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The Polyanalgesic Consensus Conference (PACC): Recommendations on Intrathecal Drug Infusion Systems Best Practices and Guidelines

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Introduction: Pain treatment is best performed when a patient-centric, safety-based philosophy is used to determine an algorithmic process to guide care. Since 2007, the International Neuromodulation Society has organized a group of experts to evaluate evidence and create a Polyanalgesic Consensus Conference (PACC) to guide practice.

Methods: The current PACC update was designed to address the deficiencies and innovations emerging since the previous PACC publication of 2012. An extensive literature search identified publications between January 15, 2007 and November 22, 2015 and authors contributed additional relevant sources. After reviewing the literature, the panel convened to determine evidence levels and degrees of recommendations for intrathecal therapy. This meeting served as the basis for consensus development, which was ranked as strong, moderate or weak. Algorithms were developed for intrathecal medication choices to treat nociceptive and neuropathic pain for patients with cancer, terminal illness, and noncancer pain, with either localized or diffuse pain.

Results: The PACC has developed an algorithmic process for several aspects of intrathecal drug delivery to promote safe and efficacious evidence-based care. Consensus opinion, based on expertise, was used to fill gaps in evidence. Thirty-one consensus points emerged from the panel considerations.

Conclusion: New algorithms and guidance have been established to improve care with the use of intrathecal drug delivery.

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INTRODUCTION AND RATIONALE

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 and outcomes research in IT therapy is ongoing. New IT devices have been recently introduced, along with novel chronic infusion strategies (1). Thus far, research has not kept pace with the growing need for innovative IT pain management, and clinical care and decision making have largely relied on best evidence and expert opinion (2). Therefore, a consensus opinion is needed to identify the current research and address deficiencies in the data. Furthermore, as new IT therapies become available, the need to refine patient selection and pain care algorithms is required (3). With more than 80% of IT therapy in the United States employed as off-label (4,5), there is a continuing need to help navigate careful decision-making surrounding IT therapy.

Consensus Point 1. An update of the best practices of IT drug delivery is needed due to many changes in patient care since the last version of this living document.

Consensus Point 2. Evidence for practice guidance has been improved since 2012, but additional expert guidance is needed to fill the current gaps in clinical practice.

The Polyanalgesic Consensus Conference (PACC) panel was formed to improve the safety and efficacy of IT therapy. PACC was initiated in 2000 to address the research gaps and review the existing data regarding IT therapy (2). This expert panel was composed of health care providers within the field of IT therapy. The panel developed an IT drug selection algorithm on the basis of best evidence and expert opinion, prepared supplemental reports that included a relevant literature review, reported on results from a survey of peers engaged in IT therapy, and described future directions in the field of IT therapy. The PACC panel reconvened in 2003 (6) and 2007 (7) to evaluate the most up-to-date 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, adding a supplement on IT granuloma and describing new insights on recommended maximal concentrations and daily doses of IT agents (8). Since then, renewed interest regarding noncancer pain management employing IT agents has resurfaced, along with new interests on infusion schema. This present update focuses on redefining patient-centric trialing strategies and the recommended observation period for trialing, algorithmic care for the near end-of-life patient, and the importance of catheter position congruent with regional location of the pain. The overarching theme of this present PACC update is to continue to modify and adapt this living document.

Brief History of PACC

In spite of thorough discussions of various factors impacting patient responses to IT therapy, previous PACC versions did not tailor algorithmic approaches to patient-specific characteristics that likely impact IT therapy (2,6–9). A number of clinical factors play important roles in shaping specific IT interventions and medication choices. These factors have been previously described (10), and include patient diagnoses and expected survival time (11), patient age (12,13), previous exposure to opioids (13–15), location of pain (diffuse vs. localized), type of pain (nociceptive, neuropathic, or mixed), the physiochemical properties of lipid solubility of the IT medications employed (16,17), cerebrospinal fluid (CSF) flow dynamics and pharmacokinetics (18,19), IT catheter location (20), pump and catheter characteristics, kinetics of the IT infusate (20), and psychological status (21–23) of the patient with chronic pain. A detailed discussion of these factors will be entertained in the following sections. Each component to be considered requires careful and deliberate attention. Interestingly, unpublished industry reports suggest that many practicing physicians in the United States and Europe do not follow the PACC guidance of 2012 (24). Physicians and scientists have been impacted by the advice given in this process, with nearly 100 citations of the 2012 guidance. The effort of the 2016 PACC is to provide recommendations based on evidence and consensus and to continue to disseminate best practice insights to practicing physicians worldwide.

Consensus Point 3. The 2016 PACC will continue the historical goal of improving safety and efficacy of the global use of IT therapies.

METHODS

The PACC of 2016 was designed to address the deficiencies and innovations emerging since the previous PACC of 2012 regarding IT therapy. Participants were chosen based on an executive panel from the International Neuromodulation Society (INS), with participants from previous PACC guidelines automatically nominated. Other nominations were made by board members based on a needs assessment of topics to be addressed. All participants were identified to have an area of needed expertise, which could include extensive experience in IT drug device management, basic science research, clinical studies, or expertise in evidence assessment or publication. Invitations were subsequently sent to potential participants and accepted prior to formal engagement. Meetings were held periodically during the composition and drafting of the manuscript, with meetings to rank evidence and develop consensus surrounding IT therapy, as defined below. The authorship publication standards outlined by the journal *Neuromodulation* and Wiley Publishing governed the working consensus group.

Literature Search Methods

A broad literature search was conducted to identify preclinical and clinical data on IT therapy published from January 15, 2007, through November 22, 2015. MEDLINE®, BioMed Central®, Current Contents Connect®, Embase™, International Pharmaceutical

Table 1. Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force, Ref [25]).

Evidence level	Study type
I	At least one controlled and randomized clinical trial, properly designed
II-1	Well-designed, controlled, nonrandomized clinical trials
II-2	Cohort or case studies and well-designed controls, preferably multicenter
II-3	Multiple series compared over time, with or without intervention, and surprising results in noncontrolled experiences
III	Clinical experience-based opinions, descriptive studies, clinical observations or reports of expert committees.

Table 2. Meaning of Recommendation Degrees (U.S. Preventive Services Task Force, Ref [25]).

Degree of recommendation	Meaning
A	Extremely recommendable (good evidence that the measure is effective and benefits outweigh the harms)
B	Recommendable (at least, moderate evidence that the measure is effective and benefits exceed harms)
C	Neither recommendable nor inadvisable (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified)
D	Inadvisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low quality or contradictory evidence; the balance between benefit and harms cannot be determined.

Abstracts®, and Web of Science®, Google Scholar, and Pubmed 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." Each author performed independent literature searches and the information was cross-referenced and compiled for evidence analysis and consensus review. These searches yielded 391 articles, which were examined for relevance to the IT treatment of chronic pain. Google Scholar was again searched 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 drug class are provided, along with a summary of preclinical studies, followed by critical review. Literature published before the dates stated above is cited when relevant. After reviewing the literature, the PACC panel convened to develop

NACC/PACC Title: _____

Author: _____

Topic: _____

Key Statements (2-5 total)	**Supporting References** List the references that support the key statement.	**Levels of Evidence** Use Table 1 below to determine the level of evidence for each reference that supports a key statement.	**Recommendation Strength** Use Table 2 below to assign a degree of recommendation to each key statement based on the supporting evidence.
1.			
2.			
3.			
4.			
5.			

Figure 1. Contributor evidence assessment.

Table 3. Strength of Consensus.

Strength of consensus	Definition*
Strong	>80% consensus
Moderate	50–79% consensus
Weak	<49% consensus

*Quorum defined as 80% of participants available for vote.

recommendations for IT analgesia. Supporting literature is included following these recommendations and discussions of the panel.

Evidence-Based Analysis vs. Opinion

Similar to the Neuromodulation Appropriateness Consensus Conference (NACC) of the International Neuromodulation Society publication in 2014, and fostered from the previous PACC statements, the goal of this present PACC effort was to create a living document, with continued refreshment and evidence synthesis ongoing, as appropriate. Unlike the PACC of 2012, the effort of the 2016 PACC was to apply a validated evidence-ranking system, outlining management and implementation of IT therapy. This effort was underscored by unpublished survey data suggesting poor adoption of the previous proposed algorithms (personal communication with Medtronic plc. and Jazz Pharmaceuticals). It is clear, however, that IT granuloma identification and management were significantly impacted and improved on since the PACC of 2011 supplement was published (24).

Evidence Ranking

The United States Preventative Services Task Force (USPSTF) created hierarchies of studies and degrees of recommendations based on evidence rankings as outlined in Tables 1 and 2 (25). The PACC of 2016 has adopted these classifications, just as the NACC previously adopted weighted recommendations for neurostimulation.

Authors of this manuscript were asked to complete reference forms for their section's assessment (Fig. 1). These forms were then reviewed by the executive committee of the working group and averaged. They served as the basis for review and consensus development. The working group developed recommendations based on evidence ranking, or consensus when evidence was lacking, followed by assigning consensus rankings. The consensus determination was performed during in-person meetings or via teleconference with a quorum of 80% of the contributing authors determining recommendation strength. Consensus rankings were outlined as strong, moderate, or weak based on agreement, as defined in Table 3.

As with any guideline, this document serves as a recommendation regarding implementation and management of IT therapy. The opinions and recommendations offered are not intended to promote off-label uses of medications and devices. Additionally, these recommendations should not be construed as a standard of care. We will explore an evidence-based algorithm of pain care, patient selection, drug selection, trialing strategies, implantation, and concentration and dosing. Physicians should consult their national approval processes when making clinical decisions.

It is important to address the conflicting nature of evidence and the need for consensus. Evidence and consensus are not mutually exclusive, which may be the perception at first glance. Evidence assessment, regardless of the strength, needs interpretation for clinical application whenever used.

RECOMMENDATIONS OF PACC 2016

In this manuscript, we will explore the evidence-weighted and consensus recommendations of the PACC regarding the following topics:

- Evidence assessment
- Pain care algorithms
- Disease-specific indications and considerations
- Patient-selection considerations
- Medication-selection recommendations and considerations
- Use context of neuropathic and nociceptive pain
- Recommended starting dosages
- Variables affecting chronic intrathecal therapy
- Conclusions

EVIDENCE ASSESSMENT

It is generally regarded that IT therapy offers a reliable, accurate, safe, and efficacious treatment for both cancer and noncancer pain, as well as for end-of-life pain care. There have been multiple reviews discussing the efficacy and safety of IT therapy (26–29). Recently, IT therapy options came under scrutiny by the state of California, with success of continued access available only after a demonstration of evidence was ruled favorable (30). A more thorough understanding of the pharmacokinetic properties of IT medications (20) and CSF flow dynamics within the IT space was the catalyst in creating better IT therapy strategies (31). Furthermore, as defined previously, there is evidence to support its use (26), based on the USPSTF criteria for data ranking and evidence strength. USPSTF strength of evidence for IT therapy was level II-3 for noncancer pain and level II-2 for cancer pain. A best practice article was written in 2014 by Prager et al., providing evidence in support of IT therapy and the needed placement of IT therapy in the algorithm for cancer and noncancer pain (27) (Table 4). The support for efficacy of IT opioid administration for the management of chronic noncancer pain comes largely from prospective and retrospective noncontrolled trials. Ziconotide has been

Table 4. Recommendations for Evidence Assessment of Intrathecal Therapy by the PACC Using USPSTF Criteria.

Statement	Evidence level	Recommendation grade	Consensus level
Intrathecal therapy should be utilized for active cancer-related pain with opioids.	I	A	Strong
Intrathecal therapy should be utilized for active cancer-related pain with ziconotide.	I	A	Strong
Intrathecal therapy should be utilized for noncancer-related pain with opioids.	III	B	Strong
Intrathecal therapy should be utilized for noncancer-related pain with ziconotide.	I	A	Strong

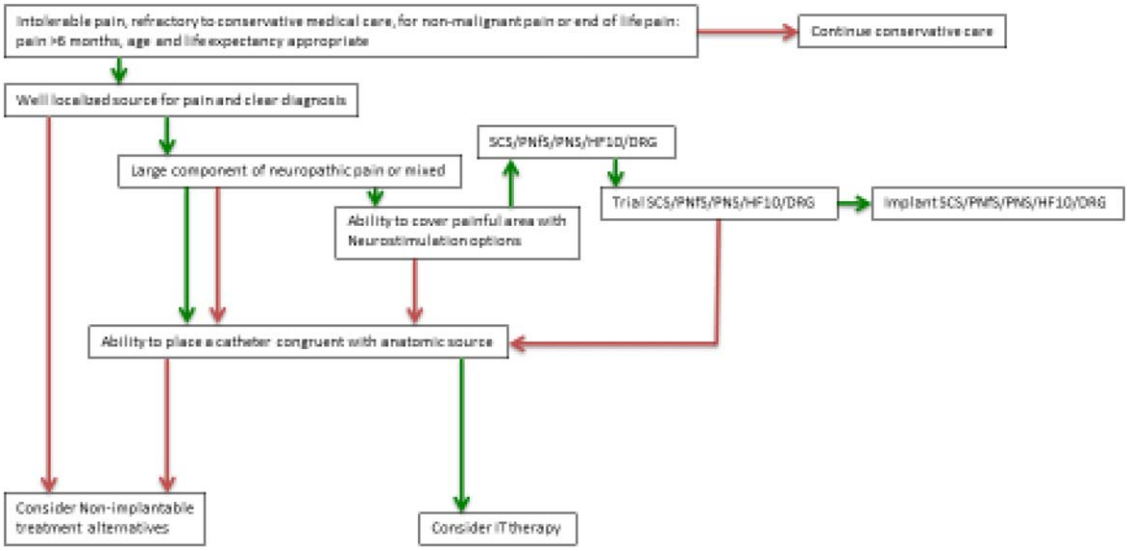

Figure 2. Algorithm for placement within the pain care algorithm for noncancer or non-end-of-life pain. DRG, dorsal root ganglion; HF10, high frequency stimulation; PNfS, peripheral nerve field stimulation; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation. Green arrows indicate affirmation or positive response; red arrows signify negative response.

robustly studied in three randomized, placebo-controlled trials, demonstrating safety and efficacy for both cancer and noncancer pain (32–34). In a randomized controlled trial (RCT) in cancer pain, which compared efficacy and side effects for IT delivery of opioids vs. systemic delivery via conservative management, IT delivery of opioids was superior (11).

At the present time, there is an ongoing investigative effort, with FDA oversight, by Mallinckrodt Pharmaceuticals (St. Louis, MO) to move IT hydromorphone from a compounded to a branded, formally manufactured, FDA-approved product. This endeavor involves two clinical trials. The first trial is a controlled, two-arm, parallel group, randomized withdrawal study followed by an openlabel single-arm safety study of hydromorphone. Further, critical evaluations regarding sustainability and cost effectiveness have been performed, with focus on sustainability and safety.

Consensus Point 4. The use of evidence ranking is a critical piece of the formatting of the 2016 PACC. This is the first time this important point has been included in the PACC methods.

Consensus Point 5. In areas where evidence is strong, peer-reviewed references are noted for the PACC recommendation. When evidence is weak or lacking, consensus opinion is used to make recommendations.

PAIN CARE ALGORITHM

Careful consideration of patient selection is foundational for successful, sustainable patient care. The fact that no recommendations were made regarding patient survival and IT therapy, or anatomic region of pain, were deficiencies of the previous 2012 PACC. Therefore, the PACC of 2016 is presenting evidence and consensus-based recommendations regarding patient survival, disease process, and medication usage for IT therapy. Attention was directed to the age of the patient, although the contributions of age are reflected in dosage sustainability, which is addressed elsewhere in the recommendations.

Algorithmic Treatment of Pain

The landscape of pain medicine and IT therapy has evolved (35). Neuromodulation literature supports that it is more cost effective, more efficacious, and no longer appropriate to position IT therapy as a salvage therapy (36). The choice of neuromodulation therapy rests on many factors, including the regional location of the pain, type of pain, life expectancy, and malignancy, to name a few. Generally, and most significantly, IT therapy is not salvage therapy after failure of systemic high-dose opioid-based medicines. IT drug delivery devices (IDDs) should be suggested for refractory pain, as recently defined (37):

> Pain is defined as refractory, regardless of etiology, when 1) multiple evidence-based biomedical therapies used in a clinically appropriate and acceptable fashion have failed to reach treatment goals that may include adequate pain reduction and/or improvement in daily functioning or have resulted in intolerable adverse effects, and when 2) psychiatric disorders and psychosocial factors that could influence pain outcomes have been assessed and appropriately optimized.

A proposed algorithm has been described (27,38). A modified version of the algorithm is suggested here (Fig. 2).

Important decision-tree aspects of this algorithm deserve mention. IT opioid infusion within the algorithm deserves special consideration. Compared to systemic opioid delivery, IT opioids appear to be safer based on mortality and morbidity data (39) and have fewer diversion risks. From 2003 to 2013, opioid use disorder increased in the United States, significantly increasing mortality, with more than 16,000 deaths reported annually (40). This has led the Centers for Disease Control (CDC) to draft new guidelines for chronic opioid therapy for noncancer pain. The first recommendation of those guidelines stresses the need for nonpharmacological and nonopioid treatments before resorting to systemic opioids. Along with neurostimulation, IT therapy should play an important role in the pain treatment continuum. The reported challenges associated with IT therapy (41,42) have been increasingly mitigated by vigilance and mindful patient selection (43).

