

The Polyanalgesic Consensus Conference (PACC): Recommendations for Trialing of Intrathecal Drug Delivery Infusion Therapy

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Introduction: Intrathecal (IT) drug infusion is an appropriate and necessary tool in the algorithm to treat refractory cancer and noncancer pain. The decision-making steps/methodology for selecting appropriate patients for implanted targeted drug delivery systems is controversial and complicated. Therefore, a consensus on best practices for determining appropriate use of IT drug infusion may involve testing/trialing this therapy before implantation.

Methods: This current Polyanalgesic Consensus Conference (PACC) update was designed to address the deficiencies and emerging innovations since the previous PACC convened in 2012. A literature search identified publications available since the previous PACC publications in 2014, and relevant sources were contributed by the PACC members. After reviewing the literature, the panel determined the evidence levels and degrees of recommendations. The developed consensus was ranked as strong (>80%), moderate (50–79%), or weak (<49%).

Results: The trialing for IT drug delivery systems (IDDS) remains an area of continued controversy. The PACC recommendations for trialing are presented in 34 consensus points and cover trialing for morphine, ziconotide, and medication admixtures; starting doses and titration practices; measurements of success; trial settings and monitoring; management of systemic opioids during trialing; and the role of psychological evaluation. Finally, the PACC describes clinical scenarios in which IT trialing is required or not required.

Conclusion: The PACC provides consensus guidance on best practices of trialing for IDDS implants. In addition, the PACC recommends that no trial may be required in certain patient populations.

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INTRODUCTION

Intrathecal (IT) therapy has been a mainstay in the treatment of refractory pain since the mid-1980s (1). Since its introduction, interest has been high in developing a patient selection strategy to suggest reliable, long-term outcomes. Trialing modalities were introduced to offer the clinician and the patient a preview of what could result with longer term infusion by implanted pump. Unfortunately, no trialing method has proven to be superior to another in regards to predicting long-term efficacy of IT infusion (2). Considerations for this divergence may be an evolving pharmacokinetic and dynamic understanding of the IT space, an improved appreciation for the IT environment itself, and an understanding that meaningful changes in neuromodulation and function occur over a longer time frame. This manuscript serves as a companion manuscript to the other Polyanalgesic Consensus Conference (PACC) offerings (3,4), refreshing a living document with the most recent developments, innovations, evidence and consensus. This article incorporates the same evidence-based, recommendation-weighted strategies as described by the Neuromodulation Appropriateness Consensus Committee (NACC) in its 2014 publication (5). Specifically, we focus on IT trialing for intrathecal drug delivery systems (IDDSs).

METHODS

This PACC was convened in 2014 (with publication in 2016) and was designed to address the current IT therapy deficiencies and innovations that have emerged since the previous PACC convened in 2012 (with publication in 2014). New members were chosen from the International Neuromodulation Society (INS), with participants from the previous PACC committee and other invited experts. Members were international experts with either extensive experience in IDDS management, basic science research, and clinical studies, or expertise in evidence assessment or publication. The working consensus group

was governed by the authorship publication criteria of the journal *Neuromodulation* and Wiley Publishing, which conform to International Committee of Medical Journal Editors' standards.

Literature Search Methods

A broad literature search was conducted to identify clinical data on IT therapy trialing available since the last PACC publications in 2014. Authors also performed independent literature searches and the information was cross-referenced and compiled for evidence analysis and consensus review. These searches yielded articles, which were examined for relevance to IT trialing. After reviewing the literature, the PACC panel convened to develop recommendations for IT trialing. Supporting literature is cited in this manuscript following these recommendations and discussions.

Evidence Ranking

Unlike the PACC publications of 2014, the current PACC applied a validated evidence-ranking system. The United States Preventative Services Task Force (USPSTF) created hierarchies of studies and degrees of recommendations based on evidence rankings as outlined in Tables 1 and 2 (6). As the NACC used this validated tool to weigh recommendations for neurostimulation, so the current PACC uses this tool for IT therapy.

Authors were asked to complete reference forms for their section assessment, and these forms were then reviewed by the senior editors and averaged. The averaged reference forms served as the basis for review and consensus development. The group-developed recommendations based on evidence ranking, or consensus when evidence was lacking, were then assigned consensus rankings. The consensus strength determination was performed during in-person meetings or via teleconference with a quorum of 80% of the contributing authors present. Consensus rankings were outlined as strong, moderate, or weak based on agreement, as defined in

Table 1. Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force, Ref [6]).

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

Table 3. The resulting summary tables and consensus points appear throughout this document.

As with any guideline, this document should serve as a recommendation regarding IT trialing. These recommendations should not be construed as a standard of care, but rather as the result of our explorations of the evidence and the years of clinical experience of trialing for IDDS. It is important to address the conflicting nature of evidence and the need for consensus. Evidence assessment, regardless of the strength, needs interpretation for clinical application.

HISTORY OF TRIALING AS A PREDICTOR OF OUTCOME

Several concepts are important when considering the process of IDDS implantation. First, patient selection should be based on the patient's disease state, pain character, psychosocial status, and algorithmic thought or previous treatment failure with more conservative options. After a patient is considered an appropriate candidate for the therapy, the trial can be carried out. Since the inception of IDDS as an option for medication delivery, the requirement of a pre-implantation trial has been considered the standard of care. This was not based on evidence, but rather on the reasonable assumption that before considering an implantable pain-control device some measure of efficacy should be established. While the pre-implantation trial has been and continues to be standard of care and is, in fact, required by many insurers, the necessity and predictive value of the trial has come under increasing scrutiny (7).

Only a few reports examine the predictive value of an IT pump trial on long-term patient outcomes after implant. Dominguez and colleagues reviewed 157 patients with chronic noncancer pain who underwent serial inpatient, single, IT-bolus dosing trials, over a 5-year period from 1996 to 2001 (8). The trialing protocol consisted of sequential IT injection by lumbar puncture on consecutive days. Patients were typically trialed with 0.5 mg preservative-free morphine intrathecally, and those who experienced >50% pain relief for >8 hours were considered positive responders. Positive responders who experienced intolerable side effects were trialed with 0.25 mg

morphine the next day. Those who did not respond to 0.5 mg IT morphine bolus were then trialed with 1 mg preservative-free morphine the next day, and the dose was doubled the day after if no response was noted. All injections were single-blinded and patients who were positive responders underwent injection of one or two placebo doses to confirm response to morphine and rule out a placebo effect. All patients were admitted for 2–4 days for the trial and underwent at least two lumbar punctures. Patients who could not tolerate morphine were trialed on equipotent doses of hydromorphone or sufentanil. Patients with a positive response to the 0.5 mg morphine dose were referred to as “standard-dose” responders, those with a positive trial response to 0.25 mg morphine as “low-dose” responders, whereas those with a response to ≥ 1.0 mg morphine equivalents (MEs) as “high-dose” responders. All patients were followed for up to 30 months. Of the 157 patients trialed, 134 (85%) proceeded to permanent implant with programmable IT pumps, but complete medical records were available for review from only 86 patients (31 patients were lost to follow-up and 17 underwent explant for various reasons).

