibition of proinflammatory cytokines.
Haroutiunian et al. 2009 (78)	IT, epidural, and IV methadone	Rat model (tail-withdrawal and tail-flick tests)	• IT and epidural administration of methadone provided analgesia superior to that of IV methadone; no difference in analgesic effect between IT and epidural methadone was noted.
Pharmacokinetic studies			
Flack et al. 2011 (15)	IT morphine	Ambulatory pig	• Spinal distribution of IT morphine was very limited, and morphine concentration decreased exponentially as a function of distance from catheter tip (concentrations within 5–10 cm of the catheter tip ranged from approximately 5–24% of peak concentrations).
Stability studies			
Bianchi et al. 2008 (273)	IT morphine, bupivacaine, clonidine, and hydromorphone	Simulated IT administration	• IT mixtures of morphine + bupivacaine + clonidine and hydromorphone + clonidine were found to be stable for 90 days.
Shields et al. 2007 (79)	IT morphine, ziconotide, and clonidine	Simulated IT administration	• IT mixtures of ziconotide + clonidine + morphine were found to be 70% stable for 20 days.
Shields et al. 2008 (80)	IT fentanyl, sufentanil, and ziconotide	Simulated IT administration	• In IT mixtures of ziconotide + fentanyl and ziconotide + sufentanil, no measureable declines in the concentrations of fentanyl or sufentanil were seen during the 40-day study

IT, intrathecal; SNSR, sensory neuron-specific receptor; PKC, protein kinase C; NOS, nitric oxide synthase; CGRP, calcitonin gene-related peptide; MIA, monosodium iodoacetate; OA, osteoarthritic; CCK, cholecystokinin; NK1, neurokinin-1; GIRK, $G_{i/o}$ protein and G-coupled inwardly rectifying potassium; IV, intravenous; SC, subcutaneous; ICV, intracerebroventricular; TLR4, toll-like receptor 4; CCI, chronic constriction injury; norBNI, norbinaltorphimine; ED_{50}, 50% effective dose; CaMKIIa, calcium/calmodulin-dependent protein kinase IIa; IL-10, interleukin-10; MAP, mitogen-activated protein.

systemic opioid therapy (88,89). The mean VAS pain score decreased significantly from 8.7 cm before IT therapy to 1.9 cm after one year of IT therapy ($p < 0.001$). Significant improvements from baseline to one year were also noted on scores for the Quality of Life Questionnaire of the European Foundation for Osteoporosis subscales for pain, quality of daily life, domestic work, ambulation, and perception of health status ($p < 0.001$). In one retrospective study, investigators attempted to determine characteristics of patients for whom IT morphine therapy is effective (90). The study included 131 patients who received IT morphine monotherapy for various pain types (i.e., cancer-related, nociceptive, or neuropathic). A >50% decrease in pain was reported in 73% of all patients. No differences in responder rates were noted when results were analyzed by pain type, patient age, or morphine dosage; however, responder rates were significantly higher in men than in women ($p = 0.02$).

Combination Therapy Efficacy A number of studies have been conducted to evaluate the use of IT morphine in combination with other IT agents, such as levobupivacaine, ziconotide, and baclofen. One such open-label study included 55 patients with advanced cancer-related pain who had been unresponsive to previous trials of systemic opioids and were treated with a combination of IT morphine and IT levobupivacaine and followed up for up to six months (91). The initial IT morphine dosage was calculated from the patients' previous systemic opioid dosage by using an oral : IT ratio of 100:1 (which is notably different from the 300:1 ratio that is typically used for equianalgesic calculations). The initial levobupivacaine dosage of 12.5 mg/day was increased to 25 mg/day before the IT morphine dosage was increased and modified as needed. Significant reductions in pain intensity, along with significant decreases in the mean systemic opioid dose, were noted at one and three months after initiation of IT therapy and up to the time of death ($p \leq 0.029$). In another open-label study, one that included 32 patients with chronic noncancer pain who had >70% pain relief after a trial of low-dose IT morphine and bupivacaine, continuous IT therapy (0.1 mg/day morphine, 0.5 mg/day bupivacaine) was initiated, and dosages were titrated to a mean of 1.03 mg/day morphine and 1.15 mg/day bupivacaine (92). Mean VAS pain scores decreased significantly from baseline to Month 3 ($p < 0.01$) and remained consistently reduced through the 48-month follow-up.

The addition of IT morphine in 25 patients with suboptimal pain relief on stable dosages of IT ziconotide was investigated in an open-label study (93). VAS of Pain Intensity (VASPI) scores for these patients improved by a mean of 26.3% by Week 4 of combination therapy, and mean systemic opioid consumption decreased by 49.1%. Notably, stability data regarding ziconotide and opioid admixtures may provide guidance for frequency of pump refills (see Table 9) (80,94).

Safety There are a number of safety concerns with IT infusion of morphine. In the previously mentioned retrospective record review of patients with chronic nonmalignant pain on long-term IT opioid therapy (morphine, hydromorphone, or sufentanil), 14 complications in ten patients (infection, catheter revision, seroma, granuloma) were noted (85). Side-effects included fluid retention, urinary retention, myoclonic jerks, and nausea/vomiting.

Immunosuppression Immunosuppression is a possible concern in patients treated with IT morphine therapy. In a long-term study, patients with chronic noncancer pain treated with IT morphine (alone or concomitantly with bupivacaine) had significant increases in mu-opioid receptor levels in lymphocytes after 12 and 24 months of treatment ($p < 0.05$); increases were greater with morphine/bupivacaine combination therapy (95). Because increased mu-opioid receptor levels could result in immunosuppression, IT opioids should be used with care in immunosuppressed patients.

Respiratory Depression Since publication of the last PACC guidelines, one case report of respiratory depression in a patient treated with IT morphine has been published (96). This 65-year-old woman who had been receiving 4 mg/day IT morphine was unable to return to clinic for pump refill until 12 days after the scheduled refill date, and the pump was found to be empty at this time. Ten hours after pump refill and resumption of IT morphine infusion (4 mg/day), she experienced severe respiratory depression (respiratory rate, 5 breaths per minute). This case suggests that loss of opioid tolerance as a result of delayed pump refill could put patients at risk of severe respiratory depression.

Peripheral Edema Two cases of peripheral edema associated with intraspinal morphine therapy were published during the period of literature review. The first described a 64-year-old woman who underwent a two-week trial of epidural morphine for pain due to failed back surgery syndrome (97). During the trial, she developed bilateral leg edema and gained >12 lb. The edema resolved within two days after termination of the infusion. This case suggests that even small doses of continuous epidural morphine can cause peripheral edema in an otherwise healthy patient. The second case report described a 61-year-old woman with chronic back pain who was treated with IT morphine, titrated to 5 mg/day over the course of three months (98). She developed progressive lower extremity edema, which was complicated by severe cellulitis. The edema lessened when she was switched to IT hydromorphone but reoccurred with severe cellulitis two months later. Her IT regimen was changed to clonidine (33 mcg/day) and baclofen (67 mcg/day); her edema resolved and did not recur. The panel recommends opioid rotation to address edema, and if unsuccessful to consider nonopioid agents.

Granulomas The risk for development of inflammatory masses (granulomas) with IT morphine therapy has been an ongoing concern. During the period reviewed herein, the development of granuloma was reported in a total of 13 patients in studies or case reports of IT morphine use (alone or in combination with other drugs) (99–110). Three additional patients developed granuloma while receiving diamorphine in combination with other IT drugs, and two patients developed granuloma while receiving unspecified IT opioids (85,99). In a retrospective longitudinal study that included 56 patients on long-term IT therapy with morphine or diamorphine (either alone or in combination with clonidine, bupivacaine, and/or baclofen), granuloma development was reported in four patients: one was treated with morphine and bupivacaine, two with diamorphine plus clonidine and bupivacaine, and one with diamorphine plus bupivacaine and baclofen (99). Granuloma formulation was significantly positively correlated with opioid dose ($p < 0.05$) and yearly increase in opioid dose ($p < 0.01$) but not with flow rate or opioid concentration. In another retrospective study, the medical records of 57 patients on long-term IT opioid therapy (morphine, hydromorphone, or sufentanil) were reviewed (85). Two patients developed granuloma; however, which opioids these patients received were not specified.

Granuloma is important in the differential diagnosis of patients receiving IT therapy who have neurologic deterioration; MRI and/or CT scans should be used to investigate this possibility. Leong et al. (109) reported MRI findings in two patients with IT morphine-related granuloma. Both patients had T1- and T2-weighted low to intermediate signal intensity spinal masses with marginal rim enhancement by gadolinium, and the masses were T1/T2 hyperin-

tense. Additionally, the authors noted that CT could be used to locate an IT catheter; correlation of catheter tip location and MRI lesion can be used for surgical planning. Another report described how metallic catheter tips may produce metallic susceptibility artifacts, which distort images of local tissue, on MRI (110). Catheter tips also appear magnified, which could mask the presence of small granulomas. However, catheter tips alone are not enhanced after contrast administration, which could be useful in differentiating catheter tips from granulomas in the axial plane. The risk factors for and the identification and treatment of granulomas are discussed in further detail in the brief report titled "Polyanalgesic Consensus Conference—2012: Consensus on Diagnosis, Detection, and Treatment of Catheter-Tip Inflammatory Masses (Granulomas)."

Tolerance Finally, tolerance, another common safety concern with morphine use, was investigated in a longitudinal retrospective review of the medical records of 47 patients who received long-term IT morphine or diamorphine therapy (111). During a mean treatment period of six years, increases in opioid doses were seen, but these were generally moderate. The time to reach a dosage of 5.23 mg/day in this study was ten years. Notably, in an earlier retrospective analysis of the change in IT morphine infusion dose in patients with cancer-related pain, among patients who were infused for at least three months, 48% had a less than twofold increase in dose by Month 3 (112). A variable in the development of tolerance is the physician practice and frequency of dose change based on individualized practice preferences.

Hydromorphone

The literature review revealed no new studies investigating the efficacy of IT hydromorphone in the treatment of chronic pain. Two case reports described granuloma development in patients treated with IT hydromorphone. The first described the previously mentioned patient (see morphine section) who developed a granuloma on IT morphine; nine months after removal of the first granuloma, she developed another granuloma after one month of IT hydromorphone therapy (102). The second report described a 52-year-old man with a history of chronic lumbar spine pain who developed a granuloma while receiving high-concentration IT hydromorphone (85 mg/mL) at a dose of 19.8 mg/day (113).