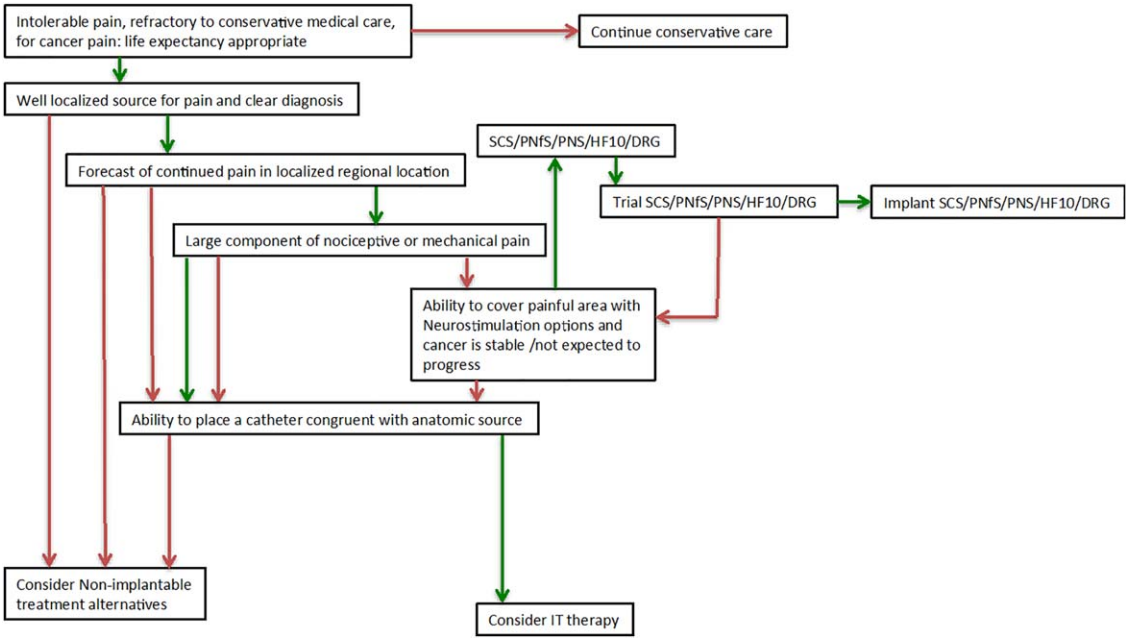

Figure 3. Pain care algorithm for cancer-related pain. DRG, dorsal root ganglion; HF10, high frequency stimulation; PNfS, peripheral nerve field stimulation; PNS, peripheral nerve stimulation; SCS, spinal cord stimulation. Green arrows indicate affirmation or positive response; red arrows signify negative response.

As can be gleaned from Figure 2, and new to descriptions of algorithmic advanced pain care, IT therapy now occupies the same line of management as neurostimulation, with important caveats. If the patient's condition can be treated effectively with stimulation therapy or IT therapy, then neurostimulation may be considered first, secondary to safety considerations (42). However, there was significant discussion among the authors surrounding the sustainability of both IT and neurostimulation therapies. Traditional spinal cord stimulation (SCS) is an effective therapy, as clearly demonstrated in multiple studies (44,45). However, there is a significant patient population (nearly 30%) that becomes tolerant to the therapeutic perceived paresthesia (46). Furthermore, Hayek and Veizi reported an explant rate from a cohort of university hospitals of nearly 23.9% (47). New stimulation therapies may help with salvage (48–50), although there is a compelling argument for a role of IT therapy, certainly after SCS failure, but also before. A significant reason for SCS explant is loss of therapeutic coverage or development of new areas of pain since implant. A registry study suggested approximately 8% of patients (13/156) developed pain outside the ability of coverage of traditional SCS at 12 months (51). Recently, data were presented at the North American Neuromodulation Society (NANS) meeting (Las Vegas, 2015) that suggested durability of care for >6 years with IT therapy (52). From a historical perspective, IT coverage may be influenced by catheter position and medication selection, providing flexibility to the clinician and the patient (8). Coverage of a common condition, such as failed back surgery syndrome (FBSS), could potentially allow for comparison of the efficacy of SCS with IT therapy, but no direct, controlled studies have been conducted in the past decade.

An algorithmic hierarchy of IT therapy for cancer pain is similar. Prognosis, likely progression of the disease into different anatomic regions/tumor characteristics, and periprocedural imaging findings are useful considerations for device selection. In patients with cancer-related pain, Smith et al. demonstrated improvement in side-effects and pain with IT therapy compared to conservative medical management (11). Staats, in a comparative trial for AIDS and cancer patients, showed improvement in the cancer population with IT ziconotide (33). Furthermore, titratability and coverage/efficacy of mechanical, nociceptive pain is less likely with SCS therapy (53). Although coverage can be extended with traditional SCS therapy by reprogramming, repositioning of electrodes, or adding new electrodes, it is not accomplished to the degree or ease of IT therapy. To that end, device selection algorithmic care is suggested in Figure 3.

End-of-life pain device selection is typically not performed if the patient has less than three months of expected longevity. The PACC

Table 5. Recommendations for Application of Intrathecal Therapy vs. Neurostimulation by the NACC Using USPSTF Criteria.

Statement	Evidence level	Recommendation grade	Consensus level
Intrathecal therapy should be considered within the same line as neurostimulation strategies to treat noncancer-related pain.	III	C	Moderate
Intrathecal therapy should be considered after neurostimulation strategies to treat noncancer-related pain if the pain is isolated and unlikely to spread.	III	I	Strong
Intrathecal therapy should be considered before neurostimulation therapy for active cancer-related pain that is mechanical and likely to spread.	III	C	Strong

Table 6. Disease Indications for Intrathecal Drug Delivery.

- Axial neck or back pain; not a surgical candidate
  - Multiple compression fractures
  - Discogenic pain
  - Spinal stenosis
  - Diffuse multiple-level spondylosis
- Failed back surgery syndrome
- Abdominal/pelvic pain
  - Visceral
  - Somatic
- Extremity pain
  - Radicular pain
  - Joint pain
- Complex regional pain syndrome (CRPS)
- Trunk pain
  - Postherpetic neuralgia
  - Post-thoracotomy syndromes
- Cancer pain, direct invasion and chemotherapy related
- Analgesic efficacy with systemic opioid delivery complicated by intolerable side effects

recommends that in the future a more objective measure, such as the Karnofsky Palliative Performance Scale (54) or Eastern Cooperative Oncology Group Performance Status (55) scores be used. The medication regimen (or the development of combination therapy strategies) may be accelerated in end-of-life pain coverage. This will be discussed with more granularity in the medication-selection section.

Table 5 presents PACC recommendations for application of IT vs. SCS therapy.

DISEASE-SPECIFIC INDICATIONS AND CONSIDERATIONS

Disease-specific indications for IT therapy have been defined previously (8,27,56). A conceptual marriage of many factors contribute to the implementation of the therapy once disease-specific indications have been fulfilled, including: survival time, opioid exposure/sensitivity, location of pain, type of pain, medication physiochemical properties, catheter location, pump infusion strategy, and psychological features and social support of the patient. Simply stated, IT therapy is indicated by the Food and Drug Administration (FDA) for moderate to severe trunk and limb pain, and intractable pain, where more conservative therapies have failed (57,58). This includes a variety of disorders, including those highlighted in Table 6. There is renewed interest to cover focal extremity pain with IT therapy, but although anecdotal reports exist, literature support is lacking.

As outlined in previous versions of the PACC and other consensus papers, it is imperative to have a clear diagnosis, an appropriate physical examination and a complete psychosocial evaluation (which may be optional for cancer pain) before undertaking a trial or implant. The PACC would point out that, in the face of psychological distress from end-of-life, not having psychological help may amplify the pain experience and compound suffering.

Table 7. Cancer Patient Classifications.

Category 1	Category 2	Category 3
Patient with imminent death or life expectancy relatively short, with palliation primary objective	Patient whose disease is stable or slowed, with high likelihood of recurrence or progression	Patient with cancer in partial remission or cured, with residual chronic pain

The cancer pain population deserves special mention, as implementation of IT therapy and medication selection, along with the sustainability of a regimen, are largely dependent on the stage of the disease and life expectancy (Table 7). Deer et al. have classified cancer patients based on categories of their disease (56). The complex interplay between disease indications and patient selection will be discussed in the following section.

PATIENT-SELECTION CONSIDERATIONS

Updating the PACC documents of 2012 and mindful of patient selection, managing patient comorbidities has been a concern since the IDD mortality data were reported in 2009 (41). Numerous reports have suggested best practice and careful consideration for the complex interplay between disease, patient characteristics, and drugs chosen for IT delivery. As outlined previously, consideration for all the variables and vigilance is required, and we will address them individually (8,9,26,27,56,60–63). Some influences of determining IT therapy are universal, spanning all patients considered, while others require risk stratification and more granularity (Fig. 4).

Procedural and Surgical Comorbid Disease Management

Careful consideration for comorbidities that impact wound healing (64) and the implementation of the therapy is crucial. Considerations also include ability to undergo the procedure, including anesthesia and assessment of bleeding risk. The 2014 NACC also reported on mitigation of surgical site infection and bleeding, with an update in review at the time of this writing (65). The PACC recommendations for avoiding surgical site infections appear in Table 8 and those for anticoagulation management appear in Table 9.

Implementation of IT infusion procedurally is just one aspect of the therapy. Decision-making regarding medication, site of delivery, and infusion strategy must also be discussed. Cardiopulmonary assessment is vital when determining the medication employed and the required vigilance surrounding the implant procedure (10,27). One of the important components of IT therapy is the fear of respiratory depression (27). It is important to understand the patient's baseline cardiopulmonary status, along with baseline medications that may play a role in sedation and influence the CO_2 response curve by shifting it down and to the right (80,81). When considering the relative risks of oral opioids with more than 16,000 deaths per year (39), the risks of IT agents appear to be considerably less, but no comparative risk studies have been performed. With that said, it should be emphasized that most IT infusion patients are already opiate tolerant, therefore, the risk of respiratory depression in such opiate-tolerant patients is extremely low.

Disease comorbidities that may impact the influence of opioid-based medications on respiratory drive include central or obstructive sleep apnea, advanced age, pulmonary disease (obstructive or restrictive), and cardiac disease (ischemic, congestive, or myopathy related). Obstructive sleep apnea has been observed in nearly 18 million people in the United States, with physiologic responses of hypercapnia and pulmonary hypertension. Numerous studies suggest opioids negatively impact respiratory drive and may lead to increased apnea duration (82–85). Age plays a role in the sensitivity to the depressive effects of opioids (85). The American Society of

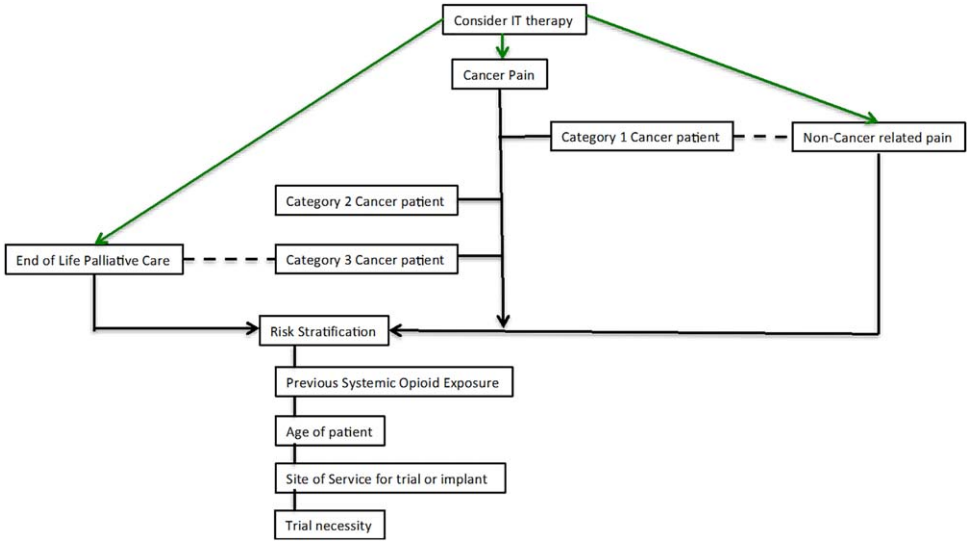

Figure 4. Algorithm of patient-selection characteristics. Green arrows indicate affirmation or positive response, red arrows signify negative response. Dashed arrows signify similarity amongst groups. Cancer pain is tiered to three categories (see Table 7).

Anesthesiologists developed consensus guidelines to mitigate risk of opioid-related respiratory depression in the acute pain population, and although the guidelines do not translate to the chronic-pain, opiate-tolerant patient *per se*, the theme is vigilance (84). Risk stratification of patients when employing IT therapy is imperative to provide safe pharmacologic care.

Given our current knowledge, understanding the role that the concomitant use of central nervous system (CNS)-active medications has on IT therapy is crucial. Careful appreciation for special populations of patients is also needed, including those with kidney or liver disorders, along with the geriatric population, as clearance and elimination (pharmacokinetics) of these CNS-active medications should be considered. It is beyond the scope of this text to describe the pharmacokinetics of systemic medications, but it is important to note that potential interaction exists between IT-delivered medications and CNS-active medications. Any CNS depressant can augment opioid-induced respiratory depression (Table 10). Creatinine kinase (CK) levels need to be checked at baseline and even intermittently during therapy with initiation of ziconotide, as clinical trials showed that levels can rise to two or three times the upper limit of normal. Causation and clinical significance of this rise is unclear, but good clinical judgment is important and symptoms need to be carefully evaluated if symptomatic CK elevation exists, with reduction or cessation of therapy to be considered. Registry data recently suggested improved tolerability of ziconotide when it was not infused with systemic medications having a similar mechanism of action and function (86). This knowledge allows for risk stratification of dosing and vigilance surrounding IT implementation. Paradoxically, nonopioid-naïve patients may have an increased margin of safety when IT therapy is initiated, although the relationship is nonlinear and overdose remains a possibility (27).

Previous Systemic Opioid Use

Discussion of patient selection requires considering all of the aforementioned factors of concurrent medications, disease states, prior treatments, and device implementation. Notwithstanding, the concept of bulk flow within the IT space is limited (8,20,90–92), with potentially very little spread from the distal end of the catheter with the CSF. It has long been appreciated that the supratentorial effects reported surrounding delayed respiratory depression with acute IT opiate delivery are different from those with chronic infusion. Chronic infusion is associated with slow, low volume, and low kinetic energy delivery wherein local rostrocaudal IT distribution is limited. Redistribution of CNS-active, IT-delivered drugs out of the IT space is likely the culprit for respiratory effects (80,81). This concept is corroborated by various recent works (8,27,55).

This new understanding has been validated in animal models, with evidence suggesting the same mechanism in humans (93). Similarly, previous exposure is relevant. More patients are taking systemic opioid medications than ever before in the United States, with increased mortality. Diversion and misuse contribute to the associated morbidity and mortality (40,94–96). The California State Medical Board has created guidelines for systemic opioids to be less than 80 morphine equivalents (MEs), while others advocate for less than 100 or 120 MEs (95,97). The CDC recently recommended chronic maintenance doses of systemic opioids of 50 ME or less, with extra vigilance and risk assessment at $>$90 ME. The history of systemic exposure is important when considering IT therapy, not just for calculating the total amount of systemic opioids, but also for considering the impact of IT opioid dose escalation, as failure of systemic opioids where side effects are not an excluding factor suggests failure of opioids intrathecally. Preclinical work has shown cross-tolerance between IT and systemic morphine (96).

In one IT opioid study of patients with chronic pain, during the washout period before randomization to another IT drug, the majority of patients were able to wean IT opioid medications but with average systemic supplementation of near 300 MEs per day (32). The patients had visual analogue scale of pain intensity (VASPI) scores of $>$80 mm, suggesting failing IT therapy. If patients are maintained on large amounts of systemic opioids before starting IT therapy, the likelihood of monotherapy failure seems to be higher (12,14,15,38,99,100). This concept supports the approach of weaning or reducing systemic opioids prior to initiating IT therapy.

This potency shift is not predictable based on previous models for systemic to IT conversion (27), and there are reports of tolerance reversal in as little as a week off IT agents (42). Veizi et al. reported a reduction of dose escalation of nearly three times when employing a local anesthetic (99). Many authors recommend weaning strategies

Table 8. Recommendations for the Avoidance of Surgical Site Infections as Recommended by the PACC.