Compared to standard-dose and low-dose responders, high-dose responders escalated their IT opioid requirements dramatically and disproportionately in the first 6 months following implant. In addition, high-dose responders were more likely to require adjuvant medications and opioid substitutions than standard- or low-dose responders. Patients older than 65 years of age escalated their IT opioid dosages at much lower rates than younger patients. This study was limited by its retrospective nature and the fact that the study population was a heterogeneous group of patients who had back pain, complex regional pain syndrome (CRPS), visceral pain, cervical pain, deafferentation pain, and painful peripheral neuropathies. Of note, patients with cervical pain had the highest rate of opioid dose escalation. However, this may have been related to placement of the IT catheter in the lower thoracic area.

A small retrospective study examined 35 patients with lumbar postlaminectomy pain syndrome implanted between 2004 and 2007 at a single tertiary care center (9). The average baseline daily opioid dose in MEs was 162.9 mg and patients were not weaned off

Table 2. Meaning of Recommendation Degrees (U.S. Preventive Services Task Force, Ref [6]).

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

Table 3. Strength of Consensus.

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

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

opioids prior to trialing with continuous IT infusion of opioids (morphine in 91.4%, hydromorphone in 8.6%) for 23 hours. At 1 year postimplant, 40% of patients were on medication combination IT therapy. Patients were not allowed systemic opioids after implant. Correlation coefficients were used to identify determinants of IT therapy success postimplant. Mean improvement in visual analog scale (VAS) scores was 26% at 1 year postimplant; however, patients with higher IT opioid dose requirement during trial had less pain relief at 1 year postimplant, and age correlated negatively with pain relief and opioid dose escalation—younger patients experienced less relief and had more frequent opioid dose escalation than older patients.

Recently, Hamza and colleagues compared trialing with a continuous method to trialing with intermittent bolus dosing (10). They prospectively studied 58 patients with a 3-year follow-up postimplant. Prior to trial, patients' oral/systemic opioids were weaned by 50%, and an inpatient trial was undertaken using single opioid boluses followed by placebo. A successful trial was defined as reduction in pain, improvement in function, lack of significant adverse events (AEs), and no report of improvement with the saline injection. A failed trial was defined as improvement with the saline injection that was superior to the opioid injection. In the study, three patients failed the trial and were not implanted. The remaining patients were implanted and reported significant improvement throughout the observation period. The authors introduced the technique as simple, easily performed with no dose conversion, and as a way of managing oral systemic opioids relative to the pump implant. At the time of 1-year follow-up there was no difference in outcome regardless of the method used for trialing. This work confirmed the work done more than a decade ago by Deer and colleagues, who determined that the long-term outcome was similar regardless of trialing via epidural or IT route and independent of single-shot, continuous, or bolus dosing (11).

Anderson et al. (12) published a study comparing IT single injection to escalating continuous epidural (CE) infusion trialing techniques. Thirty-eight patients were included in the study, 18 treated with a single dose of 1.0 mg IT morphine, and 19 trialed with a dose-escalating CE infusion ranging from 0.2 to 2 mg/hour. Trial success, defined as $\geq 50\%$ pain reduction, was 60% in the IT group and 64% in the CE group. Trial failure was due to $< 50\%$ pain improvement despite dose titration. At follow-up there were no significant differences in outcomes between the groups. The study lasted 6 months, with two observation points, and was powered to measure the safety and cost-effectiveness of the two trialing techniques. The researchers concluded that safety was comparable, however, IT trialing was more cost-effective. Following implant, all patients were started at 1.0 mg/day; at the end of observation the IT dose was 5–6 mg/day, representing a 500% to 600% increase over 6 months. Oral opioids were discontinued for at least 12 hours before trial. Following implant, systemic opioid use decreased by 57% on the medication quantification scale at the end of observation compared to

baseline dose. There was no report on a specific weaning protocol and the trials were open label. Beyond the initial random assignment to trialing group there was no blinding or randomization. However, these researchers found more frequent opioid side effects, including nausea, vomiting, diaphoresis, and urinary hesitancy in implanted patients who underwent single-bolus IT morphine trial vs. those who had undergone continuous epidural infusion. It should be noted that the studies by Hamza et al. (10), Deer et al. (11), and Anderson et al. (12) did not evaluate the response to IT therapy in patients who did not undergo a trial as part of the protocol, so no comparisons can be made in that group.

Consensus Point 1. The PACC concludes that no single study has shown that continuous IT trial is superior to other methods of IT trials in noncancer pain. There are equal levels of evidence for single-shot trialing, bolus trialing, and continuous infusion.

Psychological Screening as a Predictor of Successful IT Therapy in Noncancer Pain

Bonica and Livingston introduced the multidisciplinary approach to the assessment and treatment of chronic pain in the 1950s (13). Melzack and Wall's gate control theory in 1965 highlighted the mechanism through which psychological factors could significantly influence the experience of pain (14). The International Association for the Study of Pain (IASP) defines pain as a sensory and "emotional experience," thus establishing psychological factors as a necessary component (15). Indeed, Basbaum (16) indicated that chronic pain may not exist but for an emotional component. The use of IT therapy for the treatment of chronic pain emerged in the late 1970s and early 1980s.

The Centers for Medicare and Medicaid Services (CMS) in the United States mandate the use of preimplant psychological screening for spinal cord stimulation (SCS) in an effort to improve outcomes (17). In 1985 Daniel (18) indicated the importance of psychological assessment and treatment as part of the SCS protocol; "Electrode implantation can serve as the initial step in a treatment plan followed by psychotherapy 'to address psychological factors influencing pain'" (p. 776). The general philosophy of identifying comorbid psychological factors that could compromise treatment was carried over to IT therapy, especially in the noncancer setting. Nelson et al. in 1996 (19) proposed a list of red flags including suicidal tendency, alcohol or drug dependency, unresolved compensation/legal issues, severe untreated depression and other factors which, although not empirically derived, made sense clinically. This spurred a rule-out approach to the assessment for neuromodulation. More recent guidelines (20) have emphasized the assessment of positive characteristics such as proper expectation, social support, effective coping skills, and the notion of using psychological intervention before and after implant.

The placement of a subarachnoid catheter for IDD probably warrants consideration of psychological factors not associated with other therapies. Whether or not one can obtain any degree of "predictive" accuracy from a one-time psychological assessment remains unclear, and there is little controlled research to support this. Logically, the clinical narrative would implicate the need for identification of positive and negative characteristics preimplant, followed by periodic re-assessment to take into account changes in the patient's circumstances. Psychological interventions, therefore, would be instituted as indicated. This model is consistent with the emerging appreciation for chronic pain as a complex and dynamic disease process. This approach transforms neuromodulation from a technique/procedure into a long-term therapy. Postimplant

Table 4. Does Trialing Predict Therapy Outcome? Recommendations by the Polyanalgesic Consensus Conference (PACC).