Peripheral edema associated with IT hydromorphone infusion was reported in one patient. This previously described (see morphine section) 61-year-old woman with chronic pain developed progressive lower extremity edema, which was complicated by severe cellulitis, while on IT morphine (98). Her edema lessened when she was switched to IT hydromorphone but recurred with severe cellulitis two months later. Her IT regimen was changed to clonidine (33 mcg/day) and baclofen (67 mcg/day); edema resolved and did not recur.

Fentanyl

The literature review revealed no new studies investigating the efficacy of IT fentanyl in the treatment of chronic pain. One case report described a 34-year-old woman receiving IT combination therapy (fentanyl, bupivacaine, and clonidine) for chronic pain, who was suspected of having an epidural hematoma because of 1) inadequate pain control despite increasing doses and 2) an unsuccessful epidural steroid injection (114). Upon operation, a catheter-tip mass was noted in the epidural space, with the catheter tip in the center of it. Misplacement of the catheter (epidurally instead of intrathecally) at the time of original insertion complicated diagnosis, and the authors determined that the inflammatory mass was likely a result of drug precipitation and was not granulomatous.

Sufentanil

The literature review revealed no new studies investigating the efficacy of IT sufentanil in the treatment of chronic pain. One case report described an 86-year-old woman with failed back surgery syndrome who had received multiple IT therapies over the course of two years (115). Six weeks after beginning IT sufentanil therapy (12–17.2 mcg/day), she had lower extremity weakness, sensory changes, and intractable lumbar pain, and a CT-myelogram demonstrated the presence of a granuloma. Sufentanil was removed from the pump and replaced with normal saline. Her symptoms resolved within approximately 48 hours, and the patient was receiving oral methadone therapy for pain at the time of hospital discharge.

Methadone[1]

The efficacy of epidural methadone was investigated in a study of 32 patients with cancer-related pain that was refractory to epidural morphine (116). Patients received one of the following treatments: 2.5, 5, or 7.5 mg epidural methadone diluted in 60 mg lidocaine or 7.5 mg epidural methadone diluted in 60 mg lidocaine plus 10 mg dexamethasone. Epidural methadone was found to provide dose-dependent analgesic effects, and these effects were further improved with addition of dexamethasone. Notably, there is concern about the safety of IT methadone, since all compounds with *N*-methyl-D-aspartate (NMDA) activity have serious neurotoxic effects (117).

Meperidine

No literature published since 2007 was found regarding the preclinical or clinical use of IT meperidine for chronic pain. Results from a randomized, double-blind study with volunteers confirmed that meperidine exerts a dose-dependent conduction nerve block when administered perineurally at the level of the ulnar nerve (118). No new data support the long-term use of IT meperidine, which is known to produce high plasma concentrations of normeperidine and increase the risk for central nervous system (CNS) AEs (119).

Other Opioids

The first case of a granuloma in a patient receiving long-term IT tramadol (12.5 mg/day) was reported (120). After ~30 months on this dosage, a progressive increase in dosage (to 29 mg/day) was needed to maintain pain control, and the patient noted numbness in her lower left limb. She underwent a dorsal laminectomy, with identification and removal of a catheter-tip granuloma. The IT tramadol therapy was resumed postoperatively, and the patient has since experienced adequate pain control with no further neurological deficits. The literature search revealed no other published data regarding the safety of IT tramadol.

Nonopioids

Recently published preclinical literature regarding the IT use of nonopioid medications is summarized in Table 10 (16,70,71,80,117,121–145).

Ziconotide

Mechanism of Action Ziconotide is a noncompetitive blocker of the N-type voltage-sensitive calcium channel, which is present on primary afferents and is responsible for the depolarization-evoked release of primary afferent transmitters. The IT delivery of ziconotide

[1] Because IT methadone is associated with possible spinal cord toxicity, it is not endorsed for routine usage by the PACC panel.

Table 10. Summary of Preclinical Literature on Intrathecal Nonopioids.

Reference	Drug(s)	Model(s)	Main findings
Mechanistic/effectiveness studies			
Feng et al. 2009 (121)	IT clonidine	PSNL rat	• IT clonidine administration led to dose-dependent attenuation of PSNL-induced thermal and mechanical hyperalgesia. • Antiallodynic properties of clonidine may result from inhibition of glial activation of NF-kB and p38.
Guevara-López et al. 2009 (122)	IT clonidine	Rat	• No evidence of neurologic damage was noted in the spinal cord specimens from rats that received continuous infusion of IT clonidine (21.4 mcg/day) for 14 consecutive days.
Martin et al. 2007 (123)	IT clonidine	SNL rat	• IT clonidine reversed mechanical hypersensitivity and reduced opioid consumption in opioid self-administering rats.
Roh et al. 2008 (124)	IT clonidine	CCI rat	• Activation of spinal a-2 adrenoreceptors by IT clonidine rapidly reversed thermal hyperalgesia and mechanical allodynia in a rat model of neuropathy. • IT clonidine decreased the number of pNR1 immunoreactive neurons in the dorsal horn, suggesting that reduction in NMDA receptor phosphorylation may be a mechanism of action for clonidine.
Ando et al. 2011 (125)	IT ketamine	*Xenopus* oocytes	• Desensitization of $GABA_BR$-mediated signaling is suppressed by *S*(+)-ketamine, in part, through inhibition of the formation of protein complexes of G protein-coupled receptor kinase 4 or 5.
Boettger et al. 2010 (126)	IT ketamine	Rat model of chronic AIA	• IT ketamine applied before induction of arthritis significantly attenuated the development of acute inflammation; this effect appears to be attributable to a spinal mode of action. • IT ketamine had antinociceptive and anti-inflammatory effects in both the acute and chronic phases of AIA.
Infante et al. 2007 (127)	IT ketamine	Monoarthritic rat	• IT ketamine administration resulted in decreased expression of nNOS but increased expression of iNOS and eNOS.
Mei et al. 2009 (128)	IT ketamine	SNL rat	• IT ketamine administration downregulated expression of glial fibrillary acidic protein, suggesting that astrocyte-related mechanisms may underlie the antiallodynic effects of ketamine.
Mei et al. 2011 (129)	IT ketamine	SNL rat	• IT ketamine administration alleviated SNL-induced mechanical allodynia without interfering with motor performance. • IT ketamine also attenuated SNL-induced activation of JNK, a kinase thought to be important in spinal astrocytic activation and the development of neuropathic pain after SNL; JNK protein expression was not affected.
Walker et al. 2010 (130)	IT ketamine	Carrageenan-induced hyperalgesia in the neonatal rat	• Carrageenan-induced hyperalgesia was reversed by 3 mg/kg IT ketamine in three-day-old rats and 15 mg/kg IT ketamine in 15-day-old rats. • IT ketamine (3–10 mg/kg) in three-day-old rats resulted in acute increases in apoptosis and microglial activation in the spinal cord and altered spinal function at postnatal day 35.
Yaksh et al. 2008 (117)	IT ketamine	Dog	• After 1–5 days of 10 mg/kg IT ketamine administration, mild hind leg weakness and neck stiffness were common. • Lumbar spinal cord segment proximal to the catheter tip had perivascular inflammation and edema within white matter parenchyma.
Loram et al. 2009 (131)	IT $A_{2A}R$ agonists	CCI rat	• A single IT injection of $A_{2A}R$ agonists, ATL 313 or CGS 21680, 10–14 days after CCI, resulted in reversal of thermal analgesia and mechanical allodynia for ≥4 weeks.
Martin et al. 2007 (123)	IT adenosine	SNL rat	• IT adenosine reversed mechanical hypersensitivity but did not have opioid-sparking effects in opioid self-administering rats.
Kuroiwa et al. 2009 (132)	IT baclofen	Anemic decerebrate rigidity in rats	• IT baclofen inhibited anemic decerebrate rigidity in rats in a dose-dependent fashion. • The effective dose of IT baclofen was 300 times lower than that of IV baclofen. • IT baclofen had a substantially greater safety margin than did IV baclofen.
Lin et al. 2009 (133)	IT gabapentin	Rat formalin test	• IT administration of gabapentin 10 min before formalin injection attenuated the flinching response in the second phase of the test. • IT administration of an HCN inhibitor did not reverse the analgesic effects of gabapentin, suggesting that antinociceptive effects of gabapentin are not attributable to HCN activation.
Narita et al. 2007 (134)	IT gabapentin	Sciatic nerve ligation mouse	• Sciatic nerve ligation caused upregulation of a2d-1 calcium channel subunits at the sensory nerve terminal in the spinal cord. • IT gabapentin administration prevented the development and maintenance of a neuropathic pain-like state after sciatic nerve ligation. • IT gabapentin administration in the early stages of a neuropathic pain-like state led to persistent reduction in the nociceptive threshold, which continued seven days after discontinuation of gabapentin.
Takasusuki and Yaksh 2011 (135)	IT gabapentin	Rat formalin test	• IT administration of gabapentin had a dose-dependent effect on phase 2 flinching and acutely inhibited the release of substance P from small primary afferents.
Takeuchi et al. 2007 (136)	IT gabapentin	Partial sciatic nerve ligation mouse	• IT gabapentin administration ameliorated mechanical hypersensitivity but did not alter spinal levels of monoamines or their metabolites.
Van Elstraete et al. 2008 (137)	IT gabapentin	Hyperalgesic rat	• IT gabapentin administration 30 min before subcutaneous fentanyl injection prevented the development of hyperalgesia. • This effect is thought to be due, in part, to gabapentin binding to a2d auxiliary subunits of voltage-gated calcium channels.
Eisenach et al. 2010 (138)	IT ketorolac	Human models of experimental pain	• IT ketorolac did not affect capsaicin-induced hypersensitivity but reduced areas of UV-B-induced allodynia.
He et al. 2007 (71)	IT ketamine and clonidine	CCI rat	• IT coadministration of ketamine and clonidine had significantly more potent analgesic effects than IT administration of either drug alone, suggesting that this drug combination may have synergistic effects.
Horvath et al. 2007 (139)	IT guanine, endomorphin-1, adenosine, and kynurenic acid	Rat	• IT infusions of triple and quadruple combinations of endogenous ligands (endomorphin-1, adenosine, guanine, and kynurenic acid) had greater antihyperalgesic effects than did double combinations.
Kosson et al. 2008 (70)	IT ketamine, morphine, and biphalin	Rat model of nociception (tail-flick test)	• Infusion of IT ketamine and IT administration of either morphine or the opioid peptide analog biphalin resulted in greater antinociception than either morphine or biphalin alone; thus, lower doses of morphine or biphalin may be required if ketamine is coadministered.
Lizarraga et al. 2008 (140)	IT ketamine and ketoprofen	Sheep	• IT ketamine and ketoprofen, alone or in combination, did not have direct hypoalgesic effects. • IT ketamine and ketoprofen, both alone and in combination, prevented the development of NMDA-induced mechanical hypersensitivity.
Mei et al. 2010 (141)	IT ketamine and LAA	SNL rat	• IT administration of ketamine or the astrocytic inhibitor LAA had dose-dependent effects on alleviation of SNL-induced mechanical allodynia. • IT coadministration of ketamine and LAA appears to have synergistic analgesic effects.
Ortega-Verela et al. 2007 (142)	IT gabapentin and metamizole	Formalin-induced nociception in the rat	• IT administration of gabapentin and metamizole, both alone and in combination, resulted in dose-dependent antinociceptive effects. • Significant synergistic effects of IT gabapentin and metamizole were noted.
Park and Jun 2008 (143)	IT gabapentin and R-PIA	SNL rat	• IT gabapentin and R-PIA (an adenosine A1 receptor agonist), both alone and in combination, demonstrated dose-dependent antiallodynia and were not associated with severe side-effects. • Synergistic interaction between gabapentin and R-PIA appears to involve activation of adenosine A1 receptors.
Pelissier et al. 2008 (144)	IT ketamine and (+/-)CPP	Monoarthritic rat	• IT coadministration of ketamine and (+/-)CPP had synergistic antinociceptive effects in the capsaicin test but only additive effects in the paw pressure test.
Yamama et al. 2010 (145)	IT gabapentin and clonidine	SNL rat	• IT coadministration of clonidine and gabapentin produced synergistic inhibition of mechanical allodynia.
Stability studies			
Shields et al. 2008 (80)	IT ziconotide, fentanyl, and sufentanil	Simulated IT administration	• In IT mixtures of ziconotide + fentanyl, ziconotide was 90% stable for 26 days and 80% stable for 58 days. • In IT mixtures of ziconotide + sufentanil, ziconotide was 90% stable for 33 days and 80% stable for 68 days.
Pharmacokinetic studies			
Flack and Bernards 2010 (16)	IT baclofen and bupivacaine	Pig	• After IT infusion of a solution of baclofen and bupivacaine, distribution of the drugs was biased caudally in pigs in the vertical position and cephalad in pigs in the prone position. • In both the vertical and prone pigs, CSF and spinal cord drug concentration decreased as a function of distance from the administration site.