Recommended practice	Origin of recommended practice[§]	References and comment
Preoperative practices		
Utilization of preoperative antibiotics for trials	CDC IA and NICE	Bowater et al. (66) demonstrated that antibiotic prophylaxis is effective for reducing the risk of wound infection for all types of surgery.
Utilization of preoperative weight-based antibiotic dosing for trials	CDC IA and NICE	Weight-based dosing of antibiotics is required to achieve therapeutically effective drug concentrations (67,68).
Utilization of preoperative antibiotics for implants	CDC IA and NICE	Bowater et al. (66) demonstrated that antibiotic prophylaxis is effective for reducing the risk of wound infection for all types of surgery.
Utilization of preoperative weight-based antibiotic dosing for implants	CDC IA	Weight-based dosing of antibiotics is required to achieve therapeutically effective drug concentrations (66,68).
Utilization of preoperative nasal culture and application of mupirocin to prevent *Staphylococcus aureus* surgical site infections	CDC 1A	Universal decolonization seems associated with a low risk of mupirocin resistance in *Staphylococcus aureus* (69). Mupirocin and antiseptic body wash may reduce superficial but not deep surgical site infections (70). Mupirocin decolonization is effective in a high-risk population (71), however, compliance is low and resistance occurs (72,73). Nasal povidone-iodine may be considered as an alternative (74).
Appropriate preoperative timing (within 1 hour prior to surgical incision excluding vancomycin) of prophylactic antimicrobial administration for implants	CDC IA, NICE, SCIP	
Hair removal (when required) with electric clippers immediately before the surgical procedure	CDC IA and NICE	
Intraoperative practices		
Utilization of double gloving	CDC II and NICE	Tanner and Parkinson (75) concluded that the addition of a second pair of surgical gloves reduces perforations to the innermost gloves. Although there is insufficient evidence that double gloving reduces the risk of SSIs, NICE recommends wearing two pairs of sterile gloves when there is a high risk of glove perforation and the consequences of contamination may be serious (76).
Utilization of chlorhexidine gluconate for preoperative skin antiseptic agent	CDC IB and NICE	CDC and NICE recommend the use of an appropriate antiseptic agent (povidone–iodine or chlorhexidine-containing products). Darouiche et al. (77) demonstrated that preoperative skin preparation with chlorhexidine-alcohol is superior to povidone–iodine for preventing SSI.
Postoperative practices		
Application of an occlusive dressing following a trial	CDC IB and NICE	CDC recommends applying a sterile dressing for 24–48 hours postoperatively (category IB). NICE recommends interactive dressings. Hutchison and McGuckin demonstrated lower rates of infection with occlusive dressings (78).
Understanding maximum time criterion for defining a deep surgical site infection of an implantable device (one year)	CDC	Infection occurs within one year if an implant is in place and the infection appears related to the operation.
No continuation of antibiotics into the postoperative period for trials beyond 24 hours*	SCIP	SCIP recommends the discontinuation of antibiotics within 24 hours after surgery.
No continuation of antibiotics into the postoperative period for implants beyond 24 hours[†]	SCIP	SCIP recommends the discontinuation of antibiotics within 24 hours after surgery.

CDC, centers for disease control; NICE, National Institute for Health and Care Excellence; SCIP, Surgical Care Improvement Project of the Joint Commission; SSIs, surgical site infections.
*Examination of survey questions 22 and 23.
[†]Examination of survey questions 24 and 25.
[§]CDC recommendations. IA: Strongly recommended for implementation and supported by well-designed experimental, clinical, or epidemiological studies. IB: Strongly recommended for implementation and supported by some experimental, clinical, or epidemiological studies and strong theoretical rationale. II: Suggested for implementation and supported by suggestive clinical or epidemiological studies or theoretical rationale.

Table 9. Anticoagulation Management Practices for Intrathecal Therapy as Recommended by the PACC.

Anticoagulant	Recommendation for trial	Recommendation for permanent implant
Warfarin	Discontinue five to seven days before, INR <1.5; if bridging required, refer to bridging medication; continue cessation during duration of trial, resume 24 hours following trial catheter removal.	Discontinue five to seven days before, INR <1.5; if bridging required, refer to bridging medication; resume 24 hours postoperatively.
Enoxaparin (LMWH)	Hold therapeutic dose of LMWH 24 hours before procedure; hold for duration of trial; resume 24 hours following catheter removal.	Hold therapeutic dose of LMWH 24 hours before procedure; resume 24 hours following surgery
Clopidogrel (ADP receptor antagonists)	High-risk patients for cardiac events—discontinue at least five days before; low risk seven to ten days before; hold for duration of trial; resume 24 hours following catheter removal.	High-risk patients for cardiac events-discontinue at least five days before; low risk seven to ten days before; resume 24 hours following surgery.
Prasugrel (ADP receptor antagonist)	Discontinue seven to ten days prior to procedure, hold for duration of trial, resume 24 hours following catheter removal.	Discontinue seven to ten days prior to procedure, hold for duration of trial, resume 24 hours following lead removal.
Ticlopidine (ADP receptor antagonists)	Discontinue 14 days prior to procedure, hold for duration of trial, resume 24 hours following catheter removal.	Discontinue 14 days prior to procedure; resume 24 hours following surgery.
Abciximab, eptifibatide, tirofiban (platelet GPIIb/IIIa receptors)	Discontinue for three days prior to procedure, hold for duration of trial, restart 24 hours following catheter removal.‡	Discontinue for three days prior to procedure, hold for duration of trial, restart 24 hours following the surgery.‡
Dipyridamole, aggrenox (aspirin/dipyridamole) (phosphodiesterase inhibitors)	Discontinue seven days prior to procedure, hold for duration of trial, restart 24 hours following catheter removal.§	Discontinue for seven days prior to procedure, hold for duration of trial, restart 24 hours following the surgery.§
Naproxen, ketorolac, ibuprofen, etodolac, etc. (nonsteroidal anti-inflammatory drugs)§	Discontinue seven days prior to procedure, hold for duration of trial, reinitiate 24 hours following catheter removal.	Discontinue seven days prior to procedure, hold for duration of trial, reinitiate 24 hours following the surgery
Aspirin§	Discontinue seven days prior to procedure, hold for duration of trial, reinitiate 24 hours following catheter removal.	Discontinue seven days prior to procedure, hold for duration of trial, reinitiate 24 hours following surgery.
Herbals (ginseng, ginko, garlic)	Discontinue seven days prior to the procedure, hold for duration of trial, reinitiate 24 hours following catheter removal.	Discontinue seven days prior to the procedure; reinitiate 24 hours following surgery.
Dabigatran etexilate mesylate, rivaroxaban (direct thrombin inhibitors)	Discontinue five days prior to procedure, hold for duration of trial, reinitiate 24 hours following catheter removal.	Discontinue five days prior to procedure, hold for duration of trial, reinitiate 24 hours following surgery.
Heparin IV*	On a case-by-case basis	On a case-by-case basis
Heparin SQ†	On a case-by-case basis	On a case-by-case basis

INR, international normalized ratio; ADP, adenosine diphosphate; LMWH, low molecular weight heparin; NA, not available; IV, intravenous; SQ, subcutaneous.
*Requires inpatient hospitalization and monitoring, suggesting a special need or indication for neurostimulation and should be assessed on case-by-case basis.
†Peaks at 2–4 hours after administration, typically thrombotic prophylaxis as inpatient and may require platelet assessment if more than four-day dosing. Please refer to American Society for Regional Anesthesia guidelines and determine on a case- by-case basis.
‡Typically contraindicated four weeks following surgery. If reinitiated, careful follow-up and vigilance is suggested (79).
§Current recommendations (79) suggest variable stoppage is necessary based on clinical context, and on the specific half-life of the nonsteroidal anti-inflammatory in question. The half-life determines the time required for discontinuation in order to limit the drug's effect on platelet function.

(101), with the core concept of improving patient selection by moving away from salvaging high-dose systemic opioid failure. The predictive value of systemic dose requirement to IT opioid dose requirement is somewhat obscured with the recently described weaning strategies, but the theme is suggested (13).

Table 10. Central Nervous System-Active Medication Classes That May Interact With Intrathecal Opioids (86–88).

Benzodiazepines
Antidepressants
Anticonvulsants
Muscle relaxants
EtOH consumption

The concept of limiting systemic opioid exposure to less than 100 MEs has already been proposed (1,38), with the CDC recommending less than 50 ME for noncancer related chronic pain and increased vigilance above 90 MEs (102). Although no specific data comparing prior systemic dose to IT dose exist, enough prospective and retrospective data suggest it may be beneficial as a tool for IT dose escalation prediction (13,35). Furthermore, there does not seem to be a gender difference with opioid dose, although in one study women were more likely to continue to receive oral opioid adjuvants (97). Hatheway et al. described the use of patient-controlled boluses to minimize systemic opioid use with IT therapy (103).

Table 11. Recommendations for Patient Selection Criteria for Intrathecal Therapy by the PACC Using USPSTF Criteria.

Statement	Evidence level	Recommendation grade	Consensus level
Patients with comorbidities that negatively affect cardiopulmonary function need increased vigilance when instituting intrathecal opioid therapy.	III	C	High
Localized pain can be adequately covered with intrathecal therapy.	II	B	Strong
Diffuse pain can be adequately treated with intrathecal therapy.	III	C	Moderate
Global pain can be adequately treated with intrathecal therapy.	III	D	Moderate
Intrathecal therapy should not be used as salvage therapy for failing systemic opioids.*	II	B	Moderate

*Patients who are weaned prior to the trial have a higher likelihood of sustained success (15,101). Different titration schedules have been recommended.

Sustainability of Intrathecal Opioid Therapy

Dose escalation with chronic IT opiates has been a cause for concern. An early retrospective study noted that in cancer patients receiving IT infusion of morphine, for periods in excess of three months after initial stabilization (4.8 mg/d), 48% showed less than a twofold increase in dose by three months (104). In 52 cancer patients, initial dose (3.8 mg/d) rose by a factor of 2.5 at four months (105). In 50 cancer patients, receiving infusion for a mean of 142 days (7–584 days), the mean IT morphine starting dose, 2.5 mg/day, increased to a mean final dose of 9 mg/day (106). In a series of chronic noncancer pain patients ($n = 88$), mean IT morphine dose increased from 10 mg/day at 6 months to 15 mg/day at 36 months after initiation of therapy (107). In another study, presence of neuropathic pain seemed to be strongly predictive of IT dose escalation (108). Seemingly, patients less than 50 years old have a greater chance of opioid dose escalation intrathecally compared to patients older than age 50 (12). Mitigating strategies include proper patient selection, minimizing pre-IT therapy opioid dose, proper localization of pain, and congruent catheter placement. Local anesthetics, such as bupivacaine have been shown to have synergistic interaction with opiates (109,110). Veizi et al. reported dose escalation mitigation with concurrent use of bupivacaine, and although this is off-label, it appears logical and should be considered (99).

Psychological Assessment and Social Support Evaluation

Previous consensus guidelines, best practices, and previous PACC iterations have all commented on psychological assessment of patients for IT therapy (8,21,22,27). There has been little update on patient selection surrounding this topic. Category 1 cancer patients do not need a robust psychological screen, as palliation is the goal of IT therapy, however, they may benefit from counseling regarding death, dying and chronic illness. For all others, clear descriptions of developing a partnership and setting expectations between patient and treatment team is suggested in the literature. Importantly, ziconotide is contraindicated in patients with a history of psychosis, and alternative IT medications should be used (111).

Pain Characteristics: Regional vs. Diffuse vs. Global

There is little doubt that CSF flow dynamics and the pharmacokinetic profiles of IT agents are better understood now than ever before. Little bulk flow exists (90–92). Rostral spread within the IT space is limited from the catheter tip. Although there is limited evidence to support catheter placement congruent with the dermatomal area of pain, consensus remains high that this is a crucial component to sustained IT care. Similarly, placement of the catheter dorsal to the spinal cord delivers medication closer to the dorsal elements of the spinal cord. Localized pain examples include the band-like dermatomal challenges of postherpetic neuralgia or unilateral precise abdominal pain or axial back pain from vertebral compression fracture. Diffuse pain refers to a whole extremity involvement, back or leg discomfort, abdominal pain encompassing more than one quadrant, and so on. Global pain is total body pain.

The PACC recommendations for patient selection appear in Table 11.

Consensus Point 6. Patients with comorbidities that negatively affect cardiopulmonary function need increased vigilance when instituting intrathecal opioid therapy.

Consensus Point 7. Localized, diffuse and global pain can be adequately treated with intrathecal therapy. The evidence for global pain treatment is less well defined and should be approached cautiously.

Consensus Point 8. Intrathecal therapies should be used at an appropriate time in the algorithm and not as a salvage treatment.

MEDICATION-SELECTION RECOMMENDATIONS AND CONSIDERATIONS

Since the publication of the PACC reports of 2012, more energy by these authors has focused on patient selection, procedure standardization, and infusion therapies compared to new medications. The FDA has approved ziconotide and morphine for IT infusion for the treatment of pain. Hydromorphone from Mallinckrodt plc. is undergoing clinical trial for potential IT labeling. Notwithstanding, the PACC of 2012 provided a framework to determine which IT medications to use when differentiating the patient's pain as either nociceptive or neuropathic or mixed pain. This framework of understanding has been expanded in 2016. Off-label monotherapy or combination therapy should be considered after failure of FDA-approved medications or when these medications are contraindicated. The question of which medication or combination of medications to use is important and is based on safety. The current PACC 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.

Consensus Point 9. Off-label drug monotherapy or combination therapy is not recommended until FDA-approved drugs are tried and failed or are contraindicated. In cancer pain, the on-label drugs can be used during the trial phase. If the results are not acceptable due to lack of efficacy or side effects, an admixture with bupivacaine or the primary use of fentanyl is supported by our consensus.

Consensus Point 10. The PACC algorithms are based on improving safety and efficacy in clinical practice, which includes the use of off-label drugs.

Table 12. Cancer or Other Terminal Condition-Related Pain With Localized Nociceptive or Neuropathic Pain.

Line 1A	Ziconotide			Morphine		
Line 1B	Fentanyl			Morphine or fentanyl + bupivacaine		
Line 2	Hydromorphone	Hydromorphone + bupivacaine		Hydromorphone or fentanyl or morphine + clonidine	Morphine or hydromorphone or fentanyl + ziconotide	
Line 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine	Ziconotide + bupivacaine		Ziconotide + clonidine	Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide	Sufentanil
Line 4	Sufentanil + ziconotide	Sufentanil + bupivacaine	Baclofen	Sufentanil + clonidine	Bupivacaine + clonidine + ziconotide	Bupivacaine + clonidine
Line 5	Sufentanil + bupivacaine + clonidine					
Line 6	Opioid* + bupivacaine + clonidine + adjuvants†					

*Opioid (all known intrathecal opioids).
†Adjuvants include midazolam, ketamine, octreotide.

Consensus Point 11. The algorithms are based on evidence and consensus on safety. The patient's physician and good clinical judgment should guide individual patient care.

Considerations of the highlighted variables include patient diagnoses and expected patient survival time (11), sustainability of the IT regimen (12,13), previous exposure to opioids (14,15), location of pain (diffuse vs. localized vs. global), type of pain (nociceptive, neuropathic, or mixed), the physiochemical properties of lipid solubility of the IT drugs (16,17), CSF dynamics and pharmacokinetics (18–20), catheter location (20), pump and catheter characteristics, kinetics of the IT infusate (20), and psychological status (21–23) of the patient with chronic pain.

INTRATHECAL THERAPY IN NEUROPATHIC AND NOCICEPTIVE PAIN STATES

Employing the familiar nociceptive and neuropathic pain classification for medication selection as a framework, the reorganization of medication selection is based on many factors, including survival expectation, age, previous exposure to opioids, location of pain, type of pain, and catheter location. The pharmacokinetics of the IT medications employed (112) point toward a potentially greater spread with multiple bolus delivery compared to continuous infusion.

Nociceptive and neuropathic pain, regardless of age, expected survival, or pain location, may respond to a combination of medications and is greatly dependent on catheter location. Neuropathic pain generally responds to ziconotide, opioid plus local anesthetic, local anesthetic alone, clonidine plus opioid, and clonidine alone. Nociceptive pain generally responds to opioid, ziconotide, opioid plus local anesthetic, and local anesthetic alone. Manipulative variables that can increase drug spread include the physiochemical properties of the drug, kinetics of the injectate, and the volume delivered (16,90). Increased concentration and daily doses of opioids (except fentanyl) are associated with granuloma formation, and care should be taken when dose escalation is rapid or doses and concentrations are known to be reaching levels associated with granuloma formation (8,10). The possibility of granuloma formation should be considered when employing opioid-based medications.

Table 13. Cancer or Other Terminal Condition-Related Pain With Localized Pain: Evidence Level, Recommendation Strength, and Consensus Level.

Tier	Evidence level	Recommendation grade	Consensus level
Line 1A	I	A	Strong
Line 1B	II-1	B	Strong
Line 2	II-3	B	Strong
Line 3	III	C	Moderate
Line 4	III	I	Weak
Line 5	III	I	Weak
Line 6	III	I	Weak

The PACC 2016 recommendations allow integration of the applied 2012 PACC nociceptive and neuropathic localized and diffuse pain recommendations for cancer or terminal illness (Tables 12–15), and for noncancer pain (Tables 16–19). For medication selection within the tiered recommendations, it is important to consider age, type of pain, and anticipated duration of therapy. In cancer pain, the evidence would suggest combination therapy might be warranted as a first- line strategy, which is a different recommendation from that for treatment of noncancer pain. If the patient responds to morphine or ziconotide as single medications during a trial, we would still recommend that on-label drugs be used initially. This distinction is highlighted by the evidence-weighted tier system designation of line 1A and 1B. Line 1A represents medication with level I evidence. Furthermore, these medications are FDA approved, with the intent of honoring the evidence available. However, if the patient does not respond to on-label monotherapy during the trial phase, then fentanyl and combination therapies, including admixtures with bupivacaine, are supported by the consensus. Baclofen is FDA approved for spasticity and is sometimes helpful in managing pain associated with spasticity.

Titratability for patients with cancer pain (Category 1 and 2, see Table 7) is extremely important. There is significant evidence that suggests opioid ± bupivacaine is helpful in this population (113,114). Careful attention should be made by caregivers to escalation of dose or concentration above certain recommended levels (8). The tiered selection of the recommended medications was based on levels of evidence surrounding the safety and efficacy of the medication provided. Ziconotide monotherapy and opioid + bupivacaine share level I evidence for their use in the cancer population

Table 14. Cancer or Other Terminal Condition-Related Pain With Diffuse Nociceptive or Neuropathic Pain.

