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The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks

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Introduction: Intrathecal therapy is an important part of the pain treatment algorithm for chronic disease states. The use of this option is a viable treatment strategy, but it is inherent for pain physicians to understand risk assessment and mitigation. In this manuscript, we explore evidence and mitigating strategies to improve safety with intrathecal therapy.

Methods: A robust literature search was performed covering January 2011 to October 9, 2016, in PubMed, Embase, MEDLINE, Biomed Central, Google Scholar, Current Contents Connect, and International Pharmaceutical Abstracts. The information was cross-referenced and compiled for evidence, analysis, and consensus review, with the intent to offer weighted recommendations and consensus statements on safety for targeted intrathecal therapy delivery.

Results: The Polyanalgesic Consensus Conference has made several best practice recommendations to improve care and reduce morbidity and mortality associated with intrathecal therapy through all phases of management. The United States Prevention Service Task Force evidence level and consensus strength assessments are offered for each recommendation.

Conclusion: Intrathecal therapy is a viable and relatively safe option for the treatment of cancer- and noncancer-related pain. Continued research and expert opinion are required to improve our current pharmacokinetic and pharmacodynamic model of intrathecal drug delivery, as this will undoubtedly improve safety and efficacy.

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INTRODUCTION

Advances in pain management technology and clinical care are rapidly evolving. New indications, manufacturers, technologies, and evolving clinical evidence for intrathecal therapy (IT) guide the clinician in making choices that may improve outcomes, including safety and efficacy. The role of intrathecal drug delivery (IDD) in treating refractory pain has become a standard of care (1,2), and IDD serves as an essential strategy for a community and patient-centered pain practice. This Polyanalgesic Consensus Conference (PACC) update on improving safety and mitigating the risks of IDD is one of three companion pieces intended to improve outcomes (3,4).

METHODS

The PACC convened in 2014 to refresh its previous publications (5,6) and provide recommendations based on new evidence. The PACC members were drawn from the membership of the International Neuromodulation Society, with the strict criteria of substantial authorship in peer-reviewed journals, participation in basic and clinical research, and clinical experience with IDD. The PACC operated as a working consensus group and met the authorship publication criteria of the journal *Neuromodulation* and Wiley Publishing, conforming to the International Committee of Medical Journal Editors standards.

Literature Search Methods

A robust literature search was performed to identify publications since the PACC of 2012, searching, in addition to articles identified previously, from January 2011 to October 2016, in PubMed, Embase, MEDLINE, Biomed Central, Google Scholar, Current Contents Connect, and International Pharmaceutical Abstracts. Key search words included: intrathecal, intraspinal, drug delivery, safety, risks, morphine, ziconotide, fentanyl, alfentanil, sufentanil, methadone, adenosine, hydromorphone, meperidine, gabapentin, baclofen, ketorolac, midazolam, neostigmine, octreotide, ropivacaine, dexmedetomidine, clonidine, bupivacaine, and lidocaine. Each member of the PACC performed independent literature searches and the information was cross-referenced and compiled for evidence analysis and consensus review, using the strategy outlined previously (5,6) and evidence assessment as described in Tables (1–3), and Figure 1. All unreferenced contributions were defined as opinion and diverted to the consensus panel for consideration and review.

Evidence Ranking

Recommended evidence synthesis methods were utilized, applying the validated evidence-ranking system of the United States Preventative Services Task Force and set out in Tables 1 and 2.

The executive committee compiled the completed evidence assessment forms prepared by authors of each per section (Fig. 1), and compiled the results for the working group for consensus development. The consensus recommendation strength determination was created through in-person meetings and/or via teleconference with a quorum of 80% of all the contributing authors. Consensus rankings were categorized as strong, moderate, or weak, as defined in Table 3.

Arguably, this article serves as a critical piece in the PACC offering of 2016, and great care was taken to respect the data acquisition and consensus development, allowing for confidence when applied clinically. However, as stated previously in the PACC papers, this living document should serve as a guide in the development of a standard of care, but individualized clinical decision-making is recommended.

To guide the discussion surrounding safety, we will focus on key aspects of IDD therapy, including patient management, medications, and procedural and biologic challenges with trialing, implantation, maintenance, and explantation. Device-related complications and failures will also be reviewed, with the goal of offering guidance for avoidance and mitigation.

Table 1. Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force, Ref [7]).

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.

TARGETED INTRATHECAL DRUG DELIVERY IN PERSPECTIVE

Intrathecal therapy is a valuable tool to manage refractory pain, although the risk-benefit assessment of IDD therapy has been questioned in recent years for the treatment of noncancer-related pain and for long-term opioid infusion (8). Coffey et al. highlighted challenges with IDD therapy, demonstrating higher mortality compared with spinal cord stimulation (SCS) or lumbar laminectomy, as well as iatrogenic concerns with opioid overdose, and critical issues surrounding device implant, replacement, programming, and maintenance (9). Recently, an analysis of closed claims in the United States was performed for advanced implantable technologies for SCS and IDD therapy, revealing that most serious events were related to IDD therapy and continued to occur during follow-up and maintenance, specifically medication administration errors and delayed granuloma detection (10). In addition, the Official Disability Guidelines recently suggested eliminating IDD therapy for noncancer pain, including low-dose and patient-controlled bolus options. Recent research describing these strategies offers a different, more patient-centric point of view that supports continued use of IT therapy for noncancer-related pain.

Table 2. Meaning of Recommendation Degrees (U.S. Preventive Services Task Force, Ref [7]).

Degree of recommendation	Meaning
A	Highly recommended (good evidence that the measure is effective and benefits outweigh the harms)
B	Recommended (at least, moderate evidence that the measure is effective and benefits exceed harms)
C	Neither recommend nor advise (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified)
D	Not advisable (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.

Table 3. Strength of Consensus.

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

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

Evidence levels, recommendation grades and consensus strength from the most recent PACC update appear in Table 4 and apply to treating cancer- and noncancer-related pain (3).

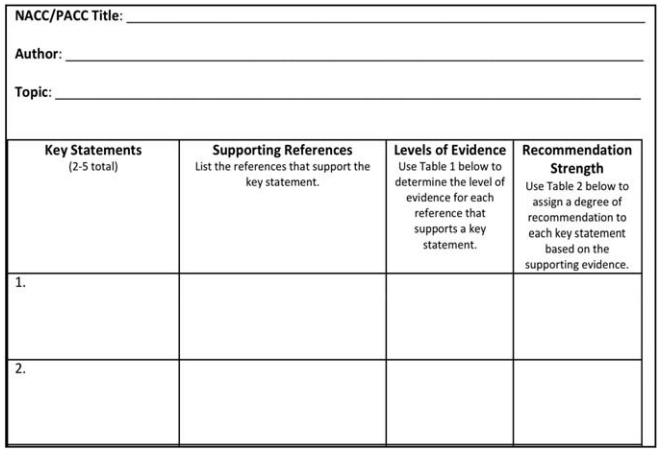
When discussing IT therapy, it is often assumed that the treatment benefits greatly outweigh the risks for treating cancer-related pain but not for treating noncancer-related pain. Given reports of adverse events (AEs) and concerns of reviewing bodies, employing chronic intrathecal infusion with opioids is at a critical juncture. Notwithstanding, many important facets are commonly overlooked. First, understanding of the complex pharmacokinetics of the IT space has improved significantly (11), and hence the ability to improve outcomes has been enhanced. Second, the morbidity and mortality attributed to IT opioids is markedly less compared to systemic opioid delivery. A recent postmarket analysis of 6398 patients demonstrated no opioid-related deaths attributed to IT infusion delivery over a ten-year period (12). Considering that systemic prescription opioid deaths number nearly 19,000 annually in the United States, IDD is potentially a safer patient option (13). Furthermore, IDD is not only a necessary treatment line to offer refractory, chronic pain patients, but IDD should be encouraged.

Consensus Point 1. The risk to benefit ratio of IDD makes it a relatively safe therapy for both cancer- and noncancer-related pain.

Consensus Point 2. IDD, as compared to chronic, long-acting systemic opioid therapy, is markedly more safe and has less associated morbidity and mortality.

MEDICATIONS USED IN INTRATHECAL DRUG DELIVERY FOR PAIN

The PACC of 2012 (5,6), and the current PACC companion articles to this manuscript (3,4), have provided an updated treatment algorithm, including an extensive evaluation and discussion of evidence,


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.			

Figure 1. Contributor evidence assessment.

Table 4. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations on Intrathecal Therapy (3).

Statement	Evidence level	Recommendation grade	Consensus strength
Intrathecal therapy should be utilized for active cancer-related pain.	I for opioids; I for ziconotide	A	Strong
Intrathecal therapy should be utilized for noncancer-related pain.	III-2 for opioids; II-3 for opioids in combination with bupivacaine; I for ziconotide	B	Strong

for intrathecal medications (3). The United States Food and Drug Administration (FDA) has approved only two intrathecal agents for pain relief: preservative-free morphine (Infumorph) and the conotoxin peptide ziconotide (Prialt). Additionally, baclofen (Lioresal, Gablofen) is approved for spasticity management, but this indication will not be addressed here. Other standard-of-care IT agents, such as the local anesthetic bupivacaine, alpha-2 agonists, and the opioids hydromorphone and fentanyl are often used off-label (3). Intrathecal drug delivery may result in AEs related to administered agents; indeed, pharmacological complications may be the most common cause of AEs in IDD (14).

Opioids

Intrathecal delivery of opioids may be associated with a number of side effects. The most serious remains respiratory depression, which may lead to death (9). Respiratory depression most often occurs with initiation of IT opioid therapy or restarting IT opioids after an interruption (15). Risk may be higher with hydrophilic opioids, such as morphine, and in cases where other central nervous system (CNS) depressants, such as benzodiazepines, are used concomitantly (16). Cardiopulmonary depression is potentially the most catastrophic complication associated with IT opioid delivery. As described in both companion papers, conservative dosing is recommended (3,4). When symptoms such as somnolence occur, reduction, elimination, or reversal of the opioid is indicated, with observation of the patient also recommended (9,17). Naloxone should be administered as required and re-dosed to prevent continued opioid depression, as dictated by the specific pharmacokinetic profile of the opioid used (18). Trialing opioid therapy in an outpatient site of service using a conservative dose has recently been recommended by the PACC. The recommendation to use a morphine dose of 0.15 mg as a single-shot injection is unlikely to produce respiratory depression, defined as a $PaCO_2$ greater than 40 or a respiratory rate less than 10 breaths per minute (3,4). Similarly, respiratory depression is unlikely with doses of dilaudid at 0.04 mg and fentanyl at 25 mcg (3,4).

