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Polyanalgesic Consensus Conference—2012: Recommendations to Reduce Morbidity and Mortality in Intrathecal Drug Delivery in the Treatment of Chronic Pain

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Introduction: Targeted intrathecal drug infusion to treat moderate to severe chronic pain has become a standard part of treatment algorithms when more conservative options fail. This therapy is well established in the literature, has shown efficacy, and is an important tool for the treatment of both cancer and noncancer pain; however, it has become clear in recent years that intrathecal drug delivery is associated with risks for serious morbidity and mortality.

Methods: The Polyanalgesic Consensus Conference is a meeting of experienced implanting physicians who strive to improve care in those receiving implantable devices. Employing data generated through an extensive literature search combined with clinical experience, this work group formulated recommendations regarding awareness, education, and mitigation of the morbidity and mortality associated with intrathecal therapy to establish best practices for targeted intrathecal drug delivery systems.

Results: Best practices for improved patient care and outcomes with targeted intrathecal infusion are recommended to minimize the risk of morbidity and mortality. Areas of focus include respiratory depression, infection, granuloma, device-related complications, endocrinopathies, and human error. Specific guidance is given with each of these issues and the general use of the therapy.

Conclusions: Targeted intrathecal drug delivery systems are associated with risks for morbidity and mortality that can be devastating. The panel has given guidance to treating physicians and healthcare providers to reduce the incidence of these problems and to improve outcomes when problems occur.

Keywords: Chronic pain, consensus, intrathecal, morbidity, mortality, opioids, outcomes

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INTRODUCTION

Targeted intrathecal (IT) drug delivery systems (IDDS) are an option in algorithms for the treatment of patients with moderate to severe chronic refractory pain. The use of IDDS has led to improved quality of life, reduced pain, and increased patient satisfaction in many with either chronic disease or those at the end of life who have failed other therapeutic options (1). IDDS has historically been known to be associated with risks that can result in serious morbidity and mortality. These issues have recently been highlighted by articles published in peer-reviewed publications (2,3). Rathmell and Miller previously suggested possible strategies to reduce these events (4). The Polyanalgesic Consensus Conference (PACC) group has examined these issues and has made recommendations to reduce the danger to patients and to improve outcomes. The need for this guidance is critical in a time of increasing focus on safety, comparative outcomes, and cost-effectiveness.

The morbidity associated with IDDS drug delivery can result from multiple sources. These include complications with implantation or management procedures, drug reactions or side-effects, device malfunction, and human error in programming or refilling the device. These problems can lead to nerve damage, endocrine suppression, peripheral edema, systemic disorders, and, in some cases, death (1,2,3).

In their extensive postmortem epidemiologic analysis in patients receiving IDDS opioid therapy, Coffey and coworkers indicated that the rate of mortality within three days of implantation of the drug delivery device was 0.088%; the rate rose to 3.89% one year after pump implantation (2). The PACC set out to determine if recommendations could be made to reduce these unacceptable numbers. We believe that with proper guidance, most of these issues can be prevented or markedly reduced in their incidence and severity.

Despite these alarming numbers, there is the possibility that they, in fact, underestimate the negative impact of IDDS therapy. The data reported by Coffey and coworkers are largely based on reporting of serious adverse events to the United States Food and Drug Administration (FDA). Many of the complications that are defined as morbidities are not reported. These issues are compounded by the complicated and sporadic reporting of complications outside of the USA. Other factors complicating the interpretation of these data include the difficult assessment of cause of death. In some cases, an IDDS may be the attributed cause of death, when a concomitant

disease is the actual cause of death. Lastly, the work of Coffey and coworkers was supported by industry, and each author disclosed a relationship with manufacturers or companies involved in IDDS, which certainly raises the issue of bias in reporting even if unintentional (5).

A careful analysis of these data suggests that both the morbidity and mortality associated with IDDS can be reduced or in many cases prevented. To improve the therapy given to many suffering patients in the USA and around the world, the PACC has established recommendations based on a careful examination of the medical literature and the extensive experience of the expert consensus panel.

METHODS

Primary literature and review articles addressing the morbidity and mortality associated with the implantation and management of IT drug infusion systems and published from January 15, 2007, through March 1, 2011, were searched. Material from previous PACC publications was used as a baseline point of information (6). Discussion was limited to medications approved for IDDS use in the management of chronic pain in the USA by the FDA, specifically morphine and ziconotide (Prialt®, Azur Pharma International, Ltd, Dublin, Ireland). Publications were reviewed for reports of serious adverse events associated with IT therapy, including respiratory depression or distress, hypertension, meningitis or other systemic infections, granuloma formation, peripheral edema, endocrine suppression, catheter- or pump-related complications, and death. Data bases searched included MEDLINE®, BioMed Central®, Current Contents Connect®, Embase, International Pharmaceutical Abstracts®, and Web of Science®. Publicly available documents and manufacturer safety reports and communications regarding risks associated with IT drug delivery systems were also reviewed, along with unpublished communications from the PACC panel members. Members of the PACC were chosen on the basis of previous participation in the consensus panel, national and international impact, publications, organized society activity, and work in shaping medical practice and policy. Other factors included geographic diversity, specialty, and various practice settings.

Physician impressions of morbidity and mortality were assessed through a multinational survey of implanting doctors. Three detailed surveys on IT infusion use, safety, and reimbursement were sent to more than 15,000 physicians and clinicians in the USA and other nations by the PACC panel in May 2011. The results are detailed in Appendix I.

Recommendations were impacted by the literature as noted above, extensive clinical experience, and physician concerns based on extensive query of their experiences.

RECOMMENDATIONS OF THE PACC TO REDUCE MORBIDITY AND MORTALITY

General Recommendations

1. The use of IDDS to treat chronic pain should be part of a treatment algorithm that involves the failure of more conservative attempts at treatment. IDDS should be considered prior to other options when unacceptable side-effects or lack of efficacy is established (7).
2. The use of IDDS should be based on an analysis of safety, efficacy, a goal of economic neutrality and appropriateness for the individual patient. These factors have been described as the S.A.F.E. principles (8).
3. Spinal cord stimulation (SCS), peripheral nerve stimulation (PNS), and hybrids of both SCS and PNS should be considered inappropriate candidates prior to considering an IDDS (9).
4. Psychological evaluation and stability should be confirmed prior to proceeding with an IDDS in noncancer patients (10).
5. In patients with cancer and those at the end of life, the use of IDDS should be combined with spiritual, psychological, and social support (11). While this practice may not change the measurable mortality and morbidity, the panel feels that this is an important component of the patient care team.
6. Prior to implanting an IDDS, the patient should undergo a trial of the planned drug with an emphasis on evaluating side-effects and efficacy (12). In some cases such as advanced cancer pain, the panel agrees that the need for a trial may be negated based on a risk to benefit ratio. In those cases, a careful analysis of life expectancy should be performed with therapy limited to those who do not have impending death in the immediate postoperative period.
7. Oral or transdermal opioids should be reduced as much as possible either prior to the implant or in the first 12 weeks of surgery. IDDS is a different route of delivering opioid, but the reduction of additional routes may improve outcome.
8. The use of concomitant drugs that effect central nervous system (CNS) function should be reduced or eliminated as much as possible in the perioperative period (2).
9. Factors which may increase the risk of infection, such as poorly controlled blood sugar, neutropenia, or a prior history of methicillin-resistant *Staphylococcus aureus*, should be addressed prior to implant (10,11).
10. Proper physician and staff training are required prior to initiating an IDDS program. This requires hands-on training, didactic teaching, mentoring, and proctoring. Failure to be properly trained can impact long-term outcomes in all areas of concern (13).
11. Infrastructure for IDDS is critical to reducing morbidity and mortality. This infrastructure includes proper nursing staffing, continuing education, proper supplies, and on-call coverage by a healthcare professional well versed in the use and complications of IDDS. Additionally, surgical backup should be arranged for those with limited surgical training or skills.

Each of these areas of concern was evaluated critically, and methods to reduce specific complications were addressed. Guidance is given in the most common areas of concern.

General Recommendations Concerning Respiratory Depression in Patients with IDDS

1. Preoperatively, patients should be assessed for the comorbidities related to the pain syndromes impacting their presentation and complaints. Of equal importance, they should be assessed for pulmonary function and the resulting risk of respiratory depression.
2. The patient should be referred for weight loss consultation or discussion with their primary care doctor if they meet the body mass index (BMI) criteria of morbid obesity. Weight loss may greatly reduce the risk of obstructive sleep apnea and subsequent respiratory depression (14).