IT, intrathecal; PSNL, partial sciatic nerve ligation; CCI, chronic constriction injury; NMDA, *N*-methyl-D-aspartate; $GABA_BR$, gamma-aminobutyric acid type B receptor; AIA, antigen-induced arthritis; SNL, spinal nerve ligation; JNK, c-Jun N-terminal kinase; nNOS, neuronal nitric oxide synthase; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; $A_{2A}R$, adenosine 2A receptor; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; CSF, cerebrospinal fluid; LAA, l-a-aminoadipate; R-PIA, N^6-(2-phenylisopropyl)-adenosine *R*-(-)isomer; (+/-)CPP, (+/-)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid.

has been shown to have potent effects on a variety of tissue and nerve injury pain states in rodent models (146,147).

Preclinical Safety Ziconotide was approved by the US FDA in 2004. Its approval was supported by a comprehensive preclinical safety evaluation in a variety of species (reviewed by Skov et al. (148)).

Long-Term Use Long-term use of IT ziconotide was investigated in an open-label, multicenter study including 644 patients with mostly chronic noncancer pain (149). The median duration of ziconotide therapy was 67.5 days, and 119 patients received ziconotide for ≥360 days. The median ziconotide dosage at last infusion was 8.4 mcg/day. Among the 394 patients who had VASPI scores ≥50 mm at baseline, 129 (32.7%) had a ≥30% improvement in VASPI scores after one month of ziconotide treatment. Additionally, objective measures of cognitive function did not appear to be affected by ziconotide therapy. Webster et al. (150) conducted an open-label, three-year, multicenter study that included 78 patients with chronic malignant or nonmalignant pain who had participated in previous ziconotide studies. The median ziconotide dosage was 6.48 mcg/day at initial visit and ranged from 5.52 to 7.20 mcg/day across all study visits, and VASPI scores were generally stable throughout the study.

Interim analysis of data from the Patient Registry of Intrathecal Pain Management in Europe found 23 patients who received ziconotide monotherapy and 13 who received ziconotide plus another IT agent (151). Six patients (26.1%) who began ziconotide monotherapy continue to receive it after one year. The mean change from baseline to Month 4 in VASPI score was 12.5 mm for patients on ziconotide monotherapy and –6.63 mm for patients on ziconotide plus another IT agent (negative change indicates improvement). Vogt et al. (152) reported that, in a prospective study of ziconotide use in ten patients with severe neuropathic pain, four patients continued ziconotide therapy after a mean follow-up of 395 days.

A retrospective review article described ziconotide use (as monotherapy or adjunctive therapy) in seven patients with CRPS (153). Initial ziconotide dosages ranged from 0.5 to 13 mcg/day, and the last available ziconotide dosages ranged from 0.06 to 146 mcg/day. Duration of therapy ranged from 26 days to 8 years. Five patients had >30% improvements in VAS scores and had increased activity levels. Edema and skin abnormalities resolved or markedly improved in all three patients who reported these symptoms. McDowell et al. (154) described a series of five cases of ziconotide use (as monotherapy or adjunctive therapy) in patients with chronic malignant pain. Initial ziconotide dosages ranged from 0.46 to 1.5 mcg/day, and ziconotide dosages at last assessment ranged from 1.16 to 7.26 mcg/day. Numeric pain intensity scores were reduced by 25% to 83% with ziconotide therapy in these patients.

Safety Analysis of AE reports from the FDA Adverse Event Reporting System data base for the five years following ziconotide approval revealed 314 AE reports, which most commonly included pain, confusion, hallucinations, and nausea (155). Twenty-six fatalities were reported, and the AEs most commonly associated with these fatalities included malignant neoplasm progression, myocardial infarction, respiratory failure, and renal failure. There were 34 reports of rhabdomyolysis, of which 5 were confirmed by Standard MedDRA Query.

Notably, ziconotide has been suggested to be associated with an increased risk of suicidality, even in patients without symptoms of depression (46). Other AEs commonly associated with IT ziconotide therapy include psychiatric AEs, dizziness, gait abnormalities, headache, diplopia, cognitive AEs, urinary retention, nystagmus, speech disorder, nausea, nervousness, and somnolence (149,150,152–154,156). In one study, cognitive AEs (e.g., mental slowing, confusion, difficulty concentrating, memory impairment, impaired verbal expression) were associated with higher ziconotide doses and longer times to onset (149). Thus far, there is no evidence of cumulative toxicity with long-term ziconotide therapy (149,150).

Combination Therapy In a phase 2, open-label study, the addition of IT ziconotide was examined in 26 patients with suboptimal pain relief on IT morphine therapy (157). Ziconotide therapy began at a dosage of 0.6 mcg/day and was titrated to a maximum of 7.2 mcg/day. Reduction in VASPI scores was noted after two weeks of combination therapy, with a 14.5% mean VASPI score improvement by Week 5. This decrease in pain was small but meaningful in this cohort of patients with a long history of highly refractory pain. Notably, use of systemic opioids was reduced in these patients. A retrospective observational study of severe chronic pain of noncancer origin included 16 patients who had inadequate analgesia with IT opioid therapy and had ziconotide added to their IT regimen (158). Ziconotide therapy began at a dosage of 0.5 mcg/day and was titrated to a mean dosage of 2.64 mcg/day over the course of 12 weeks. At the end of this titration period, 20% of patients had ≥4-point decreases in scores on the 11-point VAS, and 20% reported increased functional capacity.

Combination therapy with ziconotide and other IT agents has been described in numerous case reports. In one case series, the addition of ziconotide to existing IT baclofen therapy in five patients with chronic neuropathic pain and spasticity was reported (159). The mean baseline VASPI score in these patients was 91 mm, and the baclofen dosage was stabilized at a mean of 266 mcg/day. The addition of ziconotide resulted in a mean 50.3% improvement in VASPI scores. The mean time to onset of pain relief was 15 weeks at a mean ziconotide dosage of 3.7 mcg/day. An additional case report described a 23-year-old woman with a spinal cord injury associated with both at-level and below-level neuropathic pain (160). The patient's at-level pain, but not below-level pain, had responded to IT hydromorphone therapy. Ziconotide therapy was initiated at a dosage of 2.4 mcg/day and titrated every 12 to 14 days in increments of 0.5 to 0.6 mcg/day. Addition of ziconotide led to substantial reduction of below-level pain. The best pain control was achieved on a regimen of 11 mcg/day ziconotide and 1.3 mg/day hydromorphone. Another case report described a 59-year-old man with spinal cord injury pain that was not adequately controlled with a combination of IT morphine and baclofen therapy (161). Ziconotide was added at an initial dosage of 2 mcg/day. The combination of IT morphine (8.5 mg/day), baclofen (1050 mcg/day), and ziconotide (6.7 mcg/day) provided adequate pain control and 85% reduction in systemic analgesic use. In another case, a report of a 43-year-old man with spinal cord injury pain, ziconotide was added after one month of treatment with IT morphine and baclofen (161). On a regimen of morphine (3.4 mg/day), baclofen (1700 mcg/day), and ziconotide (4.2 mcg/day), the patient's pain decreased by >50%, sleep improved, anxiety lessened, and oral analgesic use decreased by 45%. Somnolence was the only reported AE.

Trialing Trialing of IT ziconotide was described in a report of 11 patients with established IT pumps who received single-shot trials of ziconotide (1.2–5 mcg) (162). AEs were similar to those reported in traditional titration trials and included one case each of urinary retention, hallucinations, and motor weakness. Trialing of ziconotide is discussed in further detail in the brief report titled, "Polyanalgesic Consensus Conference—2012: Consensus on Trialing for Intrathecal Drug Delivery."

Use in IT Morphine Detoxification The use of ziconotide in IT morphine detoxification was investigated in an observational study in which two methods of switching from IT morphine to ziconotide therapy (i.e., equivalent detoxification and fast detoxification) were compared (163). In the equivalent detoxification method, the IT morphine dosage was gradually substituted with an equivalent oral morphine dosage over the course of a month, and IT ziconotide therapy started when detoxification was complete. In the fast detoxification method, IT morphine was substituted with slow-release oral morphine, clonidine, ketoprofen, and lorazepam for three days, followed by slow-release oral tramadol, clonidine, and ketoprofen for ten days; IT ziconotide therapy was started when detoxification was complete. Both methods were successful in preventing opioid withdrawal symptoms and increased pain, and the authors recommended the fast detoxification approach.

