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Best Practices for Intrathecal Drug Delivery for Pain

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Objective: The objective of this study was to identify best practices and provide guidance to clinicians to ensure safety and optimize intrathecal drug delivery for chronic intractable pain.

Methods: Twelve experienced pain medicine practitioners—eight anesthesiologists, one neurosurgeon, one physiatrist, one clinical psychologist, and one advanced practice registered nurse—from the United States, Australia, and Europe gathered to identify and publish consensus on best practices in three areas related to safe intrathecal therapy for pain: safety and monitoring, patient and device management, and patient selection and trialing.

Conclusions: Intrathecal drug delivery is a valuable alternative drug delivery system for many patients with severe chronic or end-of-life pain. While device-related complications (mostly with catheters) and surgical-site infections can occur, the main therapy-related safety issues associated with intrathecal drug delivery arise primarily with inadequate patient monitoring (e.g., respiratory depression), inflammatory mass (e.g., high doses and concentrations of opioids), wound healing, dosing errors (e.g., medication concentration and pump programming), pump fills or refills (e.g., pocket fills), and interaction with concomitant systemic medications (e.g., opioids and benzodiazepines). Many of the reported adverse events and complications of intrathecal drug delivery can be prevented by adequate clinician training, implementation of best practices, and experience. In adopting the therapy, patients must be apprised of its risks and benefits. Physicians and patients must partner to achieve both safety and effectiveness.

Keywords: Best practices, chronic pain, intrathecal drug delivery, intrathecal catheter, intrathecal pump, morphine, opioid, ziconotide

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has received compensation for consulting fees, honoraria, speaking fees, travel fees, or expert testimony fees that he provided for Medtronic Inc. Dr. Caraway is on the scientific advisory boards for Medtronic Inc. and Spinal Modulation Inc. He is a paid consultant for Medtronic Inc., Spinal Modulation Inc., and St. Jude Medical Inc. Dr. Cousins has no conflicts of interest to report. Dr. Jacobs is on advisory committees at Medtronic Inc. for Development of Refractory Chronic Pain Screening Tool, IDD Best Practices, and Sympathetically Mediated Pain Best Practices. She received consulting fees for these. She was also reimbursed for travel expenses by the North American Neuromodulation Society (NANS) for a preconference workshop on Pain Psychology (2011). Gail McGlothlen has received honoraria, speaking fees, and travel fees from the International IDD Best Practices Panel. Dr. Rauck has no conflicts of interest to report. Dr. Staats holds equity/stock options and is on the Board of Directors of Electrocore Medical LLC. He is a paid consultant for Medtronic Inc. and St. Jude Medical Inc. Dr. Stearns is an advisor for Medtronic Inc. She is a paid consultant for Medtronic Inc. in neuromodulation and for Insys Therapeutics Inc.

INTRODUCTION

Since the first reservoir for intrathecal medications was implanted in 1981 (1), experience with more than 300,000 implanted pumps (for all indications) (2) has established intrathecal drug delivery (IDD) as a safe and effective route of administration for medications (3) used to treat intractable pain and spasticity in appropriately selected patients (4). IDD has evolved within the pain treatment continuum to include patients with chronic, noncancer pain. In 2000, the Joint Commission for Accreditation of Healthcare Organizations recommended making pain assessment the fifth vital sign (5) and in 2010, the World Pain Summit, hosted by the International Association for the Study of Pain, passed the Declaration of Montreal asserting that pain management is a fundamental human right (6).

The safety and efficacy of IDD have been documented in the peer-reviewed literature (7–9). Safety and durability have improved with each generation of pumps through technology development (10). Nonetheless, a 2009 analysis by Coffey and colleagues indicated that IDD-associated mortality has been higher than previously appreciated (11). Their examination of nine cases (reported to the manufacturer or identified in a systematic literature and data base search) found that respiratory depression was a primary or contributing cause in each case (11,12). Eight of the nine patients died within 24 hours of device implantation. A subsequent comprehensive review resulted in consensus guidelines for the selection of patients with noncancer pain for IDD and concluded that intrathecal therapies were effective, cost neutral, and appropriate (13,14). While device-related complications (mostly with catheters) and surgical-site infections can occur, the main therapy-related safety issues surrounding IDD are associated primarily with inadequate monitoring (e.g., respiratory depression), inflammatory mass (high doses and concentrations of opioids), wound healing, dosing errors (e.g., medication concentration and pump programming), pump fills or refills (e.g., pocket fills), and interaction with concomitant systemic medications (e.g., opioids and benzodiazepines). All of these issues are amenable to improvement based on a change in practice, education, monitoring, or a combination of these factors. Consequently, a consensus panel was convened in February 2011 to improve the care of patients receiving IDD by identifying best practices and providing positive guidance to clinicians to ensure safety and optimize therapy.

Methodology

Twelve experienced pain practitioners—eight anesthesiologists, one neurosurgeon, one physiatrist, one clinical psychologist, and one advanced practice registered nurse—from the United States, Australia, and Europe gathered to identify and publish consensus on best practices in three areas related to safe intrathecal therapy for pain: safety and monitoring, patient and device management, and patient selection and trialing. Figure 1 delineates the clinical path of a patient being considered for and treated with intrathecal therapy. Vertical arrows connect events along the clinical path to the three main areas discussed by participants—safety and monitoring, patient and device management, and patient selection and trialing. Specific issues within the three areas are listed in the tinted boxes. The best practices contained in this manuscript and summarized on line are based on the literature and the collective expertise of the participants. While consensus best-practices recommendations do not necessarily meet the criteria of evidence-based medicine, evidence does support many of the recommended best practices identified and documented herein. None of these practices are intended to supplant physician judgment, and their application must be individualized to each patient and practice setting.

Safety and Monitoring

PUMPS MUST BE IMPLANTED AND MANAGED BY PROVIDERS TRAINED AND SKILLED SPECIFICALLY IN IDD.

IDD is an alternative medication delivery system approved by the United States Food and Drug Administration (FDA) only for preservative-free morphine sulfate or ziconotide for chronic intractable pain and preservative-free baclofen for severe spasticity. As an intrathecal infusion of a class II narcotic or ziconotide, IDD must be initiated and managed by a physician. We will not be addressing any off-label uses of IDD.

Proper and sufficient training is essential for successful use of IDD. Although pump implantation is a relatively straightforward surgical procedure, correct placement of the spinal catheter can be complicated by anatomical abnormalities, comorbidities, or improper training (13). Starting or restarting intrathecal medication requires pharmacologic knowledge as well as competency with the use of the pump and its programming. In addition, patients require regular follow-up and attentive management for as long as they continue on IDD. Physicians prescribing the therapy should be prepared to invest time in their own training, as well as the training of their staff, in managing patients (13,15).

CLINICIANS MUST BE FULLY FAMILIAR WITH THE PRESCRIBING INFORMATION FOR ALL THE DEVICES AND DRUGS THEY USE IN IDD.

IDD requires a candid therapeutic partnership in which the patient takes responsibility for adherence to the physician's recommendations, self-monitoring, and vigilance for adverse effects. A patient who cannot partner in this way or who (in the case of disability) does not have a caregiver who can fulfill this role should not be implanted. Comprehensive patient/caretaker education and informed consent are essential elements of the therapy. During the

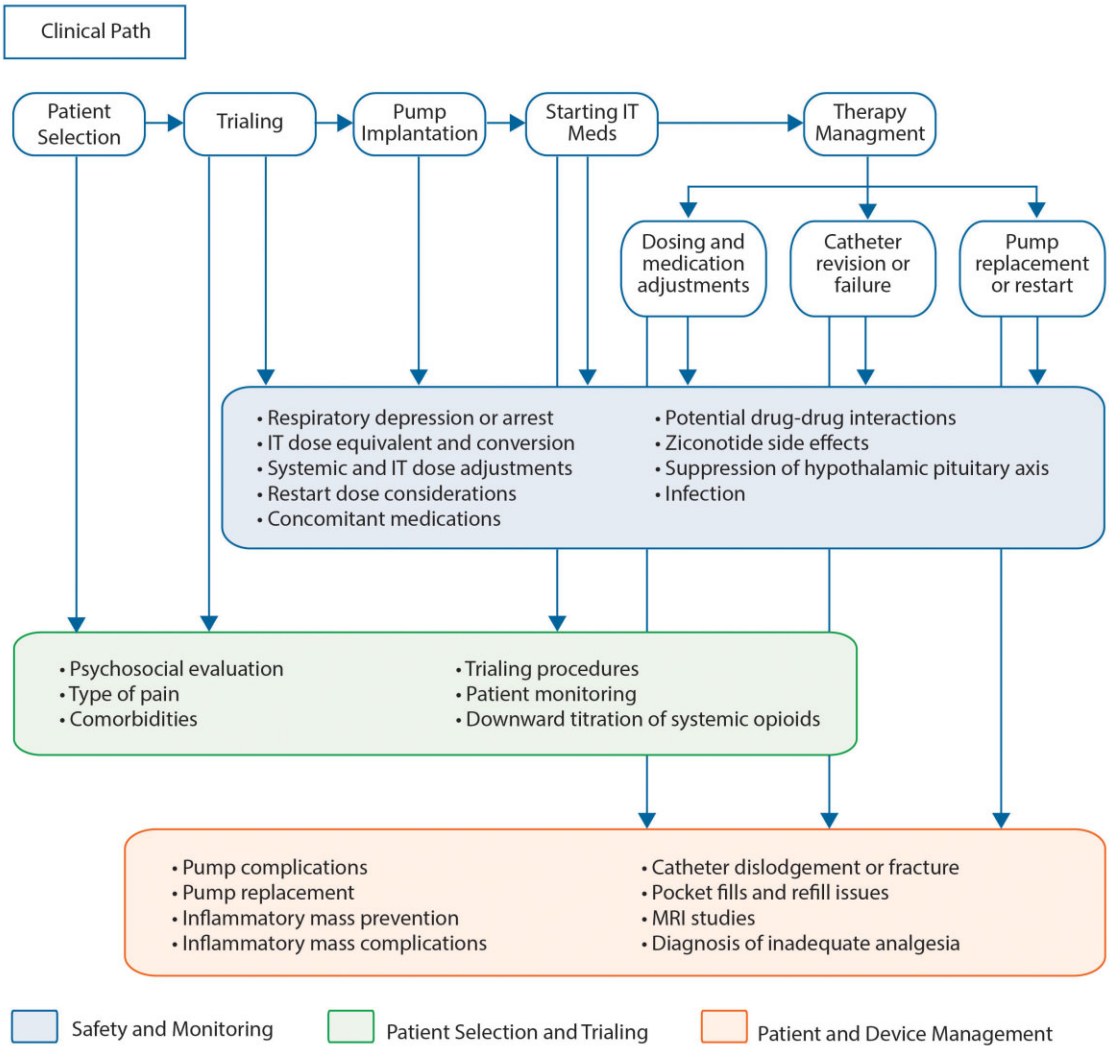


Figure 1. The clinical path of a patient being considered for an intrathecal drug delivery system entails multiple therapy considerations and potential areas for complications that require clinician attention. IT, intrathecal; MRI, magnetic resonance imaging.

patient selection and trialing process, patients, their families, or caregivers have the opportunity to learn about implantable pumps, suitability for IDD, the individual efficacy and side effects of IDD during the trial, and the risks and benefits associated with the therapy. Comorbidities such as obstructive sleep apnea, diabetes, obesity, metabolic syndrome, or chronic lung, cardiac, or kidney disease or smoking increase the risk of complications (13). Patients should also know that achieving an appropriate balance between pain management and side effects takes time and may require slow titration with continuing adjustments.