Sudden interruption of opioid infusion as a result of catheter or device malfunction may result in opioid withdrawal (19). Similar to oral opioids, IT opioids may also be associated with nausea, vomiting, pruritus, constipation, urinary retention, and neuroendocrine dysfunction (20). Indeed, long-term opioid therapy may result in suppression of the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis (21). Compared to a similar chronic pain group of 20 patients not receiving opioids, the majority of 73 patients receiving IT opioids suffered from decreased libido (23 of 24 men and 22 of 32 women) (22). The average daily dose of IT morphine was 4.8 mg and the average duration of treatment was 26.6 months. Irregular menstrual cycle or amenorrhea occurred in all 21 premenopausal women and ovulation occurred in only one woman. Serum hormone levels were significantly decreased in the IT opioid group compared to the nonopioid group.

Intrathecal opioids may also produce lower extremity edema, even at low doses (23–25). While the mechanism of opioid-induced edema is poorly understood, it is hypothesized that cephalad migration of hydrophilic opioids, such as morphine or hydromorphone, stimulates posterior pituitary secretion of vasopressin, resulting in water retention and peripheral edema. A number of techniques have been recommended to manage peripheral edema related to IT opioid administration, including compressive stockings, diuretics, opioid dose reduction or discontinuation, and opioid rotation (6,23). A recent case series described successful resolution of IT hydromorphone- or morphine-related peripheral edema by rotating the opioid to low-dose fentanyl, although more controlled prospective data are needed (25).

Urinary retention is a known complication of administering IT opioids, resulting from sphincter spasm. Although adapting postsurgical results to a population receiving chronic infusion may not accurately reflect the experience with long-term administration, a review of 30 patients who underwent orthopedic surgical procedures, receiving 0.2 mg morphine with hyperbaric bupivacaine or bupivacaine alone, demonstrated that the morphine group had higher rates of catheterization, longer catheter retainment, and longer time to micturition compared to the group receiving local anesthetic alone (26). In a similar review of 1306 anesthetic records between October 2010 and April 2011, the incidences of nausea, vomiting, and pruritus were 21.5%, 14.8%, and 59.5%, respectively, for doses of IT morphine of less than 0.3 mg. Intrathecal doses greater than 0.2 mg increased the incidence of side effects (27).

Development of IT catheter tip granuloma is a complication unique to IT opioids with potentially serious neurological deficits. Granuloma formation and risk mitigation are discussed later in this article. The PACC recommendations for opioid therapy appear in Table 5.

Ziconotide

Ziconotide is a 25-amino acid peptide that is the synthetic form of a marine snail conotoxin and possesses a high blocking affinity to the neuronal N-type voltage-sensitive Ca^{2+} channel in the CNS. It is the only FDA-approved nonopioid medication for IT use (28), and has been extensively studied in three randomized controlled trials and an open-label study, and described in multiple pharmacologic reviews (29–38). Ziconotide has a narrow therapeutic window and requires careful and strategic dosing for efficacy and for reducing side effects (39,40). Rapid titration has been associated with cognitive and neuropsychiatric AEs (41). While the recommended daily maximal dose is 19.2 mcg, much higher doses have been accidentally administered, reportedly without long-term consequences (42). CNS AEs include nausea, nystagmus, dizziness, dysmetria, ataxia, agitation, hallucination, and coma (43). The neuropsychiatric AEs may occur after many months of asymptomatic infusion and represent the main reason for ziconotide discontinuation (44). It should be noted that abrupt discontinuation of ziconotide does not result in withdrawal or

Table 5. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations for Intrathecal Opioid Therapy and Risk Mitigation.

Statement	Evidence level	Recommendation grade	Consensus strength
Intrathecal opioid delivery is a relatively safe and effective method for chronic infusion to treat cancer and noncancer-related pain.	II-2	A	Strong
Respiratory depression can occur with intrathecal opioid administration, and careful dosing is critical to avoid this complication.	II-3	B	Strong
Concurrent use of sedative medications in patients receiving opioids should be minimized or avoided.	II-2	A	Strong
Single-shot trialing with intrathecal opioids is a safe strategy, with an observation period of at least six hours, in an outpatient or inpatient site of service. Outpatients should have continued observation after discharge with a responsible adult.	II-3	B	Moderate
Endocrinopathic side effects are a consequence of intrathecal opioids, and preoperative surveillance and monitoring is recommended.	II-3	A	Strong
Lower extremity edema can occur by an unknown mechanism and can be mitigated by transition to a more lipophilic opioid.	III	C	Strong
Urinary retention is a complication that may be mitigated by the administration of parasympathomimetic medications.	III	C	Moderate
Nausea, vomiting, and pruritus are consequences of intrathecal delivery of opioids and, although they typically resolve with time, should be considered when employing opioids for chronic infusion.	III	C	Moderate
Consideration of patient candidacy for intrathecal opioid therapy is crucial, and evaluation should consider the pain generator(s), patient age, location and type of pain, previous opioid exposure, and patient comorbidities (3).	II-2	B	Strong

rebound effects. Although elevation in serum creatinine kinase can be seen in up to 40% of the patients, significant elevation typically occurs in the first two months after initiation of ziconotide therapy and only three cases of rhabdomyolysis have been described (45,46). Periodic monitoring of creatinine kinase should be considered if patients have symptomatic muscle weakness while receiving IT ziconotide (45). There is no antidote for IT ziconotide overdose. However, overdoses up to 912 mcg/day were reported in clinical trials with no evidence of respiratory depression, and most patients recovered within 24 hours after the infusion was stopped (45).

It has been suggested that ziconotide should be first in pump, as longevity and efficacy of the monotherapy appear to be greater than if ziconotide is introduced later in IT therapy (47). Furthermore, other ziconotide infusion strategies have been suggested to improve longevity of monotherapy (48). Hayek et al. published on ziconotide longevity in three patients who received ziconotide first; two continued on therapy at the conclusion of the study follow-up (44). However, six of eight patients in whom ziconotide was added as an adjuvant to existing intrathecal medications experienced predominantly neuropsychiatric effects necessitating removal of ziconotide.

Off-label applications are common practice when trialing ziconotide. As referenced in the companion article on trialing (4), single-shot bolus trials are advocated for in the evaluation of candidacy for ziconotide IDD. PACC recommendations for ziconotide appear in Table 6.

Consensus Point 3. Ziconotide should be considered as a first choice in the treatment of cancer- or noncancer-related pain, in the absence of psychiatric comorbidity or significant baseline renal disease.

Clonidine

Clonidine is an alpha-2 adrenergic agonist that possesses analgesic properties with spinal administration, especially in neuropathic pain (49–52). Clonidine use may be advantageous intrathecally as it lacks respiratory-depressant effects, urinary retention, gastrointestinal effects, pruritus, or sensorimotor blockade. Clonidine, in combination with morphine, was associated with granuloma in a case report (53). Clonidine also has significant cardiovascular effects, peripheral edema, and may cause sedation in a dose-dependent fashion (52). Clonidine can cause hypotension at lower doses and, paradoxically, hypertension at higher doses, likely through a peripheral vasoconstrictive effect (54–56). Clonidine discontinuation can lead to severe withdrawal reaction including life-threatening hypertensive crisis and stress-induced cardiomyopathy (57). Accidental massive injections of clonidine in the subcutaneous tissue during pump refills have been reported in two cases—12,240 mcg in one case and 18,000 mcg in the other (58,59). Both patients experienced rapid loss of consciousness, myocardial infarction within 24 hours and blood pressure instability with episodes of hypertension and hypotension—among other complications. Initial symptoms of oral clonidine overdose include sedation and feeling of dizziness, followed by varied manifestations of hypothermia, altered consciousness, apnea, miosis or mydriasis, bradycardia, and fluctuations in blood pressure (60). PACC recommendations for clonidine appear in Table 7.

Bupivacaine

Bupivacaine is a lipophilic local anesthetic that blocks sodium channels. It possesses a sensorimotor differential neuronal blockade, whereby at lower doses or concentrations bupivacaine predominantly blocks the smaller nerve fibers involved in pain conduction; higher doses/concentrations block larger nerve fibers involved in touch perception, and even higher doses/concentrations block motor nerve fibers (61). Hence, use of bupivacaine intrathecally (usually in admixtures) has been associated occasionally with numbness and rarely with weakness (62). A case reported that an IT catheter-tip chalk-like white precipitate mass was excised adjacent to an

Table 6. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations on Intrathecal Ziconotide Therapy and Risk Mitigation.

Statement	Evidence level	Recommendation grade	Consensus strength
Ziconotide has no cardiopulmonary side effects when delivered intrathecally.	I	A	Strong
Ziconotide use is contraindicated in patients with a history of psychosis.	I	A	Strong
Ziconotide can cause predictable increases in creatinine kinase and it is recommended to perform baseline laboratory testing prior to initiation, and repeat testing if muscle-related symptoms occur.	I	B	Strong
It is recommended that ziconotide therapy be introduced initially if appropriate (or "first in pump") and not as an adjuvant therapy.	I	A	Strong
Ziconotide needs to be titrated slowly with recommended amounts of less than 1 mcg/day each week.	II	B	Moderate
If side effects occur, and depending on their severity, titration to half the dose with continued infusion may be helpful.	III	C	Strong

inflammatory mass in a patient receiving a mixture of clonidine (1500 μg/mL), hydromorphone (10 mg/mL), and bupivacaine (20 mg/mL) for 14 months (63). Prior to that admixture, the patient received IT morphine monotherapy for seven years. Bupivacaine is known to precipitate in the presence of sodium bicarbonate (64), but this was unlikely in this case. In addition, bupivacaine has been shown to be stable in admixture with opioids and clonidine (62,65,66). The authors hypothesized that the presence of an adjacent catheter tip mass may have altered local infusate mixing with the CSF, resulting in bupivacaine precipitation (63). PACC recommendations for bupivacaine appear in Table 8.

Compounding

For IDD there is considerable need for pharmacy compounding of preservative-free custom formulations of medications. Commercially available medications approved by regulatory bodies, including those in Europe and the United States FDA, have undergone comprehensive testing in animal and human subjects demonstrating safety and efficacy, while the manufacturing process is continuously evaluated to ensure high quality standards are met (67). In the United States, pharmacy compounding is not regulated by the FDA but rather by state boards of pharmacy, incorporating the United States Pharmacopeia (USP) chapter Pharmaceutical Compounding—nonsterile and sterile preparations (67). As the FDA does not regulate these processes, quality assurance is left to the individual pharmacy. 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.

The USP classifies manipulations of sterile products in aseptic conditions as low-risk compounding; however, addition of nonsterile components would constitute high-risk compounding (67). With regard to 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 (67–69).

The last PACC 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 (68). Debate concerning the use of compounded medications continued, since essentially all medications could be construed as compounded to some degree (70). Around this time, one IDD device manufacturer reported that off-label medications or admixtures could result in corrosion to the infusion system and device failure (71). 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 (70).