Local Anesthetics

Bupivacaine

Use in Head, Neck, and Upper Limb Pain The use of IT bupivacaine in head, neck, and upper limb pain was described in a report of six cases of patients with head and neck or upper limb cancer-associated refractory pain (164). IT bupivacaine and diamorphine (with clonidine and/or baclofen in some cases) were administered via a catheter in the cervical or upper thoracic spine for 13 to 87 days. All patients reported improvements in pain and reduced the use of systemic opioids/adjuvants. AEs were reported in four patients and included leg weakness, arm weakness/numbness, urinary retention, hypotension, catheter dislodgment, and respiratory depression. It should be noted that these infusions were performed by an external catheter with higher flow rates than normally given by implanted intrathecal drug delivery system.

Combination Therapy In the previously described study that included 32 patients with chronic noncancer pain who were treated with IT morphine and bupivacaine combination therapy (see morphine section) (92), VAS pain scores decreased significantly from baseline to Month 3 ($p < 0.01$) and remained consistently reduced through the 48-month follow-up. Additionally, a prospective, open-label pilot study was conducted to evaluate the stability and tolerability of high-dose bupivacaine (4–21.4 mg/day) in 12 patients already receiving IT opioids and low-dose bupivacaine (165). After a mean of 29 days between initial pump filling and refilling, concentrations of bupivacaine and morphine or hydromorphone remained at >97% of the concentration for the formulation at the time of manufacture. Premature withdrawals from the study included one for reversible leg weakness, one for depression worsening, and two for unrelated accidental burns. One patient required bupivacaine dose reduction because of motor weakness. No significant changes in pain or disability scores were noted. In a randomized prospective study, Mironer and colleagues showed that the addition of bupivacaine to opioid did not significantly change the pain scores (166). The authors advised exercising caution in the use of high-dose bupivacaine over prolonged periods.

Levobupivacaine

The literature search revealed little published information regarding the use of IT levobupivacaine for the treatment of chronic pain. In one study, combination IT morphine and levobupivacaine therapy was investigated in 55 patients with cancer-related pain that was highly refractory to systemic opioid therapy (91). Significant decreases in mean pain intensity from baseline were noted at the time of hospital discharge, at Months 1 and 3, and up to the time of death. Significant decreases from baseline in the intensity of drowsiness and confusion were also noted in the first month of combination therapy. The IT morphine dose significantly increased (threefold) between baseline and hospital discharge and remained relatively stable thereafter, and systemic opioid consumption was significantly lower than at baseline at all time points examined. Complications of IT levobupivacaine/morphine therapy included the need for bladder catheterization ($N = 6$), reoperation for bleeding or changes in catheter position ($N = 4$), headache ($N = 4$), mild bleeding ($N = 2$), local infection ($N = 2$), stroke ($N = 1$), and spinal cord compression ($N = 1$). One death occurred, but it was judged to be unrelated to treatment.

Ropivacaine

Ropivacaine was introduced in 1996 as a new long-acting amide local anesthetic agent with better CNS and cardiovascular safety results than those seen with bupivacaine, which is considered the pattern drug among local anesthetics for use in IT infusion for the treatment of chronic pain. The differentiating characteristics of ropivacaine include its being a pure S-enantiomer with a high pK_a and relatively low lipid solubility. Ropivacaine is virtually identical to bupivacaine in terms of onset and quality and duration of sensory block, but it seems to produce less motor block. The lower degree of toxicity of ropivacaine as compared with bupivacaine has been confirmed in numerous animal experiments and human studies, including studies that accounted for the presumed lower potency of ropivacaine. In fact, reduced cardiovascular toxicity, as compared with bupivacaine, may be a distinct feature of ropivacaine.

Animal Studies: Neurotoxicity Results from previous studies have suggested that the clinical safety profile of ropivacaine appears to be more favorable than those of other local anesthetics. Zhong et al. (167) examined the possible neurotoxicity of multiple doses of IT ropivacaine in rats via an implanted IT catheter for 48 hours. In a dose-dependent manner, both 0.75% and 1.0% ropivacaine induced neuronal injury characterized by infiltration of inflammatory cells, vacuolation of myelin sheaths and axons, abnormal morphology of neurons, and apoptosis in the spinal cord (mainly in posterior roots and the adjacent posterior white matter). No significant differences between ropivacaine-treated (any dose) and control rats were noted for results of neurologic tests to determine antinociceptive inhibition of reactions to heat or mechanical stimulation.

Yang et al. (168) explored alterations of myelin basic protein concentrations in the plasma and ultrastructure in the spinal cord 48 hours after continuous IT infusion of various ropivacaine concentrations in rats by using polyurethane microspinal catheters. For the 1% ropivacaine group, concentrations of myelin basic protein significantly increased over time and were signifiantly higher than in the normal saline group. IT infusion of 1% ropivacaine was also associated with pyknosis of neurons, dilation of rough endoplasmic reticulum, and vague structure of mitochondria and endoplasmic reticulum.

Zhang et al. (169) showed that IT administration of different concentrations of ropivacaine did not affect the percent maximum possible effect of paw withdrawal latency to heat and mechanical stimulation (von Frey filament). Electron microscopic examination showed different degrees of ultrastructural changes in the spinal cord, depending on the ropivacaine concentration used. Using a rabbit model, Malinovsky et al. (170) explored the relationship between IT doses of ropivacaine, spinal effects, and local neurotoxic effects. Complete motor block was observed with ropivaciane doses >1.5 mg. No neurologic clinical lesions were observed in rabbits receiving saline or ropivacaine within the seven days after the last IT injection, and histopathologic study revealed no sign of neurotoxicity in these groups. The authors concluded that ropivacaine

induced dose-dependent spinal anesthesia and did not induce neurotoxicologic lesions. Yamashita et al. (171) demonstrated that IT local anesthetics significantly increased CSF glutamate concentrations, and hence may provide a clue to elucidate mechanisms of related neurotoxicity. Among the anesthetics used in the study (2% tetracaine, 10% lidocaine, 2% bupivacaine, and 2% ropivacaine), 2% ropivacaine appeared to be the least neurotoxic. Finally, by using a rat model of peripheral nerve injury, Whitlock et al. (172) analyzed the effects of intrafascicular or extrafascicular ropivacaine injections and extraneural (topical) ropivacaine. Extrafascicular ropivacaine injection and extraneural placement of ropivacaine were both associated with damage to the perineurium, with focal demyelination surrounded by edematous endoneurium. Intrafascicular ropivacaine injection resulted in a wedge-shaped region of demyelination and focal axonal loss with some regeneration, bordered by a region of normally myelinated axons in a background of edematous endoneurium. Notably, the inherent limitations of the rodent model must be considered when evaluating these data before conclusions can be made about a direct toxic effect on the nerve.

Median Effective Dose and Relative Potency Michalek-Sauberer et al. (173) examined clinical experience and determined that the median effective dose for IT ropivacaine was 22.6 mg. The relative analgesic potency ratio of the median effective dose of IT bupivacaine to ropivacaine was 0.50. However, Geng et al. (174) found a relative potency ratio of 0.80 (95% confidence interval, 0.74–0.85) for IT ropivacaine/bupivacaine in patients undergoing cesarean section. Lee et al. (175) studied the median doses at which 50% of patients have effective analgesia (ED_{50}) and the relative potencies of local anesthetics for IT anesthesia in lower limb surgery. The ED_{50} for ropivacaine was 7.6 mg, and the relative anesthetic potency ratios were 0.65 for ropivacaine/bupivacaine and 0.68 for ropivacaine/levobupivacaine. Although these data were obtained in studies of surgical anesthesia, they should be considered when using IT ropivacaine infusion for chronic pain management.

Combination With Opioids In a model of labor analgesia, Ortner et al. (176) showed that the ED_{50} of IT ropivacaine was 4.6 mg and that the addition of sufentanil resulted in dose-independent prolongation of analgesia. Addition of sufentanil at ED_{20} significantly decreased the ED_{50} of IT ropivacaine to 2.1 mg ($p < 0.005$), and a similar reduction was seen with addition of sufentanil at ED_{40} ($p < 0.005$). In another study that included obstetric patients scheduled for cesarean section, Parpaglioni et al. (177) demonstrated that the addition of 3.3 mcg sufentanil to IT ropivacaine reduced the minimum local anesthetic dose, did not affect its potency ratio significantly, and resulted in enhanced spinal anesthesia. Levin et al. (178) showed that ropivacaine doses of 2 or 4 mg were clinically indistinguishable from bupivacaine doses of 2.5 mg when combined with 10 mcg sufentanil for labor analgesia. Considering these data, the combination of opioids with ropivacaine appears to result in potentiation of spinal analgesia and therefore may be an alternative in the clinical management of patients with pain refractory to monotherapy.

Chronic Pain Management: Case Report Only one published case report has described the use of IT ropivacaine in the management of chronic pain. The report described an eight-year-old girl with CRPS and severe pain in both feet that began without any recalled trauma or inciting event (179). Epidural ropivacaine provided complete pain relief in the right foot but no change in pain in the left foot. Subsequently, IT ropivacaine (0.5% block followed by 0.2% infusion for seven days) plus concomitant physical therapy and institution of oral gabapentin led to substantial reduction in pain (VAS score, 0–3). The patient regained nearly full range of motion, strength, and sensation in the two months following IT ropivacaine therapy. Further research and additional case series to corroborate these findings should be considered.

Tetracaine

The literature search yielded no new literature regarding the use of IT tetracaine in the treatment of chronic pain.

Lidocaine

The literature search uncovered one case report of the use of IT lidocaine in the treatment of chronic pain (179). A 28-year-old woman with spastic diplegia and severe neuropathic and somatic pain had spasticity scores on the Ashworth and Tardieu scales of 4 and 5, respectively, and a VAS pain score of 10 out of 10. The patient underwent selective bilateral adductor myotomies and implantation of a pump for IT lidocaine infusion. Her postoperative spasticity and pain were dramatically decreased (scores of 0 on the Ashworth, Tardieu, and visual analog scales for pain), and control of pain and spasticity were maintained during the 36-month follow-up period.