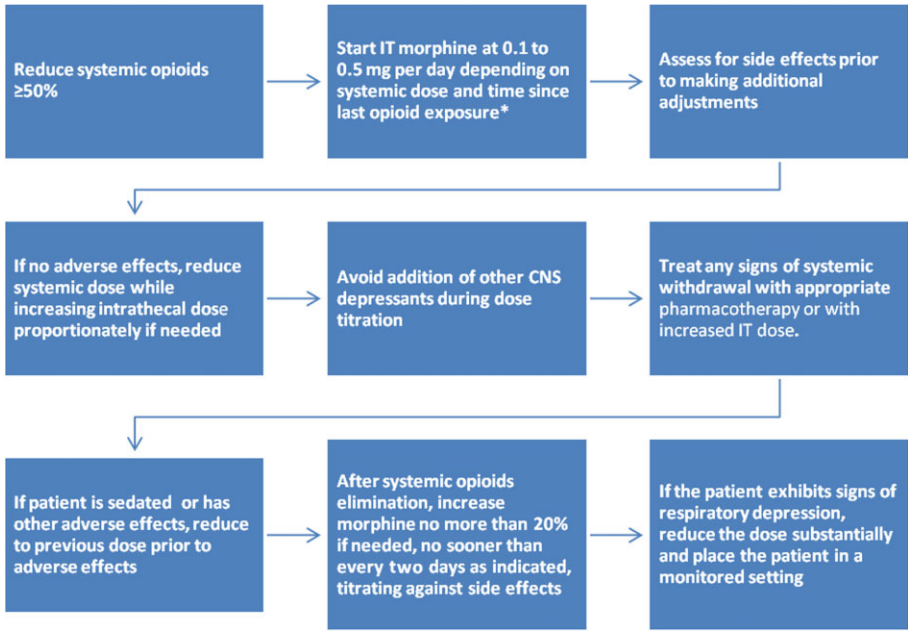
THE PATIENT IS A PARTNER IN THERAPY.

At every visit, clinicians must ask patients to list all of the medications they take, including over-the-counter and complementary medications and those prescribed by other physicians. Undisclosed alcohol or illicit drug use complicates IDD and can make it dangerous. It is reasonable for the treatment team to order periodic urinary drug screening to gauge patient compliance. At each visit, patients should be encouraged to report and should be examined for any changes in pain perception, and new or worsening side effects also need to be assessed at each visit.

Obtaining informed consent before implantation is mandatory, and the panel experts also recommended renewing the informed consent periodically (16). Elements of informed consent might include refill appointments, prescribing physician supervision, dosing adjustments, illegal drug or alcohol use, and discontinuation of pump medication (17). Appendix I on line contains a sample informed consent form for IDD that can be adapted according to physician preferences and practice settings.

RESPIRATORY DEPRESSION IS THE KEY THERAPY-RELATED SAFETY ISSUE ASSOCIATED WITH IDD.

Respiratory depression comprises a clinical spectrum from clinically irrelevant to respiratory arrest. The American Society of Anesthesiologists (ASA) characterizes respiratory depression in the context of neuraxial opioid administration as reduced respiratory rate (<10–12 breaths per minute), reduced oxygen saturation (arterial oxygen saturation <90–92%), hypercapnia/hypercarbia (arterial CO_2 tension >50 mmHg), or clinical signs such as drowsiness, sedation, periodic apnea, and cyanosis (18). Many cases of respiratory depression can be prevented or minimized by collaboration with providers who prescribe central nervous system (CNS) depressants.



*In certain clinical settings where patients' systemic doses cannot be reduced, physician discretion may dictate a higher intrathecal starting dose (20).

Figure 2. Algorithm to guide appropriate dose titration. CNS, central nervous system; IT, intrathecal.

Physicians must insist on full disclosure by the patient and coordinate prescriptions with other treating physicians. A drug screen may be considered prior to trial or permanent implant.

CONSIDER THE CLINICAL RAMIFICATIONS BEFORE ADDING ANY CNS-ACTIVE DRUG.

Between 1999 and 2006, the number of all-cause fatal opioid poisonings more than tripled in the United States from 4000 to 13,800 deaths (19). Thirty-seven percent of the fatalities in 2006 were attributable to opioid analgesics, and in about half of the cases, more than one type of drug contributed to death; benzodiazepines were implicated most often. In the IDD-associated fatal respiratory depression cases investigated by Coffey et al. (20), patients were taking between one and nine concomitant drugs, including sedatives, hypnotics, oral and transdermal opioids, antidepressants, tranquilizers, and antihistamines. All but one death occurred in outpatient settings where appropriate administration of concomitant drugs depended on patient compliance. These data underscore the necessity of supervising *all* of a patient's CNS-active medications and of fully weighing the implications of using any nonessential CNS-active drug, particularly during the trialing and perioperative period. In cases of psychiatric disease, this may not be possible. In those cases, it is important that the psychiatrist and the interventional pain specialist or implanting surgeon be in proper communication.

Great care must be taken in selecting dosing regimens for IDD. Knowledge of intrathecal dose labeling for each drug placed in the pump is essential. The goal of fine-tuning the opioid dose is to reach the lowest efficacious dose to minimize side effects (18,21). In practice, conversion of opioid doses from one route of administration to another can be problematic (12,22,23). Individual variations exist in patients' responses to opioids (24), no safe ceiling doses have been established, and the consequences of inappropriate dosing and rapid titration can be life threatening (25). In addition, many other factors affect drug delivery, including catheter tip location, cerebrospinal fluid (CSF) flow, and stenosis. Safety is ensured by erring on the side of conservatism. Dosage can be titrated up to alleviate pain in a relatively short period of time based on patient response to previous dose. Therefore, when starting intrathecal therapy, eliminate systemic opioids, if possible, and reduce systemic opioid doses by at least 50% when elimination is not feasible (7,26). The recommended initial lumbar dose range in patients with no tolerance to opioids is 0.1–0.5 mg per day. The upper daily dosage limit for each patient must be individualized (27). Start with low doses and escalate slowly when changing from one medication to another as well (13,25).

The medication-related side effects of intrathecal opioids are highly individual and not linearly dose dependent (28). Titrate dose increases slowly to minimize adverse effects and allow patients to develop tolerance (25,29). After reaching a stable dose, per-episode dose increases should generally be limited to no more than 20% in stable patients with noncancer pain (Fig. 2). More rapid dose titration may be suitable for patients with cancer pain (29). Dose increases can occur at once-weekly intervals for frail or elderly patients and at more frequent intervals for younger, healthier patients (25). When supplementing a daily infusion, increases should not exceed 20% of the *total* infused daily dose. This recommendation applies especially when the patient-controlled analgesia device is added to IDD, which should prompt the setting of dose limitations within a time frame to minimize risk of overdose (13). The use of patient-controlled analgesia devices with implanted pumps has resulted in high patient satisfaction (>80%) for various reasons, but especially because of the sense of control over pain the device provided (30,31).

Opioid receptor affinity mediates almost all of the side effects associated with IDD (Table 1) (26,32). Hydrophilicity (or lipophilicity) determines to a large extent how far a drug will spread in the CSF (3). Morphine is more hydrophilic, which results in potentially greater CSF diffusion because of the partition coefficient than more lipophilic compounds (39) and its effects linger, resulting in slower

Table 1. Incidence and Management of Side Effects Associated With Intrathecal Morphine Therapy.

Side Effect	Incidence	Treatment
Pruritus	0–100% (32) 14% for long-term ITT (33)	Treatable with mu antagonist naloxone
Nausea and vomiting	30% with acute ITT (32) ~21% in long-term ITT (33)	Antiemetics Improved by lowering dose
Urinary retention	42% (34) to 80% (35) ~3% in long-term ITT (33) Dose dependent More common in men with enlarged prostates	Cholinomimetic agents (e.g., bethanechol or distigmine [used in the UK]); catheterization if medication is ineffective
Constipation	30% (33)	Stool softener, bowel stimulant or laxatives
Edema (preexisting venous insufficiency and edema are relative contraindications to intrathecal therapy (38))	3% (33) to 16% (36)	Leg raising, elastic stockings, compressive air pumps, salt and fluid restrictions, diuretics
Mental status change (sedation and lethargy, paranoid psychosis, catatonia, euphoria, anxiety, delirium, hallucination)	10–14% in long-term ITT (33)	Lower opiate dose first Treat sedation with psychostimulants (modafinil) or neuroleptics (haloperidol)
Sexual dysfunction	68.8% in women, 95.8% in men (38) Due to opioid-induced hypogonadism	Lower opiate dose Rotate opioids Prescribe hormone replacement therapy
Respiratory depression	Cause of some fatalities soon after the start of ITT	Start ITT with low dose Monitor vulnerable patients for 24 hours after start or change of ITT (25) Readily reversed with naloxone or nalbuphine

Adapted from Ruan X. *Pain Physician*. 2007;10:357–365. ITT, intrathecal therapy.

onset of action and long-lasting antinociception and respiratory depression (3). The decreased clearance of morphine from the CSF allows rostral spread to the brain stem, which tends to amplify side effects. It should be noted that the most common side effects of intrathecal opioid therapy—pruritus (32), nausea and vomiting (32), urinary retention (34), and constipation (33), which frequently appear at the start of therapy—usually can be managed and generally resolved during the first three months of IDD therapy (15,40).