3. The patient should be seen and optimized by the primary care doctor or pulmonologist if severe lung disease is present, such as chronic obstructive pulmonary disease, restrictive lung disease, or cystic fibrosis.
4. Smoking cessation should be encouraged, and collaboration with the primary care doctor treating the patient should be available in the event the patient wants to be treated with medications to assist in this goal (15).
5. Sleep apnea testing and treatment should be encouraged if the patient is at moderate to high risk (16).
6. The use of CNS depressants, including opioids, benzodiazepines, barbiturates, antipsychotic drugs, and other applicable drug classes, should be assessed and doses reduced or discontinued if possible prior to implant. The primary care doctor and those involved in the patient care team should notify the doctor managing the IDDS when adding drugs that may impact brain stem respiratory centers.
7. Alcoholism and other illicit drug habits should be evaluated and addressed prior to implant. The addition of any CNS suppressant can worsen outcomes and those that are illicit may greatly increase risks (17).
8. Avoid rapid IDDS drug escalation and doses that exceed the PACC guidelines (18).
9. When therapy is discontinued because of catheter disruption, pump failure, or elective stoppage of the pump, the therapy must be reinitiated at a starting dose consistent with that of an opioid-naive patient. Starting at a dose higher than those recommended can potentially lead to death.
10. The PACC recommends starting at the lowest reasonable dose of opioid when initiating IT drug therapy, or after revising a pump following an interruption in drug delivery.
11. In the elderly, the use of IDDS is often very helpful since they may have difficulty tolerating oral or transdermal medications. They may also exhibit extreme sensitivity to opioid dosing, and a lower dose should be initiated in the elderly or chronically ill.
12. When filling pumps with medication, attention should be given to the shape and contour of the device. A template should be used to identify the refill port. If there is difficulty the physician should consider the use of fluoroscopy or ultrasound to avoid inadvertently injecting the drug solution into the subcutaneous space surrounding the pump (colloquially referred to as a "pocket fill") (19).
13. During the refill procedure, clinicians can increase the confidence that the medication solution is being injected into the pump reservoir by the ability to aspirate 1 to 2 mL of the solution after each 3- to 5-mL injection (20).
14. If a full or partial pocket fill is known or suspected, the patient should be monitored in a high dependency or intensive care unit for symptoms of drug overdose. The occurrence of a pocket fill may be verified by completely emptying the pump and comparing the expected volume of the infusate with the actual volume. A discrepancy between the expected and actual volumes of the infusate is suggestive of a pocket fill. Ultrasound may be used to assess fluid in the pocket after a suspected pocket refill (19,21).
15. The panel recommends that if drug infusion is interrupted for more than 24 hours, the patient's dose on reinitiation of therapy should be reduced to that appropriate for the starting dose for an opioid-naive patient. Hospital admission is required to access the risk of respiratory depression or withdrawal.

Recommendations to Minimize the Occurrence of Respiratory Depression in Hospitalized Patients Receiving IT Therapy

1. The health-care team should monitor for adequate ventilation, oxygenation, and level of consciousness. Any change in these issues should lead to pump adjustment or IT drug cessation, and increased vigilance in monitoring.
2. The first 12 hours after implant is a very important window for monitoring for respiratory depression. In any high-risk patient, this monitoring should be hourly for the first 12 hours and then every 2 hours for the next 6 hours.
3. The frequency of monitoring should be increased in high-risk and opioid-naive patients.
4. If frequent monitoring is not possible, administration of very low starting doses of opioid is recommended.
5. The risk of respiratory depression is limited with ziconotide, and the degree of monitoring for patients receiving ziconotide therapy is currently based solely on physician judgment. The PACC does recommend an overnight admission in these patients despite the low risk of respiratory depression.

Recommendations for the Treatment of Respiratory Depression

1. Once respiratory depression is identified, the clinician should consider transfer to a higher acuity unit to maintain constant monitoring of respiratory rate, oxygen saturation, and vital signs.
2. The clinician should attempt to eliminate and avoid adding other drugs that may affect respiratory status (e.g., barbiturates, benzodiazepines, anticonvulsants, antispasmodics). The physician should consider administering reversal agents for these medications, such as naloxone or flumazenil, if possible.
3. Discontinue any systemic postoperative pain medications, and treat pain with ice and nonsteroidal anti-inflammatory agents or acetaminophen if either drug class is appropriate.
4. Support the airway, breathing, and cardiovascular system. Start resuscitation as indicated, as would be performed with any case of respiratory depression.
5. Turn off the pump if possible. If the device is nonprogrammable, the pump should be aspirated of all drug and, if possible, the catheter should also be aspirated. Turning off the pump may result in a future motor stall, and upon reinitiating the drug careful monitoring is needed.
6. Rule out other causes of respiratory distress (e.g., pulmonary embolism, myocardial infarction, aspiration). Obtain consultation with the proper doctors to help treat these comorbidities.
7. Maintain the pump in the *off* position until the patient returns to baseline status, then reassess and restart the drug only after recovery is confirmed. Follow guides to restarting infusions after cessation described in the PACC recommendations for the treatment of chronic pain.

Recommendations for Infection Control and Reduction in Patients with IDDS

1. Patients should be assessed preoperatively for an increased risk of infection. Comorbidities such as uncontrolled diabetes, immunosupressive drugs for systemic diseases, immunosupression from disease such as malignancy or HIV, or a history of poor

wound healing should be addressed (11,22). In patients with a history of staphylococcal infection or colonization, extra precautions should be considered. Possibilities include the use of intranasal Bactroban ointment for five days or greater, perianal Bactroban ointment for five days or more, chlorohexidine bathing prior to surgery, and preoperative antibiotics that are consistent with coverage for that organism (23).

2. The externalization of a trial catheter dramatically impacts the infection rate. The permanent implant should be performed with a new, sterile catheter.
3. The doctor should consider rapid internalization if an external tunneled catheter for IDDS is considered.
4. The physician should consult with local experts on bacterial resistance to antibiotics in their facility and consider antibiotic choice based on these facts. This may vary based on geographic location, institution, and patient populations.
5. A laminar flow, restricted access operating room should be used for the implantation of an IDDS. It is not acceptable to do this procedure in other settings.
6. Antibiotic solution should be used vigorously to irrigate the wounds intraoperatively. The choice of antibiotics should be based on local flora. High volume irrigation has been shown to reduce the risk of wound infection (24).
7. Wound closure should be performed with careful attention to detail since poor wound closure can lead to dehiscence and bacterial introduction to the wound (25).
8. The use of preoperative antibiotics is well established and should be completed prior to incision. The choice of preoperative antibiotic administration should be based on local pathogens and sensitivity. The use of postoperative antibiotics is lacking in the literature, but the majority of the PACC do use postoperative antibiotics (26).

Recommendations to Prevent, Recognize, and Treat IT Granulomas (IG)

The PACC has made exhaustive recommendations on this topic (6,27).

1. The evidence supports a direct effect of high concentrations of some opioids as a major factor in the development of IG (6,28).
2. These agents exert their effect presumably by triggering local arachnoid mast cell degranulation.
3. The most commonly used IT agents associated with IG are morphine and hydromorphone.
4. The concentration of IT opioids should be kept at the lowest reasonable level to achieve clinical utility and acceptable refill intervals.
5. High doses of IT opioid can necessitate the need for higher concentrations; therefore, it is recommended that dose elevation be minimized as clinically appropriate.
6. Replacement of the opioid with IT ziconotide should be considered when the opioid dose becomes elevated or efficacy is inadequate. There have been no confirmed cases of ziconotide causing IG.
7. The addition of adjuvant drugs to opioids may reduce the risk of granuloma by opioid-sparing effect (29–31).
8. The reduction in pain relief from an ongoing infusion that does not respond to subsequent dose increases should raise concern that a granuloma is developing. This is particularly the case if multiple drug increases do not change the patient's level of pain or function.
9. Any changes in motor, sensory, or proprioceptive function should alert the healthcare team to the possibility of granuloma.
10. If there is concern for possible granuloma formation, plain x-ray films should be obtained to identify the location of the catheter tip, followed by cross-sectional imaging at the level of the catheter tip.
11. A magnetic resonance imaging (MRI) with and without gadolinium using narrow slices through the level of the catheter tip is the imaging procedure of choice. In those who cannot obtain an MRI, a computed tomography (CT) myelogram may be helpful in diagnosing the lesion (32,33).
12. Once a granuloma is identified, the management depends on both the presence of spinal cord or nerve compression and the patient's clinical presentation.
13. If significant neural compression is present, consultation of a spine surgeon is needed. The surgeon and managing physician should collaborate to determine the best options for treatment.
14. If there is no significant spinal or nerve compression and if the patient is asymptomatic, discontinuation of the offending opioid alone may lead to the resolution of the IG. The use of ziconotide as an alternate to the opioid can be considered in these cases. The replacement of the offending drug with saline is another possible option (27).
15. In the symptomatic patient, several treatment strategies are available based upon their degree of symptomatology. The IDDS can be changed to saline and the patient can be followed with serial MRI or CT myelography.
16. Other options in the symptomatic patient include revision or replacement of the catheter or removal of the system and a consideration of other pain management options. Since IDDS are often placed as a therapy of last resort, these other options may be limited.