Adrenergic Agonists

Clonidine

Mechanism of Action Growing evidence suggests that activated spinal cord glial cells contribute to enhanced pain states through the release of proinflammatory cytokines, such as tumor necrosis factor-α, and IL-1 and IL-6 (180,181). In addition to its analgesic effects as an a_2-adrenergic agonist, clonidine may ameliorate enhanced pain states via immunomodulation. Recent research suggests that IT clonidine may exert antiallodynic effects by inhibiting the activation of glial cells and by activation of nuclear factor κB and p38, thus inhibiting the production of proinflammatory cytokines (121).

Animal Studies: Neurotoxicity Results of studies in large animals treated with epidural clonidine for 28 days (concentrations up to 2 mg/mL and doses up to 7.7 mg/day) revealed no notable histopathologic findings (182). Additionally, IT infusion of clonidine (2 mg/mL at 2.4 mL/day) monotherapy for 28 days was not associated with direct evidence of spinal histopathology (82). In the same study, in dogs that received admixtures of clonidine and morphine, the severity of spinal histopathology decreased in a clonidine dose–dependent manner.

Clinical Studies Combination therapy including IT clonidine was described in a case report of a 79-year-old man with chronic lower extremity pain (183). Approximately one year after beginning IT therapy with fentanyl, bupivacaine, and clonidine, the patient reported night terrors, insomnia, severe dry mouth, and increased depression. Three days after discontinuation of clonidine therapy, his depression improved and the other symptoms resolved; the symptoms have not recurred after >2 years of clonidine-free IT therapy.

Dexmedetomidine

The authors are unaware of any large systematic preclinical studies of IT dexmedetomidine. However, safety concerns regarding the use of IT dexmedetomidine exist. Although perineural administration of the drug in the rat appears to be safe (184), the drug has been found to have demyelinating effects when administered epidurally in the

rabbit model (185). One case report suggests that IT dexmedetomidine could be a beneficial adjuvant to IT morphine therapy in patients with cancer pain (186).

Moxonidine

The literature search yielded no new literature regarding the use of IT moxonidine in the treatment of chronic pain.

NMDA Antagonists

Mechanism of Action

The NMDA ionophore was one of the first receptor systems found to be associated with the development of hyperpathia after tissue and nerve injury. Results from studies in preclinical models have shown that its blockade has profound effects on facilitated states of spinal nociceptive processing (187). The NMDA receptor can be inactivated by agents that directly and competitively block the glutamate binding site or by agents that block the channel directly (i.e., noncompetitively).

Ketamine[2]

Animal Studies: Neurotoxicity Ketamine is an antagonist that noncompetitively blocks the glutamate NMDA ionophore. IT ketamine infusion (10 mg/mL delivered at 2.4 mL/day) in chronically catheterized dogs resulted in mild to severe spinal pathology ranging from local demyelination to necrotizing lesions of spinal parenchyma near the catheter tip. This effect was shared by other NMDA antagonists, including MK801, memantine, amitriptyline, and S-methadone (117).

Clinical Studies In a randomized, double-blind study, the use of epidural ketamine plus bupivacaine vs. epidural bupivacaine plus saline in 53 patients undergoing lower limb amputation was compared (188). In both treatment groups, persistent phantom and stump pain were less than what was seen in comparable studies and did not differ significantly between groups. In the ketamine/bupivacaine group, significant decreases from preoperative anxiety and depression levels were noted and persisted through the one-year follow-up point. Additionally, a case report described a 49-year-old woman with severe cancer-related upper back and abdominal pain (189). Her numeric rating scale pain score was 6, despite 96 days of IT therapy with a combination of morphine and bupivacaine. IT ketamine was added to her regimen, and her numeric rating scale score decreased to 3.

Other Nonopioids

Adenosine

Mechanism of Action Adenosine is an endogenous, fast-acting neurotransmitter that modifies pain signaling by both peripheral and central effects but does not produce effective analgesia. There are at least four subtypes of adenosine receptors: A1, A2a, A2b, and A3. A2a receptor activation decreases inflammatory cytokine release and increases the release of the anti-inflammatory cytokine IL-10. In a rat model of chronic constriction injury, a single IT dose of the A2a receptor agonist ATL 313 or CGS 21680 produced a reversal of mechanical allodynia and thermal hyperalgesia for at least four weeks (131). Antibody neutralization of ATL 313 reversed the effect. This effect is most likely mediated through suppression of microglial and astrocyte activation. Although neuropathic pain model studies have suggested that A2a receptor activation is antiallodynic and antihyperalgesic, it is not analgesic (131). This effect is also not opioid mediated. The latter concept was reinforced by the work of Martin et al. (123) who demonstrated that, although adenosine reversed mechanical allodynia in nerve-injured rats, it did not attenuate the rate of opioid consumption in a self-administration model. Whereas A2a receptor activation does not produce analgesia, the potent and long-lasting analgesic effect of prostatic acid phosphatase is mediated through the A1 receptor (190).

Tsuda et al. (191) demonstrated that activation of the adenosine triphosphate (ATP)-gated ion channel subtype P2X4 receptors in the spinal cord produce upregulation of microglia after nerve injury and that this process is necessary for the production of neuropathic pain. Nakagawa et al. (192) further demonstrated that although acute allodynia is due to activation of P2X2/3 receptors, the maintenance of allodynia (one day after ATP administration) is mediated by the activation of astrocytes and not microglia. Because ATP is rapidly hydrolyzed, the long-lasting effect is thought to be attributable to activation of P2X receptors. If the NMDA receptor antagonist MK-801 is coadministered with ATP, ATP-induced allodynia is completely blocked, but if MK-801 is administered after ATP, allodynia is not attenuated, which suggests that, although NMDA receptors may play an important role in the induction of acute ATP-induced allodynia, they are not involved in the maintenance thereof (193).

Animal Studies: Neurotoxicity IT infusion of adenosine (concentrations up to 3.0 mg/mL delivered at 2.4 mL/day) in chronically catheterized dogs for 28 days resulted in no behavioral or spinal histological evidence of neurotoxicity. Concurrent studies in rats also failed to show evidence of spinal histopathology associated with IT adenosine (194).

Clinical Studies Few clinical studies have investigated the use of IT adenosine in the treatment of patients with chronic pain. One small study included seven patients with neuropathic pain who had an inadequate response to SCS and were given adenosine boluses, with SCS initiated 30 min after injection (35). IT adenosine administration was frequently associated with back pain and headache. However, when bupivacaine was added to counteract vasodilatation (a likely contributor to headache), the mixture was found to be unstable, and after approximately one week, the pain-relieving effects of bolus administration diminished by >60%. Few patients in the study chose to receive adenosine alone, but all who did wished to terminate therapy after one year; thus, further IT adenosine/SCS combination studies were abandoned.

Baclofen

Mechanism of Action Baclofen is an agonist of the γ-aminobutyric acid (GABA)-A receptor. In preclinical studies, the GABA-A receptor, a chloride ionophore, has been shown to exert antihyperalgesic effects at the spinal level (195,196). Concurrent with these effects, baclofen at the GABA-A receptor can have prominent effects on motor tone via direct hyperpolarization of the motor horn cells.

Animal Studies: Neurotoxicity IT baclofen infusion (at rates of up to 2 mg/mL/day) for 28 days in chronically catheterized dogs has been shown to result in no behavioral or spinal histological evidence of neurotoxicity (197). Additionally, preclinical evaluation suggested that IT baclofen at doses up to 2 mg/mL/day were not associated with granulomas in dogs (197).

Neuropathic Pain Recent reports of the use of IT baclofen for the treatment of patients with neuropathic pain include two studies and two case reports. In a double-blind study, the effect of different

[2] Because IT ketamine is associated with possible spinal cord toxicity, it is not endorsed for routine usage by the PACC panel.

IT baclofen infusion rates (i.e., 0.75 or 3 mg/mL baclofen solution infused at a consistent rate) on pain and dystonia was investigated in 14 patients with CRPS who had not responded adequately to previous IT baclofen therapy. (21) Overall, faster baclofen infusion rate was not associated with improvements in dystonia or pain but was associated with increased frequency of AEs. However, in a subset of six patients for whom AEs had previously prohibited dose escalation of IT baclofen, all but one preferred the faster infusion rate, reporting that the effects of faster-infusion IT baclofen on pain and dystonia outweighed the severity of AEs. One report described two cases of baclofen and ziconotide combination therapy (159). The first patient was a 48-year-old man with neuropathic pain who had received ziconotide (2.4 mcg/day) for approximately three months when baclofen (110–115 mcg/day) was added to his IT regimen for spasticity control. His ziconotide dosage was then reduced to 1.7 mcg/day over the course of one month. After eight months of ziconotide/baclofen therapy, his VASPI score had decreased by 75%. The second patient was a 73-year-old man with neuropathic pain who had received ziconotide monotherapy (dosage at onset of pain relief, 14.4 mcg/day) for six months when baclofen (62 mcg/day) was added for control of spasticity. After two years on ziconotide/baclofen therapy, his VASPI score had improved from baseline by 30%. He also experienced improvements in mood and ability to perform activities of daily living during this time.

Trialing In a study that included 48 patients with neuropathic pain who had inadequate response to SCS, participants were given IT baclofen boluses (25–100 mcg). Among these patients, 14 were classified as responders (>50% improvement from baseline in pain level), and 11 had pumps implanted for continuous IT baclofen infusion (four with pumps alone, seven with SCS and pumps). Follow-up after an average of 32 and 67 months of SCS plus baclofen therapy revealed that >50% of patients maintained good treatment effects; baclofen doses approximately doubled during this time.

Spasticity The use of IT baclofen in patients with spasticity has been investigated in several studies that have included patients with numerous conditions. In a prospective study, 25 children with spasticity and/or dystonia were treated with IT baclofen therapy (198). After six months, significant improvements from baseline were noted in measures of goal achievement (i.e., the Canadian Occupational Performance Measure and goal attainment scaling). Complications were more common in patients with dystonia than in those with spasticity. In one retrospective review of records from 316 surgical procedures in pediatric patients with spasticity treated with IT baclofen, results from a follow-up questionnaire revealed that 81% of patients/caregivers were satisfied with IT baclofen therapy and 87% would recommend it (199).