In 2013, a joint statement by thought leaders from the North American Neuromodulation Society and the American Society of Interventional Pain Physicians presented the viewpoint of many physicians experienced in IDD—that IT formulations with hydromorphone, fentanyl, and other opioids are more effective with improved side effect profiles compared to morphine (70). In addition, this position statement reconfirmed the use of admixtures of bupivacaine and clonidine as outlined previously by PACC (68). The stall rate for SynchroMed pumps (Medtronic plc, Minneapolis, MN) was reported at 2.4% for approved medications (Infumorph, Lioresal and Prialt) at

Table 7. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations on Intrathecal Clonidine Therapy and Risk Mitigation.

Statement	Evidence level	Recommendation grade	Consensus strength
Clonidine is recommended as an adjuvant for both nociceptive and neuropathic pain management with intrathecal infusion.	II-3	B	Strong
Clonidine dosing can cause cardiac effects and patients should be monitored during titration.	II-2	A	Strong
Withdrawal from intrathecal clonidine can cause hypertensive crisis, and reinitiating therapy or systemic dosing is critical for treatment and supportive care.	II-3	B	Strong

Table 8. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations on Intrathecal Bupivacaine Therapy and Risk Mitigation.

Statement	Evidence level	Recommendation grade	Consensus strength
Bupivacaine is a helpful adjuvant for IDD and is recommended in the first tier of medication selection.	III	C	Strong
Bupivacaine can mitigate opioid escalation and should be considered in patients whose doses are rapidly escalating.	II-3	B	Strong
Bupivacaine titration can result in urinary incontinence, numbness and weakness at higher doses, and patients should be monitored.	II-3	C	Strong

five years and 4.5% for unapproved medications (71). The group 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.

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 (72), IDD essentially mandates use of compounded medications. Indeed, according to the Medtronic *Product Performance Report*, at one year after implant, less than 16% of implanted pumps had on-label medication (369 on-label vs. 1999 off-label) and 6% at year 5 after implant (30 on-label vs. 475 off-label) (72). According to the same report, the SynchroMed II pump failure rate at five years with on-label drugs is 2.8%; while it was 5.3% at five years with off-label drugs and 3.6% at four years. A recent report from a tertiary care center identified 13 pump failures in 144 SynchroMed II implants, a rate of 9% (73). The median time from implant to pump failure in the 13 cases was 48 months. Thus, it would be prudent to diligently monitor patients receiving IDD for the presence of motor stalls or therapy disruption. PACC recommendations for compounding appear in Table 9.

Consensus Point 4. Strict sterility and quality assurance are a necessity when delivering medications into the IT space, with increased vigilance when compounded medications are employed.

INTRATHECAL CATHETER TIP GRANULOMA FORMATION: RISK MITIGATION

Intrathecal catheter tip granuloma (ICTG) is a complication of IDD that can be quite devastating for patients. Granulomas are sterile inflammatory masses that develop proximal to the IT catheter tip. The mass consists of inflammatory cells and fibroblasts. Progressive enlargement of these IT masses can produce a mass effect on the spinal cord and induce spinal cord changes that can be potentially irreversible. Clinically, worsening pain, sensory loss, motor deficits and bowel and bladder dysfunction manifests ICTGs, which are similar to progressive compressive myelopathy. Considering the severity of the ICTG, early diagnosis and potential identification of risk factors and risk mitigation are of paramount importance. Most ICTG cases reported to date involve the use of IT morphine; however, a significant number of reports confirm observation of ICTG granulomas with IT hydromorphone, other IT opioids, clonidine (53), baclofen, and tramadol.

Pathology of Intrathecal Granulomas

The ICTG represents a mass that forms around the catheter proximal to the infusion point. These masses arise from the dura-arachnoid around the catheter tip and not from the underlying pia. Accordingly, there is often a plane of dissection between the granulomatous mass and the underlying cord. In humans (74) and animals (monkey, sheep, dogs, and guinea pigs) (75–78), the mass secondary to IT morphine infusion consists of an aseptic collection of macrophages, plasma cells, eosinophils, lymphocytes, and predominantly fibroblasts in a maturing collagen matrix. An important point is that studies using morphine indicate a close parallel between the characteristics of the IT masses observed in humans and those in animals.

Incidence of Intrathecal Granuloma

Data on IT granuloma incidence in literature are fragmented. Since North et al. (79) reported the first granuloma formation in 1991, there have been many articles describing inflammatory mass lesions at the tips of IT catheters, mostly in the form of case reports or case series (80–82). Between 1990 and 2000, Medtronic reported 41 cases of ICTGs through postmarketing surveillance to the FDA. From October 2000 to September 2007, 448 more cases of ICTGs have been reported. However, the denominator from which all the granuloma cases derived is not well defined. In a cohort of 56 patients, Duarte et al. reported an incidence of 7% ICTG in subjects treated with IT morphine or diamorphine (81). Veizi et al. described ICTGs in six of 69 patients treated with an IT hydromorphone admixture with bupivacaine for an incidence of hydromorphone-related ICTG of 8.7% (83). Overall, IT catheter tip granulomas reportedly occur at lower rates, though these numbers are believed to be conservative estimates of the actual prevalence as they are often based on the reporting of patients who have developed neurological signs (84–86). It is noteworthy that in one case series, an IT mass was diagnosed in one of seven infusion patients as evidenced by neurological signs (85),

Table 9. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations on Compounding for Intrathecal Therapy and Risk Mitigation.

Statement	Evidence level	Recommendation grade	Consensus strength
Compounded medications have been identified as a causative agent for increased risk of pump failure in the SynchroMed II pump, and care should be exercised when employing them in a regimen.	I	A	Strong
Compounded medications and polypharmacy have not resulted in early device failure with the Flowonix Prometra II pump to date.	II-3	A	Moderate
Solubility decreases unpredictably when multiple medications are combined in one solution.	II-3	B	Strong

although the first symptom is usually back pain near the tip of the catheter. Subsequent imaging of all seven patients revealed asymptomatic masses in two. Actual numbers are thus likely higher, given sporadic and voluntary reporting and lack of clear recommendations on screening or routine imaging of asymptomatic patients with undiagnosed ICTGs. ICTGs may also recur after surgical removal and changes in flow and infusion patterns have been made (87). Larger multicenter registries are needed to determine the real incidence and risks of developing granulomas, which should be taken into account when counseling patients on risks and benefits of targeted IT drug delivery with morphine or hydromorphone.

Consensus Point 5. The prevalence of granuloma varies, but may be as high as 8% in published reports, with the actual prevalence unknown. Any neurologic deterioration, new-onset neurologic symptoms, or decreased efficacy need to be interrogated for granuloma if granulomagenic (or inflmatory mass inducing) medications are employed.

Etiology of Intrathecal Granulomas

Intrathecal granulomas are localized in the rostrocaudal axis with the largest girth of the mass observed at the catheter tip, rather than along the subarachnoid catheter (74,75,79). While catheters have been reported to result in an IT reaction (76,78), this particular anatomic profile argues against the hypothesis that ICTG is a delayed hypersensitivity reaction to the material of the catheter (88) or even that it is a somehow related to surgical trauma during the implantation. Furthermore, saline infusion is not usually associated with granuloma formation (75–78). In MRI dog studies carried out at multiple times, substitution of saline for the morphine infusion resulted in at least a partial resolution of the mass (89), which argues against the catheter as the triggering factor of ICTG formation. Preclinical and clinical literature suggests that the mass is not associated with positive bacterial cultures or gram stains in humans or animal models (74,90).

In humans, ICTGs have occurred with IT infusions of morphine (74,79,86,91–109) or hydromorphone (86,110). In contrast, though less widely employed for IT infusions and with one exception (111), no granulomas have been reported in patients receiving IT admixtures with fentanyl as the IT opioid. Preclinical studies support clinical observation. Using a canine experimental model, IT granuloma formation was shown to occur following IT infusion with morphine or methadone but not in fentanyl or alfentanil-infused dogs (89,107,112). The fact that some, but not all, opiates produce a granuloma suggest the effect is independent of an opiate receptor. This suggestion is further supported by the observation that concurrent treatment with an opiate antagonist does not alter granuloma mass size or time of onset with IT morphine (113).

Consensus Point 6. Granuloma has been identified with IT delivery of medications, including morphine, hydromorphone, bupivacaine, sufentanil, baclofen, and tramadol.

Intrathecal infusion of the N-type calcium channel blocker ziconotide (Prialt) in preclinical studies failed to display IT mass formation (114), and to our knowledge mass formation has not been associated with IT ziconotide use in humans.

Consensus Point 7. Ziconotide is not associated with the formation of granuloma to date.

Dose and Concentration

Systematic studies with morphine in dogs have shown that the total dose was of less importance than concentration. The overall incidence of histologically defined granuloma rises with local concentration, but granulomatous reactions were indeed noted even at the lowest concentrations (75,89). This is supported by recent clinical reporting of ICTGs occurring in four patients receiving fairly low doses and concentrations ($\leq$1 mg/mL) of IT hydromorphone (83).

Duarte et al. performed a rigorous retrospective analysis of 56 patients (25 with well-described ICTG compared with 31 clinic patients without granuloma) in the United Kingdom and found a correlation between increasing morphine or diamorphine dose and granuloma formation (81). Four of the 56 patients had ICTGs with one patient receiving only IT morphine and three patients receiving IT diamorphine. Diamorphine, also known as diacetyl morphine or heroine, is not available for clinical use in the United States. The authors concluded that the relative risk of ICTG increased with the dose and concentration of opioids. However, rate of flow and catheter tip location were not associated with risk of granuloma formation.

Patient Age and Granuloma Formation

McMillan and colleagues compared three patients with ICTG (two asymptomatic) detected by CT myelography to four patients without ICTG on imaging and suggested that ICTGs occurred in younger patients on higher doses of morphine (85). However, no other study reported age as an independent risk factor for granuloma formation. Younger age could be a factor in opioid escalation, with younger subjects escalating opioid requirements faster than older patients (115), and that can potentially predispose to a higher risk of ICTG. Kratzsch and colleagues identified 13 ICTG cases among 159 patients with implantable drug delivery systems (IDDSs) at two European medical institutions, thus the prevalence was 8.2% (116). The authors compared the 13 ICTG cases to 54 subjects chosen from 159 patients randomly assigned to a control group, of similar age and follow-up duration. However, 24 of 54 patients in the control group had the IDDS implanted for spasticity control and 30 for pain vs. all 13 ICTG patients implanted for pain indications. Higher IT morphine dose and concentration highly correlated with ICTG formation. Intrathecal catheter ending in the middle thoracic spine ($p = 0.010$) was associated with ICTG formation, and previous spinal surgery was weakly associated with granuloma formation ($p = 0.051$).

Consensus Point 8. Granulomas likely occur because of high concentrations of medication lingering for long periods of time, with little CSF flow, surrounding the region of the catheter tip.