Statements	Evidence level	Recommendation strength	Consensus level
A trial should be considered before initiating IT drug delivery for noncancer pain.	II-3	B	moderate
A trial is not a necessity before initiating IT drug delivery for cancer pain.	III	I	moderate
If a trial is performed, delivery of the medication within the IT space is an acceptable method.	II	C	strong
IT trials should be monitored in a safe setting, with due vigilance, appropriate monitoring of the patient, and appreciation for patient comorbidities.	II-3	B	strong
IT ziconotide trials should be monitored in a safe setting, with due vigilance, and appropriate monitoring of the patient.	II-3	B	strong

management of the patient becomes as, or more, important as pre-trial or preimplant assessment. In many cases psychological involvement, therefore, extends beyond screening to intermittent but long-term patient/pain management (21).

Consensus Point 2. The PACC recommends a psychological assessment prior to any implant for noncancer pain. Preimplant psychological assessment is an important part of the patient evaluation to place an IDDS. We also recommend ongoing psychological care for those with ongoing issues identified by the mental health professional performing the evaluation. In some geographic locations, inadequate or unavailable mental health services may require modification of this recommendation.

Consensus Point 3. The PACC does not believe a formal psychological assessment is required in patients with pain due to cancer and other terminal conditions. Psychological and spiritual assessment and treatment may be of help in those who have issues concerning death, dying and grief.

PRE-TRIALING MEDICAL MANAGEMENT

Once a decision to proceed with IT trialing has been made, the patient's comorbidities that could influence the success of this therapy should be optimally managed. Disease states that potentially interface with successful outcomes of IT trialing include cardiovascular disease, respiratory disease, systemic/chronic infections and coagulopathies. The NACC is currently working on articles, slated for publication in 2016, addressing coagulation management (22) and infection prevention and control (23) for implantable devices. Particular emphasis should be placed on the patient's medical condition and on comorbidities such as pulmonary status, given that there is the possibility of opiate-induced respiratory depression after IT therapy (24). The use of concomitant medications, particularly benzodiazepines, which affect respiratory drive, should be evaluated carefully and reduced, if possible (25). Additionally, assessment of sleep apnea may be appropriate in certain patients. Lastly, there is an increasing recognition of hypogonadism associated with long-term opiate exposure, irrespective of the route of opiate delivery (26–29). This abnormality may be worthy of appraisal prior to embarking on IT delivery. Management of any of these issues may necessitate referral to the appropriate consultant.

EVIDENCE FOR TRIALING

As noted earlier, variable trialing techniques have been reported with outpatient or inpatient IT delivery vs. an epidural catheter trial (11,30–34). The three major payers in health care in the United States (Medicare, United Health, and Anthem), as well as some European countries, require a catheter trial as a condition for pump implant. The rationale has been that a catheter trial provides the opportunity to assess short-term pain relief of the therapy, begin to gauge appropriate dosing, and determine individual tolerability to the therapy (17,35,36). Many, however, have questioned the value and need for an IT pump trial given lack of studies with supporting evidence and the fact that a seemingly successful trial may not predict long-term success (25). In addition, it is not possible to trial all potential analgesics or their combinations, which may predispose to a high likelihood of false-negative trials (25,37). However, expert panels have consistently recommended that patients being considered for IDDS undergo a trial in view of information provided on individual patient response, including analgesia, functional improvement, and AEs (25,38). Setting up treatment goals prior to an IT trial may allow providers and patients to better evaluate the responses to the trial (39). A potential confounder could be the lack of uniformity with the method of trialing and the long-term infusion strategy.

Consensus guidelines have provided recommendations with regard to patient selection and trialing techniques in the setting of noncancer pain (7). The previous PACC outlined an evidence-based algorithm regarding the utilization of different medications in an IDDS (38). Many questions remain unresolved after the last publication; therefore, this present version of the PACC considers levels of evidence and expert opinion to clarify best practices (Table 4).

Historically the use of a positive response to intraspinal opioids has been critical to moving forward with IDDS (40). Earlier we discussed multicenter studies showing no difference in outcomes regardless of trialing technique. In an older study, Paice and colleagues (41) conducted a mail survey of 35 physicians from different specialties caring for patients with chronic pain and IDDSs. Four-hundred and twenty-nine patient surveys were returned from 35 physicians. The most common screening method was continuous epidural infusion at 35%, followed by IT boluses in about 34% of cases and epidural bolus injection in 25%; continuous IT infusion was reported in about 6%. Based on this analysis, there were no

statistically significant differences between patient groups defined by type of screening with respect to activities of daily living (ADL) and pain relief. Blinded testing with saline was performed in 18% of patients. No statistically significant difference was found between the blinded and the non-blinded test groups. A recent survey in Canada by Peng et al. found that direct IT infusion was the most popular trial method used (50%) (42).

In a single-site retrospective review of 86 patients, prior to pump implantation, all patients were admitted to the hospital for 2–4 days where they underwent single-blinded opioid IT trials (8). This typically consisted of single-dose opioid boluses via lumbar punctures on consecutive days. Morphine, hydromorphone, and sufentanil were used in the trial; patients with a positive response were trialed with saline to rule out a placebo effect. The study examined the impact of age, gender, primary diagnosis, and opioid needs during trial on the outcome during follow-up. However, the study did not compare different trialing techniques. Unfortunately, this study did not present a specific protocol to address managing the dose of oral/transdermal opioids and did not require patients to decrease or eliminate opioids prior to trial or implant.

VAS of pain intensity (VASPI) reduction by 50% with acceptable side effects are the usual criteria for success. (12). While many have opined regarding proper trial length, there are no generally accepted guidelines as to the length of trial, or guidelines regarding discontinuation or tapering of systemic opioids during the trial (43–45).

Other evidence exists and dates back two decades. Tutak and Doleys in 1996 used an epidural infusion for 2 weeks and defined a successful trial using multiple criteria: $\geq 50\%$ reduction of pain, discontinuation of systemic opioids, and increase in activity levels (46). Winkelmuller and Winkelmuller used IT infusion of undocumented length with the success criterion of VAS reduction by 60% (47). Angel et al. used three IT boluses of 0.125–0.750 mg of morphine during an inpatient trial of more than 3–4 days and gave a placebo dose of 0.0125 mg of morphine on the last day, again using $\geq 50\%$ reduction in pain as a success criterion (32). Without a saline placebo, this method is a dose-response trial rather than a placebo-controlled trial.

Rainov et al. (48), in a series of 26 patients, used a tunneled IT catheter for infusion of 3–10 days as a trial. After the start of IT trial infusion, systemic medication was continued for 3 days to manage breakthrough pain. Weaning of systemic medications started on day 4, and they were gradually decreased until they were finally discontinued after 7–10 days of trial infusion. If necessary, the IT morphine dose was increased during systemic opioid weaning. The trial infusion was started at 0.5 mg/24 hour morphine and titration was performed until a decremental pain response was noted. Clonidine was added at 0.015 mg/24 hour, and bupivacaine at 0.5 mg/24 hour. Midazolam's starting dose was 0.2 mg/24 hour. Four patients with failed IT infusion trial due to unspecified subjective dissatisfaction with the treatment were excluded from the study. A VAS decrease of 50% was considered as success; there was no assessment of functional improvement during trial. There was no clear description of weaning parameters.