MONITOR ALL PATIENTS IN A FULLY EQUIPPED AND STAFFED ENVIRONMENT FOR AT LEAST 24 HOURS AFTER START OR RESTART OF OPIOID INTRATHECAL THERAPY.

Respiratory depression, potentially the most serious side effect of opioid IDD, can be detected and treated if a patient is monitored following the start or restart of opioid therapy. This cautious approach is based on the observation that patients can become relatively naïve to the effects of intrathecal opioids within as little as a week's interruption in therapy (20). Other panels have recommended hospital monitoring for 24 hours for vulnerable patients, defined as the elderly, the young, opiate-naïve patients, or patients with significant comorbidities (reduced cardiac or respiratory reserve, for example) (25). While the duration of inpatient monitoring is a matter of clinical judgment, the panel recommends monitoring for all patients receiving intrathecal opioids in a fully equipped and staffed environment for at least 24 hours during initiation or reinitiation of opioid therapy. The ASA practice guidelines call for monitoring adequacy of ventilation (respiratory rate, depth of respiration), oxygenation (continuous pulse oximetry), and level of consciousness (sedation scores) (18). Vital signs should be documented at least every four hours in an inpatient setting. Pulse oximetry must have alarms perceptible to nursing staff at all times. The opioid reversal medication naloxone must be readily available. Nursing staff should be educated about the unique monitoring requirements of patients being treated with IDD.

The patient's family or caregivers can be enlisted in the surveillance for side effects after the patient is discharged or leaves the office. Thus, patient education should include the clinical signs of overdose, including dizziness, sedation, euphoria, anxiety, seizures, and respiratory arrest.

START ZICONOTIDE AT A DOSE OF NOT MORE THAN 0.5 mcg/24 HOURS, WITH INCREMENTAL INCREASES OF NOT MORE THAN 0.5 mcg/24 HOURS, NO MORE OFTEN THAN ONCE WEEKLY.

Preservative-free ziconotide (Prialt®, Jazz Pharmaceuticals, Dublin, Ireland) was approved by the FDA for IDD in December 2004, and soon joined preservative-free morphine (West-Ward Pharmaceuticals, Eatontown, NJ, USA) as a first-line intrathecal therapy (25). This highly hydrophilic drug may require several days to demonstrate efficacy (13), and the median time to onset of the most common adverse events is from three to 9.5 days (41). This slow onset of action may explain why side effects often persist despite discontinuation of ziconotide.

The current recommendations regarding the initiation of treatment are to start at a much lower dose with much slower titration than appeared in the initial ziconotide package insert (41). Table 2 shows the incidence of side effects identified and usual treatment provided in a placebo-controlled trial. Prior to introducing ziconotide, a psychiatric evaluation should be performed if the patient exhibits signs of an untreated psychiatric illness. If a patient has a history of psychosis or schizophrenia, ziconotide should only be administered in collaboration with the patient's psychiatrist. Careful observation of patients for potential side effects (Table 2) at the start or restart of therapy is warranted. No permanent direct sequelae of ziconotide have been described in the professional literature, despite reported incidences of profound inadvertent overdosing (43). However, ziconotide-associated symptoms of ataxia and poor balance can result in significant, potentially permanent consequences from falling. Psychological symptoms resolve after

Table 2. Incidence of Treatment-Emergent Adverse Events Reported in a Slow-Titration Placebo-Controlled Trial (42) or at MedWatch (41) and Management of Side Effects Associated With Intrathecal Ziconotide Therapy.*

Side effects	Incidence	Treatment: Most side effects can be treated effectively by decreasing the medication dose.
Any adverse event	93% (42)	
Body as a whole	57% (42)	
Asthenia	22% (42)	Caffeine
Headache	15% (42)	Acetaminophen or NSAID
Pain	11% (42)	Not felt to be related to therapy
Fever	7% (42)	
Digestive system	60% (42)	
Nausea	41% (42)	
Diarrhea	19% (42)	
Vomiting	15% (42)	
Anorexia	10% (42)	
Nervous system	81% (42)	
Dizziness	47% (42)	
Somnolence	22% (42)	
Confusion	18% (42) to 33% (41)	
Ataxia	16% (42)	
Abnormal gait	15% (42)	
Memory impairment	12% (42) to 22% (41)	
Hypertonia	11% (42)	Low-dose baclofen
Anxiety	9% (42)	Short-term benzodiazepine
Speech disorder	9% (42) to 14% (41)	Decrease medication
Aphasia	8% (42) to 12% (41)	Not felt to be significant
Nystagmus	8% (42)	No treatment
Dysesthesia	7% (42)	No treatment unless it worsens
Hallucinations	7% (42) to 12% (41)	Consider possible short-term, low-dose antipsychotic but most panelists recommended decreasing medication
Nervousness	7% (42)	Consider short-term benzodiazepine
Paresthesia	7% (42)	No treatment unless it worsens
Vertigo	7% (42)	Short-term meclizine
Psychosis	1% (41)	Decrease or eliminate medication
Special senses	20% (42)	
Abnormal vision	10% (42)	
Urogenital	22% (42)	
Urinary retention	9% (42)	Decrease medication, bethanechol

*When a patient experiences side effects, one clear way to deal with the problem is to decrease the dose. Physicians should use their own best judgment to validate the use of treatments for side effects.
NSAID, nonsteroidal anti-inflammatory drug.

ziconotide is discontinued, and therapy can be halted without causing withdrawal symptoms (44). Among patients who benefit from ziconotide, discontinuation rates for adverse events are similar to those for placebo, supporting a low rate of side effects (45).

CONSIDER UNDERTAKING AN ENDOCRINE EVALUATION BEFORE STARTING INTRATHECAL OPIOID THERAPY, WITH PERIODIC MONITORING FOR HORMONE SUPPRESSION.

Long-term opioid therapy, whether systemic or intrathecal, can profoundly alter neuroendocrine function (38), affecting two major hormonal systems: the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis (21). In a study that compared patients treated with intrathecal opioids with a control group of patients with a similar pain syndrome who were not receiving opioid treatment, the majority of the treated patients (23 of 24 men and 22 of 32 women) developed hypogonadotropic hypogonadism (38). Fifteen percent of the opioid-treated patients developed central hypocorticism, and a similar percentage developed growth hormone deficiency. Patients treated with opioids also had slightly more body fat and slightly higher low-density lipoprotein cholesterol than patients in the control group. Periodic evaluations by an endocrinologist or qualified internal medicine specialist allow patients to be treated for sex-steroid deficiencies or an unfavorable lipid profile before hormone deficits manifest clinically. Follow-up for any new endocrine symptoms can be coordinated through the patient's primary care physician at regular intervals.

USE VIGILANCE AND WELL-ESTABLISHED SURGICAL TECHNIQUE TO PREVENT INFECTION.

Infection control measures, scrupulous surgical technique, and vigilant monitoring of wound healing are essential. Follett et al. surveyed the literature pertaining to infections in patients undergoing IDD and found strong evidence (Category IA) for administering antimicrobial prophylaxis (46). The *Guideline for Prevention of Surgical Site Infection, 1999* (47), issued by the National Center for Infectious Diseases, recommends: Use an antimicrobial agent for those operations in which surgical-site infections would represent a catastrophe. Use an agent that is safe, inexpensive, and bactericidal with an *in vitro* spectrum that includes the most probable intraoperative contaminants for the operation in question. Time the infusion of the

Table 3. Preimplantation Checklist.

Key trial tasks
- Conduct a complete patient history and physical examination
- Ensure the patient meets indications for the therapy
- Assess and document patient's symptoms
- Evaluate patient motivation and commitment to therapy
- Assess support of patient's family and social network for this intervention
- Set treatment success goals with patient
- Obtain insurance preapproval (if appropriate)
- Educate patients and caregivers
- Obtain informed consent
- Conduct a trial
- Assess outcome for pain relief, functional restoration, tolerability, and compatibility with patient's lifestyle and treatment goals

Pain history
- Complete a baseline pain assessment.
- Assess signs and symptoms, including intensity, distribution, and impact of pain.
- Review patient's current pain therapy. Is the patient receiving oral, intravenous, or intramuscular opiates at tolerable doses without adequate pain relief? Does the patient achieve pain relief but with side effects that impair activity and quality of life?
- Obtain supplemental opiate and nonopiate history from all providers.

Functional assessment
- Evaluate functional capacities (activities of daily living)
  May use questionnaire that assesses personal care, lifting, walking, standing, sleeping, sex life, social life (e.g., SF-36, EQ-5D, Oswestry)

Psychological or psychiatric assessment
- Complete psychological/behavioral evaluation, including standardized psychological assessment measures (e.g., MMPI-2 or MBMD)

EQ-5D, EuroQol-5D; MBMD, Millon® Behavioral Medicine Diagnostic; MMPI-2, Minnesota Multiphasic Personality Inventory-2; SF-36, Short Form (36) Health Survey.

antimicrobial agent so that a bactericidal concentration of the drug is established in serum and tissues by the time the skin is incised. And, finally, maintain therapeutic levels of the drug in serum and tissues throughout the operation and until a few hours after the incision is closed. While evidence has yet to confirm its value, it is a consensus recommendation to prescribe postoperative antibiotics as well. This recommendation is controversial and subject to clinician judgment. Collaboration with an infectious disease expert can be considered to monitor infection rates and address local pathogens that could place patients at risk.

Follett et al. found Category II evidence to support the use of aseptic surgical technique (2–5 min surgical scrub, double gloving, minimal-touch technique), implantation in an operating room rather than a procedure room, applying antiseptic occlusive wound dressings, and treating threatened incisions and external CSF leaks aggressively (46). Some evidence supports using a chlorhexidine rather than a betadine prep (48). The solution must be left to dry prior to incision. When implanting hardware, irrigation may reduce wound infections. Limited evidence suggests that an antibiotic solution (bacitracin) may be better than saline for this purpose (49). Betadine is toxic to healthy tissues and should not be used for irrigation (50). There is no evidence that soaking the pump in an iodine-based solution is better than soaking it in saline before implantation (49,51). Manufacturers do not recommend soaking pumps prior to implant. An established infection usually requires removal of the infected components or the entire device, and eradication of the infection before replantation is contemplated.