Recommendations for Addressing Endocrine Issues Related to IDDS

1. Growth hormone levels can be reduced by the use of IT opioids. Low growth hormone levels can be associated with fatigue in the adult patient and growth suppression in the pediatric population (34).
2. Follicle-stimulating hormone levels should be evaluated in females who suffer from decreased libido with IT opioid use (35).
3. Luteinizing hormone (LH) levels can be lowered by **the use of IT opioids.** The initial symptoms of low LH levels may include breast discomfort (35).
4. Testostone levels can be lowered by opioid therapy including IDDS. Symptoms of hypotestosteronemia include fatigue, loss of libido, and difficulty concentrating (35). In patients in whom these issues are of a concern the panel recommends referral to an endocrinologist or proper specialist.

Recommendations for Anesthesia During IDDS Placement

1. Local anesthesia has limited risks for placement of the IDDS, but often patients cannot tolerate the procedure because of pain or may move during catheter placement creating an increased risk of injury. In patients with severe discomfort while lying in the surgical position, local anesthesia as a sole option is not recommended.

2. Monitored anesthesia care is a commonly used anesthetic technique for placing IDDS. Properly performed monitored anesthesia care allows for the patient to be responsive during catheter placement and reduces the risk of postoperative pulmonary and cardiovascular complications.
3. General anesthesia is sometimes chosen and has advantages for patients for whom positioning is painful, cooperation is difficult, or in those cases of surgeon preference. The potential risks of general anesthesia include the inability to solicit complaints of pain or paresthesias, inadvertent positioning injury, and a higher risk of potential cardiac or pulmonary events. There are significant differences in anesthetic preferences related to physician specialty.
4. Spinal anesthesia is used infrequently. With this technique, the catheter is usually placed under sedation. Disadvantages of spinal anesthesia may include high spinal block, fluid shifts and hemodynamic changes, and difficulty in recognizing nerve injury in the immediate postoperative period. New methods of analgesia may improve the tolerance of the patient to tunneling and pocketing, including transversus abdominis plane block, although further study is needed (36).

Recommendations for the Avoidance and Treatment of Post-Dural Puncture Headache (PDPH)

1. Assure adequate hydration in the preoperative period.
2. Acquire a history of previous PDPH. In these patients, an increased period of reduced activity and increased hydration may be warranted.
3. Minimize trauma to the dura during needle placement. Such trauma is minimized by using a paramedian approach, a low angle of 30 degrees or less and entry at the midline of the spinal canal.
4. In the postoperative period, assure proper hydration and minimize activity; an abdominal binder may be helpful in reducing the occurrence of PDPH.
5. Consider caffeine, oral hydration, and bed rest if a positional headache develops.
6. Consider medications for the prevention of nausea if PDPH develops. This is an important step since the inability to tolerate oral hydration can worsen the situation.
7. Consider hospital admission if the severity of the headache worsens, if visual problems develop, or if new neurological signs or symptoms develop.
8. The inability to provide sufficient oral hydration is another indication for admission and intravenous hydration.
9. A blood patch may be an option but the risk of damaging the catheter, introducing infection, or creating an additional hole in the dura should be considered. The blood patch should only be considered if all conservative options have failed.

Recommendations to Minimize Psychiatric Complications with IT Ziconotide

1. Start with a low dose infusion of ziconotide (as low as 0.2 μg/day).
2. Titrate IT ziconotide doses slowly with only small increases at weekly intervals.

Recommendations for Recognizing Failure in Long-Term Infusions Due to Catheter Obstruction

1. The managing physician should be vigilant regarding surveillance for potential catheter obstruction.
2. Warning signs may include increased pain and signs of drug withdrawal.
3. Clinical findings at the time of pump refill may include a mismatch between the expected and actual volume of solution remaining in the pump reservoir as well as an inability to aspirate the catheter. In some catheters that are patent the clinician may not be able to aspirate despite it being patent. A nuclear medicine study may be possible to access patency in these patients.
4. The diagnosis is suggested by evidence of catheter kinking or other obstruction on x-ray, MRI, or CT imaging or by the inability to aspirate fluid from the pump side port. The catheter should not be injected if aspiration is not possible (37–43).
5. Definitive diagnosis is made by surgical exploration and direct visualization of the obstruction. If upon direct visualization the cause of the catheter obstruction is not obvious the recommendation is to replace the catheter.

Recommendations to Increase the Safety of Programming When Changing Infusate Concentrations (Bridge Bolus Dosing)

1. The length of the catheter must be known to properly schedule a bridge bolus dose.
2. The concentration and dose of the drug needs to be known prior to calculating the bridge bolus (4).
3. The internal and external catheter volume must be considered prior to starting the bridge bolus dose.
4. If the length of the catheter is not known, a bridge bolus is not possible.

Recommendations to Minimize the Risk of a "Pocket Fill"

1. The patient should be examined prior to pump refill.
2. A skin template should be used when refilling a pump.
3. Once a needle of proper gauge enters the skin and is advanced to the pump, a distinct structure, the pump septum, should be engaged. The actual volume of drug removed from the pump prior to refill should be within 3 cc of the predicted volume.
4. During the refill process, the drug solution should be aspirated every 3 to 5 cc.
5. If the drug cannot be aspirated, a pocket fill should be considered. If uncertain, a protocol for respiratory depression should be initiated (20).
6. In difficult cases, fluoroscopy or ultrasound should be considered to assist in filling the pump (19).
7. If a pocket fill is suspected the pocket should be aspirated and treatment protocols should be initiated immediately.

Recommendations for Evaluation and Treatment of Peripheral Edema in Patients with IDDS

1. Prior to IDDS implantation, patients should be assessed for their risk of developing pedal edema.

2. Those with any history of venous stasis, cardiac failure, renal disease, and/or peripheral neuropathy should be considered at high risk and the initial IT opioid dose should be minimized. The panel recommends considering ziconotide in these patients as a first agent in care.
3. Peripheral edema usually develops early in the course of therapy.
4. If peripheral edema develops, the opioid dose should be lowered.
5. The use of antidiuretics, compression stockings, and leg elevation should be considered.
6. Unresolved edema may require cessation of IT opioids. Other considerations include opioid dose reduction or replacement with an alternate agent. Ziconotide should be considered.

Recommendations for the Recognition of Muscular Complications of IT Ziconotide Therapy

1. In rare cases, ziconotide can cause muscle breakdown and potential renal failure.
2. In previous communications, the need to monitor creatine phosphokinase (CPK) has been suggested (22).
3. The PACC feels the need to monitor CPK on a routine basis is controversial. If new muscle pain or weakness develops, CPK levels should be checked immediately. In the setting of an elevated CPK, renal problems should be an indicator of a need for consultation and discontinuation of the drug.

SUMMARY OF CLINICAL DATA SUPPORTING THE PACC 2012 RECOMMENDATIONS

The recommendations in this manuscript are based on a comprehensive review of the literature, clinical experience, and the consensus on best practices for IDDS.