A more quantitative approach using placebo was advocated by Levy (49). His two-phase trial involved the use of an IT catheter for a morphine bolus, dose-escalation trial measuring VASPI as the endpoint. A second phase of the trial involved a crossover double-blind trial of bolus saline vs. morphine. Using this method, 27% of patients failed to meet the criteria for implant in terms of VASPI reduction and lack of response to placebo. This protocol, however, may be too complicated, hard to reproduce, and lacks details of how to incorporate the management of concomitant oral/systemic opioids.

In a retrospective review, Maniker et al. reported that although epidural infusion is an effective screening method (50), it overestimates the IT dosages needed for pain control when a permanent IDDS is implanted. Authors did not comment on systemic opioids management in relation to IDDS implantation. Results from this group may be even more confounded since there was no established dose equivalency when considering factors such as rate of infusion and volume infused.

Krames described an outpatient, IT trial after reduction of oral opioids by 50%; he also allowed the use of rescue opioids during trial (40). Another paper by Krames gave the opinion that bolus trials were limited because of their inherent short duration, lack of mitigation to placebo effect, and lack of simulation to actual implant (43). He also noted that as a result of fibrosis after continuous epidural infusion, the epidural space might be restricted and not allow full spread of medication. More recent studies have not shown these theories to be accurate as noted previously.

Hamza et al. showed that there is no superior trialing method (10,51). Anderson et al. (12) showed that there are more side effects in those receiving bolus compared to continuous infusion, but no difference in efficacy.

Consensus Point 4. There is evidence for efficacy of single-shot, bolus, and catheter trialing techniques. If pretrial oral opioids are associated with side effects, then a trial to evaluate the possible side effects with an IT dose is important. Also, trialing to evaluate the side effects of ziconotide should be considered. The use of placebo may increase the utility of an IT trial.

Consensus Point 5. The trialing doses of IT medications should be chosen conservatively.

Regulatory Policy for Trialing

Trialing before implanting an IDDS has been a practice standard and has been included in many certification requirements. At the time of this publication there has been no prospective, randomized, controlled-study evidence to show that trialing changes long-term patient outcomes compared to not performing a trial. Proponents of trials believe that trialing eliminates poor responders and allows the physician to note improvements in function and behavior, as well as in pain relief, before moving to permanent implant. Other implanters state that trialing is unproven, expensive, and subjects the patient to procedures that entail risks in exchange for minimal, if any, benefit.

Medicare reimbursement policy in the United States covers opioids and ziconotide for the treatment of chronic refractory pain through an implanted IDDS if a patient has a life expectancy of 3 months or more, fails noninvasive medical pain management techniques, and responds to a trial of opioids through a temporary IT or epidural catheter.

Currently in the United Kingdom (UK), IDD is only approved for noncancer pain on a case-by-case basis and is indicated as a last resort for severe refractory pain. This policy includes specific diagnoses that can be considered, such as multiple compression fractures (52). IT cancer pain management is approved with specific qualifications for patient selection. Cancer pain treatment is approved as well by the newest PACC treatment algorithms (3). A trial for efficacy is required in the UK but the specifics of the trial are left to the discretion of the physician (38,52).

The policy regarding IDD in the European Union (EU) varies for individual countries and ranges from no established policy for payment to full reimbursement for both cancer- and noncancer-related

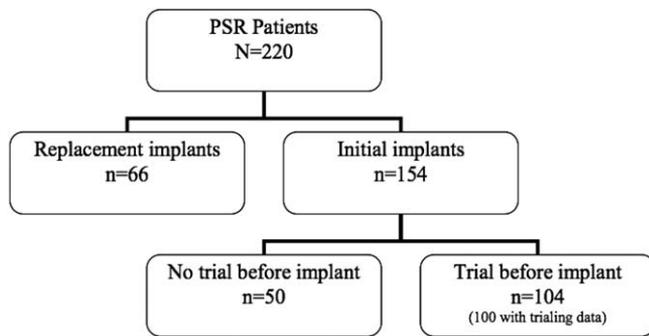


Figure 1. Distribution of Medtronic Product Surveillance Registry patients from May of 2013 until January of 2015. Data from the Medtronic Product Surveillance Registry used with permission.

pain. Physicians in the EU should reference local country policy for more information.

Policy for IDD in Australia for noncancer pain requires a psychological screening and a trial before implant. The trial can be performed by bolus or infusion and must show both pain improvement and improved quality of life or function. The official government policy for cancer pain is to externalize catheters for external delivery because of limited life expectancy (53).

The Asian use of IDD is very limited. Recently the use of IDD has increased slightly with improved access to technology. The approval for this therapy is limited and varies from country to country. No trialing policy has been determined in most jurisdictions (54).

Evidence From a Product Surveillance Registry

Both Medtronic (Minneapolis, MN, USA) and Flowonix (Mt. Olive Township, NJ, USA) have developed postmarketing product surveillance databases. These have been criticized since they only capture results from a small percentage of physicians and doctors who implant the devices, which could represent a bias toward outcomes that are not generally representative. Nevertheless, the data could have representative value and should be considered.

Since 2003, the Medtronic Product Surveillance Registry (PSR), and its predecessor, the Implantable Systems Performance Registry (ISPR), have collected data for more than 7000 patients from 55 centers across the United States, Europe, and South America (55). In 2013–2014, Medtronic expanded this data collection to include data on trialing techniques and patient-reported outcomes. Specifically, the PSR collects data on patients with IDDSs that includes the diagnosis, type of trial, length of trial, place of service, and outcomes.

Table 5. Distribution of Trialing for Initial Implants by Primary Treatment Indication.

Primary indication	Trialed before implant		
	Yes	No	Total
Non-malignant pain	59 (88.1%)	8 (11.9%)	67
Malignant pain	11 (21.6%)	40 (78.4%)	51
Spasticity	25 (100.0%)	0 (0.0%)	25
Non-malignant pain & Spasticity	7 (100.0%)	0 (0.0%)	7
Malignant pain & Chemotherapy	2 (50.0%)	2 (50.0%)	4
Total	104 (67.5%)	50 (32.5%)	154

Data from the Medtronic Product Surveillance Registry used with permission.

Patient-reported outcome measures include the Oswestry Disability Index (ODI), Numeric Pain Rating Scale (NPRS) and EQ-5D (quality of life). These enhanced data have been collected since May of 2013 and accrual is ongoing. As of January of 2016, the median follow-up time was approximately 9 months, but this will increase as patients are followed for longer periods.