Line 1A	Ziconotide			Morphine		
Line 1B	Hydromorphone			Morphine or hydromorphone + bupivacaine		
Line 2	Hydromorphone or morphine + clonidine			Morphine or hydromorphone + ziconotide		
Line 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine	Ziconotide + bupivacaine		Ziconotide + clonidine	Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide	Sufentanil
Line 4	Sufentanil + ziconotide	Baclofen	Sufentanil + bupivacaine	Sufentanil + clonidine	Bupivacaine + clonidine + ziconotide	Bupivacaine + clonidine
Line 5	Sufentanil + bupivacaine + clonidine		Sufentanil + bupivacaine + ziconotide		Sufentanil + clonidine + ziconotide	
Line 6	Opioid* + bupivacaine + clonidine + adjuvants†					

*Opioid (all known intrathecal opioids).
†Adjuvants include midazolam, ketamine, octreotide.

(11,33). Little evidence suggests that ziconotide is helpful in combination with opioids to manage cancer pain. No prospective, controlled studies of ziconotide plus opioids have been performed. Stability of admixtures becomes a concern when multiple medications are used for combination therapy (115). There is also concern that drug mixing may increase permeability of medications into the pump rotor, resulting in corrosion and pump failure (58). Reports of ziconotide plus bupivacaine have little supportive evidence. For palliative reasons in the cancer population more combinations of medicines are trialed, and Tier 6 was added to the PACC 2012 algorithm. When contemplating higher-tiered recommendations, it is crucial to consider the category of cancer pain that the patient has (see Table 7).

Consensus Point 12. The disease process should be considered when making decisions on algorithms for patient care.

Consensus Point 13. The stage of cancer and survival time should be considered when considering drug titration.

Recommendations for medication selection for noncancer localized pain need to be approached mindfully, and age and pain type should be carefully considered. As can be seen in the noncancer-pain tiered algorithm, and assuming that the catheter location is congruent to the painful area, medication recommendations are based on the physiochemical properties of the drug. Built into the algorithms are pathways for diffuse or local, nociceptive, and neuropathic pain types. The evidence behind Tiers 2–5 (or 6 for cancer or end-of-life pain) is largely dependent on experience/consensus from the PACC members, with graded strength of consensus.

Table 15. Cancer or Other Terminal Condition-Related Pain With Diffuse Pain: Evidence Level, Recommendation Strength, and Consensus Level.

Tier	Evidence level	Recommendation grade	Consensus level
Line 1A	I	B	Strong
Line 1B	II	B	Moderate
Line 2	II-3	B	Strong
Line 3	III	C	Moderate
Line 4	III	I	Weak
Line 5	III	I	Weak
Line 6	III	I	Weak

Consensus Point 14. Ziconotide has strong clinical evidence for efficacy.

Consensus Point 15. There are no cases of death from ziconotide overdose and no granuloma formation has been reported.

Consensus Point 16. Unless contraindicated, ziconotide should be the first drug selected in the population of noncancer patients discussed in this consensus.

RECOMMENDED STARTING DOSAGES

Starting dosage ranges of IT medications recommended by the PACC panel have not changed since the PACC of 2012 (Tables 20 and 21). These doses assume chronic continuous infusion. Bolus strategies have been reported (1,116), but there are limited data to support widespread adoption. IT dosing studies with bolus-only or bolus-weighted infusion strategies are presently ongoing (35). Appropriate starting opioid dosages may vary according to the patient's baseline oral intake at the time IT therapy is initiated, and it is suggested that patients be stratified by risk regarding cardiopulmonary depression and site of service initiation. Conservative initiation dosing strategies are recommended.

It is important to consider morbidity and mortality data of IT delivery when gauging appropriate starting doses. Coffey et al. reported, from device registration and Social Security death master file analyses, an IT opioid therapy mortality rate of 0.088% at three days after implantation, 0.39% at one month, and 3.89% at one year (41). All patients were initiated on an opioid dose of $>$0.5 mg/day. It is also important to contrast IT drug delivery mortality with that for prescription drug overdose death rates, which quadrupled between 2000 and 2014, from 1.5 to 5.9 deaths per 100,000 people (117).

Site of service for trialing and dosing of IT therapy is an important issue when considering morbidity and mortality. This article is accompanied by a PACC recommendation article that pays exclusive attention to trialing (118), where similar clarity is required. Conservative dosing, regardless of patient risk assessment, is highly recommended in both articles. Risk assessment not only includes the biologic disease indications and patient-selection criteria aforementioned, but also the nonbiologic site of service where trialing and dosing changes occur. It was recommended in the previous PACC to perform opioid trials and initiate monotherapy or combination opioid therapy followed by a 23-hour observation period, which

Table 16. Noncancer-Related Pain With Localized Nociceptive or Neuropathic Pain.

Line 1A	Ziconotide		Morphine	
Line 1B	Fentanyl		Fentanyl + bupivacaine	
Line 2	Fentanyl + clonidine	Hydromorphone or morphine + bupivacaine	Fentanyl + bupivacaine + clonidine	Bupivacaine
Line 3	Fentanyl + ziconotide + bupivacaine	Morphine or hydromorphone + clonidine	Ziconotide + clonidine or bupivacaine or both	Bupivacaine + clonidine
Line 4	Sufentanil + bupivacaine or clonidine	Baclofen	Bupivacaine + clonidine + ziconotide	
Line 5	Sufentanil + bupivacaine + clonidine		Sufentanil + ziconotide	

typically requires hospital admission. In review of publications and consensus opinion since that publication, we have modified our recommendation so that the site of service for IT therapy be based on several mitigating factors.

In the perioperative setting for trials, the safe IT dose of morphine was determined in a meta-analysis to be near 0.075 and 0.15 mg for a single IT bolus, although the disparity of the definition of clinically significant respiratory depression muddies the ability to determine the exact incidence (119). In a retrospective comparison study of parturients in labor investigating opioid-related side effects of morphine or bupivacaine, the incidence of opioid-related side effects did not statistically differ (pruritus, nausea, vomiting, respiratory depression). None of the 114 patients in this study had respiratory depression at doses of 0.04 mg hydromorphone or 0.1 mg morphine when observed for no less than 24 hours (120). In an assessment of 1524 postoperative patients, one patient who received a single-bolus IT dose had less than ten breaths per minute (121). In a prospective study comparing morphine and fentanyl in the parturient population for cesarean delivery, there were no respiratory depression events defined as less than ten breaths per minute (122). In a comparison of spinal analgesia for transurethral surgical procedures, in patients who received 25 mcg of fentanyl intrathecally, no patient ($n = 20$) experienced respiratory depression or complications (122). Although not specific to the chronic pain patient undergoing IT trial for candidacy of IT chronic delivery, evidence suggests low-dose opioid trialing is safe in the outpatient setting.

Does the safety profile described during IT trialing translate to the initiation of therapy as an outpatient? The mortality data for IT therapy includes data from implantation, revision, and refill of the device (41). There are no data suggesting safety or danger of IT opioid initiation in an outpatient setting. However, it is suggested by expert consensus that the 24-hour initiating IT dose be half of the efficacious/successful trialed IT opioid dose. For ziconotide, the previous recommendation of a 12-hour observation period after initiation has been revised, by consensus, to six hours as long as there are no signs of neurologic dysfunction prior to initiation. The risk of morphine overdose applies when using higher initial drug concentrations of morphine. This is important since the FDA considers drug dilution as an off-label use of drug. In settings where the initial drug concentrations create the need for a starting dose outside of the PACC recommendations, an overnight admission is advised.

Table 17. Noncancer-Related Pain With Localized Nociceptive or Neuropathic Pain: Evidence Level, Recommendation Strength, and Consensus Level.

Tier	Evidence level	Recommendation grade	Consensus level
Line 1A	I	A	Strong
Line 1B	II-3	B	Strong
Line 2	II-3	B	Strong
Line 3	III	C	Moderate
Line 4	III	I	Weak
Line 5	III	I	Weak
Line 6	III	I	Weak

No evidence suggests superiority of one trialing method over another, which includes duration of trial (15,124). However, inpatient catheter trials offer the flexibility to trial different intrathecal medications and regimens following one dural puncture, and may be helpful in the complex patient.

Special comment needs to be made here regarding patient-controlled bolus administration and IT opioid rotation or a medication switch. The 2012 PACC recommendations suggested that patient-controlled dosages be 5–20% of the total daily dosage. In a retrospective review from the Cleveland Clinic, up to 30% of the 24-hour dose could be administered safely during each patient-activated dose, up to four times daily (125). This represents a significantly larger incremental increase of the 24-hour dose, suggesting that more prospective or retrospective data are required. In another unpublished study from the Cleveland Clinic, patient-controlled IT analgesia proved to be cost-effective, paying for the IT device in eight months (126).

Consensus Point 17. The initiating dose of intrathecal opioids and ziconotide should be as low as reasonably expected to provide analgesia.

Consensus Point 18. The initiating dose of intrathecal opioids and ziconotide delivered continuously should be 50% or less of the dose used during bolus trialing.

Consensus Point 19. The PACC recommends that the primary medication be weaned and discontinued when converting medications from one single medication to a different single medication in the algorithm. The use of ziconotide and bupivacaine do not have risk of withdrawal and weaning is not needed. The abrupt stopping of an opioid is not recommended.

Consensus Point 20. The PACC recommends careful attention to side effects when adding any adjuvant drug to a primary drug.

Consensus Point 21. Medications with significant withdrawal syndromes, including clonidine and baclofen, require rescue strategies in the event of abrupt cessation or interruption in intrathecal delivery.

Maximal recommended daily doses based on preclinical studies, animal toxicity studies and consensus were published in the 2012 PACC. Preclinical work with fentanyl and sufentanil used single

Table 18. Noncancer-Related Pain With Diffuse Nociceptive or Neuropathic Pain.

Line 1A	Morphine		Ziconotide*	
Line 1B	Hydromorphone		Morphine or hydromorphone + bupivacaine	
Line 3	Hydromorphone or morphine + clonidine		Fentanyl + bupivacaine	Ziconotide + morphine or hydromorphone
Line 4	Hydromorphone or morphine + bupivacaine + clonidine	Fentanyl + ziconotide	Sufentanil + bupivacaine or clonidine	Ziconotide + clonidine or bupivacaine or both
Line 5	Fentanyl or sufentanil + bupivacaine + clonidine		Sufentanil + ziconotide	Baclofen
Line 6	Opioid + ziconotide + bupivacaine or clonidine			

*Ziconotide should be first choice in patients with >120 morphine equivalents or fast systemic dose escalation, in the absence of history of psychosis.

bolus, multiple daily boluses, or continuous infusions across many animal models (127–133). It appears that high concentrations of fentanyl and sufentanil are tolerated, exclusive of a single injection sheep study (133). Very limited continuous infusion studies exist. Although some data suggest that 50 mcg/mL has limited data supporting safety, the 2000 mcg/mL study also suggests that neurotoxicity may not be a concern, with conflicting reports with fentanyl up to concentrations of 5000 mcg/mL (127,128).

Although these animal toxicity studies do support the safety of high concentrations of fentanyl and sufentanil, there was concern among PACC members about the phraseology of the "no known upper limit" recommendation. Those expressed concerns included: 1) high daily doses may lead to opioid- induced hyperalgesia; and 2) high plasma levels of the medication from very high IT doses may limit the advantages of targeted drug delivery to the spinal dorsal horn. The majority of PACC members agreed that in most clinical settings patients would not benefit from daily doses higher than 1000 mcg of fentanyl or 500 mcg of sufentanil. Members also agreed that the lowest possible concentration should be used, as human data are limited. Therefore, the consensus was that a more conservative approach to dosing of both fentanyl and sufentanil should be taken.

The consensus panel did note the experience of several members suggesting that escalation of IT fentanyl doses was often associated with diminishing returns. Several have observed clinical responses consistent with hyperalgesia and lack of clinical efficacy in dose ranges above 1000 mcg per day of IT fentanyl. Further systemic absorption of this highly lipophilic opioid may approach systemic levels seen with transdermal systemic applications (>3 ng/dL) as higher IT doses are utilized. While there is no conclusive data to guide the panel, the PACC does suggest strong reevaluation and consideration of other approaches as doses cross the 1000 mcg per day dosing threshold. Clearly clinicians have utilized doses above the 1000 mcg per day level safely and possibly with efficacy, however, the panel does recommend this dosage currently as a reevaluation milestone.

Similarly, evidence suggests that the much higher doses of bupivacaine are well tolerated and average concentrations are reported in many studies (99,134,135). For all of the other drugs, the recommendations established in 2012 are still supported in the evidence, and we endorse the same dosing recommendations in 2016 (Table 22).

Consensus Point 22. Before proceeding with aggressive dose titration above 1000 mcg per day of IT fentanyl, clinicians should closely monitor the outcome of each dose increase and, if efficacy is not being established, consider dose reduction with consideration of intrathecal tolerance and hyperalgesia.

Table 19. Noncancer-Related Pain With Diffuse Nociceptive or Neuropathic Pain: Evidence Level, Recommendation Strength, and Consensus Level.

Tier	Evidence level	Recommendation grade	Consensus level
Line 1A	I	A	Strong
Line 1B	II	B	Strong
Line 2	II-3	B	Strong
Line 3	III	C	Moderate
Line 4	III	I	Weak
Line 5	III	I	Weak
Line 6	III	I	Weak

VARIABLES AFFECTING CHRONIC INTRATHECAL THERAPY

Spinal Anatomy and CSF Dynamics Relevant to IT Drug Delivery

Meninges are morphologically and physiologically implicated in mechanical, immunologic, trophic, metabolic and thermal protection of the brain and spinal cord. In relation to spinal drug delivery, the spinal meninges represent the main barrier to the transfer of drugs between the CSF and the spinal cord. Therefore, it is necessary to know if any of the meninges cause resistance or limitation to the free circulation of CSF, presenting a barrier or compartmental limitation. The spinal dural sac contains the subarachnoid space with the trabecular arachnoid, the pia mater, and the subpial tissue. Drugs must cross all of these structures before reaching their final target,

Table 20. Recommended Starting Dosage Ranges of Intrathecal Medications for Long-Term Therapy Delivery.

Drug	Recommendation of starting dose*
Morphine	0.1–0.5 mg/day
Hydromorphone	0.01–0.15 mg/day
Ziconotide	0.5–1.2 mcg/day (to 2.4 mcg/day per product labeling)
Fentanyl	25–75 mcg/day
Bupivacaine	0.01–4 mg/day
Clonidine	20–100 mcg/day
Sufentanil	10–20 mcg/day

*Starting doses of continuous intrathecal delivery should be half of the trial dose for opioid-based medications.

Table 21. Recommended Doses for Intrathecal Bolus Trialing.

Drug	Recommended dose*
Morphine	0.1–0.5 mg
Hydromorphone	0.025–0.1 mg
Ziconotide	1–5 mcg
Fentanyl	15–75 mcg
Bupivacaine	0.5–2.5 mg
Clonidine	5–20 mcg
Sufentanil	5–20 mcg

*Starting doses of medication in the opioid-naive patient for outpatient bolus delivery do not exceed 0.15 mg morphine, 0.04 mg hydromorphone, or 25 mcg fentanyl.

the substance of the spinal cord. Dura mater, arachnoid and pia mater are differentiated structures morphologically, with different properties and, therefore, must be considered and analyzed independently.

Dural Sac

The dura mater is the most external layer of the dural sac and is responsible for 90% of its total thickness. This fibrous structure, arising from the meningeal fibroblast, represents a collagenous membrane that confers a barrier to diffusion defined by the molecular weight of the compound crossing the membrane (136). The remaining internal 10% of the dural sac is formed by the arachnoid lamina, which is a cellular lamina that adds very little extra mechanical resistance to the compound movement (137). The arachnoid lamina is semipermeable, and influences the passage of lipophilic substances through the dural wall (136). The arachnoid limits the diffusion of injected drugs to the epidural space. Dura mater has a thickness of about 0.35 mm (0.25–0.40) (138) that it is fairly constant along the length of the spinal cord, with some small variations. It is comprised of concentric dural laminas containing fibers distributed randomly in all directions (139–142). The arachnoid lamina has a thickness of 50–60 microns (μm) (143). Its barrier effect is due to arachnoid cells strongly bonded by specific membrane junctions. This cell layer represents a small thickness of about 10–15 μm.

Trabecular Arachnoid

The trabecular arachnoid originates from the stratum of inner cells of the arachnoid lamina. These cells surround bundles of collagen fibers that form the axis of the arachnoid trabeculae. Near the spinal cord, the arachnoid cells of the trabecular structure are mixed with pial cells from the pia mater. Both types of cells share the same histochemical profile, positive epithelial membrane antigen. In the pial layer, collagen fibers and fibroblasts continue under the pial cells to form the subpial compartment. The trabecular arachnoid surrounds the structures inside the subarachnoid space, including the spinal cord, nerve roots and vessels that are found free within the space, providing cover sheaths to these structures (144,145). These sheaths are very fragile and break easily if dissected. The characteristics of the arachnoid sheaths in the cauda equina are variable; some are lax while superimposed planes of the same components with a more compact appearance form others. The thickness of an arachnoid sheath ranges from 10 to 60 μm (144,145). In some cases, a single arachnoid sheath encloses one or more nerve roots and in others the nerve root has no sheath at all (144–146).

It is possible that a microcatheter, with small diameter, could be introduced inside the arachnoid sheath. By contrast, a 20G catheter, used commonly in epidural techniques, is more difficult to introduce. If a drug is injected inadvertently or by accident inside the sheath, the drug would have a limited dilution with CSF and, therefore, could potentially be neurotoxic. Taking into account the method of administering drugs, continuous injection of local anesthetic through a microcatheter into these arachnoid sheaths could potentially be more devastating than a single injection. This is because repeated doses of small volumes may be accommodated inside the sheath, leading to nerve damage. The injection of a single larger volume instead would promote leakage of the anesthetic outside the sheath, decreasing its potential for injury.

Table 22. Maximum Concentrations and Daily Doses of Intrathecal Agents as Recommended by PACC 2012 (8) and 2016.