Other agents for IT administration have been examined. Baclofen infusion was negatively associated with ICTG formation (116). Veizi et al. did not find correlation of concentration, dose, flow rate, duration of treatment, age, or previous spinal surgery with granuloma occurrence in six patients identified with ICTG among 69 patients receiving a combination of hydromorphone and bupivacaine intrathecally. Four of the six patients were receiving hydromorphone at concentrations of $\leq$1 mg/mL (83).

Etiology of Intrathecal Morphine-Initiated Granuloma

The origin of the morphine-initiated IT granuloma is not certain. Based on morphological examination, it is evident that the mass arises almost exclusively from the dura-arachnoid (75). As noted previously, the mass is composed largely of fibroblasts and to a lesser degree inflammatory cells embedded in a collagen matrix that matures over time (78). The human and animal work suggest that the mass is initiated by several opioid molecules (89,112), which given an apparent absence of effect of concurrent opiate antagonism (113) represents an effect independent of opiate receptor activation.

Table 10. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations on Intrathecal Therapy and Granuloma Formation and Risk Mitigation.

Statement	Evidence level	Recommendation grade	Consensus strength
Granuloma represents a sterile collection of cells that appears to be dose dependent and concentration related, residing at the end of the intrathecal catheter.	I	A	Strong
Symptomatic granulomas occur at a rate of 0.5–3% and should be suspected with exacerbated previous symptoms, new focal neurologic symptoms, loss of efficacy, or rapid dose titration.	II-2	A	Strong
Granuloma has been implicated with morphine, hydromorphone, sufentanil, alfentanil, and baclofen.	I	A	Strong
It is recommended to use the lowest dose and concentration of intrathecal opioid that is clinically needed.	II-3	B	Strong
Bolus delivery appears to be an effective method for reducing the formation of granuloma.	III	C	Moderate
Advanced imaging of the area surrounding the catheter tip, including MRI with gadolinium, or CT myelogram, may be helpful in diagnosing granuloma.	II-3	B	Moderate

Current hypotheses suggest that the opiate-receptor independent degranulation of meningeal mast cells may be an intermediate link in granuloma formation (113). Importantly, mast cell degranulation enhances fibroblast chemotaxis, and products of mast cell degranulation stimulate collagen formation (117,118). Alternatively, morphine increases kidney fibroblast proliferation (119), while inhibition of mast cell degranulation leads to a *decrease* in scar formation in skin wound healing (120–122). Accordingly, a speculative hypothesis exists that opiates, such as morphine (or any agent degranulating mast cells at the concentrations achieved with chronic IT delivery), stimulate pericatheter fibrosis, through either a direct effect on meningeally derived fibroblasts and/or by the degranulation of mast cells, which enhance fibroblastic activity and collagen deposition.

Clinical Presentation

Cord compression was a common finding in most preclinical reports. The incidence of spinal cord compression was 36.4%, 76.0%, 88.9%, and 45.1% for monkeys, dogs, sheep, and rats, respectively (76). Often the presenting symptom is increased back pain. Regardless of the reaction at the catheter tip, it is the effect of these reactions on the adjacent spinal cord (and spinal nerve roots) that has the most potential to produce an AE. Compression of the cord was due to the presence of the catheter, the reaction around the catheter (inflammation and/or fibrosis), or both. Because inflammation and fibrosis along the catheter track varied between the studies, compression also varied. Similar findings were noted in symptomatic patients diagnosed with ICTGs, though granulomas are occasionally detected in asymptomatic patients undergoing imaging studies (109).

Imaging in Diagnosis of Intrathecal Granulomas

MRI with and without contrast is considered the test of choice for granulomas. If symptoms persist with a negative MRI, a CT myelogram should be considered. Alternatively, catheter side-port injection of contrast followed by CT can also detect a granuloma, which will appear as a filling defect around the catheter tip. Characterization of an enhancing lesion of various size at the catheter tip is diagnostic of an ICTG. However, it is important to rule out artifacts from the catheter tip. Indeed, metallic IT catheter tips may produce image distortion that could potentially make it somewhat difficult to distinguish from granuloma. If this is the case, CT myelogram should be considered. When evaluating possible granuloma development around an IT catheter tip, it is important to take into account the characteristic metallic susceptibility artifact and increased size of normal metallic catheter tips on MRI scans. Gadolinium enhancement improves diagnostic accuracy (123). PACC recommendations for granuloma identification and risk mitigation appear in Table 10.

Conclusions

This section on IT granuloma highlights somewhat disparate findings: on the one hand, higher dose and concentration of opiates (such as morphine and hydromorphone) increase the risk of granuloma formation, on the other hand, a mast cell degranulation response—a phenomenon seen in allergy/hypersensitivity—is implicated. While not mutually exclusive, the latter phenomenon may support recent descriptions of hydromorphone-related IT catheter tip granulomas at low concentrations (750 mcg/mL) and dose (as low as 160 mcg/day) (83). It remains unclear whether granuloma formation occurs as a generalized reaction that is determined by the local concentration and exposure to the opiate or is related to individual patient predisposition and hypersensitivity to the opioid.

BLEEDING

Bleeding Risk Stratification

Bleeding risk associated with neuraxial procedures has been very well defined recently (6,124–126). These guidelines centered on assessment of risk of hemorrhage from the procedure secondary to vascular injury, the consequence of bleeding, along with recommendations for cessation of anticoagulation based on the pharmacology of each medication and whether anticoagulation therapy was for primary or secondary prophylaxis. Based on this risk assessment, IT therapy is classified as intermediate-risk (124,125). Previous guidelines can be followed for the placement of IDDSs (124,125). Subdural hematoma can occur with violation of the dura, and care must be taken when evaluating this complication. PACC recommendations for bleeding risk mitigation and coagulation medication management appear in Tables 11 and 12, respectively.

Epidural Hematoma

Epidural hematoma is well defined in literature for neuraxial interventions and is estimated by some reports to be 0.75% in a nine-year MarketScan analysis of 5458 percutaneous placements for SCS employing a 14 G needle (127). Appreciating that the needle puncture may be similar in violating the epidural space or placing a catheter within the IT space, the incidence for spinal epidural hematoma associated with IT therapy is not well defined.

Table 11. Polyanalgesic Consensus Conference (PACC) Evidence and Recommendations on Bleeding and Risk Mitigation for Intrathecal Therapy.

Statement	Evidence level	Recommendation grade	Consensus strength
Aspirin should be discontinued six days prior to IT therapy for primary prophylaxis and four days for secondary prophylaxis.	II-3	B	Moderate
Discontinuation of anticoagulants should be shared with consultation from the prescribing/managing provider, along with the decision to bridge with low molecular weight heparin (LMWH).	III	A	Strong
NSAIDs should be discontinued based on their pharmacologic half-life and a minimum of five half-life intervals.	III	B	Strong
COX-2 inhibitors do not need to be discontinued prior to intrathecal drug delivery procedures.	I	A	Strong
Typically reinitiation of anticoagulation therapy is recommended 24 hours following surgery.	II-3	B	Strong
Discontinuation of antidepressant medications should be balanced against the risk of exacerbating psychiatric illness and bleeding risk.	III	B	Moderate

Spinal Hematoma

Spinal hematoma is a serious complication associated with dural puncture and has been reported with SCS (128). Hustak et al. reported a case of subarachnoid bleeding that required surgical evacuation following placement of an epidural blood patch for a patient with postdural puncture headache (129). Although rare, this complication may occur when an epidural blood patch is performed for management of postdural puncture headache. Magro et al. reported a case of bilateral subacute subdural hematoma that required surgical decompression following the placement of an IDDS for chronic baclofen infusion (130).

Pocket Hematoma

Pocket hematoma is often a complication requiring minimal intervention, but early surgical treatment is important to optimize outcome. Although the literature is sparse in identifying pocket hematoma as a complication, it has been known to occur. With a keen eye on cardiac literature, some general consensus statements can be made. In a study that included 2500 patients receiving an implantable cardioverter defibrillator, 56 had a meaningful, clinically significant pocket hematoma (131). Independent risk factors included older age and upgrade from a pacemaker. A multivariate analysis of 659 patients who received implantable cardiac devices and had a primary outcome of device-related infection demonstrated a sevenfold increase in risk of infection, with no effect from empiric antibiotics (132). A subanalysis of the same study population demonstrated no statistically significant influence of bleeding risk and body mass index (133).

Consensus Point 9. Pocket hematoma should be treated aggressively if discovered, and intraoperative techniques should be refined to reduce dead space and ensure hemostasis prior to pocket site closure.

Device site would likely have an influence on surgical rate of hematoma surrounding the pocket. There is no peer-reviewed literature identifying this risk. The choice for the location of pump reservoir placement varies, but consideration of patient preference, ease of refill, physiological conditions, and physical location able to accommodate the hardware should play a role in decision making.

Consensus Point 10. A clear appreciation for anatomy is critical for the appropriate surgical dissection and plane of device placement. Commonly, the programmable implantable device is placed either in the abdomen or the back, with historical preference for the former.

INFECTION

Infection is a major complication of any surgery, and meningitis and encephalitis can occur with implantation near the spine. Many principles referenced from surgical-site infection mitigation for neurostimulation therapy apply to IDD as well.

Many medical conditions demonstrably increase the risk of surgical site infections (SSIs) in other implant procedures, including spinal and cardiac device implantations. Factors associated with an increased risk of SSI include anemia, smoking (134,135), diabetes mellitus (136,137), cancer, malnutrition, obesity, cardiovascular disease (other than hypertension), and active drug and alcohol abuse (138). Smoking and tobacco history should be assessed as the habit increases the risk of SSI and poor wound healing (134,135). Smoking cessation is advised prior to elective IDDS surgery. The optimal time of smoking cessation is approximately two months prior to surgery (139,140). PACC recommendations for infection risk management appear in Table 13.

The patient's immune status should also be assessed. This includes questioning the patient about infection susceptibility and history of previous surgical infections. Medical conditions and medications that are likely to affect the patient's immune competence should be reviewed, and include but are not limited to HIV, prior organ transplant, cancer/cancer treatment, and systemic inflammatory diseases that require immune-modulation therapy. Patients with these conditions are at increased perioperative risk for infectious complications and extreme care must be taken to mitigate risks to the extent possible. Patients who are taking immune-modulation medications, including corticosteroids, disease-modifying antirheumatic drugs, and many of the chemotherapeutic drugs, are at a significantly increased risk for SSI. The implanting team should work closely with the managing medical teams to optimize the timing of the surgery in these clinical scenarios (138).

Preoperative consultation with an infectious disease specialist may be considered for high-risk patients. Patients with poorly controlled diabetes are at increased risk for perioperative complications including infection and poor wound healing and may require an endocrinology consultation (141,142). Preoperative assessment in patients with diabetes should routinely include a hemoglobin A1C level and an assessment of the patient's overall glucose management and therapy compliance. Patients with diabetes mellitus should have their diabetes optimized prior to surgery. A hemoglobin A1C should be checked prior to surgery and should be <8. If the HgbA1C is >8, the surgical team should consider the option of postponing the procedure and refer the

Table 12. Recommended Anticoagulation Management for Neuromodulation Targets.