Respiratory Depression/Distress

Respiratory depression is defined as the diminished ability of the CNS to increase minute ventilation in response to an increase in the arterial partial pressure of carbon dioxide. Although respiratory depression occurs consistently with all opioids regardless of route of administration, there is no direct measure of the disorder. It is a dose-dependent phenomenon that may initially avoid clinical detection, but produces somnolence, bradypnea, and respiratory distress in more advanced stages. Some patients may develop tolerance to this effect of opioids, but the phenomenon is unpredictable and should not be relied upon to ensure the safety of chronic opioid administration. The risk of opioid-induced respiratory depression is increased by comorbidities such as obesity, smoking, the use of other CNS depressants, drug abuse, and central apnea of unknown origin.

Prospective data do exist evaluating the impact of increasing opioid doses on respiratory depression (Table 1). In a high quality cohort study of patients receiving IT morphine or other opioids for the treatment of cancer pain, complete data were available for 45 of 55 patients who were followed from treatment initiation to time of death (6). The average dosage of morphine was 5.76 mg/day at treatment initiation, 14.9 mg/day at hospital discharge, and 19.7 mg/day at a time close to death. One patient experienced bradypnea accompanied by severe drowsiness that was reported as a likely consequence of opioid overdose. IT therapy was discontinued in this case, and the patient recovered (44). In another prospective study, 110 patients with cancer-related or nonmalignant pain received IT therapy with morphine; dosages ranged from 0.03 to 42 mg/day, depending on patient requirements (37). Respiratory complications were noted in two patients, although it is unknown whether these complications were treatment related (37). A retrospective study of 34 patients aged 65 to 86 years with chronic noncancer pain documented IT therapy with morphine at a starting dosage of 0.1 mg/day (45). At three months after treatment initiation, the mean ($\pm$standard deviation) morphine dosage was 0.51 $\pm$ 0.33 mg/day, and the dosage increased to 1.03 $\pm$ 0.61 mg/day at four years after implantation. Bradypnea was noted as a side-effect of IT therapy in one patient. In many of these cases, the use of opioid monotherapy required rapid dose escalation to daily doses greater than the PACC consensus recommendations. Using the PACC algorithm should be considered since adjuvant IT agents such as bupivicaine have been shown to have an opioid-sparing impact (29,30).

A case report documented respiratory depression in a patient in whom IT therapy with morphine was reinitiated at the same dosage (4 mg/day) after a delayed (12 days) pump refill (46). The 65-year-old woman became unresponsive and experienced respiratory failure ten hours after reinitiation of IT infusion. She responded to 0.6 mg naloxone intravenously, and IT morphine was continued at a dosage of 1 mg/day. This case illustrates both the importance of using naloxone to counteract the impact of opioid-induced respiratory

Table 1. Respiratory Depression/Distress.

Citation(s)	Study design	IT medication(s)	Treatment-related adverse events
Coffey et al. 2009 (3) Coffey et al. 2010 (2)	Postmortem epidemiologic analysis	Opioid drugs	Nine deaths within three days of implantation of a new device, pump replacement, or catheter replacement, most likely as a consequence of respiratory depression resulting from opioid drug overdose
Mercadante et al. 2007 (44)	Prospective cohort study	Morphine and other opioid drugs	One of 55 patients (1.8%) receiving IT therapy developed bradypnea
Raffaeli et al. 2008 (45)	Retrospective review	Combination therapy with morphine and a nonopioid analgesic	One of 34 patients (2.9%) developed bradypnea*
Ruan et al. 2010 (46)	Case study report	Morphine	Respiratory failure in patient after a delayed pump refill
Rauck et al. 2010 (37)	Prospective multicenter study	Morphine	Respiratory complications in 2 of 110 patients (1.8%)*

*Publication did not specify whether respiratory complications were related to IT therapy.
IT, intrathecal.

suppression, and the need to significantly decrease or stop the infusion of the offending drug.

In patients with chronic nonmalignant pain, IT opioid dosage can markedly increase with time as they develop a tolerance to the drugs (38). Susceptibility to respiratory depression can, however, persist irrespective of the tolerated opioid dose. Particular danger may be encountered when reinitiating IT opioids after a period of drug cessation or when starting IT drug administration for the first time. Coffey and coworkers documented nine cases of death after initiation or reinitiation of IT opioid therapy (2,3). The most probable cause of death in all nine cases was respiratory depression resulting from opioid overdose (2). Compared with mortality rates of SCS, mortality rates of IT opioid therapy were 7.6-, 3.6-, and 2.2-fold higher at 1 day, 30 days, and 1 year after therapy initiation/reinitiation, respectively (3).

The higher mortality rate of IT opioid therapy as compared with SCS is not surprising in that mortality from SCS should be very low and approach that of any other elective spine surgery. The IT-opioid-related deaths are also not surprising in that the morphine-equivalent starting doses for these patients ranged from 0.75 to 12.6 mg/day; in seven of these nine patients, the starting IT opioid dose exceeded the PACC recommendations of 0.2 to 1.0 mg/day (2). These factors suggest that the risk of mortality should be minimized by ensuring proper clinical practice. All nine patients died within three days after the initiation or reinitiation of IT opioid therapy. Eight of the nine patients (seven with noncancer pain and one with cancer pain) died within 24 hours after implantation of a new device, pump replacement, or catheter revision (3,4). Seven deaths occurred after implantation of new IT devices (2–4); of the remaining two deaths, one occurred after catheter replacement and the other occurred after pump replacement (2). These data further suggest that two of the most vulnerable groups of patients are those at initiation of IT opioid therapy and those where a revision is required to address either a nonfunctioning pump or catheter.

Patient Risk Factors

While clinicians should be concerned about the possibility of complications in all patients receiving IT drug therapy, particular concern should be directed toward those with increased BMI values (12). In an observational study of 392 patients receiving long-term opioid therapy without documentation of the route of administration, there was a correlation between patients with high BMI and increased apnea–hypopnea severity indices (47).

Procedural Risk Factors for Respiratory Depression

Procedural risk factors that may contribute to respiratory depression in patients receiving IT therapy include inadvertent pocket fills, device programming errors, and reinitiation of IT opioid therapy at the last administered dose after a temporary interruption of infusion. Potential drug, dosing, and programming errors are listed in Table 2. It should be noted that each of these issues is avoidable by vigilance and proper clinical practice.

A pocket fill occurs when an IT drug solution is mistakenly injected into the subcutaneous pocket in which the pump is implanted instead of into the pump reservoir. The estimated incidence of inadvertent pocket fill is 0.01%; however, the actual rate may be higher because of underreporting and the possibility that partial pocket fills may go unnoticed because they are not clinically relevant (20). In February 2011, after reports of pocket fills in patients who were implanted with SynchroMed® infusion pumps (Medtronic, Inc., Minneapolis, MN, USA), the FDA classified corrections to product labeling as a Class I recall (21). From May 1996 to September 2010, the manufacturer of SynchroMed infusion systems received 351 reports related to the occurrence of pocket fills (20). Serious or life-threatening injuries were reported in 270 cases (76.9%), and fatalities were reported in 8 cases (2.3%). Injury did not occur or was judged to be nonserious in 58 cases (16.5%); the severity of consequences was unknown in 15 cases (4.3%) (20).

In an "Urgent: Medical Device Correction" letter issued to healthcare professionals (20), the manufacturer of SynchroMed infusion devices provided recommendations to avert and manage the occurrence of pocket fills. This letter may serve as a guide to improving patient practice, but does not answer all issues such as refill in the patient with a difficult body habitus. To address this later group, Gofeld and McQueen (19) recently suggested that ultrasound-guided IT pump access is feasible to prevent pocket fills. In cases where there is a concern of pocket fill, ultrasound may show drug in the subcutaneous pocket. A pocket fill can also be verified by com-

Table 2. Drug Filling, Dosing, and Device Programming Errors.