Drug	Maximum concentration	Maximum dose per day
Morphine	20 mg/mL	15 mg
Hydromorphone	15 mg/mL	10 mg
Fentanyl	10 mg/mL	1000 mcg
Sufentanil	5 mg/mL	500 mcg
Bupivacaine	30 mg/mL	15–20 mg*
Clonidine	1000 mcg/mL	600 mcg
Ziconotide	100 mcg/mL	19.2 mcg

*May be exceeded in end-of-life care and complicated cases as determined by medical necessity.

Lumbar Subarachnoid Ligaments

Trabecular arachnoid and subarachnoid ligaments may be related to embryonic tissue remnants found in the subarachnoid space, where the cellular component is progressively replaced by fibrous connective tissue. These ligaments anchor the lateral, anterior and posterior sides of the spinal cord to the dural sac (147,148). Subarachnoid ligaments are similar to trabecular arachnoid, although contain more collagen fibers, and therefore more resistant to mechanical forces. A number of 21 dentate ligaments from each side of the spinal cord hold to the dural sac. Each ligament is composed of a flat fibrous membrane between the anterior and the posterior nerve roots, and its medial edge is in direct contact with subpial tissue covering the spinal cord. Laterally, these ligaments give rise to pyramidal projections that attach nonuniformly to the arachnoid lamina. The most cephalic ligament is found opposite the margin of the foramen magnum between the vertebral artery and the hypoglossal nerve. The lowest dentate ligament lies between the exit of the 12th thoracic and first lumbar spinal nerve roots; this ligament is a thin band stretching downwards from the medullary cone. Less commonly, posterior ligaments (*posticum*) are found giving shape to thin, inconsistent bands that attach the spinal cord to the inner surface of the dural sac (147,148). There are also less resistant fenestrated posterior-lateral ligaments, extending more laterally from the dorsal roots to the arachnoid lamina. Both posterior and posterior-lateral ligaments extend longitudinally from the cervical to the midthoracic or lumbar level. The thinner ventral ligament is found in the anterior side of the subarachnoid space. These subarachnoid ligaments do not limit free flow of CSF in most patients, due to their discontinuity along the dural sac.

Pia Mater

The structure of the pia mater includes a cellular layer and a subpial compartment. The cellular layer is made of flat overlapping pial cells with a smooth and bright appearance. It is three to five pial cells thick (10–15 μm) at medullary level and two to three cells thick

Table 23. Cerebrospinal Fluid Volume and Nerve Root Volume (mL) per Vertebral Segment (159).

	Sacral	L5	L4	L3	L2	L1	T12
Cerebrospinal fluid (mean ± SD)	2.2 ± 0.6	4.8 ± 1.3	5.1 ± 1.1	4.9 ± 0.8	5.7 ± 0.9	5.8 ± 1.6*	4.7± 1.3*
Nerve root (mean ± SD)	0.1 ± 0.1	0.6 ± 0.3	1.3 ± 0.3	1.8 ± 0.5	2.0 ± 0.8	2.4 ± 0.5*	2.4 ± 0.6*

*Includes spinal cord volume.

(3–4 μm) at nerve root level. Amorphous fundamental substance is found around pial cells. The cells measure on average 0.5–1 μm (149,150).

The subpial compartment has large amounts of collagen fibers, amorphous fundamental substance, fibroblasts, and a small number of macrophages, as well as blood vessels. The subpial compartment is enclosed between the pial cellular layer and a basal membrane in contact with neuroglial cells. The subpial compartment from low thoracic vertebrae has a thickness of 130–200 μm, and here measurement variations are more significant than in the pial cellular layer. The thickness of the pia mater is reduced to 80–100 μm at the level of the medullary cone and continues to diminish down to 50–60 μm in the origins of the cauda equina. At nerve root level, the thickness of the subpial compartment is 10–12 μm (149,150).

At the level of the medullary cone, there are perforations or fenestrations over the entire surface of the cellular layer of the pia mater. These fenestrations have circular, ovoid, or elliptical shapes. While the dimensions of these fenestrations vary, most of them measure 12–15 μm in length and 4–8 μm in width. At nerve root level, the pia mater also shows similar fenestrations but smaller in size (1–4 μm) (144,149,150).

Surrounding the pial cells there are numerous macrophages. The macrophages and other inflammatory cells seen within the pia mater could possibly originate from subpial and subarachnoid blood vessels, although a small proportion of them could originate from immature pial cells as a result of an unknown stimulus. Probably the fenestrations found in the pia mater are related to the migration of some immature pial cells as part of an inflammatory response (151).

The number of cell junctions between pial cells is much lower than among arachnoid cells. For this reason, pia mater is a permeable structure allowing the passage of drugs through intercellular spaces. However, in the area of the conus medullaris the permeability could be higher if the fenestrations are present in the patient.

Cerebrospinal Fluid

The volume of the CSF has obvious relevance as a determinant of dilution of drugs in the subarachnoid space (152). About 500 mL of CSF is formed each day, mainly by the choroid plexuses of the cerebral ventricles with uncertain contribution from ependyma, pia, and brain parenchyma. A small proportion of CSF leaves the skull and enters the spinal subarachnoid space, passing downwards, posterior to the spinal cord and returning upwards, anterior to the spinal cord (153), with little bulk flow. The rate of absorption through the arachnoid villi varies and is adjusted to maintain a pressure within normal range.

There are oscillations of the CSF pressure, which are synchronized with intracranial arterial pulsations for both respiratory and circulatory motors. These changes of pressure could help the dilution of drugs injected in the CSF to reach a homogenous concentration around the nerve roots and spinal cord. Their amplitude is about 9 mm per cycle in the cervical CSF and about 4 mm at the thoracic-lumbar junction, with minimal movement in the distal part of the lumbar sac (154,155). Pulsations probably increase with the elevation of intra-abdominal pressure. The oscillatory CSF pulsations have a significant impact on the spreading of drugs after subarachnoid injection (156). CSF flow dynamics reveal latencies of the systolic and diastolic peaks of cervical and lumbar CSF pulsations, contrary to the hypothesis of a continual wave theory. Furthermore, fast flow velocity reappears in the thoracolumbar spine, correlating to a large respiratory influence in the thoracolumbar spine (18).

Magnetic resonance imaging (MRI) allows the estimation of CSF volumes from human axial images under physiological and pathological conditions (157–160). There is a great variability of CSF volume between patients, although this variation also depends on the method used to study the CSF. Sullivan et al. (159) in 2006 estimated a CSF volume of 35.8 ± 10.9 mL (range 10.6–61.3 mL) between a perpendicular plane in the intervertebral midpoint of T12 to L1 and the lowest limit of the dural sac. Edsbagge et al. (160) in 2011 studied the complete spine and found a total CSF volume of 81 ± 13 mL (52–103 mL). In the cervical region, there was 19 ± 4 mL, in the thoracic region, 38 ± 8 mL, and in the lumbosacral region 27 ± 8 mL. Another group estimated that the total volume of CSF from L5-S1 to T11-T12 was 36.1 ± 6.7 mL (161). These individual differences of CSF volume affect the final concentration of a local anesthetic drug administered in the dural sac of different individuals, even with the same dose, volume and concentration given. Therefore, having considered other relevant factors such as position of the patient or vertebral level selected for subarachnoid injection, it may be that doses below 7.5 mg of bupivacaine do not ensure an adequate level of blockade in all patients.

Nerve Roots, CSF, and Subarachnoid Catheters

The relationship between CSF volume and nerve root at each vertebral level is an unknown subject that may be of interest when we consider the concentration of drugs in CSF and the amount of nerve tissue that must be crossed (161–163). In the cadaver it is possible to measure the volume of each nerve root, but more difficult to determine the amount of CSF related to each nerve root. Recently Prats-Galino et al. estimated the volumes in the segments from L5-S1 to T11-T12 (162). The total volume of CSF was 29.95 ± 5.66 mL (Table 23) and the volume of the nerve roots was 10.38 ± 2.4 mL. The total mean volume of CSF at each lower thoracic and lumbar level is around 5 mL per segment, but with a wide range of results between the different levels (162) (Table 23).

The existence of concentration gradients for many compounds in the CSF along the spinal canal was established in the 1990s (139,140). These gradients imply de facto that the CSF cannot be a circulatory system, and recently MRI evidence has confirmed that movements of the CSF through oscillations rather than a flow (139). The velocity of CSF oscillation waves has been calculated at 4.6 m/sec (SD 1.7 m/sec) (140). This new knowledge has been surprising to many practitioners and should be considered in all future pharmacokinetic studies of IT drugs.

Very little is known about the mechanisms of drug dispersion in the human CSF. The best available *in vivo* data are still derived from

a sophisticated porcine model developed by Bernards (16,20,152). Overall these studies suggest that all drugs that have been tested for IT infusion and are relevant to the algorithms are poorly dissipated in the CSF. This is due to a combination of factors including the low kinetic energy (low flow rate) provided by all implantable pumps currently on the market, limited liquid/liquid diffusion coefficient, and the absence of meaningful CSF bulk flow. Local IT mechanisms related to the interaction of the oscillation of the CSF across obstacles, such as nerve roots and ligaments, as well as irregularities in diameters and contours of the walls of the spinal canal, combine to form regional vortices that increase the dispersion of drugs by several orders of magnitude (164).

CSF Dynamics

Factors that affect the dynamics of CSF flow include heart rate, blood pressure (156), and the pulmonary ventilation, which appears to be one of the most important drivers (165). Traditional knowledge and experience with local anesthetics, opioids, and novel agents administered in the lumbar spinal subarachnoid space for surgical anesthesia and analgesia unfortunately contribute little understanding to the complexities of IT catheter-targeted drug delivery for chronic pain and spasticity management. In the former, technical factors such as bolus injection speed or rate, volume, baricity, and patient factors such as height and posture, significantly influence drug distribution. In the latter, drug distribution is highly influenced by CSF flow dynamics, where multiple recent studies have led to a new understanding of drug distribution, which in time may lead to improved efficacy and safety of IT drug delivery.

The intended action of intrathecally delivered drugs is the spinal cord and to a lesser extent the brain, and they are delivered into the CSF through a catheter connected to an implanted pump. The CSF is secreted by the choroid plexus and brain parenchyma at a rate of 0.3–0.4 mL/min and the total volume ranges from 90 to 150 mL. Approximately a third of the total volume is contained in the compliant spinal subarachnoid space. Choroid plexus and brain parenchyma are not the only sites of CSF production, as glial cells, water transporters know as aquaporins, and other bidirectional mechanisms produce flow rates greatly exceeding traditional net CSF secretion rates (166). Absorption traditionally has been considered to take place at arachnoid villi, and the resultant bulk CSF flow was thought to influence drug distribution to the spinal cord and brain to a greater extent than by simple molecular diffusion. This bulk flow concept has been shown to be outdated from several perspectives, however.

Current understandings from imaged-based and computational fluid dynamics (CFD) show CSF to behave as a poorly mixed volume with little net flow, but significant oscillatory flow, originating from CSF pulsations, which are, in turn, influenced by blood pressure, stroke volume, and intrathoracic pressure variations associated with respiration. Because of the noncompliant skull, and to a lesser extent spinal canal features, these pulse volumes are transmitted as CSF pulses, and in the compliant spinal canal lead to oscillatory inflow and outflow at velocities up to 10 mm/sec (167). This pulsatile mixing is orders of magnitude greater that that seen with simple molecular diffusion (164).

This oscillatory flow interaction with the various IT structures such as nerve roots, ligaments, and objects such as catheters induces secondary flow patterns known as: 1) steady streaming, which may be more or less than oscillatory flow, but also greater than molecular diffusion (167), and 2) enhanced diffusion caused by shear forces at liquid/solid interfaces (168). Velocity and amplitude variations also occur in various locations within the spinal canal (169).

In a small-volume (spinal anesthetic) CFD model, speed of drug transport (i.e., mixing) was strongly affected by the frequency and volume of CSF pulsations (156). Large-volume bolus injection of more than 10% of total estimated CSF volume has been shown to result in rapid substantial mixing throughout the entire spinal axis independent of pulsatile mixing, but this is orders of magnitude greater than clinically used in simple continuous or intermittent patient-activated bolus mode through an implanted catheter (164).

Many animal studies have shown a rostral-caudal gradient from the catheter tip (20,81,91), and the recent work of Wallace and Yaksh confirms this in a human study (170). In patients receiving IT morphine, CSF morphine concentrations decreased by distance from the catheter tip with a gradient that correlated with the infusion dose, and over a range of infusion rates of 0.1–1.0 mL/day.

Just as volume and flow rate of injection in spinal anesthetics compared to continuous catheter infusion limit the applicability of spinal anesthetic data, such discrepancies may also explain the apparent initial "failures" of IT drug delivery when the catheter location, volume, and rate of delivery vary from the trial methodology and lead to varying and lesser drug distribution reflecting pharmacokinetic differences. This has been described with the lipophilic drug bupivacaine (171), and when simple addition of lipophilic bupivacaine to an existing hydrophilic opioid pump mixture was shown to be of no benefit (172).

Given all these variables, the amount of drug present at a particular site along the neuraxis distant from the injection site is difficult to determine and is not likely to be uniformly distributed from a CFD perspective (167). Experimentally, drug distribution is limited to a few centimeters around the tip of the catheter (171,173), and dispersion around the cord is also limited (90). This leads to factors to consider when placing a permanent catheter.

Catheter Location and Placement

The traditional teaching of many instructors has reasonably recommended placing the catheter tip close to the target receptors of the spinal segment(s) associated with the dermatome/sclerotome/viscerotome of the primary pain generator. This issue of delivery location reflects on: 1) the fact that analgesic medications (mu opioid, alpha 2 adrenergic, N type calcium channel blockers), aside from the local anesthetics, exert their effects on the target receptors/channels that are located on the terminals of the primary afferent and at the level of the first order spinal synapse; and 2) the need for the drug to reach the spinal levels associated with the spinal segments processing the pain information (where the target receptors are located), and the absence of robust infusate redistribution (as discussed in the previous sections). The ability to determine this location is, for the most part, difficult, and may be easier to determine when local anesthetics are administered (174); it is far less clear when baclofen is infused to treat spasticity or morphine to relieve pain. An important issue is the appreciation that the receptors associated with the target dermatome are not restricted to the spinal segment associated with the root dermatome. Afferent input into any given segment may send collaterals up to several segments rostrally and caudally. It has been argued that the IT drug must accordingly reach the cells and afferent terminals in these distal dermatomes (112,175,176).

Consensus Point 23. Limited data exist as to appropriate and best catheter tip placement. The catheter should ideally be centered

in the spinal dermatome associated with the pain generator. The consensus recommendation is that the doctor use clinical judgment based on the clinical setting.

Pharmacokinetics of IT Analgesic Agents

Compared to epidural administration, IT administration has long been shown to result in higher analgesic efficacy and lower rates of treatment failures and technical complications (177). The principal advantage of IT therapies involves bypassing the blood-brain barrier. This results in higher concentration of administered agents in the CSF while using lesser amounts of medication. Evidently, greater efficacy is realized with IT drugs that do not freely cross the blood-brain barrier and when the target receptor is predominantly located in the CNS in close proximity to the administered IT agent. Medications deposited in the IT space, through catheters placed near the level processing the patient's pain, lie close to but not at the target sites. Except for local anesthetics and baclofen, the receptor sites for IT drugs are located in the dorsal horn of the spinal cord, in particular in lamina II, also known as substantia gelatinosa (178). In order to reach their target receptors at neuronal synapses in the superficial dorsal horn, intrathecally administered medications must diffuse across the pia arachnoid and white matter of the spinal cord—a distance of up to 1–2 mm from the surface of the cord (179). Diffusion across the pia is typically considered to be unimpeded given its structure of a single layer of cells without intercellular junctions. Work with large molecules has, however, suggested that the diffusion of drugs into the parenchyma may occur though fluid pathways paralleling the intraparenchymal vasculature (180). The spinal cord white matter consists of myelinated axons making it hydrophobic (e.g., dorsal column), whereas the grey matter consists of cell bodies in the various laminae and is hydrophilic (181). Continuous IT infusion results in stable CSF drug concentrations, which establishes a gradient driving parenchymal diffusion into the spinal cord. At equilibrium with slow constant IT infusion, concentrations of small molecules in the CSF are thought to be equivalent to those in the interstitial fluid in the superficial aspect of the dorsal horn (179).

A number of factors intrinsic to the IT medication play important roles in determining drug uptake. Among these, lipid solubility and molecular weight are the most important physicochemical characteristics of an intrathecally administered drug. Hydrophilic medications administered intrathecally may have a clinical advantage over hydrophobic or lipophilic IT agents. Compared to lipophilic medications, hydrophilic agents have longer half-lives, reflecting the faster clearance into the vasculature demonstrated by lipophilic agents (16) and smaller volumes of distribution, resulting in potentially deeper cord penetration and more rostral spread (182). However, lipophilic medications have the advantage of limited spread when precise targeted delivery is desired.

Safety and the Compounding of IT Drugs

Medications approved by the FDA have undergone comprehensive testing in animal and human subjects to demonstrate safety and efficacy, while the manufacturing process is continuously evaluated to ensure that high quality standards are met (183). Despite these good manufacturing processes and preclinical testing of medications before FDA approval, there remains considerable need for custom formulations of medications that are not commercially available for IT use or commercially unavailable concentrations of medications. The practice of creating these mixtures of medications, known as pharmacy compounding, is not regulated by the FDA but rather by state boards of pharmacy, incorporating the United States Pharmacopeia (USP) chapters Pharmaceutical Compounding—nonsterile and sterile preparations (183). As the FDA does not regulate these processes, quality assurance is left to the individual pharmacy or to national compounding associations that offer credentialing. The FDA defines pharmacy compounding as combining, mixing or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner's prescription (183). If a physician chooses to use a compounding pharmacy, the physician should be familiar with quality control procedures of that pharmacy.