As of January 2015, the last time the data were analyzed, the PSR had captured trialing information on 154 patients enrolled from May of 2013. Fifty patients had no trials and 104 patients had trials before implant (Fig. 1). In this cohort, 67 of 154 patients had noncancer pain, 51 patients had cancer-related pain, and 25 patients had spasticity. Several patients had overlapping diagnoses. Eighty percent of the noncancer pain patients had trials, and 21.6% of cancer-related pain patients had trials. All spasticity patients had a trial (Table 5). However, data on patients with cancer pain were heavily skewed by information provided by one center, which does not routinely do trialing. Thus, the conclusions regarding common cancer-based practice cannot be determined. In summary, 58% of the trials were performed in the hospital inpatient setting, 28% of the trials were outpatient, and 12% were listed as other settings (Fig. 2). Forty-five percent of the trials were performed with a continuous IT infusion, 44% were trialed with single-shot IT bolus injections, 7% used multiple IT bolus injections, and 4% of the patients were trialed using continuous epidural infusion (Fig. 3). The median duration of IT infusion was 6.5 days. Eighty percent of the patients with cancer-related pain were trialed with single, IT bolus injections; 68.4% of the patients with nonmalignant pain were trialed with continuous IT infusions; and 79.2% of the spasticity patients were trialed with either single or multiple IT bolus injections (Table 6).

Future analysis of this data will provide a more robust snapshot of practice patterns in the United States, Europe, and South America, since all participating sites will have converted from the ISPR to the PSR protocol where trialing information is collected. Thus, there should be adequate data to evaluate associations between trialing techniques and patient-reported outcomes and to determine whether trialing improves outcomes and whether any single trialing method should be preferred. This registry will provide real world information, but may be limited because of participating centers, patient demographics, and variability in selection criteria. The registry of the Flowonix Prometra pump is very limited at present. Perhaps a pooling of registry data will be helpful in the future. Work is being done in the UK to create a national registry. Registries that include all data of all patients selected for IDDS, and subsequently implanted with pumps from all manufacturers, would be extremely helpful in future discussions and best practice recommendations.

Consensus Point 6. The PACC recommends a randomized, prospective, multicenter evaluation of trialing methods to determine if a trial or method of trialing has any impact on patient outcomes.

The literature suggests that no trialing methodology can help predict long-term success (2,10). As described recently, this may result from poor translation of the trial IT pharmacokinetics to the conditions of permanent implant. Bolus-only strategies have been developed for IDD to better emulate a bolus-style trial.

Trialing for Low-Dose IDD (Microdosing)

In many practices the current dosing strategy for IDDS has been based on provider experience with scientifically unproven recommendations and rough approximations of equianalgesic dosing (56). Those who have adhered to the previous PACC recommendations have adopted a reduced daily dose and lesser concentration for long-term infusions. It might be possible to postulate that

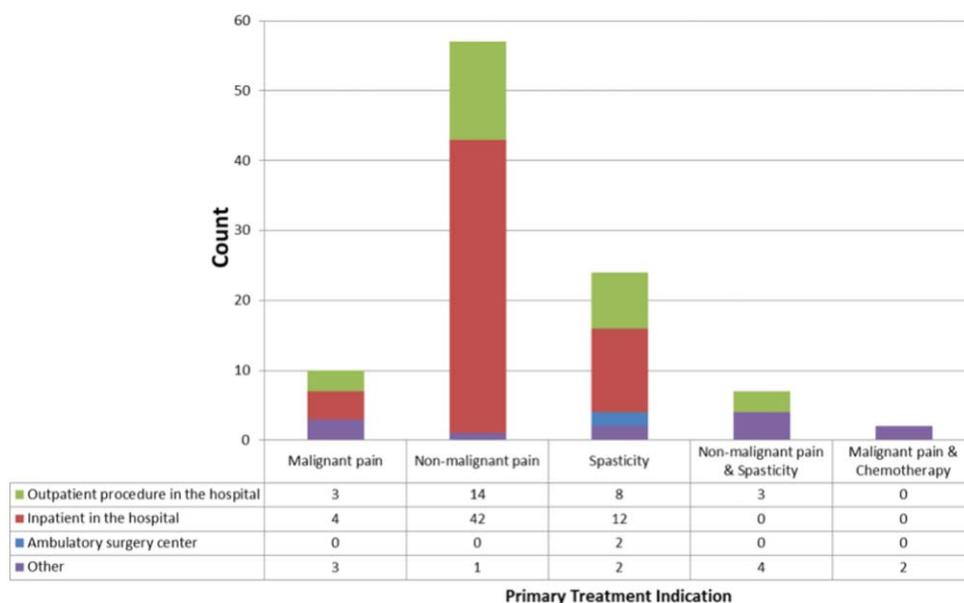


Figure 2. Trialing site of service by primary treatment indication. *Other represents trialing performed at “pain management center” (n=7), or “in-clinic” (n=5). Data from the Medtronic Product Surveillance Registry used with permission.

adherence to previous PACC recommendations may lead to a reduction in side effects, granuloma formation, and morbidity (38).

The term “microdosing” has been introduced based on observations that opioid cessation coupled with microgram-dosed morphine IT trialing resulted in improved outcomes for patients with IDDS. The term has evolved to actually represent a philosophy of trialing followed by maintenance dosing of IT opioids (occasionally in combination with adjuvant medications) with the express goal of reversing or slowing opioid tolerance and perhaps hyperalgesia by significantly reducing or eliminating concomitant systemic opioid therapy. Although the low-dose concept is intriguing, it has not been studied in any large, multicenter, randomized, controlled, prospective studies.

The previously discussed study by Hamza et al. continued to follow patients for 36 months after a successful trial. Patients were

initially weaned from their baseline systemic opioid dose to 50% of the original amount (51). This is a common practice that has been recommended for many years and was first suggested by Krames (43). After 50% weaning off systemic opioids, patients underwent a trial by placing an IT catheter (tip at T12-L1) and were given a bolus of either IT preservative-free saline or morphine (0.25 mg or 0.5 mg) on 3 consecutive days. Only three patients had more relief with saline than morphine and were considered trial failures and did not proceed to implantation. The rest of the patients were then weaned off systemic opioids over 3–5 weeks on an outpatient basis, and after 7–10 days of being off opioids were implanted with an IDDS. This concept of weaning prior to implanting the permanent device is a new concept and part of the microdosing strategy. Shortly after implant, IT opioid titration stabilized at approximately 1.5 mg ME/day of IT opioid. This was somewhat in contradistinction to the

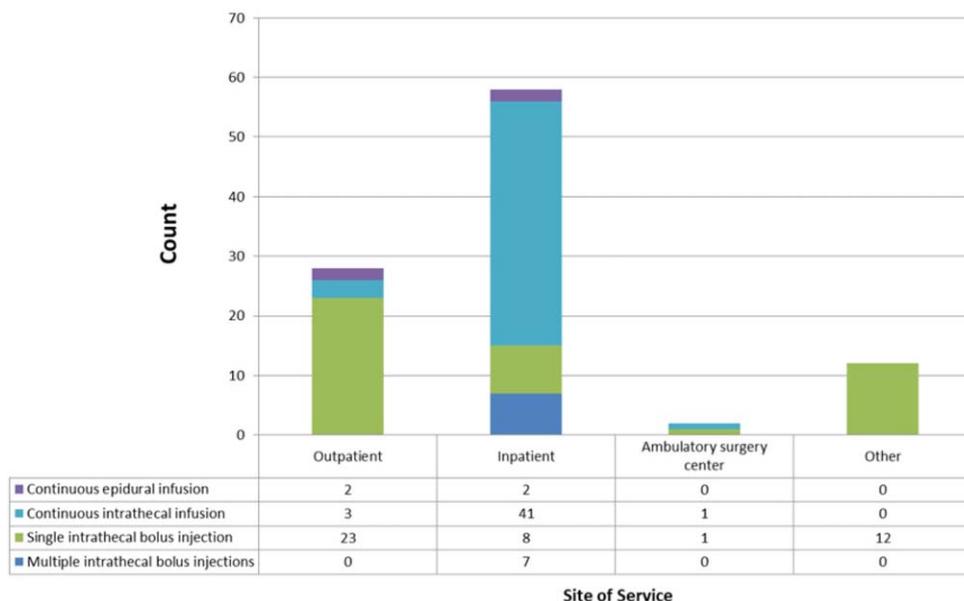


Figure 3. Trialing method by site of service. Data from the Medtronic Product Surveillance Registry used with permission.