In a ten-year follow-up study of 252 patients who received IT baclofen therapy for spasticity of spinal (63%) or cerebral (37%) origin, all patients were found to have improvements in spasticity (200). Notably, baclofen doses were much higher in patients with cerebral spasticity than in those with spinal spasticity. In another retrospective study, review of medical records from 30 patients with supraspinal or spinal cord injury-related spasticity who began IT baclofen therapy after inadequate response to oral antispasticity agents revealed that significant improvements from baseline to one year were noted in spasticity scores, spasm frequency, motor function, and pain (201). IT baclofen appeared to be effective in treating both cerebral- and spinal-associated spasticity. Results from a third retrospective review of records (from 57 patients) suggested that there were no significant differences between patients with spasticity of spinal origin and those with spasticity of cortical origin in daily dosage, dosing changes, and mode of IT baclofen delivery (202). Subgroup analysis revealed that, at six months, the mean baclofen dosage was significantly higher in patients with multiple sclerosis than in those without multiple sclerosis. One case report described a 38-year-old woman with spasticity after removal of a cervical-dorsal ependymoma (203). Adjunctive intramuscular botulinum toxin type A was found to increase the therapeutic effect of IT baclofen in this patient. The use of IT baclofen in patients with spasticity of cerebral origin was evaluated in one study, results of which revealed no correlation between IT catheter tip position and clinical response of the patient (204). Results from a small case series of patients with spasticity of various etiologies suggest that spasticity control can be improved in some cases with the use of a decreased concentration of IT baclofen at the same dose rate (205).

Amyotrophic Lateral Sclerosis The use of IT baclofen for the treatment of amyotrophic lateral sclerosis was studied in a retrospective review of records from a cohort of eight patients (206). After exhibiting spasticity relief following a test injection of 25 or 50 mcg baclofen, these patients had IT pumps implanted for continuous IT baclofen infusion. IT baclofen appeared to be safe and effective in this group of patients with intractable spasticity. Reduction in pain scores with continuous IT baclofen infusion appeared to be predicted by reduction in pain scores associated with the IT baclofen test injection.

Cerebral Palsy Results from a number of studies suggest that IT baclofen therapy is useful in reducing spasticity, decreasing pain frequency and severity, and improving gross motor function in patients with cerebral palsy (207–211). One review of records from IT baclofen-treated patients with cerebral palsy and patients with cerebral palsy who did not receive IT baclofen suggested that IT baclofen therapy does not increase mortality and may improve life expectancy (212). This suggestion is based on a small retrospective single center study and more research is needed. Results from a retrospective review of records from 164 patients on IT baclofen therapy for cerebral palsy or static encephalopathy suggested that, for some patients, switching from simple continuous dosing to a complex dosing regimen may be helpful in treating predictable daily fluctuations in muscle tone and in optimizing the effects of IT baclofen (213). Results from another study suggested that patients with cerebral palsy who receive IT baclofen and undergo posterior spinal fusion do not appear to be at greater risk for infections (214).

Brain or Spinal Cord Injury Findings from small studies and case reports suggest that IT baclofen can be useful in treating spasticity related to brain or spinal cord injury (215–217). Even patients with long-standing (>14 years) traumatic brain injuries have been reported to show improvements after initiation of IT baclofen therapy (216). One case report described a 41-year-old man with spasticity related to spinal cord injury who developed episodes of priapism (218). Oral baclofen had minimal effect, but a trial of IT baclofen alleviated priapism for ten hours, and continuous IT baclofen infusion reduced spasticity and prevented further episodes of priapism. Results from a single-subject study in a patient with incomplete spinal cord injury suggest that control of spasticity with IT baclofen can be attained without adversely affecting strength (217). These results imply that strength testing may be useful in the comprehensive clinical assessment of spasticity, such that baclofen dosing can be adjusted to levels that provide control of spasticity without adverse effects on strength.

Stiff-Person Syndrome Two case reports have described the successful use of IT baclofen in patients with stiff-person syndrome (219,220).

Tolerance Tolerance is an important consideration when using IT baclofen, as it may occur in approximately 22% of patients treated with long-term IT baclofen (221). Tolerance may develop even after very long-term treatment, as was described in a case report of a patient who developed tolerance 16 years after initiation of IT baclofen therapy (222). A drug holiday of ≥24 hours (with careful monitoring for withdrawal symptoms) may be helpful. Additionally, limited data in four patients suggest switching to a pulsatile bolus infusion model may help address tolerance (221).

Safety Issues

Withdrawal Abrupt cessation of IT baclofen therapy could result in baclofen withdrawal, a serious, life-threatening situation that can be severe and prolonged (223). Baclofen withdrawal may mimic serotonin syndrome (224) and has rarely been associated with hallucinations (225). One case report described baclofen withdrawal after removal of an IT baclofen pump in a 45-year-old woman with paraplegia and severe lower extremity spasticity (226). She was treated with oral baclofen, lorazepam, phenytoin, and tizanidine and gradually improved over the course of seven days. She was discharged on phenytoin, linezolid, and metoprolol, with no need for oral spasticity therapy. It is also important to note that IT baclofen withdrawal may result from catheter leakage (227), so clinicians should be aware of the signs and symptoms of baclofen withdrawal and be watchful for them in any patient who receives IT baclofen. One report described the successful weaning of a patient from high-dose IT baclofen therapy through use of a lumbar drain and standard PCA pump in continuous infusion mode as a means to avoid withdrawal (228).

Overdose Baclofen overdose is a potentially life-threatening condition, the signs and symptoms of which may include somnolence, hypotonia, seizures, autonomic instability, bradycardia, and respiratory depression (229). One case report described baclofen overdose associated with a change in IT baclofen concentration combined with the performance of a catheter dye study (229).

Scoliosis Results from some retrospective medical record reviews suggest that the implantation of IT pumps and initiation of IT baclofen therapy are associated with increased rates of development and progression of scoliosis (230,231). However, other findings suggest that IT baclofen does not significantly affect the progression of scoliosis (232,233).

Infection As with other IT therapies, infection is a potential concern for patients treated with IT baclofen therapy (214), but some recent reports have described means to avoid or treat infection in IT baclofen-treated patients. One case report described the management of a patient who developed meningitis as a result of contamination of his IT infusion pump reservoir during refill. As an alternative to IT pump removal and replacement, an antibiotic was coinfused with IT baclofen, thus maintaining uninterrupted antispasticity treatment (234). In another case, pump pocket infection was successfully treated with gentamicin-impregnated collagen sponges in a patient for whom baclofen withdrawal and pump removal would have resulted in severe problems (235).

Granuloma The development of granulomas is rare with IT baclofen therapy (200). Granuloma formation was reported in two patients receiving IT baclofen monotherapy (236). However, these reports, plus another, were later reevaluated, and other scientifically plausible explanations (e.g., baclofen precipitation) were posited for MRI findings in these patients who were originally reported to have IT baclofen-induced granulomas (237). The association between IT baclofen therapy and granulomas is further discussed in the brief report titled, "Polyanalgesic Consensus Conference—2012: Consensus on the Diagnosis, Detection, and Treatment of Catheter-Tip Inflammatory Masses (Granulomas)."

Other Safety Concerns Additional safety issues associated with IT baclofen therapy include post-dural puncture headache (238), seizure (239), psychiatric AEs such as delirium (240), transient global amnesia (241), and various pump and catheter complications, including pump and/or catheter migration and catheter obstruction (198–200,214,242–249). Additionally, one case report described deep vein thrombosis and pulmonary embolism in a 65-year-old woman who received a 100-mcg bolus trial of baclofen (250), and another report described severe cardiac AEs (bradycardia, hypotension, hyperventilation, decreased oxygen saturation) in a 53-year-old man treated with IT baclofen (251).

Droperidol

There are no systematic preclinical studies evaluating the safety of IT droperidol. The literature search yielded no new literature regarding the use of IT droperidol in the treatment of chronic pain.

Gabapentin

Mechanism of Action Gabapentin likely acts by binding to the α2δ auxiliary subunits of voltage-sensitive calcium channels (252). Such channels are expressed in dorsal horn neurons and in the dorsal root ganglia. Although the exact effects of this binding and their relevance to the behavioral effects of IT gabapentin are not known, spinal delivery of the drug has been shown to have pronounced antihyperpathic effects in a wide variety of preclinical models of tissue and nerve injury (253).

Clinical Studies The literature search yielded no new literature regarding the use of IT gabapentin in the treatment of chronic pain. In a recent prospective randomized study, no efficacy of IT gabapentin was demonstrated (254).

Ketorolac

Mechanism of Action Results from preclinical studies have suggested that a variety of peripheral tissue injuries and the resulting hyperalgesia can be attenuated by the spinal delivery of cyclooxygenase (COX) inhibitors, including ketorolac. This effect is believed to involve input from small, high-threshold primary afferents, which activate spinal neuronal and nonneuronal cells that have constitutively expressed COX-1 and COX-2. Activation of these cells leads to the release of prostanoids, which can then act through eponymous receptors presynaptically on small primary afferents to enhance opening of voltage-sensitive calcium channels and thereby increase excitatory input (255) and also act postsynaptically to reduce the inhibitory activity of glycine interneurons (256). These effects account for a central component of the hyperalgesic action of COX inhibitor-sensitive systems.

Animal Studies: Neurotoxicity IT ketorolac infusion (concentrations of 5 mg/mL given at 1.2 mL/day) for 28 days in chronically catheterized dogs has been shown to result in no behavioral or spinal histological evidence of neurotoxicity (257).

Clinical Studies A double-blind, randomized, placebo-controlled, crossover study evaluated the use of IT ketorolac (2 mg) or saline treatment in patients with chronic pain who had been receiving IT

morphine via an implanted IT pump for ≥6 weeks (258). Although VAS scores for pain and unpleasantness decreased significantly from baseline, these decreases did not differ between ketorolac and saline treatments. No significant differences in response rates (defined as the proportion of patients who had ≥30% or ≥50% improvement in pain) were noted between ketorolac and saline treatments. The incidence of AEs was similar in the ketorolac and saline groups; AEs associated with ketorolac injection included mild sedation, mild dizziness, hot sensation in the back, headache, urinary retention, and hives. In an open-label study, 15 patients with chronic pain who had received IT morphine for ≥3 months were treated with 0.5, 1, or 2 mg IT ketorolac as add-on therapy (258). AEs in the study were mild or moderate in severity, not dose dependent, and most commonly included headache and nausea. Pain scores declined in a dose-independent manner; peak reduction was noted one to three hours after IT ketorolac injection. Additionally, results from subgroup analyses showed that pain was reduced in IT ketorolac-treated patients with high resting CSF prostaglandin E2 concentrations but not in those with normal resting prostaglandin E2 concentrations.