Type of error	Adverse consequence
Accidental injection of the drug solution into the subcutaneous pocket (pocket fill)*	— May lead to a sudden drug overdose or underdose; life-threatening overdose or withdrawal symptoms may ensue
Errors in programming bridge boluses†	— Drug overdose if the residual drug volume in the catheter or pump tubing is unaccounted for or estimated to be lower than the actual volume — Drug underdose if the residual drug volume in the catheter or pump tubing is estimated to be higher than the actual volume
Not accounting for dead space volume in inner pump tubing†	— Results in a higher-than-intended drug concentration in the catheter and pump tubing, even if the pump is refilled with a lower concentration of drug than was previously used
Compensation for the minimum pump flow rate with a high drug concentration†	— May result in a minimum programmable drug dose that exceeds the dose that was originally intended
Insufficient caution with equianalgesic dose conversions†	— Patient who tolerated a high dose of systemic opioids may remain susceptible to respiratory depression when receiving an equianalgesic dose of IT opioids
Assumption that the maximum IT trial dose is an appropriate starting dose for long-term IT therapy†	— The maximum dose of drug tolerated during an IT drug trial may still induce a drug overdose if administered immediately after implantation of the pump device
Reinitiation of IT opioid infusion at the titrated dose after a temporary interruption in therapy†	— Patient can become susceptible to the adverse effects of opioids within days after the cessation of IT opioid therapy

*Information derived from Medtronic Inc. Urgent: Medical Device Correction. Important Clinical Information about Pocket Fills. SynchroMed® II and SynchroMed EL Implantable Drug Pumps [news release]. January 2011 (20).
†Information derived from Coffey et al. *Pain Med*. 2010;11 (7):1001–1009 (2).
IT, intrathecal.

pletely emptying the pump and comparing the expected volume in the pump reservoir with the actual aspirated volume; a discrepancy between these volumes is essentially diagnostic of a pocket fill (20). The device programmer should not be used to confirm actual reservoir volumes, because current devices show only a calculated volume based upon the device programming. Other indications of a pocket fill include swelling at the injection site or patient reports of a burning or stinging sensation during drug injection; it must be noted, however, that these indications do not manifest in all patients and should not be considered a definitive finding in all patients (20).

Device programming errors that do not correctly account for the residual volume of IT drug solution in the inner pump tubing can result in an overdose or underdose and potential symptoms of drug withdrawal. Furthermore, the drug concentration must be manually entered during programming of the IT device, which provides additional opportunity for human error (4). The data presented by Coffey and coworkers suggest that the error of not accounting for the residual volume when programming can lead to death (2). In a retrospective analysis of 131 patients who received IT therapy with morphine, overinfusion was noted in one patient (48).

Meningitis and Other Infections

Meningitis is an infrequent complication of the implantation and maintenance of IDDS. Surgical implantation and refill of IDDS can result in bacterial meningitis and other infections (49). Chemical- or drug-induced aseptic meningitis can also result from hypersensitivity to medications or interaction of the drug or drug metabolites with serum antibodies (50). The incidence of meningitis or other infections (Table 3) in patients receiving IT therapy was documented in nine published reports that comprised four retrospective studies (38,45,48,51), four prospective studies (37,39,52,53), and one case series report (40).

In a retrospective study of 131 patients who received IT monotherapy with morphine via implanted pump devices, meningitis was reported during the test phase in three patients (48). In another retrospective review involving 34 patients who received IT combination therapy with morphine and a nonopioid analgesic via implanted pumps (45), one patient developed septic meningitis as a consequence of a pump refill and required urgent removal of the entire device. Meningitis was reported in two prospective, multicenter, open-label studies of long-term IT therapy with ziconotide via external pumps (39,52). Meningitis was noted in five patients (39), bacterial meningitis was confirmed in two patients and suspected in two patients, and aseptic meningitis occurred in one patient who recovered without sequelae. The duration of symptoms ranged from 9 to 33 days, and the occurrence of meningitis was deemed unrelated to ziconotide itself. Meningitis occurred during the titration phase of the study in four of the five patients, one of whom had a history of diabetes mellitus; two patients had no predisposing factors, and a breach in device sterility was a contributing factor in one patient. The remaining patient developed meningitis during the extension phase of the study, three days after detection of fluid leakage from the catheter filter (39). Although the 7% rate of meningitis in these patients was within the expected range of 0% to greater than 9%, the authors noted that the occurrence was increased among patients receiving long-term IT therapy via external infusion systems (39).

In an open-label, multicenter, prospective study of IT ziconotide therapy in 644 patients, 242 patients (37.6%) had external pump

Table 3. Meningitis and Other Infections.

Citation	Study design	IT medication(s)	Treatment-related adverse events
Reig and Abejón 2009 (48)	Retrospective review	Morphine	Meningitis in 3 of 131 patients (2.3%)
Kongkam et al. 2009 (40)	Case series report	Morphine or other opioid and nonopioid drugs	Meningitis in 2 of 13 patients (15.4%); paraspinous abscess with bacterial meningitis during IT pump use in one patient required pump removal; subclavian venous catheter sepsis and intracardiac fungal ball during IT pump use in 1 of 13 patients (7.7%); CNS infection in one patient during IT pump use required pump removal
Raffaeli et al. 2008 (45)	Retrospective analysis	Combination therapy with morphine and a nonopioid analgesic	Bacterial meningitis in 1 of 34 patients (2.9%)*
Ver Donck et al. 2008 (39)	Prospective open-label study	Ziconotide	Confirmed bacterial meningitis in 2 of 71 patients (2.8%) and suspected bacterial meningitis in two patients (2.8%)†; aseptic meningitis in one patient (1.4%)
Wallace et al. 2008 (52)	Prospective open-label multicenter study	Ziconotide‡	Twenty of 644 patients developed meningitis: 19 cases of meningitis possibly related to the external infusion system; one case of "chemical meningitis" related to ziconotide
Rauck et al. 2010 (37)	Prospective multicenter study	Morphine	Infection or cellulitis in 6 of 110 patients (5.5%)
Atli et al. 2010 (38)	Retrospective review	Morphine and other opioid drugs	Wound infections in 5 of 57 patients (8.8%)
Saltari et al. 2007 (53)	Prospective cohort study	Morphine	Wound infection in 1 of 24 patients (4.2%)
Pasutharnchat et al. 2009 (51)	Retrospective review	Morphine combination therapy§	Catheter-related infection in 1 of 29 patients (3.4%)

*Patient was excluded from the study.
†One patient developed meningitis during the extension phase after completion of titration.
‡Thirty-one of 644 patients also received other epidural medications; 580 patients also received strong analgesic drugs including morphine derivatives and other opioid drugs.
§Twenty-five patients (86.2%) received morphine and a nonopioid analgesic; 4 patients received morphine monotherapy.
IT, intrathecal; CNS, central nervous system.

devices at study initiation; 130 of these patients (53.7%) were later switched to an internal infusion system (52). Device-related adverse events occurred in 68.2% of the 242 patients who had external pump devices and in 29.1% of the 532 patients with implanted infusion systems. Meningitis occurred in 20 patients, 19 of whom received IT therapy via external pump devices. Of these 19 patients, 18 recovered without sequelae and 1 died from end-stage heart disease. In a case series report of 13 patients with chronic pancreatitis who received IT therapy with morphine and/or other opioid or nonopioid medications via internal pump devices (40), meningitis was documented in two patients. In one patient, meningitis was accompanied by subclavian venous catheter sepsis and an intracardiac fungoma that necessitated cardiac surgery and pump removal. In the second patient, meningitis was accompanied by a paraspinous abscess that also prompted pump removal (40).

Catheter infections, implant site wound infections, or both were documented in five studies (37,38,40,51,53). In a retrospective cohort study of 29 patients who received combination therapy with morphine and nonopioid analgesics via implanted pumps for the treatment of cancer pain (51), a catheter-related infection was reported in one patient at six months after implantation; the infection necessitated removal of the catheter. In a retrospective study of IT therapy with morphine or other opioid medications, wound infections prompted removal of the implanted IT device in 5 of 57 patients (38). Wound infections were also noted in two prospective studies of IT morphine monotherapy in patients with implanted infusion devices (37,53). In one study, infection or cellulitis occurred in 6 of 110 patients; surgical removal of the device was required in four patients with implant site infections (37). In the other study, among 24 patients receiving IT morphine monotherapy for pain related to osteoporosis, one patient developed a wound infection that required antibiotic treatment (53). Thus the rate of infection, although low, is an obvious area for improvement in clinical outcomes of IDSS therapy. The PACC has identified issues to consider and the recommendations are presented earlier in this article.

Granuloma Formation

Granuloma formation has been primarily associated with IT opioids (38,41) and opioids in combination with nonopioid medications (48). Risk factors for granuloma formation include high drug dose (54), high drug concentration (55,56), and the duration of infusion (57). A detailed discussion of granulomas is provided in the accompanying article, 2012 PACC Consensus on Diagnosis, Detection, and Treatment of Catheter-Tip Inflammatory Masses (58). Recommendations to avoid, detect, and treat granuloma are noted in the section above.