Table 6. Trialing Method by Primary Treatment Indication.

	Malignant pain		Non malignant pain		Spasticity		Non-malignant pain & spasticity		Malignant pain & chemotherapy		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Continuous intrathecal infusion	2	20.0%	39	68.4%	4	16.7%	0	0.0%	0	0.0%	45	45.0%
Single intrathecal bolus injection	8	80.0%	15	26.3%	12	50.0%	7	100.0%	2	100.0%	44	44.0%
Multiple intrathecal bolus injections	0	0.0%	0	0.0%	7	29.2%	0	0.0%	0	0.0%	7	7.0%
Continuous epidural infusion	0	0.0%	3	5.3%	1	4.2%	0	0.0%	0	0.0%	4	4.0%

Data from the Medtronic Product Surveillance Registry used with permission.

Grider et al. retrospective case series that evaluated patients following a 6-week opioid-free period after trial and implantation (57). Average IT morphine doses were 140 mcg/day at trial and stabilized at an average 335 mcg/day of IT ME 12 months after implant. Improvements in pain scores and function were recorded during the trialing and early maintenance phase. The last PACC briefly discussed microdosing using these studies to support a proof of concept that was believed to require further investigation (38). Additional work has been done regarding low dosing since the 2012 PACC, and the evidence has improved.

Recently several investigators have reported success with some degree of microdosing. Hatheway et al. published a study involving 389 subjects and reported a 51% success rate in eliminating systemic opioids within 1 year of implantation of an IDDS (58). While the aim of the study was to evaluate the impact of IDD and systemic opioid administration on health care expenditures, the evidence supported the prior observation that IDD in general, and low-dose approaches specifically, enable the elimination of oral opioids in many subjects. Likewise, Caraway and colleagues reported that systemic opioid use was eliminated in 92% of subjects ($n = 99$) by 5 years, with the majority of subjects (68%) eliminating systemic opioids during the first month following IDDS implantation (59). More importantly, the mean IT starting dose in the Caraway et al. study was 360 mcg per day of IT ME, which was within the range reported by both Grider et al. and Hamza et al. This was accomplished without the opioid-free interval initially described anecdotally by Witt and later reported as a protocol by Grider (57).

This opioid-free interval method was also evaluated in a prospective 36-month study that reported similar degrees of analgesia at 36 months compared to the retrospective study (60). In this expanded and prospective study, an attempt was made to determine epidemiologic patient factors that could be identified to predict success with IDD using a low-dose approach. This study suggested that

patients with mechanical or nociceptive low back pain were more responsive than patients with pure neuropathic pain syndromes to low-dose IT opioids (60). Again, similar to studies by Hamza et al. and Caraway et al., sustained analgesia was seen at IT doses significantly lower than previously reported in the literature (51,59,60).

The broader concept of microdosing, however, remains unproven because of a lack of effectiveness studies comparing this strategy to conservative medical management (CMM) or other IT therapy approaches. Micodosing preselects patients who are willing and able to wean off opioids and may not be applicable to all patients, especially those with progressive cancer-related pain. In addition, opioid usage, both IT (including dose escalation) and systemically, are not solely dependent on patient feedback but also on practitioner preferences and biases. The general lack of objective methodologies for IT opioid and systemic opioid titration and delivery in IDDS-implanted patients somewhat detracts from the value of these important outcomes. The studies considered here strengthen the evidence that microdosing may be helpful in a subgroup of patients (Table 7). It is important to note that most patients who underwent this type of low-dose trialing had either their doses of systemic opioid reduced or were totally weaned off before trialing.

We suggest that the term *microdosing*, which is not descriptive and surrounded by a mythology of sorts, be replaced with the term *low-dose IT opioid therapy*. The concept of low-dose IT opioid therapy describes a methodology of identifying, trialing and maintaining subjects, who are largely opioid naïve and have chronic benign pain, with the goal of transitioning from systemic opioid therapy to IT analgesia. The stated goal is to maximize the benefit of IT drug delivery while minimizing exposure to the risks and side effects of combination IDD and systemic opioid administration. Drastically reducing, if not eliminating, systemic opioid therapy accomplishes this goal. Additionally, it does not appear to matter whether the trial is a single-shot or catheter-based trial (10). While the original

Table 7. Recommendations for Low-Dose IT Therapy by the Polyanalgesic Consensus Conference (PACC).

Statements	Evidence levels	Recommendation strength	Consensus level
Sustainable analgesia can be achieved at lower doses without the need for systemic opioid supplementation.	II-3	B	moderate

approach of IT, low-dose, opioid therapy recommended pretrial opioid elimination, the recommendation was not based on strong clinical or experimental evidence. The works of Hamza et al., Hatheway et al., and Caraway et al. strongly suggest that similar analgesic results can be obtained with opioid elimination occurring during or shortly after trial (51,58–60). Pretrial opioid taper may be beneficial for those subjects who are opioid tolerant or have opioid-induced hyperalgesia, or for those who may be at higher risk of opioid-induced respiratory depression in the hours or days after implantation of an IDDS. The duration of opioid tapering in existing studies was variable, and the optimal duration of tapering before IT therapy has not been established. The balance of the data, however, suggests that many, if not most, patients can undergo trialing and implantation with elimination of systemic opioids following transition to IDD (51,58–60).

As highlighted in the PACC 2016 publication presenting treatment algorithms (3), previous systemic opioid exposure needs to be considered prior to IT medication selection. The PACC recommends that systemic opioid therapy be markedly reduced or eliminated when IT therapy is instituted. Assessing the risk associated with trialing IT medications in different practice settings (hospital, surgery center, etc.) will be addressed in the subsequent discussion.

Consensus Point 7. The term *microdosing* should be replaced by the descriptive term *low-dose IT therapy*.

Consensus Point 8. A goal of IT therapy should be the reduction or elimination of systemically delivered opioids.

Consensus Point 9. Elimination of systemic opioid therapy can be accomplished before trialing, during trialing, or after implantation of an IDDS (38,51,57–60).

Consensus Point 10. Unless contraindicated, IT ziconotide should be considered as an alternative to opioids, and in certain specific circumstances, should be considered first-line therapy (3).