Drug/Drug class	When to stop	When to restart*
ASA and ASA combinations	-Primary prophylaxis: six days -Secondary prophylaxis: shared assessment and risk stratification[†]	24 hours
Drug/Drug Class	5 half-lives	24 hours
NSAIDs		
Diclofenac	1 day	
Ketorolac	1 day	
Ibuprofen	1 day	
Etodolac	2 days	
Indomethacin	2 days	
Naproxen	4 days	
Meloxicam	4 days	
Nabumetone	6 days	
Oxaprozin	10 days	
Piroxicam	10 days	
Phosphodiesterase inhibitors		
Cilostazol	2 days	24 hours
Dipyridamole	2 days	
Aspirin combinations	Follow aspirin recommendations	
Anticoagulants		
Coumadin	5 days, normal INR	24 hours
Acenocoumarol	3 days, normal INR	24 hours
IV heparin#	4 hours	24 hours
Subcutaneous heparin, BID & TID#	8–10 hours	24 hours
LMWH: prophylactic	12 hours	24 hours
LMWH: therapeutic	24 hours	24 hours
Fibrinolytic agents	48 hours	48 hours
Fondaparinux	4 days	24 hours
P2Y12 inhibitors		
Clopidogrel	7 days	12–24 hours
Prasugrel	7-10 days	12–24 hours
Ticagrelor	5 days	12–24 hours
Cangrelor[‡]	1-2 hours	[‡]
New anticoagulants		
Dabigatran	4–5 days 6 days (impaired renal function)	24 hours
Rivaroxaban	3 days	24 hours
Apixaban	3–5 days	24 hours
Edoxaban	3 days (5–6 days in renal patients)	24 hours
Glycoprotein IIb/IIIa inhibitors[§]		
Abciximab	2–5 days	8–12 hours
Eptifibatide	8–24 hours	8–12 hours
Tirofiban	8–24 hours	8–12 hours

ASA, aspirin; INR, international normalized ratio; LMWH, low molecular weight heparin.
*When to restart after lead removal for trials (medications should be discontinued during the whole trial) or after permanent implant.
[†]In patients taking aspirin for secondary prevention with high risk factors for cardiovascular disease, and when discontinuing aspirin is not recommended, this should be considered a relative contraindication for brain neuromodulation.
[‡]Cangrelor is a new intravenous P2Y12 inhibitor that was recently approved by the Food and Drug Administration. Neuromodulation procedures in patients on cangrelor are rarely encountered.
[§]It should be noted that neuromodulation procedures are mostly elective procedures and these medications should be assessed case-by-case.

patient to the treating physician for further evaluation and management (143).

Nasal screening and treatment for staphylococcal colonization has been shown to reduce SSI in some implant procedures, including those for orthopedic and cardiac implantable devices. While no such data currently exist for IDDS implants, it should be recognized that nasal colonization with MSSA and MSRA increases the risk of SSI (144,145). The Centers for Disease Control and Prevention (CDC) guidelines for infection control to reduce the risk of SSIs should be followed. Accordingly, surgical drapes should not be touched by members of the surgical team during the procedure. Other steps to consider include preoperative skin-cleaning protocols and screening for staphylococcal colonization. Showering with chlorhexidine soap the evening before and the morning of surgery has been shown to decrease the rate of SSI. Staphylococcal colonization detection is best performed via a nasal swab polymerase chain reaction assay. If the nasal swab assay is positive for staphylococci, then it should be cultured to determine MSRA vs. MSSA (146).

Table 13. Polyanalgesic Consensus Conference Recommendations on Intrathecal Therapy for Infection and Risk Mitigation.

Statements	Origin of recommended practice*	Evidence levels	Recommendation strength	Consensus strength
Preoperative practices				
Identify and treat all remote infections for neuromodulation trials and implants	CDC IA	II-2	B	Strong
Optimize glucose control for neuromodulation implants	CDC IB	II-2	B	Strong
Discontinue tobacco use for neuromodulation implants	CDC IB	II-2	B	Strong
Decolonize MSSA and MSRA carriers through the application of mupirocin nasal ointment and chlorohexidine baths		I	A	Strong
Utilize preoperative antibiotics for neuromodulation trials and implants	CDC IA and NICE	I	A	Strong
Utilize preoperative weight-based antibiotic dosing for neuromodulation trials and implants	CDC IA and NICE	I	A	Strong
Use appropriate preoperative timing (within one hour prior to surgical incision excluding vancomycin) of prophylactic antimicrobialadministration for neuromodulation trials and implants	CDC IA, NICE, SCIP	I	A	Strong
Remove hair (when required) with electric clippers immediately before the surgical procedure	CDC IA and NICE	I	A	Strong
Perform preoperative surgical scrub for a minimum of 2–5 min with an appropriate antiseptic prior to neuromodulation trials and implants	CDC IB and NICE	II-2	B	Strong
Keep nails short and do not wear artificial nails for neuromodulation trials and implants	CDC IB and NICE	II-3	B	Strong
Do not wear hand or arm jewelry for neuromodulation trials or implants	CDC IB and NICE	III	B	Strong
Intraoperative Practices				
Wear a surgical mask for neuromodulation trials and implants	CDC IB	II-3	B	Strong
Wear a cap or hood to fully cover hair for neuromodulation trials and implants	CDC IB	II-3	B	Strong
Use sterile gown and gloves for neuromodulation trials and implants	CDC IB	II-3	B	Strong
Double glove	CDC II and NICE	II-1	B	Strong
Utilize chlorhexidine gluconate for preoperative skin antiseptic agent	CDC IB and NICE	I	A	Strong
If an incise drape is used, then iodophor-impregnated drape for neuromodulation implants are recommended	NICE	I	A	Strong
Use laminar flow and HEPA filters in OR for neuromodulation implants	CDC IB	I	A	Strong
Limit procedure room traffic for neuromodulation trials and implants	CDC II and NICE	I	A	Strong
Keep procedure room doors closed during neuromodulation trials and implants	CDC IB	II-3	B	Strong
Limit tissue trauma, maintain hemostasis, eradicate dead space, and avoid electrocautery at tissue surface	CDC IB and NICE	III	B	Strong
Irrigate with saline through a bulb syringe prior to closure of surgical wound		I	B	Strong
Employ implant strategies to limit operative time		II-2	B	Strong
Postoperative practices				
Apply an occlusive dressing following neuromodulation trials and implants for 24–48 hours	CDC IB and NICE	II-2	B	Strong
Do not routinely use topical antimicrobial agents for surgical wounds that are healing by primary intention	NICE	I	B	Strong
Understand maximum time criterion for defining a deep surgical site infection of animplantable device (one year postimplant)	CDC	III	B	Strong
Do not continue antibiotics into the postoperative period for neuromodulation trials and implants beyond 24 hours	SCIP	I	A	Strong
Educate patient and family on proper incision care, symptoms of SSI, and importance of reporting symptoms	CDC II and NICE	III	B	Strong
Wash hands before and after dressing changes	CDC IB	III	B	Strong
Use sterile technique for dressing changes	CDC II and NICE	III	B	Moderate
When SSI is suspected, prescribe an antibiotic that covers the likely causative organisms. Consider local resistance patterns and culture results in choosing an antibiotic	NICE	III	B	Strong

*The origin of recommended practice defines the supporting surgical guideline.
CDC, Centers for Disease Control; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; NICE, National Institute for Health and Care Excellence; SCS, spinal cord stimulation; SCIP, Surgical Care Improvement Project; SSI, surgical site infection.

There is increasing interest in orthopedic implant, spinal implant, and cardiac device surgical practices regarding wound application of antibiotics. For example, there is mounting evidence in the orthopedic and spinal implant practice that application of vancomycin powder directly to the wound following irrigation and prior to closure reduces the rate of SSI and may be cost-effective. In the cardiac device practice, there is evidence that applying an antibiotic-eluting mesh envelope around the generator prior to closure can reduce the rate of SSI. While it is premature to recommend the use of wound antibiotics or mesh pouches for all IDDS implants, this is

an area of significant investigation and the implanter should keep abreast of developments (147).

GENERAL SURGICAL MANAGEMENT CONSIDERATIONS

Technical complications related to placement of an IDDS detract from therapeutic effectiveness, often require surgical revision, and result in patient dissatisfaction. Careful consideration to all aspects of the surgical procedure—including preoperative preparation, intraoperative technique and postoperative care—is critical to ensuring optimal outcome. Specifically, trialing and preoperative preparations and consideration are outlined in the companion papers of this updated version of the PACC (3,4). Patient selection and disease indications, major drivers of improved outcomes, are underscored there and the reader is encouraged to review them.

Preoperative Care

Obtaining a careful history and physical examination, identifying the pain generator(s), and excluding physical and psychological variables that predispose to suboptimal outcomes are minimum requirements before contemplating implementation of IDD. These matters have been addressed in related publications (3,4). In particular and relevant to complications, it is important to identify patients at high risk for infection or wound dehiscence, such as those with malnutrition, immune compromise, connective tissue disorders, diabetes mellitus, or staphylococcus colonization. It is also important to inquire about known allergy to any of the components of the IDDS or the anticipated perioperative and IT medications.

Preoperative imaging should be reviewed prior to the planned surgical procedure. Cross-sectional spine imaging, either MRI or CT, should be available and reviewed prior to IT catheter placement. The important information to be noted includes: 1) the position of the conus; 2) the presence of a potential obstruction, such as stenosis or tumor that could reduce capacity of the spinal canal to safely allow passage of or contain the IT catheter; and 3) spinal conditions that could affect access to the thecal sac, such as scoliosis or severely narrowed interspaces.

Finally, the patient should be examined prior to the planned procedure to be sure that there is a satisfactory location for the pump to be placed safely. This is especially important in patients with cancer-related pain. Factors that need to be considered include the presence of ostomies, drain tubes, feeding tubes, future radiation targets (this should be discussed ahead of time with the radiation oncologist), prior radiation sites, and previous surgical procedures.

Consensus Point 11. Preoperative assessment includes a mindful forecast of catheter location, age of patient, previous pain management strategies and opioid exposure, disease comorbidities, preoperative imaging, lab assessment, and location for pump implantation.

Consensus Point 12. PACC recommends obtaining preoperative labs to survey concurrent infections and coagulation status prior to IT drug delivery; include complete blood count, basic metabolic panel, coagulation profile, erythrocyte sedimentation rate, C-reactive protein, urinalysis and creatinine kinase, along with a nasal swab for MSSA or MRSA.