The USP classifies manipulations of sterile products in aseptic conditions as low-risk compounding; however, addition of nonsterile components would constitute high-risk compounding (183). With regard to IT drug delivery (IDD), dilution of commercially available products such as Infumorph (Baxter Health Care, Deerfield, IL, USA) would constitute low-risk compounding, whereas combining an aseptic product with a powder formulation, such as bupivacaine, may constitute high-risk compounding. Beyond the quality assurance issues that lie with the individual compounding pharmacy (and are largely out of the control of the prescribing practitioner), there has been considerable discussion about the role of compounded medications for IDD (8,183,184). It should be noted that drug dilution is also considered an off-label use of IT medication. This fact, along with lack of efficacy, has led to the off-label use in the majority of IT clinical practice.

The PACC of 2012 commented on the role of compounding, identifying the risks associated with the practice and outlining basic considerations surrounding the practice, such as training of personnel, segregated sterile compounding facilities, air quality of the compounding area, certification and calibration of equipment, standardized disinfection and quality assurance programs (8). Debate concerning the practice of using compounded medications continues to this day, since essentially all medications could be construed as compounded to some degree (185). Around this time, one IDD manufacturer reported that off-label medications or admixtures could result in corrosion to the infusion system and device failure (186). This bulletin suggested that preservative-free morphine (maximum approved concentration 25 mg/mL) was approved for use, however, the bulletin also stated that compounded formulations of baclofen and morphine had resulted in motor stall, leading to some confusion on the part of practitioners as to what constituted safe use of morphine.

In 2013, a joint statement by thought leaders from NANS and the American Society of Interventional Pain Physicians presented the viewpoint of many physicians experienced in IDD: that medication formulations with hydromorphone, fentanyl, and other opioids are more effective than morphine and have fewer side effects (185). In addition, this statement reconfirms the use of admixtures of bupivacaine and clonidine as outlined in the PACC of 2012 (8). The stall rate for Synchromed pumps (Medtronic Inc., Minneapolis, MN) was reported as 2.4% for approved medications (Infumorph, Lioresal, and Prialt) at five years and as 4.5% for unapproved medications (185). The PACC suggested that compounded medications were the de facto standard of care, and peer-reviewed literature exists to support use of both on- and off-label medications.

An infinite number of drug combinations exist and some physicians recommend that drug mixtures be utilized only where drug stability information is available. If a study suggests that a high-concentration drug combination is 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-concentration drug

combinations do allow for longer refill interval and delivery of higher daily doses, alterations in pH in high drug-concentration solutions can lead to pump and catheter failure and patient symptoms. For example, precipitant has reportedly caused catheter obstruction, pump corrosion, and failure of IT drug therapy (187,188).

Given that few clinicians utilize IT medications that are completely devoid of some pharmacy manipulation (dilution, concentration, etc.) and that most clinicians utilize compounded off-label medications and admixtures, IDD essentially mandates use the of compounded medications. Also, since the incident rate of motor stalls for approved and nonapproved medications is similar, it seems prudent that diligence in monitoring patients receiving IDD for the presence of motor stalls or therapy disruption be underscored to detect and treat these possible outcomes.

Review of IT Medications

To date there has been considerable controversy and little consistency in the trialing of opioids, although trialing with morphine or hydromorphone is common and advised (27,59). The use of pretrialing systemic opioid dose conversions to derive an appropriate dose for IT opioid trialing is not recommended because of pretrial weaning of systemic opioids and differences in pharmacology between systemic and IT opioids.

Morphine

Mechanism of Action. Morphine is the most widely used IT medication. It is a mu opioid agonist (189).

Neurotoxicity. Preclinical evaluation in several large animals models showed morphine's propensity to initiate space occupying masses or IT granulomas (190–193). These masses, constituted of fibroblasts, maturing collagen and interspersed with inflammatory cells, arise from the dura/arachnoid, with the mass size largest proximal to the catheter tip (188,194). This profile has been observed with several opiates, including hydromorphone and methadone (131). The association between IT opioid therapy and granulomas is further discussed in a PACC 2012 publication (60).

Clinical Studies. Clinical data on IT morphine continue to support its use as a first-line therapy. From 1983 to 2000, there were many studies showing efficacy of the long-term infusion of morphine and morphine/adjuvant admixtures, as reported by PACC 2012 (8). Recent results from several long-term studies support the efficacy of IT morphine in treating patients with chronic pain, including pain from cancer and noncancer diseases. 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 (195). 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 (Prometra® Infusion Pump, Flowonix Inc., Mt. Olive, NJ, USA), 110 patients with chronic pain were treated and followed up for approximately one year (196). 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 (197). The limited 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 systemic opioid therapy (198,199). 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 (200). The study included 131 patients who received IT morphine monotherapy for various pain types (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 ($p = 0.02$).

Raphael et al. conducted a randomized, double-blind controlled trial of IT morphine efficacy in noncancer pain (201). One group had no change in morphine dose while the other had a 20% reduction every week for ten weeks. Seven of ten patients, all in the dose-reduction group, withdrew from the study prematurely. Within-group VAS and Oswestry Disability Index differences were statistically significant between baseline and the last observation for the intervention group, with statistically significant greater pain and worsened disability in the dose-reduction group. These results suggest the efficacy of IT morphine for long-term treatment of noncancer pain.

Hydromorphone

Mechanism of Action. Hydromorphone is a mu opioid agonist (202).

Neurotoxicity. Preclinical studies of IT infusion of hydromorphone in large animal models showed space occupying granulomas at higher concentrations (131,203).

Clinical Studies. 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 a patient 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 (204). 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/d (205).

Mallinkrodt Phamraceuticals (St. Louis, MO, USA) is enrolling patients in a study to develop a branded and formally manufactured, FDA-approved hydromorphone product. The first trial is a controlled, two-arm, parallel-group, randomized withdrawal study. Subjects in this trial will already have implanted IT pumps and will be transitioned to IT hydromorphone. They will then be titrated to a level where oral opiate medications are eliminated up to a dose of 5 mg of IT hydromorphone per day. Subjects who attain stabilization and meet criteria for randomization will be assigned to either remain at their current dose of hydromorphone or be titrated off therapy in a blinded fashion. The primary efficacy end point of this study is the proportion of subjects who are treatment failures during the

double-blind randomized withdrawal period. The second trial is a Phase 3, open-label, single-arm safety study where subjects can either directly enter the study from the previously described trial or be transitioned directly to IT hydromorphone. The two formulations of IT hydromorphone being investigated are a 2 mg per cc and a 10 mg per cc concentration, respectively. These trials are actively recruiting subjects and results are expected in 2017.

Peripheral edema associated with IT hydromorphone infusion was reported in one patient. This 61-year-old woman with chronic pain developed progressive lower extremity edema, which was complicated by severe cellulitis, while on IT morphine (206). 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/d) and baclofen (67 mcg/d); edema resolved and did not recur.

Fentanyl

Mechanism of Action. Fentanyl is a lipophilic mu opioid agonist (132,207).

Neurotoxicity. Preclinical studies of IT infusion of fentanyl or alfentanil in large animal models showed no space occupying granulomas at the highest concentrations examined (132,133).

Clinical Studies. 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 inadequate pain control despite increasing doses and an unsuccessful epidural steroid injection (208). On operation, a catheter-tip mass was noted within the epidural space, with the catheter tip in its center. Misplacement of the catheter (epidurally instead of intrathecally) at the time of original insertion complicated diagnosis. Histopathological analysis revealed a proteinaceous mass, which the authors determined was an inflammatory mass, not a granuloma, and was likely a result of drug precipitation.

Sufentanil

Mechanism of Action. Sufentanil is a potent mu opioid agonist (209).

Neurotoxicity. No canine continuous infusion trials with sufentanil have been reported. Repeated bolus delivery in the canine mode showed no histopathologic changes (132).

Clinical Studies. 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 FBSS who had received multiple IT therapies over the course of two years (210). Six weeks after beginning IT sufentanil therapy (12–17.2 mcg/d), 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.

Ketamine

Mechanism of Action. Ketamine is a noncompetitive antagonist that blocks the glutamate NMDA ionophore (211).

Neurotoxicity. IT ketamine infusion (10 mg/mL delivered at 2.4 mL/d) 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 (10). Similar pathology was observed in neonatal rats (213). This effect was shared by other *N*-methyl-D-aspartate (NMDA) antagonists, including MK801, memantine, amitriptyline, and S-methadone. Notably, these studies unfortunately did not establish a no effect level nor correlate the lower doses with an antihyperpathic action.

Clinical Studies. A randomized, double-blind study compared the use of epidural ketamine plus bupivacaine vs. epidural bupivacaine plus saline in 53 patients undergoing lower limb amputation (214). In both treatment groups, persistent phantom and stump pain were less than that 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 (215). Her numeric rating scale (NRS) 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 NRS score decreased to 3. There were no signs of motor paralysis, psychomimetic alteration, neurological dysfunction, or infection in this terminally ill patient. This contrasts with subpial vacuolar myelopathy, which was found postmortem in a cancer patient treated with 5 mg/day IT ketamine for three weeks (216).

Methadone

Mechanism of Action. Methadone is a racemic compound in which the d-isomer has NMDA receptor antagonist activity and the l-isomer is a mu opioid agonist (189).

Neurotoxicity. Notably, there is concern about the safety of IT methadone, since all compounds with NMDA activity have serious neurotoxic effects (212). Continuous infusion of the isomers in a dog model revealed spinal toxicity and granulomas with either isomer (131).

Clinical Studies. The efficacy of epidural methadone was investigated in a study of 32 patients with cancer-related pain that was refractory to epidural morphine (217). 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 provided dose-dependent analgesic effects, and these effects were further improved with the addition of dexamethasone. A prospective study of IT methadone was performed in 24 patients (218). Thirteen patients experienced improvement of their pain control with methadone, nine continued to receive this agent for six months with good pain relief.

Ziconotide

Mechanism of Action. IT ziconotide is first-line therapy for both neuropathic and nociceptive pain, and is FDA approved. Its mechanism of spinal action is to block presynaptic N-type calcium channels in the dorsal horn of the spinal cord (219,220). This targeting is distinctly different from mu agonism and allows ziconotide to be helpful in the opioid-tolerant patient (32).

Table 24. Recommendations Regarding Intrathecal Clonidine Treatment by the PACC Using USPSTF Criteria.

Statements	Evidence levels	Recommendation strength	Consensus strength
Intrathecal clonidine in CRPS patients decreases pain scores over time as well as allodynia, hyperalgesia, and mean arterial blood pressure.	I	A	Strong
Clonidine increases analgesia duration and decreases morphine use in the acute postoperative setting.	II-2	B	Strong
Clonidine may precipitate hypotension in patients with baseline hypertension.	II-3	B	Strong
Ziconotide concentration decreases over time when mixed with clonidine.	II-3	B	Strong

Neurotoxicity. Ziconotide (Prialt) has undergone extensive preclinical safety evaluation in multiple species (221) without spinal toxicity in the concentrations employed.

Clinical Studies. Many methods have been employed to trial ziconotide, from continuous infusion to single-shot bolus. There is no evidence to suggest one trialing strategy is better than another, appreciating that on-label FDA trialing is performed by a microambulatory delivery device, or via the Medtronic Synchromed II device.

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 narrow therapeutic window and the side effect profile is more closely related to the rate of dosage increase. 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 alternative 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.

Bupivacaine

Mechanism of Action. Bupivacaine is an amide local anesthetic with high lipid solubility that is often used off-label in IT therapy (99,134,222,223). Several mechanistic properties give it utility with spinal delivery: 1) differential efficacy at low concentrations that alters sensory processing while sparing motor function (224–227); 2) absence of tachyphylaxis in patients with neuropathic or somatic pain (174,228–230); and 3) potent synergy with other IT analgesic targets in animal models (110,231) and in humans (226,227,229,230).

Neurotoxicity. In early rat studies with continuous bupivacaine infusion, modest increases in neuronal vacuolation, was observed at concentrations of 0.5% (232). Bolus delivery in dogs of bupivacaine (0.75%) resulted in minor leptomeningeal cellular infiltration (233). IT infusion of 2.5–3.8 mL/d of 0.25% bupivacaine for 3–11 weeks resulted in mild leptomeningeal cellular infiltration in two of eight animals (233). In combination with morphine in human cancer patients no significant histopathology was noted on autopsy (234,235). IT infusion of bupivacaine has a long track record of safety and efficacy alone or in combination with morphine.

Clinical Studies. Though not FDA-approved for continuous IT use, bupivacaine is the most common local anesthetic used in spinal anesthesia and is used off-label in IT therapy. Compared to the epidural route, IT drug delivery results in higher patient satisfaction, fewer catheter complications, better pain relief and sleep (174). Combinations of bupivacaine and opioids have shown synergistic efficacy in acute postoperative and labor pain studies (110,236–239).

In chronic pain settings with continuous IT drug delivery, however, the effect is less clear. A retrospective study of 109 patients, who were managed with a solution containing a mixture of IT bupivacaine and opioids after an initial period of IT opioid-only treatment, found improved pain control and decreased oral opioid consumption with combination therapy compared to opioids alone (134). The average daily bupivacaine dose in that study was 10 mg. A small double-blind randomized prospective study suggested that addition of bupivacaine (up to 8 mg/day) to IT pumps infusing morphine or hydromorphone did not result in improved pain control in patients with low back pain, mostly in the setting of postlaminectomy syndrome (172). However, a large study in noncancer pain patients revealed blunting of opioid dose escalation in IT-therapy patients receiving bupivacaine in addition to IT opioids. The average bupivacaine daily dose in those patients was 9.8 mg at one year postimplant (99). Nevertheless, the difference in pain scores between the group receiving IT opioids and the group receiving IT opioids plus bupivacaine was not statistically significant. A similar effect of blunting IT morphine dose escalation was noted in a small cancer pain study (240).

The high lipid solubility of bupivacaine limits its spread intrathecally and highlights the need to place the catheter in the posterior IT space at the site of processing-pain pathology (20). No formal studies have been performed to assess starting and maximal doses of bupivacaine in IT therapy. In addition, there are no prospective studies of chronic IT bupivacaine administration as a sole agent. The most recent PACC guidelines have suggested a maximal concentration of 30 mg/mL, a starting dose of 1–4 mg/day and a maximal daily dose of 10 mg (8). However, this maximal dose is similar to the average dose noted to be effective in previous studies (99,134). Additional bupivacaine is sometimes self-administered in boluses by patients through a personal therapy manager (PTM) device (241). Serious cardiotoxic side effects can occur when significant amounts of bupivacaine reach the bloodstream. This should not be of concern with IT bupivacaine infusion (224). Clearly, the limiting factor in bupivacaine infusions would be sensorimotor loss. Nevertheless, IT bupivacaine doses as high 5 mg/hour (or 120 mg/day) and bolus doses as high as 7.0 mg in the high cervical IT space have been reported with no apparent untoward manifestations (242). Catheter tip location, CSF dynamics, and patient mobility likely play important roles in sensorimotor loss in response to bupivacaine. The most recent version of PACC guidelines suggested that, in neuropathic

Table 25. Recommendations Regarding Intrathecal Baclofen Treatment by the PACC Using USPSTF Criteria.

Statement	Evidence level	Recommendation grade	Consensus strength
Baclofen should be considered an intrathecal medication for use to treat spasticity.	II-2	A	Strong
Baclofen can be used as an adjuvant to treat pain.	II-3	B	Moderate
Care regarding mitigating withdrawal from baclofen is suggested.	II-2	A	Strong
Ancillary resources regarding physical therapy to aid in titration and assessment when employing baclofen is recommended.	III	C	Moderate
Using bolus or flex dosing strategies to improve spasticity demonstrates promise.	II-3	B	Moderate

pain, bupivacaine in combination with morphine is considered first line but second line in combination with morphine, fentanyl or hydromorphone in nociceptive pain (8). It should be noted that there is no basis for such an assertion. Recent data suggest efficacy of IT bupivacaine in combination with hydromorphone as first-line therapy (135). Average daily dose of bupivacaine at 24-month post-implant was 12.1 ± 0.9 mg including on average 3.7 ± 0.6 PTM boluses of 0.78 ± 0.05 mg bupivacaine each.

Clonidine

Mechanism of Action. Clonidine is an alpha2 adrenergic agonist (243). Clonidine may exert antiallodynic effects by inhibiting the activation of glial cells and by activation of nuclear factor κB and p38 (MAP kinase), thus inhibiting the production of proinflammatory cytokines (244). Increasing 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 (TNF α), IL-1, and IL-6 (245,246).

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/d) revealed no notable histopathologic findings (245). Additionally, IT infusion of clonidine (2 mg/mL at 2.4 mL/d) monotherapy for 28 days was not associated with direct evidence of spinal histopathology (191). 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 (246). 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. Clonidine has been evaluated in many studies, with improvement in analgesia and opioid-mitigating effects (247–250).

The PACC recommendations for IT clonidine appear in Table 24.

Baclofen

Baclofen is commonly used for intractable spasticity and is FDA approved for use in IT pumps. Baclofen has limited use as a monotherapy option for the primary treatment of chronic pain. It is used most commonly in combination therapy to treat pain with spasticity (Table 25).

Mechanism of Action. Baclofen is an agonist of the gamma-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 (251,252). 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.