PATIENT AND DEVICE MANAGEMENT

Implantation Technique

Proper pump and catheter implantation techniques have been described in the professional literature by Follett et al. (52) and by manufacturers. Some manufacturers also support training courses and on-site peer-to-peer education. We will describe placement of the pump in the abdomen rather than the buttocks, because manufacturers recommend abdominal placement, and other locations have not been vetted in the literature. A preimplantation checklist can be used to prepare for the procedure (Table 3). Once the catheter has been placed, the system can be implanted under general or spinal anesthesia, or under local anesthesia with sedation, depending upon the physician's and patient's preferences, and the patient's condition. If general anesthesia is used, special care must be taken both at the time of needle placement and of catheter advancement to avoid trauma to the spinal cord, because the ability to utilize patient feedback as a form of monitoring is eliminated. There was a significant minority opinion that general anesthesia should be avoided for percutaneous placement of an intrathecal catheter, except under special circumstances such as a patient's inability to be still during placement despite moderate sedation (e.g., due to spasticity or cancer).

Preoperative examination should include investigation of spinal deformities, previous spinal or abdominal surgeries, and other relevant comorbidities. A full surgical scrub, sterile draping, and a wide bio-occlusive, adhesive antiseptic drape are recommended. The needle is inserted at the L2-3 or L3-4 level unless anatomy, disease, previous surgery, or other unusual circumstances require alternative placement. Insertion of the catheter above L2 increases the risk of conus medullaris injury. Anecdotal evidence suggests that insertion in the more mobile lower lumbar spine may expose the catheter to greater risk of dislodgement or damage (52).

The use of a shallow-angle, paramedian, oblique needle-insertion angle and trajectory avoids the catheter crossing the spine, which could result in damage or dislodgement later. The entry point of the needle should be approximately one to two vertebral levels below the interlaminar space selected for dural puncture, and lateral to the midline, ipsilateral to the intended pump pocket. Entry into the

subarachnoid space allows a return of CSF through the needle. If the implanter chooses to align the bevel of the needle on entrance in a longitudinal direction, then the needle should be rotated 90 degrees before advancing the catheter.

According to one manufacturer's clinical reference guide (53) and expert consensus, if the catheter must be withdrawn during positioning, it should not be withdrawn through the needle with or without the stylette in place. Doing so could weaken, nick, or sever the catheter (52). A rare exception might be made, based on clinical judgment to avoid repeat dural puncture, to gently withdraw the catheter in the *absence of any resistance*. Placing the catheter under fluoroscopic guidance is required for positioning the tip at the desired level. Depending on the implanter's experience and comfort with the procedure, and the complexity of the patient's anatomy, lateral fluoroscopy may be helpful. Remove the needle from the spinal canal first, hold the catheter gently at its site of entry into the fascia, and then slowly remove the guidewire. Various catheter-anchoring techniques reduce the likelihood of dislodgement. Elbow, butterfly, and V-wing-shaped devices can be used. The catheter should be secured to the lumbodorsal fascia, *not* to the subcutaneous fat. For the pump, if suturing to the abdominal fascia is not possible, a mesh pouch should be considered (deploy per manufacturer's instructions), and a pump pocket created with special care to make it as small as possible to merely allow the pump to fit in.

While Level I evidence to support anchoring as a best practice does not exist, observational data published by Follett et al. indicated that meticulous anchoring can reduce the likelihood of dislodgement and other complications (52). Manufacturer instructions also recommend that anchors always be used. Anchoring should be performed in a manner that prevents tensile forces at the catheter entry site, allows gentle loops to avoid catheter kinks, and secures the catheter to the anchor and the anchor to the fascia with nonabsorbable sutures (52,53).

The catheter is passed from the smaller spinal incision to the larger pump pocket within the abdominal wall by using a tunneling tool. The pocket size should be approximately 120% of the volume of the pump, large enough that the incision does not overlie the pump after wound closure, and sufficient to permit the catheter segment that attaches to the pump to be looped and placed behind the pump. A pocket that is the same volume as the pump will result in tension on the wound and subsequent dehiscence. A pocket that is too large can lead to pump movement or flipping. Attach the connector to the pump and place the pump in the pocket with excess catheter coiled behind. If there is any question of the integrity of the catheter system between the pump and catheter, the panel advises aspiration of the side port to ensure that CSF can be obtained as final confirmation of catheter patency (53). If CSF cannot be obtained, it is necessary to troubleshoot the entire system. The length of the implanted catheter should be noted in the operative report. Place the pump at a depth of 1–2 cm so that the reservoir access port can be easily palpated before refilling and proper telemetry with the programmer can be maintained. Use meticulous closure technique to prevent infection or dehiscence.

Managing Pump- and Catheter-Related Complications

Clinicians should familiarize themselves with the manufacturer's manual and with potential pump- and catheter-related complications. Mechanical pump malfunction is uncommon and has declined with each generation of pumps[1] (54,55). One documented and preventable cause of pump failure can be corrosion from compounded (i.e., off-label) drug formulations that results in permanent pump stalls (56). The overall failure rate of the Medtronic SynchroMed II pump at 78 postimplant months is 2.4% when used to dispense approved drugs (Medtronic Product Performance Clinical Registry) and 7.0% when used to dispense unapproved drugs (57). Intermittent motor stalls also occurred in the Medtronic SynchroMed EL pumps near the end of their service life. These pumps were designed without a hard stop for end of service and without an alarm for motor stalls. Pump stalls invariably result in underdosing, which becomes evident clinically as decreased efficacy or withdrawal symptoms. To aid in end-of-service planning, the SynchroMed II pump was designed with a seven-year hard shut-off and a motor stall alarm to help clinicians determine if intervention is appropriate. Because of the variety of considerations that can delay a reimplant procedure, a plan for replacement or discontinuation should be formulated immediately when the 90-day elective replacement indicator activates. These available data are based on the performance of the SynchroMed II pump. No performance data, based on actual market experience, have been reported by any other system manufacturer. The data regarding pump failure are complex. At this time, no additional conclusions can be drawn regarding specific medications and concentrations.

Catheters are the most vulnerable component of the system for damage or dislocation. Caution patients that an active lifestyle that involves repetitive bending or twisting of the spine could increase the risk of damage or dislodgement of the catheter. Catheter complications—such as microfracture, leaks, disconnection, breakage, kinks, migration, partial occlusion, fibroma, or inflammatory mass—are more common than pump failures. The symptoms of catheter problems are often subtle and noticed by the patient as reduced efficacy, increased pain, and possibly withdrawal symptoms. The diagnostic work-up for inadequate analgesia should follow a logical progression, as shown in Figure 3, and begins with a review of the patient's history, which frequently offers clues to the underlying cause. The algorithm described in Figure 3 represents the panel's view of a sound approach to assessing a patient for suspected inadequate analgesia.

When troubleshooting catheter problems, identify the catheter tip location and flow rates, and determine to the degree possible the drug distribution characteristics. Although CSF plays a crucial role in the distribution and elimination of intrathecal medications, our knowledge of CSF movement comes mainly from studies in immobilized animals and drugs other than morphine or ziconotide (58). In anesthetized pigs treated with slow intrathecal infusions of baclofen and bupivacaine, there was very limited distribution of the drugs in CSF after eight hours. This led to the conclusion that catheter tip location is critical to efficacy, given the small area of drug distribution (59). Other investigators assert that in humans, CSF is replaced three to four times daily at a rate of 0.3 to 0.4 mL/min (17,60), which would favor wider drug distribution, especially in a conscious, ambulatory person treated for longer periods of time. It should be noted that even partial catheter occlusion can have an impact on efficacy because of the small volumes and slow infusion rates of intrathecal medications.

Replacing a functioning catheter is unnecessary and could pose a risk to the patient. Investigation of suspected catheter dislodge-

[1] Combined survivability for the Synchromed II 20-mL and 40-mL pumps at five years is 97.7% (*Medtronic 2011 Product Performance Report, for Synchromed II*). Survivability is defined as the percentage of implanted devices that remain free from product performance-related events at various time points.

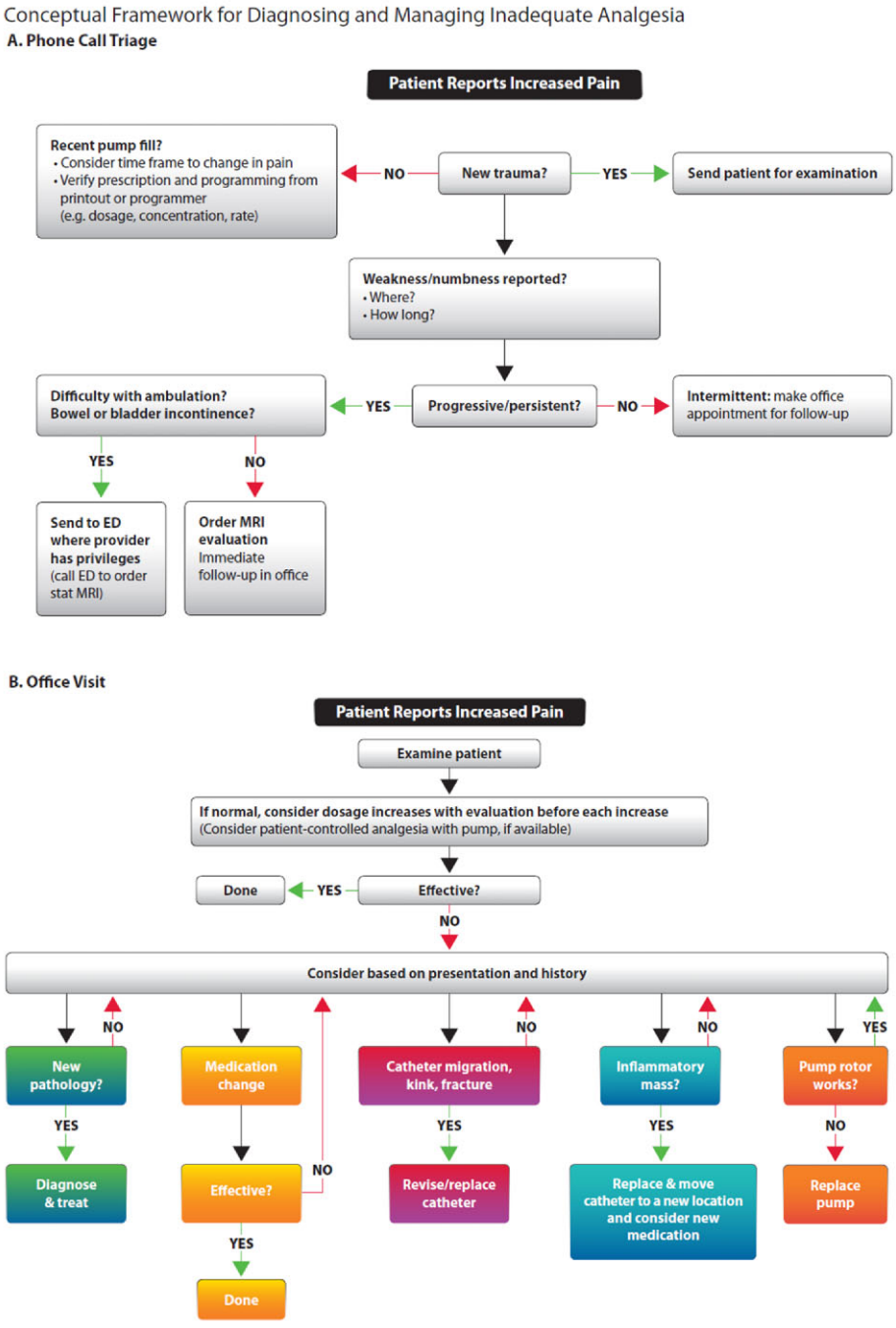


Figure 3. Algorithm for diagnosis of inadequate analgesia. Reprinted with the permission of Medtronic, Inc. © 2013. ED, emergency department; MRI, magnetic resonance imaging.