Surgical Technique

The implanting physician should be skilled not only in basic surgical techniques but also in the surgical peculiarities of IDDS implantation. A minimum number of yearly implants similar to that recommended for SCS is preferable (148). Pump placement should be discussed with the patient preoperatively and with regard to body habitus and patient preferences. The surgeon should carefully plan and mark the incision sites for catheter placement and for pump placement. Targeting the proper dermatome with catheter tip positioning is crucial for optimizing results of IT therapy (149).

The majority of published guidelines recommend that general anesthesia or heavy sedation be avoided during spinal needle and/or spinal catheter placement. The ability of the patient to report a paresthesia is an added safety measure to reduce the risk of needle or catheter trauma to the neural elements. Accordingly, when patient factors allow, it is preferable to perform the spinal puncture and IT catheter placement under sedation that is light enough to allow the patient to reliably respond and communicate with the surgical team. The PACC recognizes that patient factors, such as severe pain, spasticity, age, and neurological status may necessitate heavy sedation or general anesthesia.

Consensus Point 13. Needle and catheter placement should be performed with patient feedback whenever possible to avoid neurologic injury or irritation to existing nerve roots heralded by new-onset radicular pain.

Patient positioning should be planned for reservoir placement and should be performed to avoid re-prepping and repositioning if possible. Placement of the programmable pump in the lateral abdominal wall requires lateral decubitus positioning.

The preferred insertion site is L2-3 or L3-4, provided that the patient's anatomy allows for one of these levels. The presence of fusion hardware or bony fusion at the catheter-entry level may warrant involvement of a spine surgeon. It is important to review preoperative cross-sectional imaging to be sure the conus is at the expected level. A low-lying conus could affect the choice of needle-entry level. The needle entry and trajectory should be planned to maximize the ease of catheter threading and minimize shearing forces on the catheter after it is implanted. The ideal approach is a paramedian, shallow angle (approximately 30°) from the skin technique, with the needle-entry site 1.5–2 vertebral segments below the expected dural-entry site. Ideally, the needle-entry site should be on the same side as the pump placement so that the catheter will not cross the spinous processes. Intraoperative imaging (fluoroscopy) should be used to verify the needle-entry level and final catheter tip position. Free-flowing CSF should be observed from the needle before the catheter is passed; however, occasionally CSF flow may be scant and needle advancement within the spinal canal in the lateral fluoroscopic view should cease at the earliest sign of patient paresthesia—even in the absence of CSF flow. The catheter should be passed with the use of intermittent fluoroscopy to guide the catheter tip to its final destination. Since most of the currently used IT medications are effective at the spinal levels proximal to the catheter tip, the final tip position should be in the posterior thecal sac at the spinal level needed to target the painful area.

Consensus Point 14. PACC recommends posterior catheter location with the catheter tip at the dermatome level congruent with pain if anatomically indicated.

After the catheter is in final position, the stylette should be removed and CSF droplets should be clearly emerging from the catheter tip. Care should be taken during needle placement to minimize the amount of CSF loss from the needle, since significant CSF loss during needle placement may reduce the flow of CSF through the small-bore catheter, leading to uncertainty about intradural placement. If there is a question regarding whether or not the catheter is in the IT space, a small amount of myelogram contrast can be

administered, provided there are no contraindications. The physician should double-check for IT compatibility before injecting.

If the catheter is trimmed, the amount removed must be accurately measured and recorded and the final catheter length should be entered into the pump program such that this information is available to those managing the device. The catheter should be secured to the dorsal fascia (not to subcutaneous adipose tissues) to reduce the risk of catheter migration. Double anchoring should be considered in patients who undergo regular wheelchair transfers because the tension on the skin during transfer puts the patient at greater risk for catheter migration. The catheter should be anchored in accordance with the manufacturers' recommendations and the catheter anchor should be secured with nonabsorbable suture material (e.g., polyester). The catheter attachment to the pump should be meticulously performed in accordance with the manufacturers' recommendation, as a catheter disconnect can be catastrophic in the case of IT baclofen or clonidine therapy.

For most patients, the pump will be placed in a subcutaneous pocket in the abdomen. Ideally, the site chosen should minimize the potential for the pump to infringe on or put pressure on the costal margin and/or the anterior iliac spine and iliac crest, as this can be a significant source of long-term patient discomfort. There are rare circumstances in which anatomic factors will eliminate the abdominal wall as the pump site. Some examples include extensive prior abdominal surgery with adhesions or the presence of multiple ostomies and/or drainage tubes. Other placement options include the buttock/posterior iliac fossa or the lateral chest wall below the axilla, with subpectoralis placement.

Pump preparation needs to be performed by an experienced person within the operating room theater with all personnel fully scrubbed. Removal of the prepackaged solution is required if initiation with the desired medication at the time of implant is performed. In some circumstances, initiation of ziconotide therapy can be delayed, and later started in the office.

The pump incision should be slightly longer than the pump diameter, just enough to comfortably allow the pump to be placed into the pocket but snug enough to reduce the risk of seroma collection, excessive pump movement, or pump flipping. The pump should fit in the pocket such that there is no tension on the wound during closure. The pump sometimes is anchored to the underlying fascia with nonabsorbable (e.g., polyester) sutures.

Prior to wound closure, all wounds should be copiously irrigated with a sterile saline solution, as wound irrigation has been shown to reduce the risk of SSI. Some practitioners use an antibiotic solution for irrigation. The addition of antibiotics to the irrigation solution has not been shown to confer additional benefit in clean surgeries (vs. bowel surgery). Wound closure should be in accordance with excellent surgical technique. A watertight, layered closure to minimize dead space is recommended. Masterful surgical technique, including gentle tissue handling, is essential for optimal surgical results. Following wound closure, a sterile occlusive dressing should be applied and left in place for 24–48 hours. If the dressing needs to be changed sooner, sterile technique is recommended.

Hygroma

Hygroma and postdural puncture headache can result from violation of the dura during catheter placement. A review by Nitescu et al. of IT therapy for refractory cancer pain noted that among 200 patients with tunneled nylon catheters and Millipore filters postdural puncture headache occurred in 15.5% and CSF hygroma (pseudomeningocele) in 1.5% (150). Although this is data from an externalized pump, it likely represents the upper limit of implantable programmable systems. Limiting dural punctures when placing the catheter, using purse string sutures around the catheter, and choosing the appropriate angle of the catheter for anchoring may limit leakage surrounding the catheter. If leakage occurs, management centers on stopping the CSF leak. Infection risk needs to be assessed and prophylactic antibiotics started if needed; oftentimes it is recommended to consult with an infectious disease specialist.

Seroma

It is commonly appreciated that some fluid undoubtedly accumulates around the reservoir site. However, large amounts of fluid can represent a seroma. Glucose testing can help differentiate between third spacing fluid and CSF. Seroma within the axilla following sentinel lymph node biopsy was reviewed retrospectively in 667 women, with an incidence of 19% (151). Of those with seroma, 77% required further intervention for symptom relief, which included aspiration (treatment success in 83% after mean of 1.3 aspirations). Seroma in IT therapy is managed with escalating techniques that include: pressure dressings, aspiration and pressure dressings, and surgical intervention or resection of the pocket. Prevention is the best treatment, and can be improved by employment of the abdominal binder to close dead space surrounding the device.

Education and Training in Intrathecal Drug Delivery Safety

There is evidence, both in the neuromodulation implant practice as well as other interventional procedure specialties, that experience and training affect outcomes. PACC believes that uniform training and education guidelines are important components for the safe practice of IDDS implantation and management. Hospital credentialing bodies should carefully evaluate and scrutinize physicians seeking privileges for IDDS implantation and management. While PACC understands that there are limited data regarding IDDS implanter experience and outcomes, we feel that implanting physicians should have a minimum number of proctored implants in order to be qualified to independently implant IDDS devices.

The Accreditation Council for Graduate Medical Education program requirements for pain medicine in the United States specify the following in regard to Interventional pain and neuromodulation: there should be formal didactic training in the following areas—anatomy, physiology and pharmacology of pain, patient selection criteria, fluoroscopic imaging and radiation safety, epidural and IT medication management, and IT drug administration systems; a minimum of 25 image-guided spinal procedures; a minimum of five neuromodulation procedures; and at the conclusion of training, "the Program Director must prepare a final report clearly documenting the specific interventional techniques with which the Fellow demonstrates competence."

Consensus Point 15. There are *minimum* competencies necessary to implant and manage IDDSs. In addition to these training minimums, the implanting physician should have experienced a minimum of five supervised implants including all of the following components: proper CSF access, safe catheter passage, surgical dissection, catheter anchoring, pump pocket formation, wound closure and management, and postoperative wound management. The supervising or proctoring physician or program director should explicitly document the trainees' competency.

Consensus Point 16. To maintain competency, the implanting physician should participate in regular and high-quality continuing medical education to keep up with the latest advances and pertinent updates in the field. To maintain competency, the implanting

physician should participate in at least ten neuromodulation implants per year, two of which should be IDDSs.

IDDS implantation and management is a multidisciplinary practice and requires the skill and expertise of many specialists. All implanting physicians should at a minimum, have immediate access and availability of key members of the team. Specific personnel include: preimplant patient selection team (including psychological evaluation), pain medicine specialist, spine surgeon, and allied health personnel. For example, a fellowship-trained pain management physician may be competent to implant and manage the device but needs spine surgeon support in the case of complications, such as spinal hematoma or infection. Similarly, a neurosurgeon or orthopedic spine surgeon may be competent to implant and manage the device but may not have the experience or training to manage the complex opioid and analgesic regimens that many patients are receiving. The implanting physician is responsible for assuring that members of the team, including allied health personnel, are properly trained and experienced in the components of care that each member is responsible for providing. This includes surgical assistants, and personnel performing pump programming, pump refill, postoperative wound evaluation and management, pump medication selection and dosing, IT catheter granuloma surveillance, and side effect surveillance and management.

CATHETER ISSUES AND DEVICE MANAGEMENT

Most complications of IDDS are due to catheter-related dysfunction, which blocks or alters drug delivery or distribution (152). Potential catheter-related problems include catheter tip migration, kink or occlusion, catheter fracture, inadvertent puncture, or loosening of connections. In one study, catheter migration was reported in 7.3% of cases, catheter tear in 6.4% and catheter occlusion in 1.8% (153). Catheter-related problems occurred in 7.4% (28/380) of patients in an older large retrospective study, with total delivery system complications occurring in 21.6% (82/380) (154). A recent study of 57 patients with lumbar postlaminectomy syndrome, trialed, implanted and managed for 24 months with hydromorphone/bupivacaine by a single implanter, revealed a total of 36 catheter dye studies on 29 patients (155). Of those, nine (25%) were abnormal, revealing three catheter migrations out of the IT space, three catheter punctures with leak and three cases of catheter kink with obstruction of flow. All nine catheter complications necessitated surgical revision of the catheter. Such complications may lead to drug withdrawal, can result in significant morbidity, and there is a potential possibility of mortality in the case of baclofen withdrawal.