Neurotoxicity. IT baclofen infusion (at rates of up to 2 mg/mL/d) for 28 days in chronically catheterized dogs has been shown to result in no behavioral or spinal histological evidence of neurotoxicity (253). Additionally, preclinical evaluation suggested that IT baclofen at doses up to 2 mg/mL/d were not associated with granulomas in dogs (254). The development of granulomas in humans is rare with IT baclofen therapy (255). Granuloma formation was reported in two patients receiving IT baclofen monotherapy (256). However, these reports, plus another, were later re-evaluated, 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 (257). 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)" (60).

Clinical Studies

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 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 complex regional pain syndrome (CRPS) who had not responded adequately to previous IT baclofen therapy (258). Overall, the faster baclofen infusion rate was not associated with improvements in dystonia or pain but was associated with increased frequency of adverse events (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 the faster-infusion IT baclofen on pain and dystonia outweighed the severity of AEs. One report described two cases of baclofen and ziconotide combination therapy (259). The first patient was a 48-year-old man with neuropathic pain who had received ziconotide (2.4 mcg/d) for approximately three months before baclofen (110–115 mcg/d) was added to his IT regimen for spasticity control. His ziconotide dosage was then reduced to 1.7 mcg/d 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/d) for six months when baclofen (62 mcg/d) was added for control of spasticity. After two years on ziconotide/baclofen therapy, his VASPI score had improved from baseline by 30%. He

Table 26. Intrathecal Drug Delivery Systems.

	Codman 3000	Medtronic Isomed	Flowonix Prometra II	Medtronic SynchroMed II
Catheter material	Polyurethane with titanium reinforced coil	Radiopaque silicone rubber with titanium tip	Radiopaque silicone rubber with tungsten tip	Radiopaque silicone rubber with titanium tip
Pump material	Titanium/silicone rubber	Titanium/silicone rubber	Titanium/silicone rubber	Titanium/silicone rubber
Pump mechanics	Continuous flow propellant	Continuous flow propellant	Valve gated programmable	Peristaltic titanium/ plastic programmable
MRI compatibility	No effects 3T	No effects 1.5T	MRI conditional 1.5T with valve shut-off	MRI conditional 3T
Patient-controlled intrathecal analgesia (PCITA)	None	None	Patient therapy controller (PTC)	Personal therapy manager (PTM)

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) (260). 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 plus 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.

Tolerance. Tolerance/tachyphylaxis is an important consideration when using IT baclofen, as it may occur in approximately 22% of patients treated with long-term IT baclofen (261). 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 (262). 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 may help address tolerance (261).

Withdrawal. Abrupt cessation of IT baclofen therapy could result in baclofen withdrawal, a serious, life-threatening situation that can be severe and prolonged (263). Baclofen withdrawal may mimic serotonin syndrome (264) and has rarely been associated with hallucinations (265). 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 (266). 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 (267). 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 delivering continuous infusion of IT baclofen as a means of avoiding withdrawal (268). It should also be noted that symptoms of baclofen withdrawal might be the first indication of IT catheter migration. Since baclofen is a water-soluble agent, migration of the catheter into the epidural space will result in symptoms of baclofen withdrawal.

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 (269). One case report described baclofen overdose associated with a change in IT baclofen concentration combined with the performance of a catheter dye study (269).

Combinations of IT Drugs

A number of studies have been conducted to evaluate the use of IT morphine in combination with other IT agents, such as bupivacaine, 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 alone and were treated with a combination of IT morphine and IT bupivacaine and followed for up to six months (270). 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) (271). The initial bupivacaine dosage of 12.5 mg/d was increased to 25 mg/d 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, which 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/d morphine, 0.5 mg/d bupivacaine) was initiated, and dosages were titrated to a mean of 1.03 mg/d morphine and 1.15 mg/d bupivacaine (272). 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 (273). 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 (115,274).

INTRATHECAL DRUG DELIVERY SYSTEM CHARACTERISTICS AFFECTING IT THERAPY

Pump and Catheter Materials and Mechanics

Intrathecal pumps can be mainly differentiated into systems that are continuous flow or variable flow. The driving mechanisms may include peristalsis, fluorocarbon propellant, osmotic pressure, piezoelectric disk benders, or the combination of osmotic pressure with an oscillating piston (Table 26). Pump materials are similar with the pump shell being titanium and filling ports containing silicone

rubber. Physical orientation of the filling and side ports are largely consistent, with differences in negative pressure or positive pressure confirmation strategies (275).

Pump delivery mechanics include continuous flow propellant or programmable features. Propellant pumps (Codman 3000 and Medtronic Isomed) do not require batteries and deliver a continuous flow for the life of the pump. The programmable pumps require battery replacement, based on labeling, at a maximum of five to seven years for the Medtronic Synchromed II and maximum of 10 years for the Flowonix Prometra II.

The programmable pump systems feature differences that deserve mention. The Medtronic Synchromed II (Minneapolis, MN, USA) system uses a peristaltic rotor system of internal tubing to deliver medication from the reservoir to the external catheter system. The Prometra II Flowonix Pump (Mount Olive, NJ, USA) employs a valve-gated bellow delivery mechanism. Each pump has the ability for patients to deliver patient-controlled dosing by using a patient-held programmer (Patient Therapy Manager or PTM for Medtronic and the Patient Therapy Controller or PTC by Flowonix). Both pumps support MRI conditional labeling, with the Medtronic pump up to 3 Tesla and the Prometra pump at 1.5 Tesla. Of note, both pumps require interrogation following a scan. For the Medtronic system, exposure to a magnetic field will create a motor stall, which typically resolves following removal of the magnet and can occur within 20 min to 2 hours, with a failure of motor stall recovery on rare occasions. For this reason, it is suggested to interrogate after the scan (276).

The Flowonix Prometra I system requires removal of all medication within the reservoir prior to MRI exposure, as failure can result in emptying of the reservoir contents into the patient. The Prometra II system remedied this concern with the flow activated valve (FAV) that is triggered when exposed to a magnetic field, blocking drug delivery from the reservoir to the patient after delivery of less than or equal to 10 μL (275). If the contents of the reservoir are expected to be less than 1 mL, they should be removed prior to the MRI because the FAV may not activate. After the MRI, the contents of the reservoir have to be removed entirety to manually reset the FAV, the pump interrogated and the contents replaced in sterile fashion, with elapsed time of 3 min (275).

The Medtronic Synchromed II System has a minimal flow rate of 0.048 mL/day to allow for programming, while the Prometra II system can be at zero flow. Accuracy of the Prometra system is greater (97.8%) compared to the Medtronic Synchromed II system (2 vs. 14.5%) (276–279). The Medtronic system has two reservoir sizes, 20 and 40 mL, while the Prometra II system has a 20 mL reservoir only.

Although it is beyond the scope of the PACC, the consensus group felt it necessary to comment briefly on the warning letters surrounding the Medtronic Synchromed II system, and the recent consent decree agreement between the FDA and Medtronic in April 2015. Prior to this, warning letters were released regarding overinfusion, corrosion of the internal tubing with the use of off-label medications or combinations or medications, and priming bolus errors (280). The complexity this introduces for use of the Medtronic Synchromed II system is unknown, with a recent editorial offering a foundation for discussion (5).

Intrathecal Infusion Rate

Intrathecal therapy offers advantages over systemic therapy in that IT delivery bypasses the blood-brain barrier with direct access of the drug delivered to receptor sites in the dorsal horn of the spinal cord (283). The efficacy of this therapy is dependent to some degree on drug distribution within the spinal canal; however, the biophysiologic properties that determine drug distribution in the spinal canal are incompletely understood. Many factors have been proposed and evaluated as contributing to differential drug distribution in the CSF. For instance, anatomic variation, postural changes, drug solution density, binding characteristics of drugs at the dorsal horn, CSF volume and variations in CSF pulsatile flow with heart rate, stroke volume, and respiratory cycle have been examined (20,156,170,281,283). Additionally, it has been suggested that the rate of dispersion in the CSF cannot be explained by diffusion alone (156,283).

CSF convective transport within the spinal canal has been studied exclusively, and it is now known that CSF flow is pulsatile with oscillatory displacements creating microenvironments with eddy currents resulting in complex micromixing of infused drugs with no net bulk flow (20,156,281,283). A recent study based on computer modeling of microanatomic structures in the spinal canal suggested that the spinal nerve roots themselves serve as a significant barrier to laminar flow and may create much of the geometric-induced flow patterns observed and postulated through various experimental designs (281). With regard to rostral-caudal spread of hydrophilic medications such as morphine, it has been demonstrated that a rather steep concentration gradient exists as samples are taken at points further removed from the catheter tip. The authors of this finding suggested that drug dilution over distance and drug concentration at the site of action may be important in providing analgesic efficacy (170). Given these data, simplistic views of CSF dynamics do not provide insight into the possible clinical implications of decisions made surrounding drug-infusion rate and drug dispersal within the CSF. Much of what is known clinically is derived from observations utilizing spinal anesthesia for surgical intervention (282). Despite this complexity there are some basic observations that have been reported in the literature that provide insight into the clinical utility of IT drug delivery flow-rate manipulations on treatment outcomes.

Basic Science

Detailed examinations of the effects of the flow rate in IT drug delivery have been conducted by the late C. Bernards in a porcine model (20). This model has a number of advantages over previous models in that it mimics IT therapy, namely a closed model with no CSF loss or disturbance due to sampling, preservation of the effect of cardiac and respiratory cycles, an upright position and the ability to study drug concentrations in both spinal fluid and spinal cord.

Bernards compared flow rates of 20–1000 mcL/hour and a bolus group receiving a bolus of 1000 mcL/hour administered more than 5 min every hour (20). These rates were chosen to be representative of regular and maximum clinical pump flow rate as well maximum speeds achieved by bolus administration. The most prominent finding was the limited distribution of bupivacaine and baclofen from the site of administration, especially in the 20 mcL/hour group. For both bupivacaine and baclofen, most of the drug recovered in the CSF and spinal cord in this group was found within 1 cm of the site of administration. Diffusion of both bupivacaine and baclofen in CSF or spinal cord parenchyma was increased in the 1000 mcL/hour and bolus groups compared with the 20 mcL/hour group. Evidence of greater distribution comes from the dose-normalized CSF area under the curve and spinal cord concentration data. Evidence that the bolus group achieved better drug distribution than did the 1000-mcL/hour group was more subtle but still present. Bernards concluded that CSF is a poorly mixed medium, that CSF motion is limited and that the spread of drug molecules in CSF is largely dependent on the kinetic energy imparted to the drug molecules by the infusing mechanism. The clinical implications of Bernards' work

Table 27. Recommendations Regarding Infusion Rate by the PACC Using USPSTF Criteria.

Statements	Evidence levels	Recommendation strength	Consensus strength
Rate of dispersion in cerebrospinal fluid cannot be attributed to diffusion alone.	II-2	B	Strong
Flow rate may not impact analgesia.	II-2	C	Weak
Bolus dosing may improve analgesia.	II-2, II-3	B	Strong

are that the location of the tip of the catheter relative to the targeted spinal cord segment may be critical given the limited capacity for CSF to distribute drugs away from the catheter tip. Limited distribution of morphine away from the catheter tip may predispose to formation of IT granulomas, and development of methods to improve drug distribution may decrease the risk of granuloma formation.

Flack et al. went on to confirm these findings in a chronic ambulatory pig model receiving IT morphine over a period of 14 days (90). In this experiment, four pigs were implanted with IDD systems and an infusion of morphine delivered at 20 mcL/hour. The authors concluded that the chronic data confirmation of limited CSF distribution in the ambulatory animal may help to explain clinical situations in which a drug delivered as an IT bolus at trial stage is effective at relieving patient symptoms but, when delivered at the very slow infusion rates used for chronic infusion, was not effective (i.e., pharmacokinetic failures of chronic IT drug delivery). Specifically, although bolus IT injection produces relatively widespread drug distribution, that was not the case with chronic infusions.

Clinical Studies

Two clinical studies have examined the effect of varying the infusion rate for baclofen and varied mixtures of analgesics, respectively. Both studies utilized a similar double-blind crossover design over two-week periods with a constant daily drug dosage throughout but an infusion rate varying at random from the patient's baseline rate to twice and four times this value. In the baclofen study van der Plas et al. (258) randomized patients who experienced no beneficial response or excessive side effects to intrathecal baclofen (ITB) infusion for dystonia to either slower infusion rate delivery or four-times faster infusion rate delivery (FIRD) for two weeks. Patients crossed over after a one-week washout period. The authors observed no significant differences between the two groups for the median change of numeric rating scale dystonia (−0.3 [interquartile range {IQR} −1.1 to 0.5]), pain (0.1 [IQR −0.8 to 1.3]). However, they found that the frequency of AEs was significantly higher during FIRD (12 vs. 2). Only patients who were included because side effects to ITB prevented dose escalation preferred FIRD. Investigators concluded that given a fixed daily dose, a four-times higher infusion rate enhances the IT distribution of baclofen as evidenced by the significantly higher number of AEs. However, in CRPS a fourfold higher infusion rate was not associated with clinically overt improvement of dystonia or pain. Patients in whom side effects restricted further dose escalations of ITB favored the faster rate because of subjective improvement of dystonia and pain. Therefore, the utility of a faster rate of delivery should be further investigated for this group.

To date no clinical studies have compared bolus to continuous infusion, although the authors understand that such an experiment is in progress (282).

The use of bolus dosing in addition to continuous flow is possible with commercially available IDD systems. One prospective registry of 168 patients suggested that patient-controlled bolus therapy with concomitant constant infusion resulted in improved patient satisfaction and reduced need for oral medication supplementation (241). Recently, it has been reported that patient-controlled IT analgesia with bolus dosing results in better patient satisfaction in cancer-related pain (282). No further work on bolus dosing with IDD has been done to our knowledge (283–285).

All told, these data suggest a lack of benefit from increasing infusion rate and, in fact, there may be a clinically significant deleterious effect, as decreased quality of life has been reported with increasing flow rate (283). The one preliminary report using intermittent bolus dosing in addition to constant infusion suggests a positive impact on patient outcomes but has not been replicated. Reck et al. demonstrated, in a blinded crossover study of ten patients comparing bolus to continuous infusion, a statistically significant reduction of numerical rating scores with intermittent, programmed, bolus delivery, compared to continuous infusion (286). No conclusions regarding safety and efficacy can be drawn from the limited data currently published. However, with the technology now available making it possible for bolus therapy in multiple applications to be provided to patients, this therapy is being utilized by increasing numbers of providers and data will be forthcoming. Caution and a conservative approach is advised when choosing to utilize intrathecal bolus therapy as our understanding of flow dynamics, oscillatory mechanisms and drug bioavailability are still evolving.

The PACC recommendations for infusion rate appear in Table 27.

Baseline Dose of Opioids: High vs. Low or None

The impact of oral opioid therapy on subjects trialed and implanted for IT therapy has been examined in several recent studies (14,15,100,198,284,285). The techniques surrounding management of oral opioid therapy in those considering IDD range from leaving the patient on oral opioids and adding IDD to pretrial/implant taper of opioid medications. Anderson et.al. in 2003 reported outcomes after taking subjects off opioids 12 hours before the trialing period (284). This was followed by several case studies that described various methods of tapering mediations during the trialing period (101,195). Shaladi et al. (198) lowered oral opioid doses as IT doses increased during the trial, while Kim et al. (100) discontinued opioids 4–12 hours prior to trialing.

Subsequent larger studies examined the role of eliminating oral opioids and the effects on the efficacy of IDD (14,15). Grider et al. in a small case study and later in a larger retrospective study reported discontinuing oral opioids for six weeks prior to trial/implant. In that study the pretrial VAS score on oral opioids was compared to the VAS following opioid taper and six weeks in an opioid-free state, demonstrating that patient-recorded VAS scores were virtually identical after discontinuation of oral opioid therapy (14). Hamza et al. likewise demonstrated analgesic efficacy in subjects trialed and maintained on low-dose IT opioids, with most subjects dramatically reducing or eliminating oral opioid use (15). However, it should be emphasized that studies on microdosing were not controlled or randomized. Such findings underscore the importance of RCTs.

Several studies have examined the impact of pretrial opioid use on postimplant IT analgesia. Kim et al. found that pretrial systemic

Table 28. Recommendations Regarding Patient Characteristics Affecting Intrathecal Therapy—Baseline Dose of Opioids, High vs. Low, by the PACC Using USPSTF Criteria.

Statements	Evidence levels	Recommendation strength	Consensus strength
Pretrial opioid dose does not appear to be predictive of intrathecal drug delivery outcomes.	II-3	C	Moderate
Effective sustainable analgesia is achievable with intrathecal drug delivery without systemic supplementation.	II-2	B	Moderate

opioid requirement was a poor predictor of IT dose, efficacy, or need to change medication at one year postimplant (100). This study did find that the trial IT opioid dose was a good predictor of success with IT therapy. Likewise, Mekhail et al. reported no link between systemic opioid requirement and efficacy with IT opioids (108). A recent analysis has suggested a significant cost benefit to the elimination of oral opioid therapy in those transitioning to IDD (103).

Taken together, these data suggest that the goal of limiting or eliminating oral opioid therapy in those transitioning to IDD can be accomplished in many ways. No large-scale trial has compared preimplant opioid cessation with postimplant cessation, however, in the two largest studies to date analgesic efficacy was achieved with both methods, albeit at lower doses in the pretrial taper study. There appears to be little value in the preimplantation opioid dose as a predictor of success with IT therapy (100,108). The impact on response to ziconotide based on preimplant opioids has not been determined.

The PACC recommendations regarding patient characteristics that affect IT therapy appear in Table 28.