ment should begin with plain anteroposterior and lateral radiographs of the abdomen and spine or fluoroscopic study. Catheter fractures occur most often where the catheter passes through the intraspinal ligaments or in the pump pocket. "Overexposure" may be necessary to see the entire catheter clearly (55). The catheter can be aspirated and flushed if the pump has a catheter access port. The procedure requires careful surgical preparation to prevent infection. Aspirate at least 1.5 mL to remove medication from the catheter tip. The catheter tip is probably not obstructed if 2–3 mL of CSF can be aspirated easily; aspiration is more difficult if the tip is partially occluded. A hole in the catheter may allow CSF to be aspirated but not in a steady flow. In some cases, catheter fracture allows CSF fluid to collect in a pocket where it can be aspirated from the catheter access port. After medication has been removed, 2–4 mL of contrast media suitable for intrathecal use can be infused and radiographs repeated to verify catheter tip location.

TO AVOID OVERDOSE, CONTRAST MEDIA OR OTHER LESS VISCOUS SOLUTIONS INTENDED TO CLEAR THE CATHETER SHOULD NEVER BE INJECTED IF NO SIGNIFICANT FLUID CAN BE ASPIRATED FROM THE ACCESS PORT (53).

The most informative test of catheter integrity is a nuclear medicine evaluation using radiolabeled indium. A nuclear scan should

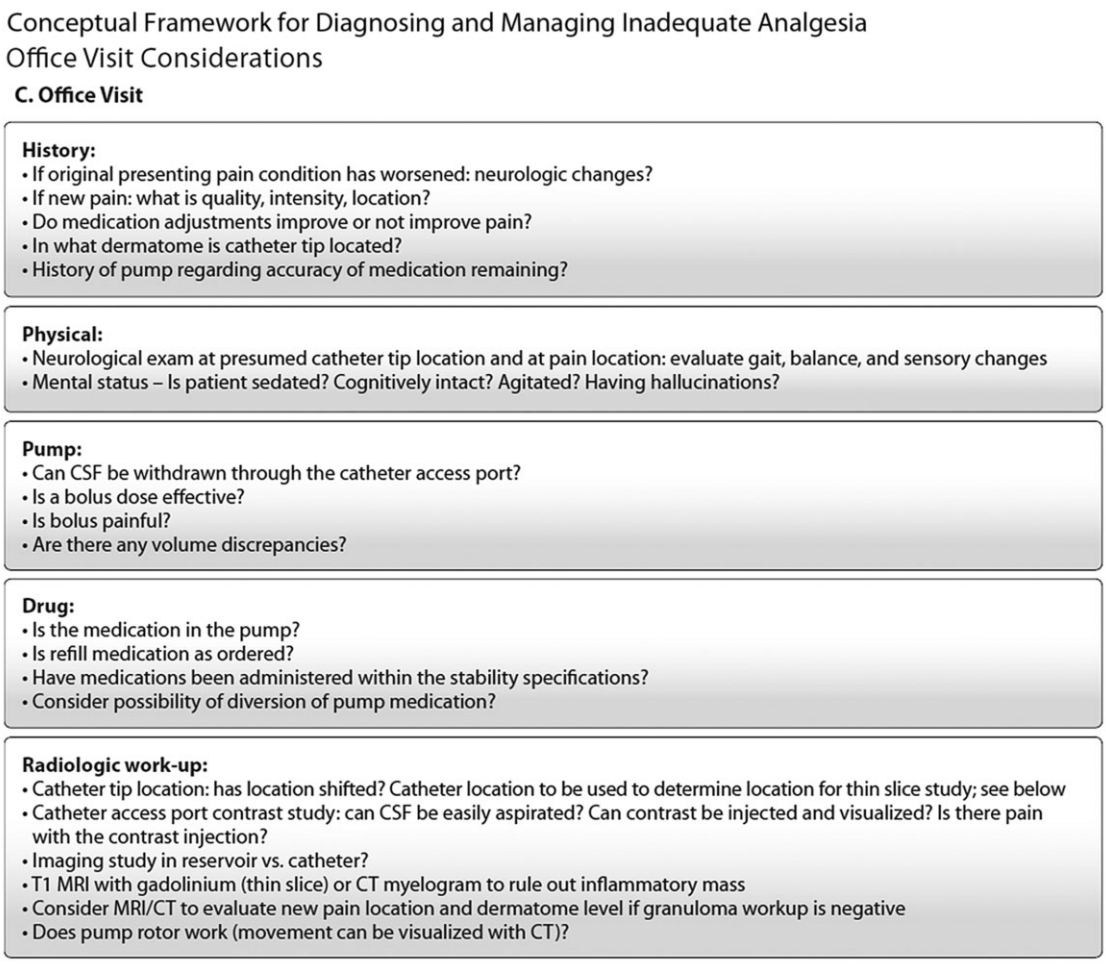


Figure 3. *Continued*

only be considered if the patient is stable, not expected to undergo withdrawal in 24–48 hours, and indium is available. Before performing a nuclear study, the pump reservoir volume, drug concentration and dose, and the catheter length and volume must be determined so that the correct volume of infused indium can be calculated. The flow rate must also be determined so that the time it takes for the tracer to reach the catheter tip will be known. Sequential analysis during the appropriate time frame should document the tracer's flow out of the pump, into the catheter, and into the CSF if the catheter is intact. Anterior, posterior, and oblique views may be needed to fully visualize the pump and catheter.

Pocket Fills

A pocket fill is the inadvertent injection of all or some of the prescribed drug into the patient's subcutaneous tissue, which includes the pump pocket, instead of the pump. From May 1996 to September 2010, 351 such incidents were reported to the manufacturer, for a frequency of 1 per 10,000 refills (0.0101%), assuming that pumps are refilled six times per year (61). Among the reported incidents, there were 8 deaths, 270 interventions for serious or life-threatening injury, and 58 cases requiring no medical intervention. Pocket fills can result in immediate overdosing, withdrawal as a result of treatment for overdose, and delayed underdosing due to incomplete pump refill if not corrected.

Overdose symptoms typically occur immediately or within several hours. Underdose may become clinically apparent within days or weeks, when the pump has run out of drug at an earlier-than-expected date. Sometimes pocket fills are accompanied by swelling at the injection site or by the patient's reporting an unusual sensation, such as burning or stinging. However, absence of these signs or sensations does not rule out a pocket fill. At every refill, patients and caregivers should be reminded of the signs and symptoms of overdose, underdose, and withdrawal, and instructed to seek immediate medical assistance should they experience any of the symptoms.

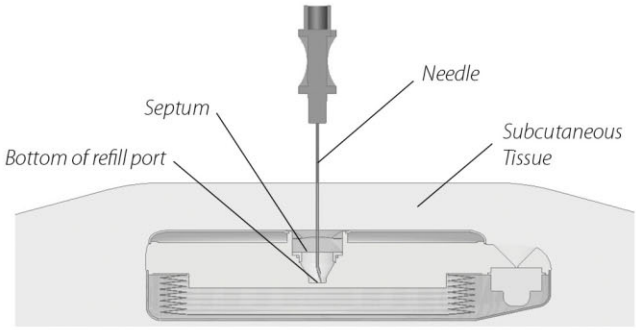
If the possibility of a pump pocket fill is recognized immediately, management should begin in the physician's office. Diagnosing a pocket fill is made by emptying the pump completely and comparing the expected reservoir volume to the actual reservoir volume. Fluid detection and pump emptying can be facilitated by ultrasound guidance if readily available, although not detecting fluid does not necessarily rule out pocket fill. A volume discrepancy may indicate a pocket fill, and the patient should be monitored overnight. Note: Do not use the programmer to determine the actual volume of drug in the pump. The programmer and pump do not measure the actual volume of drug in the pump. The medication should be replaced with saline (or the pump turned down to minimal rate) and the patient monitored, perhaps overnight. If a pocket fill is suspected or known, monitor the patient closely for

Table 4. Avoiding and Responding to Pocket Fills.

Inserting the Needle

When inserting the needle you should feel the needle:

1. pass through the patient's skin and subcutaneous tissue,
2. hit the silicone septum,
3. pass through the septum, and
4. hit the metal bottom of the refill port.



Inserting the Needle

(Note: This illustration represents a cross-section view of the SynchroMed II 20 mL pump.)

- Needle placement within the pump septum should always be checked throughout the procedure to help perform a successful refill as illustrated.
- Correctly accessing the port can be affected by factors such as: obesity, scar tissue, seroma, implant depth, patient position during refill, patient movement during refill, postimplant patient weight changes, pump orientation in the pocket, and pump movement within the pocket.
- The actual amount of drug aspirated from the pump should be compared with the expected reservoir volume, as an indicator that the refill needle is properly positioned in the pump reservoir.
- If all or part of the drug is known to have been injected into the pocket during the refill procedure, aspirate as much drug as possible from the pocket.
- Monitor the patient closely for signs and symptoms of overdose in an appropriate facility for a sufficient amount of time or until the symptoms have resolved. Seek emergency assistance and follow emergency procedures for overdose as necessary.
- Using ultrasound to guide refills has recently been described in the literature (62). This may be a promising approach. Insufficient information and experience are available to support a recommendation at this time.

sedation, hypotension, and respiratory depression. Emergency measures may be required to prevent hemodynamic instability or severe respiratory depression. Panel experts agreed there should be a very low threshold for additional monitoring. Recommendations for avoiding pocket fills appear in Table 4. Figure 4 illustrates an overdose emergency algorithm. Patients reporting symptoms from a remote location should be directed to proceed to the emergency department of the nearest hospital.