Hormonal Changes

The panel concurred that increased awareness of the endocrinologic effects associated with IT opioid therapy is needed. To determine if a patient's gonadotropic hormone levels have changed, sensitive inquiry about his or her libido should be included during clinic assessments. Many chronic pain patients have a low testosterone at baseline and the assessment may have nothing to do with the IT infusion. Regardless, if hormonal changes are detected, the patient should be tested and treated appropriately. Weaning the patient from IT opioid therapy and switching to IT ziconotide or other opioid drugs should be considered. The panel advised that the risks associated with hormone replacement must be considered before treatment is initiated. The panel recommends that patients be followed by their primary care physicians to monitor important changes in hormones, including testosterone and free testosterone in men, and estrogen, follicle-stimulating hormone, and LH in women. Hormonal replacement can be complex and should be done in collaboration with the patient's primary care physician, urologist, or gynecologist or in consultation with an endocrinologist.

Hormonal Suppression

IT opioid administration can induce hypogonadotropic hypogonadism, leading to low levels of estrogen and testosterone (34,49). A retrospective study of 73 patients published in 2000 showed that a large majority of men and all women developed hypogonadotropic hypogonadism after long-term IT opioid therapy (34). No new reports of hormonal suppression as a result of IT opioid therapy were identified in our literature search from 2007 to 2011, which suggests that this adverse event may go unrecognized in clinical practice and may thus be underreported. The recommendations of the PACC are noted above.

Anesthesia for IT Pump Placement and Revision

The PACC has made recommendations regarding anesthesia for IDDS implantation. An examination of the closed claim project, a legal analysis of settled or dismissed cases by the American Society of Anesthesiology, shows no cases directly attributed to the choice of anesthetic in those receiving pumps. Clinical experience suggests that an awake patient may be best able to complain of pain or paresthesias, and that someone undergoing spinal anesthesia may be slow to assess in the event of a neurological event (59). The choice of anesthetic should be tailored to the patient's best interest.

PDPH

In the event of PDPH in patients with newly implanted IDDS, the use of an epidural blood patch must be carefully considered because of the increased risk of infection. Supine positioning of the patient, caffeine supplementation, and hydration, possibly accompanied by the administration of intravenous dexamethasone and analgesics, may be attempted before a blood patch is considered. If persistent headache is accompanied by nausea and vomiting, the panel recommends that a CT scan be performed to evaluate for the possibility of intracranial hemorrhage. Placement of fibrin glue at the catheter insertion site may alleviate PDPH.

Psychiatric Considerations with Ziconotide

Ziconotide has been shown to be an efficacious IT analgesic agent in the appropriately selected patient. The window between therapeutic effect and significant side-effects can be quite narrow with rapid titration; therefore, slow dose titration and patient monitoring are recommended. One of the concerns with rapid titration is the psychological side-effects that may limit the drug's use. These adverse events typically resolve on discontinuation of the drug. Patients who are being considered for IT ziconotide therapy should be assessed with a careful psychological evaluation, with special attention to their premorbid psychological state and functioning. The patient's stress management and coping skills as the pain disorder has progressed over time offer valuable information for medical decision making about the use of ziconotide. It has been theorized that prior mental disorders may predispose the patient to

Table 4. Peripheral Edema.

Citation	Study design	IT medication(s)	Treatment-related adverse events
Atli et al. 2010 (38)	Retrospective cohort study	Morphine and other opioid drugs	Marked peripheral edema reported in 5 of 57 patients (8.8%)
Webster et al. 2008 (70)	Open-label multicenter study	Morphine and ziconotide	Peripheral edema reported in 3 of 25 patients (12.0%) during the titration phase and in 3 of 24 patients (12.5%) during the extension phase
Sadiq and Poopatana 2007 (69)	Retrospective study (70)	Morphine* and baclofen	Bilateral lower limb edema in 1 of 9 patients (11.1%)

*Only morphine was used for the treatment of chronic pain.
IT, intrathecal.

an increased risk of adverse psychiatric events with the use of this agent, but that has not been shown in a prospective fashion. Considering recent reports of increased suicidality associated with ziconotide, worsening of mood disorders and increased suicidal ideation are possible sequelae of ziconotide therapy (60). Cognitive impairment, new onset of psychosis, and changes in consciousness are other possible reported adverse events (60,61). Given these risks, patients with a history of psychosis are not candidates for ziconotide therapy (61,62). Even when an IT trial with ziconotide is successful, patients undergoing this therapy require ongoing assessment of their psychological functioning and a thorough mental status examination by the pain practitioner. Consultation with a psychologist or psychiatrist should be considered if side-effects develop (63).

Catheter Obstruction, Kinking, Migration, or Occlusion

The IDDS requires an intact system to deliver the desired drug. This involves the properly placed and intact non-occluded catheter, a properly functioning IT pump, and the appropriate drug. Catheter malfunction is the most common cause of system failure in those undergoing IDDS (37–39,42,64–66).

Peripheral Edema

IT opioid administration is associated with peripheral edema (particularly in the legs and feet). Although the mechanism underlying this edema remains unknown, both the sympathetic (67) and neurohypophysial systems have been implicated. It is unclear whether the antidiuretic effects of opioid therapy are mediated by arginine vasopressin, as both human and animal studies of opioids and opioid analogs have yielded contradictory findings (Table 4) (68). The consensus panel noted that patients must be screened for peripheral edema before initiating an IT opioid trial. Peripheral edema was documented as a treatment-related or treatment-emergent adverse event in three published reports of IT opioid therapy (38,69–71) and in one case report of an epidural morphine trial (72).

In a prospective, multicenter, open-label study, 25 patients received adjunctive IT morphine (initial morphine dose = 0.07–1 mg/day) while receiving long-term treatment with IT ziconotide (median ziconotide dose = 4.85–8.12 μg/day) (70). Peripheral edema was reported in three patients during the titration phase of the study and in three patients during the extension phase of the study (70). In a retrospective study of nine patients with multiple sclerosis who received combination therapy with IT morphine (0.8–9.5 mg/day) and IT baclofen (0.005–1.2 mg/day), bilateral lower limb edema was noted in one patient (69). In another retrospective study of 57 patients with chronic noncancer-related pain ($N = 54$) or cancer-related pain ($N = 3$) who received IT morphine or IT therapy with other opioid medications, 47 patients (82.5%) completed a three-year follow-up (38). The average dosage of morphine or opioid equivalent was 6.5 mg/day at the time of hospital discharge and 12.2 mg/day at three-year follow-up, corresponding to an 88% increase in opioid dose compared with the dose at discharge (38). Of the 54 patients for whom data on adverse events were available, marked peripheral edema was noted in five patients; however, no further details were provided. In a case report of a patient-controlled epidural morphine analgesia trial, a 64-year-old female patient received an epidural morphine dose of 6.3 mg/day. Bilateral peripheral edema was documented on the fourth day after trial initiation (22). By the end of the two-week trial, the patient had gained 12 lb (72).

Predisposing risk factors for peripheral edema include previous leg edema and venous insufficiency (67). In the case report noted above, the patient had none of these risk factors nor any known history of endocrine, hepatic, cardiac, renal, or vascular disease (72). None of the other aforementioned studies of IT opioid administration identified these risk factors in their patient populations.

Catheter- and Pump-Related Complications

Commonly reported catheter-related complications include catheter dislodgment or migration, obstruction, occlusion, or breakage (Table 5). Catheter-related complications were reported in three of ten studies (64–66), published in a meta-analysis of the efficacy and safety of programmable IT opioid drug delivery (43). In another study, spontaneous catheter dislodgment from the spinal canal into subcutaneous locations occurred in 3 of 18 patients (65); in two additional patients, catheter occlusion as a result of kinking at the fascial/ligamentous anchor was reported (65). In the third study, catheter obstruction resulting from loss of elasticity or collapse of catheter tubing occurred in 7 of 26 patients (66). Collapse of the tubing was usually located at the dural entry site, and affected patients experienced periods of opioid withdrawal (66).

Catheter breakage was noted in 1 of 26 patients at the dural entry site approximately 23 months after implantation (66). In a prospective multicenter study of 110 patients receiving IT monotherapy with morphine (37), catheter-related complications were reported in 17 patients. Catheter migration occurred in eight patients, catheter tear or breakage occurred in seven patients, and catheter occlusion occurred in two patients. Surgery to replace a catheter or to correct catheter function or placement was required in 13 of 17 patients: for catheter migration in 8 of 13 patients, for catheter

Table 5. Catheter- and Pump-Related Complications.