PSYCHOLOGICAL CONSIDERATIONS

The general belief that identifying comorbid psychological factors, which could compromise treatment success, was borrowed from neurostimulation practice and guidelines and applied to IT therapy, especially in the noncancer pain setting. Nelson et al. in 1996 (287) proposed a list of "red flags" to success of treatment that included suicidality, alcohol or drug dependency, unresolved compensation/legal issues, severe depression, and so on, which, although not empirically derived, made sense clinically. This spurred a "rule-out" approach to the assessment for neuromodulation in general. More recent guidelines (56) have emphasized the assessment of positive characteristics such as proper expectation, social support, effective coping skills, and so on, and the importance of using psychological intervention before and after internalization of an IDD device. Some third-party payers mandate this screening process for authorization of the procedure.

Four questions summarize the practical considerations related to psychological assessment for IT interventions: 1) Should psychological evaluation be performed? 2) If so, when is the best time for evaluation? 3) Who should perform the psychological evaluation? 4) What are the best practice guidelines for psychological evaluation? These and other aspects of psychological screening are discussed more thoroughly in a PACC companion article on screening trials for IT therapy (118).

A review of the published IT literature from 1998 through 2010 reveals few psychological evaluations in the studies identified (288). Furthermore, there appear to be few, if any, systematic studies with sufficient follow-up to determine the contribution of psychological evaluation to outcome. There has also been criticism of reliance on psychological assessment as a component of the selection criteria (289). The continuing emphasis is on identification of predictive characteristics. Yet identification of patient states or traits that predict outcome is not scientifically valid. A more reliable approach is to assess for and identify psychological symptoms (e.g., depression) and/or psychiatric diagnoses (e.g., post-traumatic stress disorder), which could be barriers to a positive outcome.

As noted already, the approach to a patient with cancer-related pain should be somewhat more flexible. For patients with significantly compromised life expectancy (Category 1, Table 7), psychological evaluation should be considered optional. We encourage psychological evaluation for patients in whom the disease process has been arrested but there is a significant probability of reoccurrence (Category 2, Table 7). Patients whose cancer has been eradicated by appropriate therapies and continue to manifest chronic pain secondary to medical treatment/anatomical/disease-related damage, but wherein life expectancy is only minimally compromised, should be considered in the same context as chronic noncancer pain patients (Category 3, Table 7).

Consensus Point 24. Psychological assessment, counseling, and after care are recommended in appropriate candidates. The use of an assessment is critical in all noncancer patients receiving an intrathecal drug delivery system. An extensive discussion of the proper tools and techniques of this screening process is presented in the PACC trialing recommendations (118).

Consensus Point 25. Psychological screening is not required for end-of-life patients, but psychological counseling should be considered.

EDUCATIONAL REQUIREMENTS FOR IMPLANTING AND/OR MANAGING IDDS THERAPY

The extensive scope and breadth of this sixth edition of the PACC guidelines is a reflection of the growth of knowledge related to the safe implementation of implantable IT therapies. In addition to the rapid growth of the preclinical and clinical science knowledge, there has also been an increase in the number of commercially available implantable IDDSs. While all of these devices function by pumping medication from an implantable reservoir to the IT space via an implanted catheter, their propellant mechanism, MRI compatibility, and device-specific engineering limitations vary substantially. Rapidly advancing clinical and scientific knowledge combined with the variability of pump designs and function make it imperative that providers throughout the health care continuum are thoroughly trained and credentialed to provide appropriate and safe care to patients implanted with these devices. The specific training recommendations are largely dependent on the scope of practice of the individual provider, the disease state being treated, and the device

being used. Every patient should have a comprehensive pump manager who is accessible throughout the continuum of medical care. The NANS in partnership with the INS is focused on education and credentialing as a strategy to continue to improve safety and efficacy of these therapies by promoting improved implementation and maintenance training and assessment. Credentialing by the hospital site of service is currently the mechanism of certification, and inherently this is nonuniform.

First Responders

All health care providers, and especially first responders to disease or trauma, as part of their core curriculum and training, should be trained to identify patients with implanted systems. They should be aware that there are multiple different types of implanted systems, including pacemakers, SCS devices and implanted pumps, and should be able to distinguish between them. When an implanted infusion pump is suspected (most often large circular device vs. neurostimulator, pacemaker, or other smaller implanted device), the first responder should have information available to them and be trained to contact a pump manager or a representative of the pump manufacturer.

Suggested Training Milestones

Suggested training regarding implanted neuromodulation devices, their indications and the processes for monitoring and refilling them, should be performed in nursing schools, medical schools and schools that train allied health professionals. Likewise, this same information should be provided in continuing medical education courses for further education of these health care providers. Currently most programs in Europe, Asia, Australia, and the United States do not include this information.

Consensus Point 26. The PACC recommends an overview of intrathecal drug delivery be added to the basic curriculum of physicians in training, nurses, and allied health care professionals.

Pump Interrogator

All patients admitted to a medical facility should have their IDDS, medications, and daily dosage of IT medication documented as part of the medical record. For programmable pumps this often requires an electronic interrogation of the pump and documentation of the drug concentrations and delivery modes. Documentation of type and manufacturer of pump identification for drug delivery should be considered the standard of care prior to performing an MRI or pursuing elective surgery, and is imperative for all patients admitted to a hospital. The interrogator of the IDDS is expected to be appropriately trained to perform the following:

- Data gathering and communication skill set
- Interrogate an IDDS without altering programming
- Determine manufacturer, model, and when the device was implanted
- Determine the drug(s) and dosage(s) delivered in a day
- Determine the drug refill alarm dates
- Access and interpret alarm logs
- Contact a physician pump manager

Suggested Training Milestones and Credentialing for Pump Interrogators

Detailed didactic lectures reviewing all currently available devices and techniques for pump interrogation are essential. These lectures should include the x-ray imaging of all commercially available devices to better identify them for patients who are unable to provide detailed information regarding their pump. For credentialing purposes, a minimum of ten interrogations per year for each make is recommended prior to independently interrogating a pump without the assistance of an industry representative or another supervising provider. These ten interrogations can be performed in one setting as part of a hands-on training workshop. The PACC feels that most programs do not currently meet these standards.

Consensus Point 27. The PACC recommends each accredited facility have the ability to evaluate an indwelling implanted device, including pump and catheter system. We encourage manufacturers and facilities to collaborate on this important issue with a goal of meeting compliance by the next scheduled PACC in 2019.

Personnel Who Perform Maintenance and Programming/ Reservoir Refill of IDDS

Virtually all patients implanted with an IDDS will need pump interrogation and refill at regular intervals, whether they are inpatients, outpatients, or homebound patients. The provider of this service may or may not be the managing physician but should be under the supervision of a managing physician. The provider of this service is expected to be appropriately trained to perform the following and have a supervising IDDS physician pump manager. In many settings these tasks are accomplished by licensed nursing infusion company employees. These service providers should be properly trained and supervised.

Programming and Refilling Skill Set

- Perform pump interrogation and programming
- Safely perform an aseptic pump refill (preferably with and without image guidance)
- Diagnose and detect a pocket fill and notify a credentialed physician pump manager for management
- Identify residual volume discrepancies and notify a credentialed physician pump manager for management
- Be familiar with medication formulations that are appropriate and inappropriate for intrathecal drug delivery (PACC recommendations)
- Have supervision by a credentialed physician pump manager

Suggested Training Milestones

Training should include the detailed didactic lectures described above and should also include added lectures on the medication choices for IT therapy and pharmacodynamics and pharmacokinetics of IT drug delivery. Additional didactic lectures on the indications and contraindications for implementing IDDS therapy as well as evaluating and recognizing serious AEs such as pump pocket fills, granuloma formation, and signs and symptoms of medication over/ underdosage should apply. For training purposes, a minimum of 20 supervised pump refills is recommended for initial assessment prior to refills being performed independently. A minimum of ten pump refills per year is suggested to by consensus in order that physician pump managers maintain clinical competency for each make of device. If these minimums are not achievable for every make, the pump refill should be directly supervised by a physician pump manager, a credentialed nurse who has met these requirements, or by a manufacturer representative.

Consensus Point 28. The training of all personnel for device evaluation and refilling is an important part of patient care. This training should be device specific and supervised carefully. The PACC

recommends that 20 refills be supervised before independent practice is approved. Two or more trained individuals should check all reprogramming.

IDDS Implanting Physician

Intrathecal pump implantation and/or explantation requires basic surgical skills necessary to perform the procedure safely. Not all implanters are IDDS managers and not all mangers are IDDS implanters. In those cases, where the manager and implanter are not the same individual, the two providers should be in close communication regarding appropriate planning for the placement of the pump and catheter and to determine the concentrations and types of medications to be infused by the pump. In addition, prior to implantation, a designated manager must be identified and available to manage the pump immediately after implantation and to monitor for adverse side effects of IT medications. In cases of explantation, the manager should inform the explanter of the systemic medication to be delivered once the IDDS is removed. The IDDS implanter is expected to be appropriately trained to perform the following procedures and have a supervising IDDS physician pump manager available before the case to address potential drug overdose and underdose.

Implanter Skill Set

- Appropriately place a pump subcutaneously and tunnel a catheter from the pump site to the catheter insertion site
- Appropriate and complete medical training in the area of Pain Medicine or Surgery, with a focus on implantable technologies, recognized by the country and area of practice.[1]
- Diagnose and troubleshoot potential intraoperative surgical complications
- Diagnose and troubleshoot potential postoperative and chronic complications of IDDS therapy requiring surgical intervention, for example, granuloma formation, catheter breaks, catheter occlusions

Suggested Training Milestones

The implanter should have also completed the basic didactic training required of the refill provider as previously described. A minimum of ten supervised implant and/or explant cases should be performed under supervision of a credentialed implanter. Another five cases over the course of two years should be completed to maintain clinical competency. For intracerebroventricular placed catheters, implanter must be credentialed in neurosurgery.

[1]Special comment is necessary regarding the suggested formal medical and surgical education. As this manuscript serves as a living, international document, it is clear that no uniform credentialing body exists to measure (or test) specific training criteria over such a diverse group. However, basic skill standards can be measured. Each implanter must undergo appropriate surgical tissue management training, with specific experience with implanting IT therapy. Internationally, the World Institute of Pain (WIP) created an exam to standardize internationally delivered interventional pain management, and there is discussion surrounding this effort through the educational committee collaborations of NANS, INS, and WIP. In the United States, since the inception of an American Council of Graduate Medical Education (ACGME) certified training program in Pain Medicine and surgical subspecialties of Neurosurgery or Orthopedic Spine Surgery, it is recommended that implanters have underdone and completed such training. This recommendation, does not, however, impact "legacy or grandfathered" practitioners for whom no such training was available.

Consensus Point 29. In order to offer intrathecal therapies regardless of primary specialty, the physician should be supervised in a minimum of ten implant and/or explant cases.

Consensus Point 30. In order to maintain skills, the implanter should be involved in five cases more than two years, or should undergo additional hands-on certified educational training to refresh skills.

Physician Pump Manager

All patients with IT pumps should have a designated physician pump manager. This individual will provide the coordination of care amongst other providers across the health care spectrum.

Pump Manager Skill Set

- Be a leader who can manage therapy and complications associated with IDDS
- Diagnose and manage overdose and underdose (withdrawal syndrome)
- Perform dye studies, rotor studies, interpret imaging (fluoroscopy, CT, MRI)
- Understand the pharmacology of IT drug delivery
- Responsibilities include, but are not limited to: patient and device selection, pump fills, prescribing, altering therapy, interactions with non-IT medications and systems (e.g., MRI)

Suggested Training Milestones

If the manager is also the implanter this individual should meet all the requirements previously described, in addition to being competent at performing dye studies/side access port procedures for each make of pumps prior to performing management services independently. For specific manufactured devices where fewer than ten cases have been completed, another manager with skills in that device should proctor or assistance be obtained from the manufacturer. In addition to the information provided in the didactic lectures previously listed, the manager should also be knowledgeable about all of the advanced intrathecal pharmacokinetic and pharmacodynamic principles and current medical guidelines. This same knowledge base is required for the managers who are not implanters.

Consensus Point 31. The training to manage an intrathecal device is critical to the long-term success of the therapy. All pump management physicians should have ongoing educational training that includes knowledge of all current and FDA-approved devices and future devices approved by regulatory bodies for research, and found to be clinically relevant. Managing physicians who are not implanting physicians are expected to be trained at the same level as those who both implant and manage devices.

Consensus Point 32. To establish a national data base for all intrathecal pump-managing physicians or healthcare professionals as a repository of current pump settings, mediations, efficacy, and side effects.

CONCLUSIONS

The previous PACC work led to improved patient safety and efficacy and advanced questions that fostered additional IT drug research. In the same spirit, this present manuscript presents the next step in algorithmic thinking. The creation 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 PACC is hopeful that the time interval between now and our next update produces new insights in the field of IT drug delivery.

The creation of this consensus statement has depended heavily on available literature, clinical experience and scientific discourse. Despite our mechanisms used to create the best consensus recommendations possible, the final conclusions include a subjective component and may be controversial. The panel has addressed nociceptive and neuropathic pain pathways to best treat pain by IT infusion. The panel had considered a third pathway for mixed pain syndromes but considering the heterogeneous components of this complex patient group, the reader is advised to use best clinical judgment to choose the most appropriate pathway, with the realization that the patient may exhibit different components of pain at differing and various times.

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Authorship Statements

Dr. Deer served as primary author, project organizer and editor; Dr. Doleys, Falowski, Jacobs, Kim, and Narouze, performed literature searches; Drs. Deer, Hayek, Pope, Grider, and Erdek prepared evidence tables; Drs. Huntoon, Mekhail, and Krames served as senior editors; the remaining authors acquired or interpreted data, wrote sections of the manuscript, and provided critical reviews and editing.

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COMMENTS

This refreshing update to the Polyanalgesic Consensus Conference statement assembles current evidence in basic science, anatomy, physiology, engineering and patient care surrounding targeted drug delivery. Thirty concise and tangible recommendations are accompanied by useful flow charts, reference tables and decision trees providing guidance which can be considered for contemporary pain care in patients with targeted drug delivery systems.

The intrathecal pharmacopeia has expanded in this iteration with division of first line agents into 1A and 1B categories, and drug choices are now categorized by localized or diffuse pain conditions, as well as cancer or non-cancer related diagnosis. Most notably, the current version largely combines the previous neuropathic/nociceptive divisions presented in the 2012 consensus conference (1), instead focusing on anatomic location: diffuse or localized pain in patients with noncancer related pain.

Some guidance is sure to prove controversial; while, at times, other recommendations seem anecdotal. Ziconotide maintains a first line position in both algorithms, yet sales of ziconotide demonstrate a shrinking year-over-year minority of real-world use (2), and may continue to decrease with increasing attention on healthcare cost containment. Sufentanil monotherapy is recommended for cancer and other terminal pain conditions, but there is never a recommendation to use fentanyl monotherapy in these same patients. Bupivacaine monotherapy is placed second line for localized non-cancer pain, but never appears in isolation for the treatment of cancer related pain conditions. At times, the reader is left wondering: what is anecdote, experience or evidence?

Amongst the most demanding components of physicianship is the task of applying a paucity of high-quality clinical evidence to each unique patient at the bedside. Regardless of the comprehensiveness of any consensus committee recommendation, clinicians will continue to be required to formulate treatment plans in the absence of a randomized double-blind placebo controlled trial mimicking the patient before them. Perhaps the most notable conclusion upon reading the consensus statement is how few rigorous, well designed clinical studies exist to support clinical practice. With a growing number of patients suffering with chronic pain (3), and an observed quadrupling of deaths associated with oral opioids (4), the time is ripe for interventional pain physicians to demand funding of high-quality studies to support contemporary pain care.

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For many years the Polyanalgesic Consensus Conference recommendations are an important contribution to the management of intrathecal therapy. Again, the new version has been thoroughly revised and includes all relevant features of intrathecal therapy. Of course some points have to remain unanswered and one issue that can always be argued on is the "lines" of intrathecal drugs to choose, especially since there is an almost infinite number of possible combinations. In the end, every physician has to make an individual choice based on pain- and patient characteristics, and a recommendation can only be somewhat of a blueprint.

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The Polyanalgesic Consensus Conference recommendations on intrathecal drug delivery is a living document that continues to impact clinical practice and guide future research. The fifth iteration of these recommendations are patient-centered and crafted in a manner that condenses the last four years of IDDS research into a practical resource for practicing clinicians.

Critical assessment of evidence from multiple studies are necessary when making decisions in day to day practice. Medical literature is immense and not all information is clinically useful. The 2016 guidelines systematically ranked evidence based on the hierarchy of studies. Expert consensus was measured and the degree of recommendations were defined. Research gaps were also identified which will hopefully lead to scholarly queries and future investigations. I commend the authors for their work.

While appropriate patient selection has been identified as one of the most important factors for a successful outcome when initiating intrathecal therapy, long term management of the intrathecal device poses several challenges. Pain patterns may change due to an ongoing disease process or changes in psychological status years later. Non-medical determinants of health, such as social and economic status, may strain the delivery of needed services to maintain an intrathecal device.

Guidance regarding long term management of the intrathecal device was briefly addressed in this manuscript, but more detailed recommendations would be useful. For example, at what point should a clinician

consider discontinuation of intrathecal therapy because of lack or loss of efficacy? Is there a consensus on the timing of intrathecal therapy rotation from one opioid to another or from an opioid to Ziconotide or to combination therapy? Is there consensus on the benefit or lack there of for trailing a different intrathecal medication before rotation? Many of us have been faced with these decisions while in the trenches of clinical practice. We want to salvage this therapy which was at one point efficacious, but never ask ourselves when is enough really enough? For many clinicians with large intrathecal pump practices, long term management is probably even more complex than the initial identification of an appropriate candidate. Successful outcomes rely upon discovering the science behind the art of managing the complexities of a long term intrathecal pump.

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