Many pumps have two access ports. One port accesses the pump reservoir and the other, termed the side port, directly communicates with the intrathecal catheter. Injections into that port result in medication being injected into the intrathecal space. Newer pumps have side ports that only accept smaller gauge needles to avoid inadvertent intrathecal bolus. Inadvertent side port administration of medication has been reported, and Figure 4 describes approaches to addressing the problem. This figure also applies to situations in which programming error can produce intrathecal overdose.

Pump Refills and Replacement

Infumorph labeling is very specific on pump refill directions (27). Pump fills and refills should always be performed by adequately qualified and trained personnel. Panel experts recommended observing patients for at least 30 min after pump refill. Refill frequency should be carefully planned to avoid depletion of the reservoir. Refills should be conducted with strict attention to needle placement in an environment free of distractions to avoid accidental injection of solution into surrounding tissue or the incorrect port. Naloxone should be on hand to treat inadvertent overdoses. Patients and caregivers should also be reminded of the symptoms of overdose or inadequate analgesia (see the Figure 3 algorithm) and told to call the physician's office immediately should any unusual sensations or sedation occur. Some patients, prior to refill, have experienced withdrawal symptoms before the 2-mL residual volume pump alarm activated (63). Their symptoms resolved after pump refill and did not recur when the residual volume alarm was set at 4 mL.

Pump replacement should not be planned without first asking whether the original therapeutic goals are still being met. Of course, it is always preferable to replace a pump as an elective procedure rather than under emergency conditions because, for example, the battery has died or the pump reached its automatic shut-off date (64).

Withdrawing an established catheter often leads to a CSF leak along the catheter tract.[2] This problem has been averted by using a blood patch in the tract, placing a purse-string suture around the catheter's exit from the lumbodorsal fascia, or tying off the old catheter but leaving it *in situ* (64).

When revising a pump, the implanter may encounter scarring, poor blood flow, and increased bleeding in the area of the pocket. The panel recommends using blunt dissection when possible to decrease tissue trauma. In areas of increased scarring, a cutting electrocautery may be helpful in reducing surgical times by loosening scar tissue around the device and creating hemostasis.

[2] Subdural fluid collections are an extremely rare but serious complication of spinal analgesia, including IDD. Only three reports of subdural hematoma have been published (Velarde et al. *Reg Anesth Pain Med* 2000;25 (1):76–78. Rosenfeld et al. *Pain Pract* 2009;4:312–316. Magro et al. *Neuromodulation* 2011;14 (2):179–181.). Such occurrences may be associated with the headache and vomiting related to CSF leakage, and possibly to anticoagulation therapy (McIntyre et al. *Tech Reg Anesth Pain Manage*. 2007;11:183–192.).

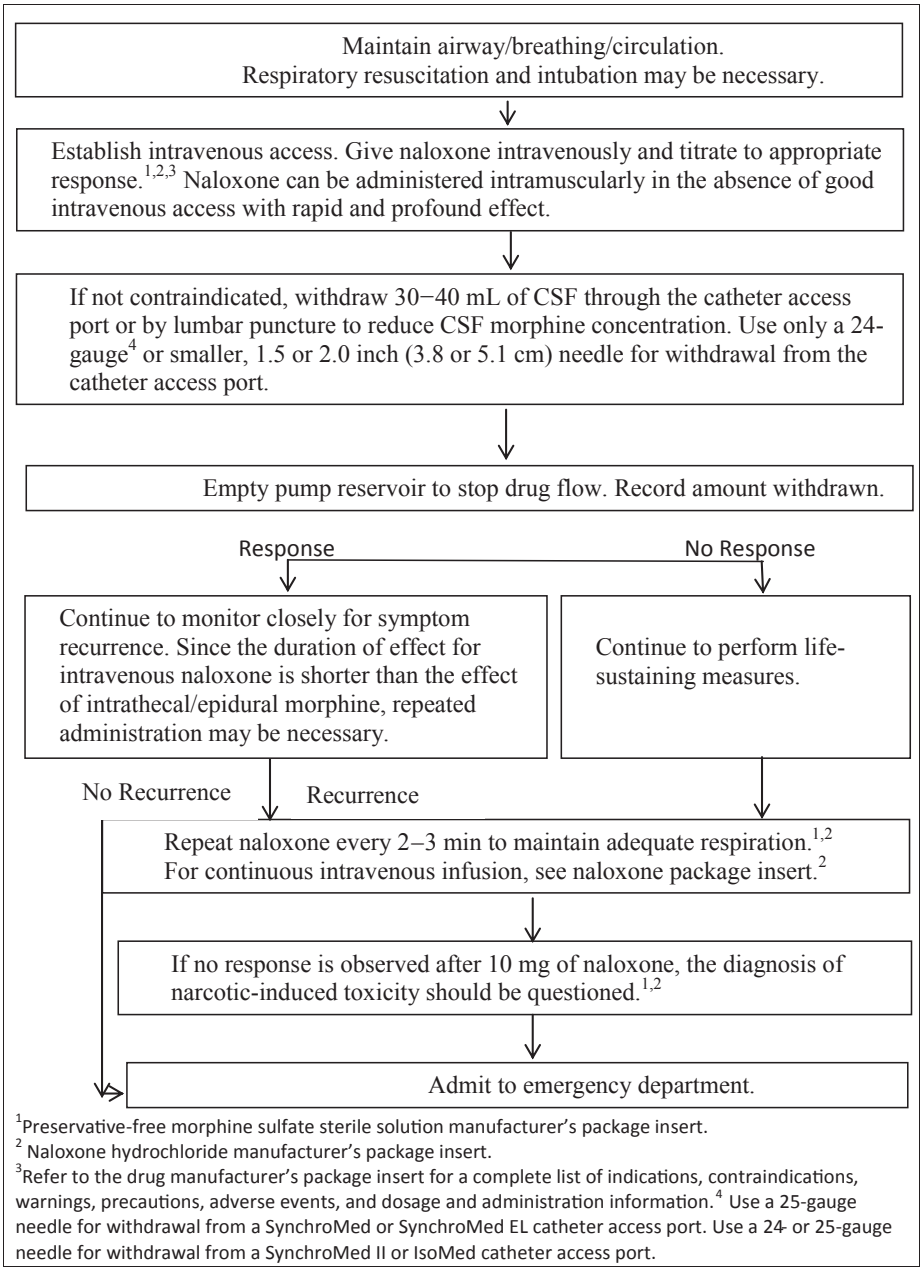


Figure 4. Morphine intrathecal/epidural overdose emergency procedure. CSF, cerebrospinal fluid.

Exercise caution when using electrocautery near the catheter. Vigorous irrigation and attention to bleeding should be performed before closure. With reimplants, it is important to assure the tissue is not constricting wound closure to avoid necrosis of the wound edges.

Surveillance, Mitigation, and Treatment of Inflammatory Mass

Development of an inflammatory mass (granuloma) at the tip of the catheter remains one of the most serious risks of IDD (25) because of the potential for temporary or permanent neurological injury. The first report of granuloma associated with intrathecal therapy was published in 1991 (65), a decade after implantable pumps were introduced. Based on current manufacturer analysis, the incidence of inflammatory mass is 0.49% for patients implanted with a drug infusion system for treatment of pain (66). The actual incidence is likely to be higher because of underreporting (67). The most frequent symptoms reported in 448 cases of inflammatory mass compiled between October 1990 and September 2007 were decreased therapeutic response/inadequate pain relief (33.5%), pain (32.6%), and neurological dysfunction (17.4%). No dose or concentration of morphine sulfate can be considered completely free of risk from inflammatory mass (68), although the risk appears to be cumulative over time and increases with higher concentrations of opioids (>25 mg/mL) or high daily doses (>15 mg/day) (69).

Early diagnosis and prompt treatment of inflammatory mass can help prevent serious sequelae. All patients on IDD should be routinely monitored for prodromal clinical signs or symptoms of inflammatory mass and for new neurological signs or symptoms (Table 5). If inflammatory mass is suspected, the diagnostic work-up starts

Table 5. Surveillance, Mitigation, and Treatment of Inflammatory Mass (66).

Surveillance

Physicians should routinely monitor patients receiving opioids for the following prodromal clinical signs or symptoms of inflammatory mass:

- Change in the character, quality, or intensity of pain
- Reports of new radicular pain, especially at or near the dermatomal level of the catheter tip
- Frequent or large escalations of the daily drug dose are required to maintain the analgesic effect
- Dose escalations alleviate increasing pain only temporarily

All patients on intraspinal opioid therapy should be monitored carefully at each visit for any new neurological signs or symptoms, including:

- New or different sensory symptoms (e.g., numbness, tingling, burning, hyperesthesia, hyperalgesia)
- New, occasional, or intermittent bowel or bladder sphincter dysfunction
- New motor weakness, change in gait, or difficulty walking
- Any neurological symptom or sign that differs from baseline (e.g., reflex changes)

In patients with new neurological signs or symptoms, consider neurosurgical consultation and the prompt performance of an imaging procedure (e.g., MRI with and without contrast or CT myelogram) to confirm or rule out the diagnosis of an inflammatory mass.

Mitigation

- **Intrathecal therapy should be administered to achieve adequate clinical response for as long as possible at the lowest effective dose and concentration.**
- Catheter tip placement in the lumbar intrathecal space may lessen the neurological consequences if an inflammatory mass develops, but may not provide as much therapeutic benefit. A lumbar mass may potentially be detected later in its time course because symptoms are not likely to develop until after the mass has reached a larger size. Patients who receive intraspinal opioid therapy should be monitored carefully at each visit for any new clinical and neurological signs or symptoms.

Treatment

Timely treatment may minimize or help to avert permanent neurological injury.

- If an inflammatory mass is detected early in its clinical course, a decrease or discontinuation of opioid delivery into the mass may cause it to shrink or disappear without the need for surgical removal.
- Note: Refer to Emergency Procedures included in the technical manual packaged with the refill kit for information on emptying the pump. Stopping the pump for more than a few days can cause the rotor to stall permanently. If therapy is to be discontinued for an extended period of time, the pump should be filled with preservative-free saline and programmed to run at the minimum rate of 0.048 mL/day.
- Depending upon an individual patient's clinical condition, intrathecal therapy may be continued after one of the following interventions:
  - Withdraw the catheter tip to a level below the inflammatory mass.
  - Remove the involved catheter and replace it with a new catheter positioned below the inflammatory mass.
  - Disconnect the involved catheter from the connector (two-piece catheter) or transect the involved catheter above the level of the lumbodorsal fascia (one-piece catheter), leaving the intraspinal catheter segment undisturbed. Ligate the exposed end of involved catheter to prevent CSF loss. Implant a new catheter with its tip below the inflammatory mass and connect the new catheter to the proximal (pump) catheter segment.
- Prompt open surgical removal of the mass or decompression of the spinal canal should be considered in patients who have a significant or progressive neurological deficit.

CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

with a complete patient history, a thorough neurologic examination, and a T1-weighted magnetic resonance imaging (MRI) performed with gadolinium (70), with a scout film performed prior to the MRI, and then with thin slices in the vicinity of the catheter tip. A computed tomography side-port myelogram is another option for assessing presence of granuloma, particularly for patients who cannot have an MRI (Fig. 5). Check the pump manufacturer's label to ensure the proper imaging option.

When an inflammatory mass is identified, treatment consists of decreasing or discontinuing opioid delivery into the mass, which may cause it to shrink or disappear (Table 4). If there is no neurologic impairment, withdrawing the catheter tip approximately 2 cm from the mass may prevent its growth. If symptoms persist, the infusion should be discontinued, and the opioid in the pump replaced with saline. Patients should be treated for withdrawal symptoms. If an inflammatory mass compresses the spinal cord or neurologic signs do not improve, the catheter should be explanted (70).

MRI

The magnetic field of an MRI scanner temporarily stops programmable pumps, suspending drug infusion for the duration of the scan (71). Upon completion of the MRI, the patient's pump should be interrogated shortly thereafter to ensure the pump has resumed proper therapy. The panel recommends following the manufacturer's recommendations (Table 6).

Radiology staff should review the patient's manufacturer-issued identification (ID) card. Patients should be advised to bring their manufacturer's ID to their MRI appointment and to alert the radiology staff conducting the MRI that they have an implanted IDD system before the procedure, so that the manufacturer's MRI guidelines can be reviewed. Appendix II is an information sheet for nonimplanting physicians who may see patients with an IDD.

Postsurgical Seroma

Should a postsurgical seroma develop, aspiration should only be considered if the amount of fluid precludes access to the pump, because of the risk of introducing infection (72).

PATIENT SELECTION AND TRIALING

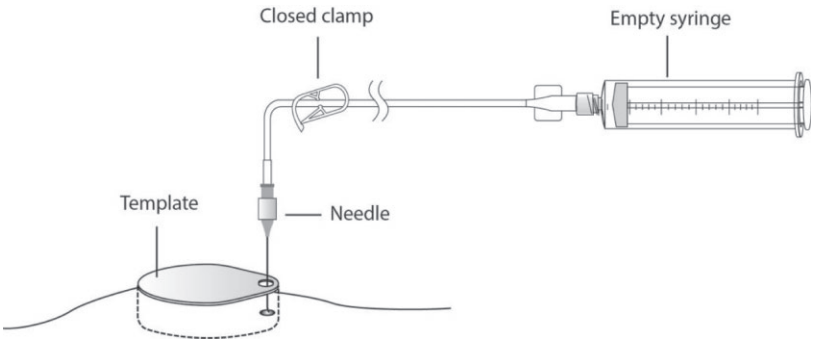
Patient Selection

PATIENTS SHOULD HAVE AN ACCURATE DIAGNOSIS OF A SPECIFIC PAIN STATE THAT WOULD LIKELY RESPOND TO INTRATHECAL MORPHINE OR ZICONOTIDE.

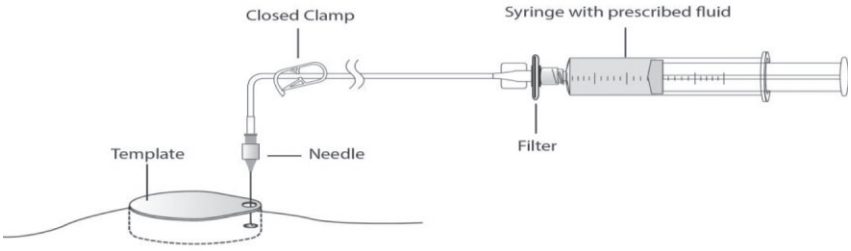
The approved indications for IDD are the chronic intrathecal infusion of preservative-free morphine sulfate sterile solution (maximum concentration of 25 mg/mL) in the treatment of chronic intractable pain, or preservative-free ziconotide (maximum concentration of

The catheter access port allows direct access to the catheter and cerebrospinal fluid and can be used for diagnostic tests. The catheter access port procedure is summarized below. The manufacturer's *Clinical Reference Guide* describes the process in more detail (53).

- Gather supplies
- Interrogate the pump
- Prepare the prescribed fluid and injection site
- Using sterile technique, aspirate drug from the catheter
- Inject the prescribed fluid
- Flush the catheter access port (optional)
- Remove the catheter access port needle
- Update the pump
- Program a bridge bolus for the total catheter volume



Aspirating drug from the catheter



Injecting fluid through a bacterial-retentive filter and into the catheter access port

Figure © 2013 Medtronic Inc., Minneapolis, MN. Used with permission.

Figure 5. Performing a side-port myelogram.

100 mcg/mL) for the management of severe chronic pain. Thus, no specific diseases are indicated or contraindicated. Intrathecal therapy has been used successfully in long-term pain management for patients with failed back surgery syndrome, complex regional pain syndrome, spinal stenosis, osteoporosis with compression fractures, pancreatitis, phantom limb pain syndrome, and peripheral neuropathies (13). Analgesic response to IDD has been seen in patients with neuropathic, visceral, deafferentation, and mixed pain. Panelists noted that patients with some conditions—such as headache, fibromyalgia, atypical facial pain, noncancer head–neck pain, and borderline personality disorder—have not had good outcomes. Although patient selection varies widely among practitioners, the goal is to identify the patients whose pain states are likely to be relieved by intrathecal medication. Using the published literature to provide data and context, clinicians can assess the potential benefits and risks of IDD for the individual patient and discuss them with the patient (13).

Comorbidities such as sleep apnea, restricted cardiac or lung capacity, venous insufficiency, obesity, metabolic syndrome, hypertension, diabetes, and immunosuppression increase the risk of IDD. These should be maximally managed before considering IDD, and all reversible causes of pain should be addressed before IDD is undertaken (73). Immunosuppressed patients require extremely careful surgical technique, and some panelists recommend more aggressive prophylaxis, including preoperative antimicrobial showers, to avoid infection. Ideally, patients should stop smoking before pump implantation, although panel experts had treated active smokers. Patients with spinal stenosis can be implanted if the catheter is placed above the conus medullaris and the patient has stable neurologic signs. Litigation by itself is not a contraindication,

Table 6. MRI Safety for Programmable Infusion Pumps.

Device	MRI conditional safe	Static magnet strength	Guidance
SynchroMed II/SynchroMed EL (Medtronic)*	Yes	1.5T, 3T	Pump should not be emptied or turned off prior to scan. Pump will alarm and automatically restart within 24 hours, usually within 20 min if delivering at least 0.048 mL/day; interrogation to confirm status is recommended. No Z-axis orientation. Do not program to "Stopped" position prior to scan.
Prometra (Flowonix)†	Yes	1.5T	Warning: Failure to empty the pump prior to exposure to MRI environment could result in drug overdose that could lead to serious patient injury or death. Upon the completion of an MRI procedure, interrogate the pump with the programmer to verify pump operation and settings. Confirm that settings are unchanged from the pre-MRI settings, e.g., flow rate must be 0.0 mg/day. Warning: If pump status cannot be properly confirmed, do not proceed since the pump is not operating properly and should be explanted and replaced.

**MRI Guidelines*. Minneapolis, MN: Medtronic Inc.; 27 Sept 2010. †*Prometra Programmable Pump Patient Guide*.
MRI, magnetic resonance imaging.

but potential secondary gains should be carefully evaluated before deciding to proceed with IDD. Absolute contraindications include active substance abuse, coagulopathy, and obstruction of CSF flow. Anticoagulation therapy was not considered an absolute contraindication by panel experts if, in consultation with the patient's cardiologist or vascular specialist, anticoagulants could be discontinued for an appropriate perioperative period. Because patients with a pain diagnosis may also have depression, anxiety, posttraumatic stress disorder, substance abuse concerns, cognitive impairment, or personality disorder, anyone being considered for IDD should have a psychological evaluation to ensure optimal outcomes.

ALL PATIENTS SHOULD HAVE EVALUATION OF PHYSICAL, PSYCHOLOGICAL, AND ENVIRONMENTAL FACTORS BEFORE COMMITTING TO A TRIAL.

Physical Evaluation

That IDD is indicated for treatment of chronic intractable pain or severe chronic pain implies appropriate application of less invasive pain management therapies before initiation of IDD. Efforts should be made to obtain records of the patient's previous pain treatments. Records from the referring or preceding physicians can supplement the patient's narrative and provide objective evidence from earlier diagnostic studies (73). A thorough physical examination documents the patient's current condition, including any comorbidity that could increase the risk of IDD. All comorbidities should be well managed before commencing IDD therapy (13). In some cases, a complete diagnostic work-up is necessary to rule out reversible and treatable causes of pain.

Psychological Evaluation

The goal of the psychological evaluation is to assess the patient's psychological functioning, rule out an underlying mental disorder, and assess the patient's understanding of the benefits and limitations of IDD. This approach derives from the understanding that pain is a highly subjective experience with pronounced emotional aspects. The experience of pain evolves and persists from the three dimensions of pain: sensory-discriminative, affective-motivational, and cognitive-evaluative (74). The transition from acute to chronic pain correlates with mental stress (75), and suffering of chronic pain increases vulnerability to mental disorder (76). The psychological evaluation for IDD is thus an essential aspect of patient selection (73). Table 7 lists the recommended components of a psychological work-up. Inclusion of psychological testing provides a comparison to normative groups and should include tests standardized on medical patients as well as standard psychiatric measures. If the patient has high psychological distress, mental health treatment can improve functioning (77,78) and prepare the patient for the procedures (79,80).

Managing patient expectations is a necessary component of preoperative preparation. A patient with realistic expectations for intrathecal therapy will likely experience greater satisfaction than one whose expectations exceed typical outcomes. If there is a significant divergence between patient expectations and what the therapist believes the physician has established, implantation should be postponed until the patient can articulate more reasonable goals. It is especially important to assess the patient's understanding that the outcome of IDD is one of pain management and not of pain cure. Furthermore, the family and social support group of the patient play an important role in the outcome because their views regarding this form of pain therapy can be influential.