Catheter Evaluation

There are no systematic studies detailing assessment or evidence in support of catheter evaluation. The evaluation for catheter dysfunction should be triggered by inadequate response to therapy despite adjustments in pump rate. The first step typically involves interrogating the pump to check that the settings agree with residual volume, and aspirating the pump to confirm the residual volume in the pump. If there is more fluid than expected, this could suggest kink, catheter blockade or reduced output by the pump motor. If there is significantly less volume, then overinfusion or pocket fill may be suspected. If pump volume is found to be within the error margin of the pump and the patient is not experiencing relief, the next step may involve radiological assessment. Simple radiographs can potentially show catheter kinking or dislodgement. Of note, some catheters such as the Ascenda (Medtronic) are not as radiopaque and a roentgenogram may be relatively uninformative.

If pump rotor malfunction is suspected, radiographs should be obtained with a programmed 90° (SynchroMed EL) or 120° (SynchroMed II) angular rotation to exclude rotor dysfunction—the so-called "rotor test" for the SynchroMed EL device or the "roller study" for the SynchroMed II system (by delivering a 0.01 mL priming bolus over one minute in the SynchroMed II pump). Of note, the Synchromed EL models are likely no longer in circulation as functional therapies. For evaluaton of the Synchromed II pump, the Synchromed II radiographs should be obtained in the perpendicular position to pump, and the pump programmed to deliver a 0.01 mL priming bolus over one minute, with fluoroscopy monitoring the rotation of the roller-heads clockwise. Next, a catheter access port (CAP) study can be performed. Aspiration through the CAP is first performed. With a normal functioning catheter, one should be able to aspirate CSF without difficulty. Greater than 1 mL should be drained to empty the catheter before injecting contrast. One should avoid injecting into the catheter port if the aspiration fails to withdraw CSF. In this case, an alternative is to fill the reservoir with saline and calculate how long it will take to clear the catheter based on the daily volume infused. It is important to see the patient at the time that the catheter clearance will be complete. Failure to do this can result in drug withdrawal. At the completion of the catheter clearance, safe injection of the CAP can be performed. If injection is considered in the absence of CSF aspiration, the clinician should anticipate over-dosing from medication in the tube, should know the amount and effect of such medication overdose, and should be prepared to manage it. Prior to the procedure, the patient should be given a detailed informed consent that includes being told of potential complications of overdose.

Catheter Myelogram

This procedure is performed under strict sterile technique with C-arm guidance. Following identification of the CAP port under fluoroscopy, a 24-gauge needle is inserted through the side port used to drain the dead space fluid column in the IT catheter before injection of intrathecally approved contrast material (such as iohexol). If it is not possible to aspirate fluid it is not advisable to inject contrast solution into the catheter due to risk of overdose. The physician should calculate the dose that would be administered if the catheter was not emptied by multiplying the internal volume of the catheter by concentration of the medication. After the appropriate amount of fluid has been aspirated from the catheter and intrathecal-approved fluid is injected under fluoroscopy, the catheter with dye is observed from the CAP into its spinal-insertion site to the catheter tip in the intrathecal space, observing leaks, contrast pooling, or loculation of contrast in the intrathecal space. It is also important to rule out contrast pooling under the pump by using a tangential view. Catheter fluoroscopy can show leaks in macroscopic perforations, and leaks, dislodgement of the catheter from the pump, and catheter tip dislodgement or migration (156). The limitation of a catheter myelogram is poor sensitivity, especially in the case of a microfractures.

High definition three-dimensional CT after a catheter myelogram should be helpful if the specific site of leak is not clear from fluoroscopy (157). This could happen especially with a small volume leak from a microfracture. If performing a postinjection CT, it is important to do the injection in the CT suite with the patient in the supine position and transferred to the CT in the supine position. Prolonged upright position of the patient after injection of the contrast can result in pooling of the contrast in the caudal sac. In a functioning

catheter with properly performed CAP injection, the post-CT should show diffuse spread of contrast throughout the CSF.

Nuclear Imaging

Injection of radionuclide material, such as Indium-111 diethylenetriamine-pentaacetic acid (^{111}InDTPA), is occasionally used to detect IDDS malfunction (158). Typically, the radioisotope is injected in the pump chamber and the radioactivity is monitored over 72 hours or more. If the isotope distributes in the spinal canal up to the basal cistern, the system is deemed functional (159–161). If the radioactivity is interrupted or accumulates along the catheter path, then catheter kink or leak is inferred. If the isotope remains in the device chamber, then pump malfunction is suspected. Note that the concentration of the drug, and the ratio of the daily dose to the concentration should be no more than 2:1 to ensure passage of the radioisotope out of the pump reservoir and through the catheter within 48 hours. However, scintigraphy has significant limitations, including poor localization, identification of early catheter kink vs. pump malfunction, and identification of catheter microfractures (160).

Radioisotope cisternography may be a useful tool in the differential diagnosis of spontaneous intracranial hypotension and related headache (162). Specifically, radioisotope cisternography provides relevant physiologic information to establish the site of a CSF leak or rule out CSF leak as the cause of headache.

PROGRAMMING AND PUMP REFILL

As described elsewhere (9,10,15), the interface between the clinician and the device is critical in all stages of management. Iatrogenic error can lead to catastrophic complications, including death. The refill procedure should be performed under strict sterile conditions, with interrogation of the device performed to allow for an anticipated reservoir volume prior to aspiration. Following aspiration of existing reservoir medication, the new prescription is injected into the pump reservoir after confirming the concentration of the individual components of the admixture with the written prescription sent to the pharmacy. The pump is programmed and validated by a second clinical individual with the final intended concentration and dose of medications prior to the patient's departure. These were a few of the strategies employed to help prevent pediatric dosing errors in a database review (163).

Ultrasound guidance has been advocated when the pump refill port is difficult to discern, secondary to placement or orientation (164). Ultrasound can also identify a pump flip, as no port is recognized. Gofeld et al. described the benefits of using doppler with direct visualization of the medication within the pump (165).

When pocket fills occur, the most important step is diagnosis. Depending on the drug admixture, different symptoms will present immediately or may be delayed and should be anticipated. If pocket fill is suspected, the pump should be aspirated to confirm volume injected into the pump reservoir and or pocket. After diagnosis, aspiration of the contents within the pocket should be attempted. Ultrasound has been reported to be helpful in this endeavor (166). The patient then needs to be monitored in a controlled setting, and it is recommended that the patient be transported to the emergency room or its equivalent. Treatment of overdose or withdrawal needs to be supportive and once the patient is stabilized, the intrathecal infusion restarted with care regarding the reinitiating dose.

Consensus Point 17. Multiple checks and balances when performing device refill procedures can minimize the risk of iatrogenic error. This can be accomplished by having a two-person validation model.

MRI COMPATIBILITY AND MANAGEMENT

Both Medtronic and Flowonix programmable pumps are labeled as MRI conditional; however, differences between the pumps do exist. The SynchroMed II pump is approved for use with less than or equal to a 3.0 Tesla in a horizontal closed MRI scanner. During an MRI, the magnetic field will stop the rotor, though this condition is temporary. Flow will resume after the study. The SynchroMed II pump has not been approved for use in standing or open MRIs. Furthermore, it can take up to 90 min to log a motor stall if the motor stops during an MRI. The pump should not be oriented so that the refill port is pointing to the patient's feet or head as the MRI could cause demagnetization of the internal pump magnets and potentially cause a nonreversible stall.

Motor recovery occurs spontaneously and pump interrogation should be performed with interrogation of logs after each MRI to ensure resumption of pump function after temporary motor stall. However, a case report described withdrawal occurring on two occasions in a patient with a SynchroMed II pump who underwent multiple MRI's (167). A memory reset solved the problem after the first withdrawal episode, but the patient required pump replacement after the second withdrawal episode. However, a retrospective study examining 86 patients undergoing MRI (168), and a prospective study of 43 patients undergoing MRI over a three-year period found no evidence of persistent motor stall or damage (169).

The Flowonix generation of pumps has MRI conditional labeling for 1.5 T scans and the preparation of the pump prior to scan deserves special comment. MRI exposure to the Prometra I pump can allow the valve gates to open, resulting in discharge of the reservoir contents directly into the CSF, as the reservoir is under positive pressure. The pump needs to be emptied before the study and the flow rate set to 0 mg per day. After an MRI, the pump should be emptied again to ensure that CSF has not flowed back into the reservoir, indicating gate dysfunction. If this occurs, the pump must be explanted and replaced. After the MRI is completed, the pump can be refilled and reprogrammed under sterile conditions. Patients are given a bracelet to wear, identifying the implanted pump as a Prometra I. As with the Medtronic pump, minor tissue heating surrounding the pump, slight tugging sensations, and image distortions immediately surrounding the pump can occur.

The Prometra II pump has a flow-activated valve, which allows the patient to have an MRI without prior removal of drug. Similar to the Prometra I generation, valve gates will open during an MRI, however, flow from the reservoir to the patient is largely prevented by activation of a flow-activated valve (FAV). The reservoir releases 0.010 mL of the pump contents into the patient, regardless of reservoir volume. If there is less than 1 mL in the reservoir, it must be removed prior to the MRI. On x-ray, the FAV is easily identified, distinguishing a Prometra I from a Prometra II model. Patient history is required to determine whether MRI exposure has occurred, as there is no reading to indicate the FAV has tripped. The FAV trip following the MRI is reset by removing the contents of the reservoir under sterile conditions, programming a demand bolus of 0.03 mL multiplied by the concentration (as the demand bolus is given in units of mg) of the drug over two minutes. The reservoir is then refilled and the pump is restarted at the desired settings.

DEVICE-RELATED COMPLICATIONS

Safety issues related to medical devices are largely independent of surgical technique. Most complications are directly related to the design of the pump itself, often stemming from the complexity of today's programmable pumps. Continuous-flow pumps are no longer used, secondary to the inability to change dosing without emptying the pump and to the increasing use of flexible programming. All drug delivery systems currently in use are programmable. It may be unrealistic to expect complication-free implantable drug delivery systems. Rather, the goal is to minimize safety concerns and maximize patient benefit.

In the United States, device complications are submitted to the FDA through the Manufacturer and User Facility Device Experience interface, known as the MAUDE Registry (170). This registry consists of mandatory reports submitted by device companies and voluntary reports that can be submitted by medical providers. However, this system is cumbersome and limited by inaccurate reports; by itself it cannot be used to reach conclusions on device-complication rates. It is also difficult to identify device complications and device-complication rates through a review of the published literature. This is due to the small populations in published studies and to the fact that most published studies are powered for detecting changes in flow rates and pain relief, as opposed to device survival and complication rates; thus, the literature cannot be reliably used for this purpose.