Midazolam

Mechanism of Action Midazolam is a benzodiazepine that is water soluble at very acidic pH. The drug augments the actions of GABA at the GABA-A receptor with associated benzodiazepine binding sites. Results from preclinical studies have shown that midazolam has effects on several hyperpathic pain states.

Animal Studies: Neurotoxicity IT infusion of midazolam in sheep and in pigs (concentrations of 15 mg/mL given at 3 mL/day) resulted in no behavioral or spinal histological evidence of neurotoxicity (259). However, in earlier preclinical literature, varying degrees of histopathology were reported in association with bolus midazolam delivery in rats and rabbits (260).

Clinical Studies The use of IT midazolam in the treatment of postherpetic neuralgia involving lumbosacral dermatomes was investigated in a randomized, double-blind, multicenter study (261). A single epidural bolus of 60 mg of methylprednisolone or a single bolus of 2 mg of IT midazolam or a combination of both and followed up for 12 weeks. Epidural methylprednisolone and IT midazolam alone each provided short-term improvement in control of pain and allodynia, but the combination of the two treatments led to a more prolonged duration of analgesia than did treatment with either drug alone. Analgesic use for breakthrough pain was lower for combination-treated patients than for patients treated with either drug alone.

Neostigmine

Mechanism of Action Neostigmine is a cholinesterase inhibitor. Administered intrathecally, it acts to increase cholinergic tone. Activation of both nicotinic and muscarinic receptors has been shown to alter nociceptive processing in animal models (262,263).

Animal Studies: Neurotoxicity IT neostigmine infusion for 28 days in chronically catheterized dogs (concentrations of 1 mg/mL delivered at 4 mL/day) resulted in no behavioral or spinal histological evidence of neurotoxicity (264).

Clinical Studies The literature search yielded no new literature regarding the use of IT neostigmine in the treatment of chronic pain.

Octreotide

The authors are unaware of any large systematic preclinical studies of IT octreotide. The search yielded no new literature regarding the use of IT octreotide in the treatment of chronic pain.

Compounding and its Considerations

The US FDA regards traditional pharmacy compounding as the combining or altering of ingredients by a pharmacist in response to a licensed practitioner's prescription, which produces a medication tailored to an individual patient's special medical needs. Compounding may also be defined as the combination of two drugs to produce a new formulation. The dissolving of drug powder suitable for parenteral or IT administration is also considered compounding. When prescribing drugs for IT administration, it is important for prescribers to perform the appropriate due diligence of the pharmacy provider, regardless of the practice setting, to ensure patient safety and protection of the practice.

The United States Pharmacopoeia (USP) has independently issued standards on compounded sterile products that have clinical, legal, and practical significance (265,266). These standards apply to compounding of solutions by various routes, including IT administration. By applying USP Chapter <797> standards, a compounded sterile product includes preparations that are prepared according to the manufacturer's labeled instructions and with other manipulations that expose the original contents to potential contamination. Compounded sterile products also include preparations that contain nonsterile ingredients or employ nonsterile components and devices that must be sterilized before the products are used.

Because incorrectly prepared or contaminated compounded sterile products, intended for delivery into the CNS, can potentially produce catastrophic effects (267,268), it is important to confirm with the compounding pharmacy that written policies and procedures are established and updated annually in order to remain compliant with the USP <797> standards. Below are considerations for evaluation and selection of a compounding pharmacy.

1. Training of personnel: Compounding personnel should be adequately trained in aseptic technique and manipulation of compounded sterile preparations. Personnel should undergo scheduled and periodic evaluations, appropriately use gowns and gloves, have a thorough understanding of compounded pharmaceuticals, and perform aseptic media fill unit testing. Training and evaluations should be documented.
2. Segregated sterile compounding area: The compounding environment must be a dedicated, enclosed area segregated from surrounding spaces to reduce the risk of contamination. Proper temperature, humidity, and air filtration controls must be used for activities and work within the sterile compounding area should be conducted only by those individuals who are directly involved with sterile compounding. The sterile compounding area should be physically designed and environmentally controlled to reduce the risk of airborne contamination.
3. Air quality of the compounding area: The sterile compounding area should be certified every six months. Primary engineering controls (i.e., IV hoods) and devices should be placed in the sterile compounding area, and the air quality should be no less than International Standards for Organization (ISO) 7 standards. Equipment must be procured and maintained as necessary to safely compound and monitor the environment. Primary laminar airflow workbenches should provide an environment of ISO 5 or

better; ISO 5 represents an air quality not exceeding 3520 particles of 0.5 microns per cubic meter. Air changes per hour must be maintained per USP standards; air pressure differential should be monitored. Environmental monitoring should be implemented to demonstrate that primary engineering controls will maintain air quality. Such monitoring consists of assessment of viable (bacteria) and nonviable (particulates) levels. Environmental air sampling should occur as an integral component of a comprehensive quality assurance program. Active air sampling should occur at least every six months to properly assess the air quality and cleaning program. An appropriate sampling plan should be developed on the basis of the size and design of the compounding area. Action levels and alerts should be established.

4. Equipment should be certified and calibrated annually, and staff must be trained and knowledgeable in its operation.
5. A cleaning and disinfection program must be implemented, with attention to the agents used in the compounding area.
6. Quality assurance program: A comprehensive quality assurance program should be in writing and implemented to include monitoring and evaluation of the compounding staff and the compounding environment. All factors associated with preparations and dispensing of products should be considered. Policies should describe specific monitoring and evaluation. A robust random sampling program to assess final product accuracy is imperative. The quality assurance program must be continuous in activity to ensure optimal outcomes. Generally, the identification of indicators and the effectiveness of the quality assurance program should be reassessed yearly. The long-term goal is to have this be the benchmark for quality in all countries where IT therapy is utilized.

Clinical Implications of Compounding Drugs

Although few studies have been conducted to evaluate the stability of combinations of two or more drugs, (269–273) in clinical experience, patient response to IT polytherapy is often suggestive of stability. Postinfusion quantitative analysis on random samples has revealed drug stability, but more studies are necessary (274,275). One major complication in long-term studies of polyanalgesic drug admixtures is infinite possible drug combinations. However, if study results suggest that high-concentration drug combinations are stable, stability can be assumed for lower-concentration combinations of the same drugs.

For most pharmaceuticals, there are established and published standards of solubility at room temperature. While high-drug-concentration solutions allow for longer refill intervals and delivery of higher daily doses, alterations in pH to develop high-drug-concentration solutions can result in unstable solutions that can lead to patient and pump complications.

CONCLUSIONS

The previous PACC work has led to improved patient safety and efficacy and advanced the questions that have led to additional IT drug research. In that spirit, this manuscript presents the next step in algorithmic thought. The advent of new algorithmic tracks for neuropathic and nociceptive pain is an important step in improving patient care. The panel encourages continued research and development, including the development of new drugs, devices, and safety recommendations to improve the care of patients whom we strive to help. The panel is hopeful that the time interval between now and the time the PACC reconvenes is a time of enlightenment in the field of IT drug delivery.

The creation of this consensus statement has depended heavily on available literature, clinical experience, and scientific discussion. Despite these mechanisms to create the best consensus recommendations possible the final conclusion includes a subjective component and may be controversial in some settings. The panel has addressed nociceptive and neuropathic pain pathways to best treat pain by IT infusion.

The panel considered a third pathway for mixed pain syndromes but considering the heterogeneous components of this complex patient group the reader is advised to use the appropriate pathway based on clinical judgment based on a realization that the patient may exhibit different components of pain at various time intervals.

APPENDIX 1

Check List of Psychological Symptoms for Patients After Ziconotide Trialing

A. Depression
   1. Suicidal ideation/intent/plan/means (access to medication, weapon)
   2. Depressed ideational themes
   3. Crying/hopelessness/despair/pessimism
   4. Amotivational/anhedonic/irritability
   5. Diurnal variations
B. Anxiety
   1. Generalized/tremor/tension
   2. Panic/flashbacks/phobias
   3. Ruminations
C. Energy level
D. Eating behavior
   1. Appetite/weight gain or loss
   2. Eating habits
E. Sleep cycle
   1. Insomnia: terminal/initial
   2. Nightmares
   3. Use of hypnotic medication
   4. Daytime naps
   5. Time spent in bed over 24 hours
F. Sexual functioning
G. Memory and concentration
H. Perception
   1. Hallucinations
   2. Delusions
   3. Idiosyncratic ideation
   4. Paranoia
   5. Dissociation

APPENDIX 2

Survey Results

In May 2011, three detailed surveys on IT infusion use, safety, and reimbursement were sent to more than 15,000 physicians and clinicians in the USA and internationally by the PACC panel. We received 196 responses to all three surveys from various geographical locations. Of the respondents, approximately 55% were licensed anesthesiologists, 8% were physical medicine and rehabilitation physicians, and 7% were neurosurgeons. Nearly half of the respondents (47.5%) were in private practice, 18% were in academic institutions, and 11% worked in private hospital systems.

More than 55% of respondents had been working in pain management for more than ten years. Seventy-five percent of respondents indicated that they dedicated at least 75% of their time to pain management, with an even distribution of neuropathic and nociceptive pain pathologies.

Most respondents (84%) believed that a behavioral evaluation continues to be necessary before IT therapy initiation. Responses regarding the percentage of patients selected for IT therapy who had a psychiatric comorbidity that required mental health services varied widely.

With respect to the 2007 PACC guidelines, 65% of respondents indicated that they currently followed the guidelines. However, in the individual commentary, respondents overwhelmingly indicated that deviations from the guidelines are occasionally warranted by patient need. Most particularly, this was noted in the case of treating cancer pain. Furthermore, although most participants indicated that they followed the 2007 PACC guidelines, quite a few respondents indicated that they felt that the maximum doses recommended in the guidelines are too high.

Forty-four percent of respondents indicated that they used IT therapy for nonmalignant pain. When trialing for nonmalignant pain, a larger proportion of respondents (45%) preferred continuous infusion to single-shot (28%) or tunneled catheter outpatient (10%) trials. With malignant pain, 35% preferred continuous infusion to single-shot (28%) or tunneled catheter outpatient (10%) trialing. Ten percent of respondents indicated that they do not perform a trial in patients with malignant pain.

With respect to peripheral edema, more than 80% of respondents indicated that they observed the onset of peripheral edema less than 25% of the time in patients treated with IT morphine.

Forty percent of respondents indicated that they significantly reduced oral and systemic opioids during an IT therapy continuous infusion trial, and 22% indicated that oral and systemic opioids were discontinued entirely. Only 15% of respondents indicated that patients were weaned off all oral and systemic opiates immediately before the trial or up to two weeks before the trial. Thirty-three percent of respondents indicated that dosages of oral and systemic opiates were unchanged before trialing.