Ziconotide (Prialt) Trialing

Ziconotide is a nonopioid, presynaptic calcium channel blocker with activity in the dorsal horn of the spinal cord, based on animal data, and the only Food and Drug Administration (FDA)-approved nonopioid-based medication to treat moderate to severe pain intrathecally (61,62). Uniquely to its large molecular size and hydrophilicity, the pharmacokinetics and pharmacodynamics of the medication require placement within the IT space. On-label delivery of ziconotide is performed via a microambulatory infusion pump or via the Medtronic Synchromed II. Ziconotide has been extensively studied in three randomized, placebo-controlled trials (63–65) and numerous prospective and retrospective studies (66–72). Recent studies suggest ziconotide is best employed when it is “first medication in pump.” As can be seen in recent work with ziconotide trialing, this has been borne out in the literature. Ziconotide trialing techniques and results from earlier poster presentations have been described in the previous PACC on trialing (38). With regard to more current trialing of ziconotide, four recent manuscripts provide guidance in describing a relatively new concept of flex dosing.

Pope and Deer (73) recently reported a trialing technique in patients naïve to IT therapy using a flex dosing algorithm. In brief, single-shot ziconotide in incremental doses of 2, 4, 6, or 8 mcg increments weekly were trialed. If efficacy at a particular dose was found the patient was re-trialed with a single shot of that effective dose 1 week later in an attempt to confirm analgesic efficacy and lack of AEs. If AEs were observed in the initial dose of 2 mcg a subsequent

study was performed at 1 mcg. Using this trial paradigm, largely based on earlier work by Mohammed et al. (74), with a different defined efficacy endpoint of >70% relief, the authors selected 16 consecutive patients with a successful trial and IDDS to undergo nocturnal flex dosing starting at 11 PM for 30–45 min and titrating up by a tenth of a microgram every week “until therapeutic efficacy was achieved that matched the success with the trial.” This study had four discontinuations due to reported AEs between 3 and 6 months postimplant: one psychiatric AE and three urinary retention AEs. The study reported excellent analgesic efficacy in a difficult-to-treat cohort similarly described in Rauck’s study of those who had failed SCS (63). This cohort was also able to virtually eliminate oral opioid therapy at the 6-month follow-up, with NPRS in the 2 of 10 range, and was the first of its kind to report bolus-weighted ziconotide dosing. Importantly, Deer and colleagues did not perform an intention-to-treat analysis or indicate how many patients were trialed. They did, however, provide a dosing strategy and a different long-term infusion management plan, attempting to match the conditions of the trial with that of permanent implantation. No patient had neurologic complications, and although clinical observation lasted 23 hours post-trial, the authors suggested that a shorter observation period would be appropriate.

Hayek and colleagues (75) reported on single-shot IT trialing in 15 subjects with ziconotide doses starting at 2 mcg, and observation for analgesic efficacy and AEs for patients who were already failing IT therapy. The retrospective protocol allowed increasing doses of 4, 6, or 8 mcg to be utilized as a titration to either analgesic efficacy, AE, or both once a week. Patients responding to a particular dose underwent a repeat injection with the same dose to minimize placebo effect. A failure of trial was defined as AEs or inadequate analgesia. This study included 12 subjects previously implanted with an IDDS who were failing to achieve adequate pain reduction (7.8 ± 6.8 months) despite combination opioid and bupivacaine admixture therapy with ziconotide. The study also reported on the outcome of three subjects naïve to IT therapy. Importantly, the definition of success was >50% relief of pain. Of 15 patients trialed, four were deemed to have trial failure and 11 had a successful trial and were given ziconotide. At the 24-month follow-up, only four of the 11 patients retained ziconotide in the IT solution. Significant improvement in pain scores occurred only at the 3-month mark after introduction of ziconotide. Six of the seven patients who discontinued ziconotide did so due to cognitive side effects and the seventh patient due to syncope. Interestingly, of the patients who remained on ziconotide, two had ziconotide first in pump. This suggests first-in-pump sustainability of ziconotide is an important factor, as two-thirds of patients with ziconotide first in pump had retained it at 24 months. Furthermore, dose titration was higher than typically reported, with average doses of 7.6 mcg/day.

The contrasting outcomes of these two most recent trialing studies raise several questions. Although both studies are excellent first steps in evaluating the trialing process for ziconotide, neither study clearly documents the concomitant or premorbid (if any) psychiatric diagnoses (e.g., anxiety or depression) present in trialed subjects, or the pharmacologic treatment of these psychiatric conditions in the subjects trialed. Other investigators observed that concomitant antidepressant/anticonvulsant treatment (which is common in subjects with neuropathic pain) may play a role in the AEs observed with ziconotide (76–78). Future studies using ziconotide should take care to document not only the pain type of the patient but also the psychiatric diagnoses (if any) and treatment in subjects trialed with ziconotide. Additionally, it is possible that combination therapy in the patients already implanted with an IDDS resulted in a difference

Table 8. Recommendations for Trialing Ziconotide by the Polyanalgesic Consensus Conference (PACC).

Statements	Evidence levels	Recommendation strength	Consensus level
A trial should be administered before initiating ziconotide.	II-2 Ver Donck II-3 others	B	strong
A bolus ziconotide trial is preferred over continuous trial.	II-3	B	strong
Patients trialed with IT ziconotide should be monitored in a clinical setting for at least 6 hours, in the absence of any neurologic findings.	II-3	B	strong
Ziconotide should be considered "first in patient" for both neuropathic and nociceptive pain.	III	B	moderate

between the outcomes in the Hayek et al. study vs. the positive outcomes reported in the Pope and Deer study, as there are many unknowns surrounding ziconotide combination therapy. This possibility is underscored by the fact that Hayek and colleagues reported a much wider array of AEs in those trialed with ziconotide, while Pope and Deer reported minimal AEs with urinary retention in three of four failures after implant with only one psychiatric AE. Furthermore, the Pope and Deer paper described a new philosophy with long-term ziconotide infusion weighted to bolus delivery, as compared to slow, low-volume, continuous delivery, as was previously performed.

A slightly different bolus dosing paradigm was performed by Mohammed and colleagues (74). In this trial, 20 patients with varied pain syndromes (including failed back surgery syndrome, neuropathic, degenerative and post-traumatic pain types) underwent single bolus IT dosing with 2.5 mcg ziconotide and were observed as inpatients for 24 hours. If patients had $\geq 30\%$ pain relief and no AE, a similar-dose single-IT bolus was injected a week later and, if similar results were obtained, the patient underwent implantation with an IDDS. If inadequate pain relief occurred, the procedure was repeated a week later with the dose increased to 3.75 mcg; if AEs were experienced the dose was decreased to 1.2 mcg. A successful trial was defined as $\geq 30\%$ pain relief by injection on two occasions without AEs. A trial failure was defined as intolerable AEs or inadequate pain relief. Using these criteria, 11 patients were deemed responders but only seven underwent implantation of an IDDS; "two withdrew because of adverse effects after their first bolus, one patient refused an implant, and one could not have an implant due to lack of funding." Overall, the mean reduction of pain scores for the group was 25%. This study is limited by the small sample number and lack of long-term follow-up.