Some medical settings may have limited access to psychological professionals capable of providing these services. While less than optimal, mid-level health practitioners can be trained to provide initial screening and patient education when fully trained psychological personnel are unavailable (81). Final approval of a patient's suitability for IDD rests with the managing physician or a multidisciplinary team. Patients who have had an IDD system may require ongoing monitoring for new onset of psychological disorders during the course of therapy.

Trialing

ALL PATIENTS CONSIDERED FOR IDD SHOULD HAVE A TRIAL.

For many years, a trial of intrathecal therapy has been considered a prerequisite for implantation. Medicare requires a continuous trial as a condition for reimbursement in the United States as do some European countries. The rationale has been that a trial provides an opportunity to assess short-term pain relief, begin to gauge dosing, and determine individual tolerability. The value and necessity of a trial has recently been challenged on the grounds that trial results do not always accurately predict the success or failure of subsequent long-term intrathecal therapy (13). Nonetheless, the panel experts concurred that all patients considered for IDD should have a trial because it allows the physician to collect information on an individual's response to IDD. There was a minority view that in some cancer patients in extreme pain, who were opioid sensitive but burdened by severe opioid side effects, trialing could be omitted in the name of expediency and especially compassion.

Table 7. Elements of the Psychological Evaluation.

- Informed consent/rationale for psychological evaluation understood by patient
- Pain description and experience
  - Pain location(s), pattern(s), intensity, and quality
  - Relationship between pain and physical/psychological function
  - Factors that increase/decrease pain and function
- Pain history
  - Onset and course of pain
  - Current pain experience and psychological consequences
  - Previous pain treatments, responses, and satisfaction with treatment
  - Beliefs about what is needed to ameliorate pain
- Specific pain behaviors
  - Activity changes in response to pain
  - Specific behaviors to prevent pain (limping, inactivity)
  - Factors that increase/decrease pain behaviors
- Review of pain treatments, efficacy, and adherence
  - Past and current medication, including dosing and side effects
  - Other pain-related treatments (injections, surgical, complementary)
  - Mental health-related therapy (psychotherapy, behavioral therapy)
  - Efficacy and adherence to these
- Current emotional functioning
  - Depression or anxiety
  - Suicidal, homicidal ideation
  - Psychosis or idiosyncratic ideation
  - Sleep, appetite, and sexual functioning
  - Cognitive functioning
  - Negative emotions (irritability, anger, guilt)
- Current situation
  - Living situation
  - Financial status
  - Daily activities
    - Employment
    - Volunteer work
    - Driving ability
  - Social involvement
  - Ability to perform ADLs
  - Family support and attitude
- Psychosocial history
  - Prior psychological symptoms, disorders, treatments in patient/family
  - Prior chemical dependency history in patient/family
  - Education
  - Vocational history and current status
  - Religion
  - Legal
    - Arrests
    - Litigation (current or past)
- Developmental history
  - Family relationships of nuclear family
  - Education
  - Activities
  - Medical history during development
  - History of trauma or abuse
  - Other issues
- Patient's concept of pain and pain treatment
  - Concept about cause of pain, prognosis, treatment goals, and expectations
  - Relationship with referring physician
  - Motivation to manage pain
  - Ability and willingness to communicate about pain
  - Fear about pain treatment or impact
- Behavioral observations
  - Grimacing, posturing, guarding
  - Use of assistive devices
  - Excessive preoccupation with pain in narrative
- Mental status examination
  - Clinical evaluation of psychological and cognitive functioning
- Psychological testing
  - Administered to supplement information gathered during interview and to assess treatment outcomes
  - Recommend one test in protocol be standardized on medical patients (e.g., *Millon Behavioral Medicine Diagnostic*) and psychiatric patients (e.g., *Minnesota Multiphasic Personality Inventory)*

ADL, activities of daily living.

No data support one method of trialing as superior (82), and the panel experts themselves differed in their trial practices. Matching the anticipated therapy conditions (medication, dose, type of catheter, infusion rate, placement of catheter tip) as closely as possible during a trial theoretically creates the best opportunity to evaluate longer-term IDD efficacy and safety. Although this assertion appears logical, unfortunately, it is theoretical and no data substantiate this hypothesis.

Another factor relating to trialing that more closely simulates permanent implantation includes asking patients with sleep apnea who use positive airway pressure equipment to bring it with them for the trial. No consensus was established on how long a trial should last, but it was noted that the pharmacokinetics and pharmacodynamics of a drug dictate how quickly its effects are likely to be seen. Single-bolus doses were not generally considered a best practice for intrathecal medication trials, although some experts found sequential bolus doses informative. Single-bolus trial doses are acceptable for ziconotide but are not considered a best practice for opioid intrathecal medication trials. If performed with opioids, the patient must be monitored overnight. Above all, the experts stressed the need for monitoring to protect patient safety during the course of the trial.

The trial is only part of the evaluation for suitability of IDD. Pain relief alone does not mean a patient will do well with IDD. In some cases, further diagnostic evaluations (e.g., imaging, electromyograms, endocrine evaluation) may be necessary before a decision can be made about implantation. A negative trial can also have predictive value. A corollary was offered: If an adequate trial cannot be conducted, do not implant the pump. The results of a trial must always be discussed with the patient, whose consent to IDD in partnership with the managing physician lays the foundation for a positive therapeutic relationship. Psychological support should be available regardless of whether the patient receives a pump.

CONCLUSIONS

The pain management experts who developed these best practices agreed that IDD is an important therapeutic option for many patients with severe chronic or end-of-life pain. In adopting the therapy, patients must be apprised of its risks and benefits, and physicians must work to achieve both safety and efficacy for their patients. The safety issues surrounding IDD derive primarily from inadequate monitoring (e.g., respiratory depression), inflammatory mass (e.g., too high doses and concentrations), dosing errors (e.g., medication concentration, pump programming), misadventures with pump fills or refills (e.g., pocket fills), and interactions among concomitant systemic medications (e.g., opioids and benzodiazepines). Many of the reported adverse effects and complications of IDD can be prevented by adequate training and experience in conjunction with the appropriate vigilance. This best practices publication is an important step toward informing and educating practitioners who treat patients with chronic pain.

SUMMARY OF BEST PRACTICES IN IDD

Safety and Monitoring

- Pumps must be implanted and managed by providers trained and skilled specifically in IDD.
- The patient is a partner in therapy.

- Respiratory depression is the key safety issue associated with IDD.
- Eliminate systemic opioids if possible, or reduce by at least 50% if elimination is not feasible.
- Consider the clinical ramifications before adding any CNS-active drug to an opioid regimen.
- Existing equianalgesic dose-conversion tables are inappropriate for IDD.
- Titrate dose cautiously while monitoring for efficacy and side effects.
- Monitor all patients for 24 hours after start or restart of opioid intrathecal therapy.
- Start ziconotide at a dose of not more than 0.5 mcg/24 hours, with incremental increases of not more than 0.5 mcg/24 hours, no more often than once weekly.
- Undertake an endocrine evaluation before starting intrathecal opioid therapy, with periodic monitoring for hormone suppression.

Patient Selection and Trialing

- Patients should have an accurate diagnosis of a specific pain state that would likely respond to intrathecal morphine or ziconotide. All patients should have evaluation of physical, psychological, and environmental factors before committing to a trial.
- Patients with comorbidities such as diabetes, coagulopathy, immunosuppressive disorders, and sleep apnea should have these conditions well controlled before considering intrathecal therapy.
- All patients considered for IDD should have a trial, and if an adequate trial cannot be conducted, the patient should not be implanted.
- Single-bolus trial doses are acceptable for ziconotide but are not considered a best practice for opioid intrathecal medication trials. If performed with opioids, the patient must be monitored overnight.
- Patients must be diligently monitored to protect their safety during the course of the trial.
- Patients must have realistic expectations for therapy and understand its possible outcomes.
- Psychological support should be available regardless of whether a patient receives a pump.

Implantation

- Use vigilance and well-established surgical technique to prevent infection.
- Use a shallow-angle, paramedian, oblique needle-insertion angle and trajectory to avoid the catheter crossing the spine, which could result in damage or dislodgement.
- Withdrawing the catheter through the needle could weaken, nick, or sever the catheter. On rare occasions, based on clinical judgment and to avoid repeat dural puncture, the catheter may be gently withdrawn *in the absence of any resistance*.
- Use an elbow, butterfly, or V-wing catheter-anchoring device to reduce the likelihood of dislodgement.

Patient and Device Management

- Physicians prescribing intrathecal therapy should be prepared to invest time in their own training as well as the training of their staff in managing patients.
- Clinicians should familiarize themselves with the manufacturer's manual and with potential pump- and catheter-related complications.
- At every refill, patients and caregivers should be reminded of the signs and symptoms of overdose, underdose, and withdrawal, and instructed to seek immediate medical assistance should they experience any of the symptoms.
- Patients should be observed for at least 30 min after pump refill.
- All patients on intrathecal therapy should be routinely monitored for prodromal clinical signs or symptoms of inflammatory mass and for new neurological signs or symptoms.
- Patients scheduled for an MRI should alert the radiology staff that they have an IDD device and should present their patient ID card so that the manufacturer's guidelines can be reviewed.

Authorship Statement

All of the authors participated in a 2-day workshop chaired by Dr. Joshua Prager, small group working sessions, and professionally facilitated discussions designed to build consensus. A first draft of the manuscript was produced from meeting notes and distributed to all authors for review and revisions. All authors contributed relevant literature searches, expert opinion, and final manuscript approval. Medtronic, Inc. provided funding for the workshop and editorial support.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix I. Sample informed consent form for intrathecal drug delivery.

Appendix II. Important information about intrathecal pain therapy.

COMMENTS

This position statement on best practices for intrathecal drug delivery for pain is going to be one of the more useful articles that the practicing IT drug therapist will read. The international authorship really have combed the literature, weighted the value of evidence and used their collective experience where needed to produce this well-balanced advice for safe and effective IT drug pump application and maintenance. Some of the flow diagrams and tables will be most useful to all staff involved. I thoroughly enjoyed reviewing this but wondered why it has taken so long to have this collective knowledge finally committed to print. We should all be grateful to those that have made this possible. Well done.

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This is an important article that provides practical safety recommendations in the area of ITDD; an excellent an concise review of the subject with clear diagrams and algorithms. In that respect it is a welcome and long overdue publication. Some of the recommendation and statements made by the authors appear to be too strong and binding given that they are entirely opinion based and do not have any backing evidence in the literature. There remains a clear and urgent need for evidence based guidance.

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