With respect to continuous flow vs. intermittent boluses, 70% of respondents indicated that they used bolus-dosing capabilities via a programming option, PCA, or a PTM system. The drug most often programmed for bolus dosing was morphine (51%). Less than 1% of respondents indicated that they would program ziconotide for a bolus dose. Patients with cancer-related pain were the ones most often identified as those for whom bolus dosing would be prescribed (40%). It was also noted that bolus dosing should be used with extreme caution in elderly patients.

Among respondents, 34.6% denied ever having had a patient who developed a granuloma while under their care, 11.2% indicated they had had a single patient in their practice who developed a granuloma, and 29% indicated they had seen between two and five patients with a granuloma. Of respondents who had seen a granuloma develop in their patient population, 38% noted that the granuloma(s) had developed while a programmable system was in use. Granuloma was confirmed via MRI more than 78.2% of the time; 32% of respondents indicated that they had confirmed granuloma via CT-myelogram, 12.3% confirmed granuloma via CT, and 23.0% of respondents confirmed granuloma via side port study (respondents were allowed to select more than one answer).

After confirmation of granuloma, 41.5% of respondents consulted a neurosurgeon, 40.0% removed and replaced the catheter, 26.1% repositioned the catheter, 13.8% left the catheter in place and merely changed the drug, and 9.2% completely removed the catheter (respondents were allowed to select more than one answer).

Ten percent of survey respondents indicated that they had noted pump stoppage as a result of corrosion; 62% indicated that this had not occurred in their patient population.

With respect to the use of IT morphine therapy, 36% of respondents indicated that they initiated therapy at <1.0 mg/day, and 25% at 1.1 to 2.0 mg/day). Thirty-seven percent of participants indicated that a dose of 5.0 mg/day was maintained for their morphine monotherapy patients.

Eleven percent of respondents indicated that, among patients in whom IT therapy with morphine is begun, <10% switch pain drug therapy; 25% of respondents indicated that 26% to 50% of their patients switch therapeutic infusion drug. Reasons for switching medications included ineffective pain control (~80%), AEs (66%), the need to control neuropathic pain pathology (15%), and morphine allergy (13%; respondents could choose more than one answer).

Regarding IT catheter tip placement, respondents indicated that the most likely catheter tip site is the lumbar spine (49%). The choices for least likely catheter tip placement were sacral spine (64%) and cervical spine (26%).

Respondents were queried regarding patient safety and the recent letter to physicians issued by Medtronic in January 2011 (276). Overwhelmingly, respondents suggested that IT pump refills should be performed by trained, experienced physicians and clinicians only. Generally, survey respondents indicated that the need for fluoroscopy and/or ultrasound to confirm pump pocket fill did not appear to be warranted; however, most respondents noted that experience in filling IT pumps was paramount to patient safety. Better education and training were recommended. Interestingly, 52% of respondents indicated that an increase in mandated safety measures (e.g., ultrasound, fluoroscopy during fill) would "decrease" or "significantly decrease" their use of IT therapy. Only 10% indicated that increased safety measures would "probably increase" or "significantly increase" IT therapy use.

Additionally, with respect to pump implantation and safety, 38% of respondents recommended that the primary surgeon should have implanted more than 15 pumps with supervision before he or she is deemed competent as an independent implantation surgeon. An additional 44% of respondents indicated that a minimum of 5 to 15 supervised implantations should be required.

When considering the economics of IT therapy in practice, 52% of respondents indicated that they were "very involved" in the business management of their practice. Forty-four percent noted that pump implantation, drug, and refill procedure costs were definite barriers to the broader use of IT therapy in their practice. Additionally, patient out-of-pocket expenses for a drug were noted to be "very important" for 60% of respondents. Among US physician respondents, 56% were "very interested" and 20% were "somewhat interested" in Medicare allowing pharmacies to bill for IT drugs, thus eliminating all reimbursement for their practice. Sixty-four percent of respondents indicated that they did not believe that reimbursement for pump management (filling/refilling/programming) is currently adequate. Fifty-two percent noted that they were unsatisfied with private payer reimbursement. Thirty-eight percent indicated that they were satisfied with workers' compensation reimbursement rates, with 26% noting dissatisfaction and 16% being "unsure." Most respondents (56%) indicated that the cost of the refill kit enters into the decision-making process of the entire reimbursement picture for IT therapy, and 48% indicated that reimbursement rates have decreased over the past five years.

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Drs. Timothy Deer, Robert Levy, and Joshua Prager chaired the project, led discussions, and garnered contributions from the consensus panel. Dr. James Rathmell performed a final review of the manuscript prior to final submission to the consensus panel for review and approval.

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COMMENTS

An excellent update from the PACC group, very well researched. I welcome the added sections and the distinctions made between neuropathic and nociceptive pains. The addition of further sections devoted to trialing and morbidity and mortality prevention is an excellent development. The guidelines however, continue to have a strong US bias; this should be addressed in future issues. The recommendation of fentanyl as first line is made on safety basis in the absence of strong efficacy data. More case series and RCTs are needed demonstrating the efficacy of fentanyl within the recommended group.

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This is the 4th polyanalgesic consensus conference with publications in 2000, 2003, 2007 and now 2012. The information drawn together by these experts is invaluable. In some areas such as the basic science and animal data there is excellent information but sadly the human data available remains of lower quality. The panel carefully draws all these data sources together and offers us advice based upon the best information currently available weighted by patient safety and quality of evidence. This PACC has started to show a difference in drug selection advice for neuropathic and nociceptive pain states. Knowledge surrounding CSF flow and catheter tip drug dispersion may in time offer us new strategies for better outcomes. There is still a lack of clinical and cost effectiveness data with this therapy. We still just have the one randomized controlled trial in cancer pain which lacked any cost benefit data collection. This should be our main future endeavor: To design a series of high quality clinical effectiveness randomized comparator trials with cost effectiveness alongside. In the mean time, we should at least maintain a national or disease specific database. I look forward to PACC 2016 when such data or study design might be presented.

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In the absence of robust studies for diagnosis or management of clinical entities, guidelines may be helpful in guiding physicians in clinical decision making. Guidelines are often developed by medical societies on topics within their domains with the intent of helping clinicians assimilate rapidly expanding medical knowledge and making appropriate decisions about health care. Guidelines generally follow strict sequential processes including collection of data, preparation of systematic reviews, weighing the strength of the evidence and grading the strength of recommendations. Assessment of adaptation and implementation of guidelines is highly desirable [1].

When evidence is significantly limited, consensus guidelines are advantageous. Unfortunately, expert opinion and consensus guidelines represent the lowest level of evidence. Observational studies are intermediate, while randomized controlled trials are believed to provide the highest level of evidence [2]. The above notwithstanding, Deer and colleagues are most esteemed in the field and are commended for establishing consensus and providing an algorithm for intrathecal (IT) therapies to improve patient safety and potentially outcomes of intrathecal therapy. These guidelines have set a framework for many, if not most, interventional pain medicine specialists.

The current consensus guidelines are the fourth iteration since the original publication in 2000 [3–6]. Given the number of intrathecal agents and potential permutations, guideline authors have attempted—using best available evidence as well as their collective experiences—to formulate "lines" of therapy. However, factors such as limited outcome data from IT studies, the "infinite" number of IT agent combinations/rankings as well as individual author biases will invariably result in highly controversial "consensus" statements. Hence, far too many questions may be raised regarding the current algorithm. For instance, why is "ziconotide + opioid" 3rd line in the Neuropathic algorithm and not a 2nd line combination? Where would "bupivacaine + ziconotide" fall into? Why does ziconotide disappear after line 2, in the Nociceptive algorithm? Why not ziconotide as third line combination agent along with opioid + bupivacaine? Though ziconotide is listed as a first line agent because of FDA approved status, how often in practice is it used as a first line agent, given its weak analgesic efficacy and difficult trialing and titration as detailed in the manuscript? In considering fentanyl as line 1 agent for nociceptive pain, where are the data on efficacy? Is safety good enough? Why not use fentanyl for neuropathic pain? . . .

One of the limitations of all previous intrathecal consensus statements has been the generalization of algorithms to all patients despite individual differences. The authors in this version of the consensus guidelines attempted to distinguish neuropathic from nociceptive pain and accordingly established different algorithms. While this is a step forward in attempting to identify pain characteristics as a means of elucidating optimal intrathecal treatment choices, it suffers from major drawbacks:

1) Though the International Association for the Study of Pain (IASP) scientifically classifies pain as nociceptive or neuropathic, mixed pain is also recognized but has not been addressed in this algorithm.
2) Classification of pain into nociceptive and neuropathic while clinically useful is difficult to establish in many patients requiring intrathecal therapy. Indeed, for the most common indication for IT therapy (post lumbar spine surgery syndrome), distinction between neuropathic and nociceptive pain is often difficult to make and most patients may suffer from a mixed pain disorder with neuropathic and nociceptive components. It is unclear if the pain is mixed in nature, which of the two proposed algorithms should be followed?
3) Such a classification takes into consideration only one symptom (the pain subtype) without regard to patient characteristics—which constitute more important determinants of success or failure of the therapy than pain subtype.
4) Important details related to the physicochemical properties of the intrathecal medications (notably lipid solubility) as well as catheter position have been omitted from discussion in the current guidelines.

Indeed, classification of pain into cancer related *vs*. non-cancer related may be more worthwhile as such diagnosis may have differential implications for therapy [7]. Within non-cancer related chronic pain, patient age plays an important role in opioid dose escalation and efficacy [8]. Along these lines, stratification of pain into (dermatomally) localized *vs*. disseminated pain is likely worthwhile [7]. Furthermore, considering pharmacokinetics of intrathecal agents, especially lipid solubility, as well as highlighting the importance of catheter tip positioning are critical to successful outcomes [7, 9–12]. Given the number of variables involved, it is obvious that simply implanting an intrathecal drug delivery system does not impart the same outcomes in different patients with different pathologies.

Given the above, polyanalgesic intrathecal consensus guidelines are a much needed endeavor. However, current guidelines are too generic and do not address critical patient characteristics that are essential for success of the therapy. Future improvements in these guidelines should focus on tailoring specific guidelines to defined patient populations taking into consideration not only particular patient characteristics but also pharmacokinetic properties of the drugs used and catheter tip location.

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Comments not included in the Early View version of this paper.