Two companies currently manufacturing programmable TDD systems in the United States maintain postmarketing device registries mandated by the FDA. The Medtronic Implantable Systems Performance Registry (ISPR) contains more than 13 years of experience with both SynchroMed EL and SynchroMed II pumps. Very few SynchroMed EL pumps are currently in use as they have either been explanted or replaced by SynchroMed II pumps, secondary to battery depletion. A new registry with more detailed patient data, the Product Surveillance Registry, has been enrolling patients since 2013. A total of 220 patients with IDD systems were followed from May 2013 through January 2015; data collection is ongoing. The Flowonix registry contains three years of data on Prometra I pumps. The Prometra II pump was recently released. The Prometra Post-Approval Study began enrolling patients in June 2013, with 85 patients enrolled as of October 2014. Postmarketing studies can help identify device complications. Coffey et al. in 2009 (9) and 2010 (15) used postmarketing data to analyze a cluster of deaths that occurred within three days of IDD device implantation/reimplantation, allowing the recognition of morbidity and mortality due to improper dosing for both new and reimplanted pumps. Deer and Chapple used data from the National Outcomes Registry to determine trial success and change in pain ratings from up to one-year postimplant in 136 patients (109).

Approximately 200,000 IDDSs were implanted between 2000 and 2013. As of July 31, 2013, 5834 patients with IT drug delivery systems had been enrolled in the ISPR registry, and 6954 pumps were implanted in this subset of patients (72). About 55% of ISPR patients were implanted for noncancer-related chronic pain, 25% were implanted for spasticity, and 20% for treatment of cancer-related pain. The most common diagnosis was failed back surgery syndrome. Catheter complications are more common than device-related complications, which include motor stalls, corrosion, and gear wear; 15% of complications were related to the drug delivery device, most of which were infections, seromas, hematomas and pain at the pump site. As of 2013, 132 events were reported secondary to device malfunction. These included 28 motor stalls, 24 corrosion and gear wear complications, and four cases of deformed pump tubing. Some of these complications were discovered only when the pump was explanted for supposed battery depletion at the end of life. Device-related complications were both determined from device explantation following clinical reports of AEs or discovered upon returned product analysis. Since July 31st of 2015, as reported in the Product Performance Registry (PPR), a total of 6953 patients have been enrolled, with 8732 pumps implanted in these patients; 57.4% were noncancer related, 22.4% were spacticity related, and 18.9% were cancer related. As of July 31st 2015, 211 malfunctions were related to the device: 89 were due to motor stalls, 28 due to gear corrosion, and 6 caused by deformed internal pump tubing.

Overall device survival probability was calculated to be 94.9% for six years for 20 cc SynchroMed II pumps and 92.1% at six years for 40 mL SynchroMed II pumps (72). The registry showed that while pump failure occurred with both on- and off-label pain medications, there was a 2.8 times greater risk of failure in the patients receiving off-label medications. The 78-month survival rate decreased from 97.2 to 90% in pumps infusing off-label medications, which was mirrored in the 2015 PPR with survival of 96.4% on-label and 88.9% off-label, with an increased risk of failure to be 2.4. However, a higher pump failure rate (9% at a median follow-up of four years) was recently reported in a large series from a tertiary medical center (73). Most off-label use occurred in patients with pumps implanted for pain as opposed to spasticity, and as expected, the majority of chronic pain patients are receiving off-label polypharmacy (72). Medtronic used ISPR data to identity the increased incidence of pump failure in pain patients receiving polypharmacy.

Pump Advisories

Adverse event reporting and information on pump safety can be found on device manufacturers' and the FDA websites. Three important advisories include: the March 2014 advisory on overinfusion (171), the June 2013 advisory on internal shorting (172), and the November 2012 advisory on use of unapproved drugs in devices (71).

Overinfusion Advisory

Medtronic estimates that the risk of overinfusion is 0.16% (171). As of November 2013, 76 pumps have been confirmed for overinfusion. There were 14 reports of life-threatening overdoses and 27 reports of non-life-threatening overdoses and/or withdrawal symptoms. There were no patient deaths. The mechanism for overinfusion has not been identified, but once it occurs, infusion rates can continue to increase. If overinfusion is identified, the pump must be replaced. It is important to note that the risk of overinfusion is low. Physicians should monitor residual volumes during pump refills over time. Maino and colleagues published a report of two cases of fentanyl overdose secondary to overinfusion of their SynchroMed II pumps (173). One patient had a fentanyl concentration of 3 mg/mL and had markedly discrepant volume at refill. The pump was replaced and examination of the inner components of the pump by the manufacturer revealed significant residue in the pump head and tube compartments. The other patient had a 6 mg/mL concentration of fentanyl and an empty reservoir instead of 5 mL at refill. A few hours after refill with 20 mL, the patient was found comatose and was resuscitated successfully with naloxone. The residual volume in the pump was 16 mL instead of the expected 19.6 mL. Examination of the explanted pump revealed residue, moisture and corrosion, with deformity of the inner tube lining around the roller head, with insufficient tube compression preventing continual infusion of drug

out of the pump, likely leading to overinfusion (173). Other causes for residual volume discrepancies include a partial pocket fill and/or a previously improperly measured fill. The advisory notes that the accuracy of SynchroMed pumps is plus or minus 15%; however, flow rates do decrease as the reservoir volume approaches 1 cc. The Prometra pump has a mean accuracy of 97.1% with a 90% confidence interval of 96.2–98.0% (153). A nearly empty pump can precipitate withdrawal syndrome. Flow rates can increase up to 3% at 40°C compared to body temperature, and flow rates decrease with low atmospheric pressures (171).

Internal Shorting Advisory

Electrical shorting can occur as ions from the drug solution permeate through the tubing inside the SynchroMed II pump (172). This can manifest as a motor stall or a low battery reset, resulting in withdrawal symptoms, increased pain and/or loss of therapy. The incidence was 0.28% at 48 months and 0.69% at 84 months postimplant. The number of adverse events reported were 380 among 181,400 implants. Prophylactic replacement of a SynchroMed II pump is not necessary secondary to the low incidence of complications. An internal electrical shorting may be suspected if pump logs reveal a motor stall, pump has reset into safe state, or is demonstrating low battery state. Prophylactic replacement is not necessary if the pump can be reset to normal function. Synchromed II pumps were modified with a durable design change to minimize rotor corrosion in 2015 and internal electrical shorting in 2016. A rotor study can show no rotor movement, or a low battery alarm may occur. A change in pump status to a "safe state" can occur as a result of a low battery alarm. This results in a minimal infusion rate. If a patient has a Personal Therapy Manager, the alarm code will show after an attempted bolus administration (172). To monitor for Synchromed II device malfunction, monitoring of the device logs should be considered at each programming session as well as electrical interrogation of the pump.

Use of Unapproved Drugs Advisory

The use of off-label drug formulations can result in decreased SynchroMed II pump life; 78-month pump survival decreases from 97.2 to 90% in patients receiving off-label pain medications. This advisory states that corrosive agents and drug formulations can permeate through the internal tubing and corrode internal components of pumps. This can damage the rotors and internal pump tubing, resulting in irreversible motor stall, loss of therapy and drug withdrawal. If baclofen is used, a potentially fatal drug withdrawal syndrome can occur. Off-label drugs include hydromorphone, clonidine, fentanyl, sufentanil, bupivacaine, any admixture, and any compounded formulation with a pH of less than or equal to three (71).

Consent Decree

Recently, Medtronic entered into a consent decree with the FDA, published on FDA.gov on April 27, 2015 (174). The legal definition of a consent decree is an agreement to resolve a dispute between two parties without admission of guilt or liability. This statute requires Medtronic to stop manufacturing, designing and distributing new SynchroMed II pumps except in limited cases such as when a physician determines that the SynchroMed II pump is medically necessary. Violations cited by the FDA included: inadequate processes to identify, investigate and correct quality problems, failure to document design changes, and failure to ensure that finished products meet design specificity. The consent decree will be lifted after the FDA confirms that Medtronic has fulfilled its part of the agreement.

The consent decree places physicians in an awkward position. As usual, an informed consent must be obtained prior to pump implantation and replacement. Physicians must discuss alternative therapies with patients. Alternatives include changing the manufacturer or continuing with medical pain management. There are websites advertising for patients for potential class action lawsuits. This is unfortunate as IDD has improved the quality of life for many patients who otherwise would have lived with poorly controlled pain. At this point, there is no equivalent device to the 40 cc SynchroMed II pump and the Prometra pump has not yet been approved for the treatment of spasticity. Overall, device complications, while potentially devastating, are not common. IT drug delivery has improved the quality of life in many patients who otherwise would have to live with untreated chronic pain or the side effects from systemic pain medications.

CONCLUSIONS

Intrathecal therapy is a viable option in the treatment of chronic to severe refractory pain. Economic data demonstrate that costs associated with IT therapy and safety are markedly better compared with systemic opioids (175). Furthermore, in defined patient groups an argument could be made suggesting improved longevity and treatment flexibility compared to SCS (48). Intrathecal therapy is a necessary strategy for the treatment of spasticity, and cancer and noncancer-related pain. Risk-mitigating strategies can be employed to promote safety and efficacy with this essential treatment option. The best practices described in this publication should be implemented in patient care with the goal of improved outcomes and to assure a more favorable risk-to-benefit ratio in treating those with diseases causing chronic pain syndromes.

Authorship Statement

Dr. Deer served as primary author, project organizer and editor; Drs. Pope, Hayek, and Lamer performed literature searches; Drs. Pope, Hayek, Veizi, and Yaksh prepared evidence tables; Drs. Lamer and Mekhail served as senior editors; all authors acquired or interpreted data, wrote sections of the manuscript, and provided critical reviews and editing.

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COMMENTS

This article, one of three produced by the Polyanalgesic Consensus Conference, provides a well-written, comprehensive update on the expert consensus regarding safety and risk mitigation with intrathecal drug delivery. Summarizing formal, rigorous literature searches, this publication provides succinct guides to best practice, supported by the best available data. This article should be read and kept at hand for frequent consultation by any clinician involved with intrathecal drug delivery for pain care.

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This important contribution outlines tangible strategies that every implanter or manager can employ today to improve safety with intrathecal drug delivery. Actionable consensus points are provided alongside supporting evidence and expert opinion allowing the publication to be read in its entirety or used as a frequent reference. By presenting known complications together with strategies to mitigate specific adverse events yields a document which serves as more than a report, but a plan for action.

While the publication outlines specific safety strategies, the first consensus point deserves even further emphasis: there continues to be widespread safety with the use of targeted drug delivery. I congratulate the authors for positioning this point first. With a continually growing number of opioid related deaths, physicians are increasingly challenged to improve safety while maintaining efficacious relief for moderate to severe pain. Because intrathecal therapy remains under the prescriptive control of the pump manager, safety is entrusted to the clinician and analgesics with narrow therapeutic windows cannot be utilized by patients ad lib or easily diverted to friends or relatives. This remains a key point in increasing the safe availability of therapy to greater numbers of patients who have proven to benefit from treatment with chronic opioids, regardless of their current route of delivery.

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