Citation	Study design	IT medication(s)	Treatment-related adverse events
Turner et al. 2007 (43)	Meta-analysis of 10 studies*	Morphine as monotherapy or in combination therapy	Catheter migration was reported in 4 of 34 patients (11.8%) in two studies (37,59); catheter breakage was reported in 1 of 26 patients (3.8%) in one study (45); catheter obstruction was reported in 7 of 26 patients (26.9%) in one study (45); pump or battery failure was noted in 4 of 34 patients (11.8%) in two studies (37,44)
Ver Donck et al. 2008 (39)	Prospective cohort study	Ziconotide	Catheter obstruction occurred in 2 of 71 patients (2.8%); device failure occurred in 13 of 71 patients (18.3%)
Atli et al. 2010 (38)	Retrospective cohort study	Morphine and other opioid drugs	Catheter migration or fracture in 3 of 57 patients (5.3%); pump malposition in 2 of 57 patients (3.5%)
Kongkam et al. 2009 (40)	Case series report	Morphine and other opioid and/or nonopioid drugs	Pump dislodgment/migration in 2 of 13 patients (15.4%)
Sorokin et al. 2008 (42)	Case study report	Combination of opioid and nonopioid drugs	Catheter migration into the subdural space
Rauck et al. 2010 (37)	Prospective multicenter study	Morphine	Among the 110 patients in the study, catheter migration was noted in eight patients (7.3%), catheter tear or break occurred in seven (6.4%), catheter occlusion occurred in two (1.8%), pump migration occurred in two (1.8%), and pump flip occurred in 1 (0.9%)
Sloan 2010 (41)	Case study report	Morphine	Catheter migration into the left L5 nerve root foramen

*Meta-analysis of studies published from 1995 to 2004.
IT, intrathecal.

occlusion in 2 patients and for catheter tear or breakage in 3 patients (37).

Catheter migration and fracture was also noted in 3 patients in a retrospective review of 57 patients who were receiving IT therapy with morphine or other opioids (38) and in two case study reports of patients receiving IT opioids (41,42). Sorokin et al. (42) documented catheter migration into the subdural space in two patients, one of whom was a 54-year-old man who had received IT opioid therapy in combination with IT nonopioid analgesic medications for chronic pain (42). The catheter was originally placed at the L4-L5 level, with the catheter tip located at the T8 level, and the patient experienced inadequate pain relief after implantation. A CT scan revealed that the catheter had migrated into the subdural space, entering the T12-L1 level. The catheter was withdrawn to the L2 level within the subarachnoid space, after which the patient experienced adequate analgesia (42). In another case report, a 51-year-old woman with breast cancer and spinal metastases experienced severe low back pain despite an increase in her IT opioid dose to 10 mg/day (41). A myelogram showed that the catheter had migrated into the left L5 nerve root foramen and appeared to be surrounded by a granuloma. The device was removed, and a new catheter was installed; the patient was subsequently switched to IT therapy with a nonopioid analgesic medication (41).

Pump-related complications were reported in two of ten studies (64,65) in a 2007 meta-analysis of IT opioid therapy (43). In one study, pump failure necessitating replacement occurred in 1 of 16 patients (64). In the other study of 18 patients, pump motor stall occurred in one patient and pump battery depletion occurred in two patients at 2.9 years and 2.6 years after implantation, respectively (65). At the time of battery failure, infusion rates were 0.9 to 1.7 mL/day (36–72 μL/h); however, no opioid withdrawal symptoms occurred in these patients (65). In a recent prospective multicenter study of 110 patients who received monotherapy with IT morphine (37), pump migration was noted in two patients and flipping of the pump occurred in one patient. All pump-related complications were resolved, and no pump failures occurred during the study period.

In an open-label, multicenter, prospective cohort study of 71 patients who received IT ziconotide, device failure was documented in 13 patients (39). In a retrospective review of 57 patients who received IT therapy with opioid medications (47), pump malposition was reported in two patients. Pump dislodgment or migration occurred in two patients described in a report of 13 patients with chronic pancreatitis receiving IT therapy with opioid medications either alone or in combination with nonopioid medications (40). In one patient, pump dislodgment and catheter displacement into the paraspinous tissue resulted in a seroma. In the other patient, pump migration within the abdominal wall interfered with bladder function and necessitated surgery to reposition the device (40).

Pump Refills and Avoidance of Pocket Fills

Notably, the residual volume estimate from the device programmer should not be considered an accurate measure of true residual volume as this is a calculated rather than a measured volume. Whenever there is question as to whether a pump refill has been performed properly, the patient should be admitted for observation. Ultrasound has recently been identified as a tool for diagnosing fluid in the pocket surrounding the pump as well as an adjunct for filling the pump in difficult cases (19). The PACC panel also recommends that all device programming be reviewed by at least two healthcare professionals before final device telemetry is performed.

Minimum training requirements for pump refill and programming procedures should include a demonstration of adequacy and competency, rather than simply the performance of a set number of pump refill procedures. Suggestions from the PACC panel for technological improvements in IT drug delivery systems include pump reservoir, needle placement, and pump volume indicators.

Reinitiation of IT Drug Delivery after Cessation of IT Therapy

When a patient has discontinued IT drug infusions for a time, the safest way to reinitiate therapy is to resume drug infusion at the

lowest effective dose and gradually titrate to a higher dose. The patient should be treated as if naive to IT agents and started at the dose that would be chosen for therapy initiation in naive patients. If the patient has been receiving oral opioids, those medications should be weaned as the IT dose is reinitiated.

In the event of catheter fracture or pump battery failure requiring an interruption in IT drug infusion, the panel recommends hospitalization and retitration of IT therapy as the safest option. In cases of pump battery failure, when the patient has received a lower dose of the drug than originally programmed, the committee recommends reducing the dosage to the lowest possible level and replacing the drug solution with saline before retitrating the dose. If the patient's status does not allow for weaning from the drug and saline replacement, the patient should be closely monitored after hospitalization and treated with a markedly reduced drug dosage. Recommendations for the starting doses of IT morphine and IT ziconotide are 0.1 to 1.0 mg/day and 0.5 μg/day, respectively. It must be noted that these general dosing guidelines are appropriate for most patients; however, exceptions may exist.

Bridge Bolus Calculation

When programming an IT drug dose bridging between two different concentrations of the drug solution, calculation of the amount of drug in the inner pump tubing and the length of catheter external to the pump must be performed. Verification of these calculations by another healthcare professional is strongly recommended as a safety measure each time the medication concentration is changed or a myelogram is performed. The consensus committee strongly recommends double-checking residual medication volume at the time of pump refilling in both hospital and home care settings.

Pump Implantation and Catheter Placement

The panel addressed several important aspects of pump implantation and catheter placement, including anesthesia, catheter positioning, and assessment of cerebrospinal fluid (CSF) flow. It was emphasized that the risk of potential spinal cord injury should be a consideration in the choice of anesthesia, particularly at the time of catheter implantation.

For IT catheter placement, a paramedian approach should be used and the needle inserted at an angle of 30 degrees or less. Removal of adipose tissue around the insertion site as necessary and securing of the catheter to the fascia using a purse-string suture are also recommended to prevent CSF leakage and catheter migration. Multiplanar fluoroscopy can assist practitioners with IT catheter positioning. The panel strongly recommends establishing a record of the catheter tip location, catheter length following trimming, catheter volume, and orientation of the side port.

Once the catheter is in place, free backflow of CSF must be confirmed. This should be checked again immediately before the catheter is connected to the pump. In the case of suboptimal CSF flow, a dye study may be considered.

New Muscular Pain with Ziconotide

In clinical studies, two cases of acute renal failure associated with rhabdomyolysis and extreme elevations of CPK levels were reported (73). However, with the advent of slower titration regimens, the incidence of this problem appears to be negligible. Monitoring of CPK muscle-type isoenzyme levels does not appear to be necessary for most patients. However, if a patient develops new or atypical muscle pain during ziconotide therapy, CPK testing should be considered.

Potential Training Requirements

The PACC panel recognizes that training requirements for clinicians who perform pump implantation procedures must be revisited. The members noted that hospital credentialing authorities should scrutinize individuals who implant IT pumps to the same extent that they scrutinize clinicians in other high-risk specialties such as cardiology. The panel also noted that the performance of a certain number of proctored implantations should be required before a clinician is deemed qualified. Once a pump is implanted, follow-up visit(s) with the clinician who performed the procedure will help to ensure continuity of care between pump implantation and IT therapy management. For patients who travel long distances for implantation, follow-up care may be provided by a local physician who is in communication with the implantation team. This may include other pain specialists, neurologists, oncologists, or specially trained primary care specialists.

For patients who travel long distances, assistance in finding appropriate care along the route should be provided. Treating physicians may help traveling patients find physicians through networking, and the IT device manufacturer may also be useful in this regard. In cases where a clinician practices outside the PACC recommendations, the ability to find another center for the healthcare team to manage the patient may be limited. This highlights the need for standardization of practice among those caring for this complex patient group.

INTERNATIONAL ISSUES WITH MORBIDITY AND MORTALITY

Despite a broad-based consensus regarding the indications for IT drug delivery, the use of this technique appears to vary greatly throughout the world. The economic conditions of many low-income countries can make these therapies difficult to obtain, but cost issues are unlikely to differ in the USA and Europe. Yet, unconfirmed information from one of the main manufacturers suggests that at least in recent years, more than twice as many pumps have been implanted in the USA than in the whole of Europe. This difference is, however, not as straightforward as it may appear. Indeed, Europe is far less homogenous than the USA in terms of reimbursement conditions, medical practice, attitude and expectations regarding chronic pain, acceptance of opioids, etc., which presumably explains variations across European countries that are perceived as significant. There is, however, no study (or otherwise published data) to support these statements.

Similarly, there are unverified assumptions that European physician tend to trial with single injections rather than continuous infusions more often than their American counterparts. Whether this has an impact on outcome is entirely speculative.

As to the choice of drugs, Europeans are perceived as "mixture users" and less enthusiastic than American physicians to prescribe morphine as a single IT drug. To some extent this is corroborated by an open-label study on bolus dosing (74) showing that mixtures of various drugs were used in nearly 40% of the cases.

The majority of pumps that are implanted today are programmable, i.e., the daily dose can be changed, the infusion can be stopped, or bolus of various doses can be administered at will. These features are perceived as significant advantages because, theoreti-

cally, they allow for the medication to be precisely tailored to the patient's needs. Whether this has any impact on the treatment outcome has not been studied and remains conjectural (75). However, anecdotal data suggest that bolus injection may have a better clinical effect than continuous injection, at least when local anesthetics are used (76). Furthermore, programmability improves the ease of use when multiple adjustments are needed.

MORBIDITY AND MORTALITY RELATED TO PUMP CHARACTERISTICS

Available IDDS fall into two categories: continuous infusion devices and programmable devices. There are several mechanical, continuous infusion pumps that have been available in the USA in the past.

At the present time, the Codman 3000 (Codman & Shurtleff, Inc., Raynham, MA, USA) is an approved mechanical pump in the USA and Europe. At present, programmable IDDS approved for pain indications in the USA are the SynchroMed family of pumps (Medtronic Inc.) and the Prometra® Programmable Infusion Pump System (Flowonix Medical, Mt. Olive, NJ, USA). These are approved to deliver Infumorph® (a preservative-free morphine sulfate sterile solution; Baxter International Inc., Deerfield, IL, USA), and the SynchroMed pump is approved for ziconotide.

The continuous flow pumps have an advantage of not requiring battery changes, which may minimize the risks to the patient. The *disadvantage* is the inability to easily change the dose, administer patient-controlled dosing, or titrate medication. The Codman pump has special bolus needles to give boluses through the same side port. A risk is present if the bolus needle is used for the routine pump refill causing an inadvertent overdose.

The programmable pump has the advantage of patient satisfaction, ease of dose change and titration, and potential to use patient-controlled analgesia. The disadvantage includes potential pump stall, battery life depletion, and rotor failure.

MRI precautions vary based on manufacturer, and the patient and physician should be aware of these issues at the time of implant.

As noted in this consensus statement, the risk of IT therapies related to morbidity and mortality is largely based on physician management choices and patient compliance. The type of pump risk is directly related to programming risks vs. refill and drug risk. There is very little data to support the safety of any particular pump design.

CONCLUSION

The morbidity and mortality that has come to the attention of clinicians by means of recent peer-reviewed reports and lengthy clinical experience significantly limits the utility of IDDS for the treatment of intractable pain. Fortunately, the causes of this morbidity and mortality are largely avoidable and can be minimized by vigilance and careful patient evaluation, surgical technique, pump maintenance procedures, and patient follow-up, with rapid recognition of complications and their appropriate treatment. Through this discussion, including an extensive update of the literature and the deliberations and recommendations of an expert consensus panel, the PACC hopes to improve the safety and efficacy of IDDS and thus improve the care of patients suffering from chronic pain.

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Drs. Timothy Deer, Robert Levy, and Joshua Prager chaired the project and led discussions; they also garnered contributions, added content, and edited materials from the consensus panel.

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Appendix I

Survey Responses: Morbidity and Mortality

In May 2011, three detailed surveys of healthcare providers concerning IT infusion use, safety, and reimbursement were sent to more than 15,000 physicians and clinicians in the USA and other nations by the PACC panel. Of the respondents, approximately 55% were licensed anesthesiologists, 8% were physical medicine and rehabilitation physicians, and 7% were neurosurgeons. Nearly half of the respondents (47.5%) were in private practice, 18% were in academic institutions, and 11% worked in private hospital systems. More than 55% of respondents had been working in pain management for longer than ten years. Seventy-five percent of respondents indicated that they dedicated at least 75% of their time to pain management, with an even distribution of neuropathic and nociceptive pain pathologies.

More than 80% of respondents indicated that they had observed new onset peripheral edema in patients treated with IT morphine less than 25% of the time. Among respondents, 34.6% stated that no patients had developed a granuloma while under their care, 11.2% indicated that a single patient in their practice had developed a granuloma, and 29% indicated they had seen between two and five patients with a granuloma. Of respondents who had seen a granuloma develop in their patient population, 38% noted that the granuloma(s) had developed while a programmable system was in use. Ten percent of survey respondents indicated that they had noted pump failure as a result of corrosion; 62% indicated that this had not occurred in their patient population.

Respondents were queried regarding patient safety and the recent letter to physicians issued by Medtronic in January 2011 (20). Overwhelmingly, respondents suggested that IT pump refills should be performed by trained, experienced physicians and clinicians only. Generally, survey respondents indicated that the use of fluoroscopy and/or ultrasound to confirm inadvertent filling of the pocket surrounding the pump rather than the pump itself was not warranted; however, most respondents noted that experience in filling IT pumps is paramount to patient safety. Better education and training were recommended. Interestingly, 52% of respondents indicated that increased mandated safety measures (e.g., ultrasound, fluoroscopy during fill) would "decrease" or "significantly decrease" their use of IT therapy. Only 10% indicated that increased safety measures would "probably increase" or "significantly increase" IT therapy use.

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

COMMENTS

This specific morbidity and mortality report from the PACC sets the benchmark for evidence-based recommendations for intrathecal opioid and ziconotide therapy to minimize complications. It represents the distilled experience and opinion derived from approximately 600 physician years of observations which makes it a profoundly grounded document and one that can fill the gaps where randomized controlled trials are lacking or fall short. This is not to dismiss the ever-present possibility of groupthink and its associated bias but nevertheless remains the best document available. I personally believe it is a more rational way of distilling experience than the Delphi method which forces participants to make choices for recommendations that may go against their actual direct practice, for example.

Contained are over 100 recommendations that if followed should minimize the risk of mortality with this therapy. First and foremost, intrathecal delivery is a continuous infusion modality which mandates continuous assessment and if necessary response. A high degree of vigilance is required but is rewarded by a low degree of complications and most especially by a rapid diagnosis of morbidity.

I can only reflect that it would have saved many lives if we had had a similar document for oral opioid therapy 25 years ago instead of our belated recognition of many similar issues.

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This is a very authoritative article on the subject with a good evidence background. It does however suffer from being lengthy and badly organized. In their eagerness to provide solid evidence to back their recommendations, the authors may have overlooked our desire as readers to be provided with a set of clear concise guidelines that are given prominence in the article. The article is also very much centered on a brand of pump which is the market leader but takes little account of the use of non-programmable pumps and other brands of programmable pumps.

Sam Eldabe, MD
Middlesbrough, UK

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