Using the same algorithm and outcome measures as Mohammed et al., a Swedish study by Backryd and colleagues examined 23 patients with neuropathic pain (77); 18 of the 23 had tried SCS. Only three of 23 (13%) patients had a successful trial though seven of 23 (30%) had $\geq 30\%$ pain reduction with at least one injection. Though no serious AEs occurred, 15 of 23 patients experienced a total of 33 AEs on 18 occasions.

In the four aforementioned studies of single-bolus, IT ziconotide injection trials there were no cases of postdural puncture headache or infection reported. Two of the studies monitored creatine kinase (CK) with one patient in each study showing transient significant elevation in CK (74,77). Each of the ziconotide studies had a different definition of responders: Mohammed et al. (74) and Backryd et al. (77) used 30% improvement, Hayek et al. (75) used 50% improvement, and Pope and Deer used 70% improvement (73).

An earlier industry-sponsored international, multicenter, continuous IT infusion study by Ver Donck and colleagues examined ziconotide titration over a 3-week study period (4 weeks in Belgian sites to

comply with local regulation) with an externalized IT catheter (79). The study was terminated before reaching target recruitment goal, in part because ziconotide became commercially available. Of 71 enrolled patients, 58 completed the titration phase. The mean ziconotide daily infusion was 2.3 $\mu\text{g}/\text{day}$ at baseline and increased to 3.43 $\mu\text{g}/\text{day}$ by the end of week 1 and culminated around 4 $\mu\text{g}/\text{day}$ thereafter. AEs occurred in 90% of the patients, with ziconotide-related AEs occurring in 60.6% of patients. Significantly, meningitis occurred in five patients (7%) completing at least 2 weeks of therapy.

Hence, overall single-bolus trial dosing of ziconotide appears to have emerged as the preferred trialing technique (73,75–77), albeit long-term results may be limited by the medication's AEs and use as salvage therapy (75, Table 8). The outcome of the study trialing subjects naïve to IDD with flex dosing nonetheless might be promising (73) and deserves consideration by clinicians considering trialing subjects for IDD, as the study replicated the findings by other studies.

Consensus Point 11. A trial of ziconotide is recommended before using it in the pump.

Consensus Point 12. A single-shot ziconotide trial appears to be adequate to predict response.

Consensus Point 13. If a continuous infusion trial of ziconotide is planned, it must be with an IT catheter.

Pharmacokinetics and Rationale for Ziconotide Trialing

Sustainability of monotherapy with ziconotide and the timing of placement within the pump may play a role in the success of the therapy (75,80). "First-in-pump" ziconotide seems to offer a therapeutic advantage, with sustainability as demonstrated in a small prospective study (73). Therefore, first-in-patient trialing of this medication is an attractive option.

The pharmacokinetics of ziconotide has been extensively described, demonstrating linear kinetics with a half-life of 4.5 hours (81,82). Many trialing options have been described for IT ziconotide therapy (38), with no clear superior strategy for predicting long-term success with long-term IT delivery (2,77). Of these, single-shot IT ziconotide trialing has emerged as a viable option (73,74,83,84). Trialing performed with a starting bolus dose of near 2 mcg, followed by observation for at least 4 hours, provides a pathway for moving forward. Because of the "penetration interval" needed for the ziconotide to reach its site of action, titration at a slower rate than the recommended dosing interval of 1.2 or 2.4 mcg per 24 hours is recommended. There is some evidence that the presence of concomitant antidepressants and anticonvulsants may increase the likelihood of AEs with IT ziconotide exposure (76). Consideration should be given to reducing or eliminating these medications in patients being considered for IT ziconotide therapy.

For patients with a pre-existing IDDS, studies have shown benefit of ziconotide in the cancer population, employed even as a salvage therapy, counter to the literature previously described for the non-cancer population. For noncancer pain, first-in-pump seems more efficacious for long-term therapy (73,75). It should be noted that the doses of open-label chronic infusion of ziconotide are higher than those reported currently in the literature, suggesting simply that there are responders and nonresponders, and high dose does not suggest capture. Dosing and methods of trialing with this patient population have not been studied, but recent registry data by one pump manufacturer suggest that the medication is more efficacious when used as a first-line medication (85).

Consensus Point 14. Trialing with IT ziconotide should be started at 1 to 2 mcgs if given by bolus, and can be repeated at higher doses if indicated.

Consensus Point 15. Trialing of IT ziconotide should be increased at not more than 1.2 mcg per day if given by continuous infusion, with consideration for a slower infusion schedule.

Consensus Point 16. Trialing of ziconotide by bolus technique does not require inpatient admission, but does require appropriate monitoring. Patients should be observed for at least 8 hours after each bolus.

Consensus Point 17. Trialing of ziconotide by short-term continuous IT infusion does require inpatient admission and monitoring.

Combination Therapy Trialing

As stated previously, FDA-labeled IT analgesics for chronic IT delivery include monotherapy with either preservative-free morphine (Infumorph, Baxter) or ziconotide (Prialt, Jazz Pharmaceutical). Despite this labeling, it is common practice amongst expert practitioners to use combinations of on-label and off-label medications to achieve good long-term outcomes. Data from product registries suggest that the majority of IT medications are compounded and are used in combination, both defined as off-label use (86–88). It has become acceptable to trial combination medications within the confines of the PACC guidance for medication algorithms (3,38).

Considering this common practice of using polypharmacy and monotherapy compounded morphine, there has been discussion regarding the impact of these medications on the devices. Some device manufacturers have issued warnings on use of unapproved medications, including any admixture, in the IDDS (89). Medtronic issued a warning regarding increased risk of motor stall with use of unapproved drugs or admixture in the SynchroMed II pump (90). Medtronic maintains a prospective longitudinal multicenter registry that has reported an overall IDDS failure rate of 2.4% with the SynchroMed II pump at 78 months when used with approved medications and 7.0% when used with unapproved medications or medication admixtures (55). Medtronic also publishes annual pump product performance reports. The 2013 report stated that of 3055 patients with noncancer-related pain, 2458 (80.5%) received off-label medications/admixtures vs. 597 (19.5%) who received on-label IT medications only (91). Among 1035 implanted patients with cancer-related pain, 998 patients (96.4%) received off-label medications/admixtures. There was no sub-analysis of the data breaking down the numbers of patients with IT medication admixtures vs. off-label monotherapy for pain. The consequence of these off-label applications may result in abrupt cessation of therapy or early device failure. A recent case series found total prevalence of motor stalls of 9.03%, with higher failure rates associated with off-

label drugs (92). However, failure occurred with approved medications as well. A Cleveland Clinic retrospective analysis suggested that an average Medtronic pump survives 5.9 years (93). The other commercially available programmable device (Flowonix, Prometra II) has not had issues with off-label medications to date. It does not have a rotor mechanism, and the suggested longevity is 10 years at a flow rate of 0.25 mL/day (94).

Despite the prevalent use of admixtures in the real world, there is a paucity of data on IT trialing with combinations of medications. Rainov and colleagues reported a prospective observational pilot study on 26 patients with lumbar postlaminectomy pain syndrome who received an IT regimen consisting of morphine combined with bupivacaine, clonidine or midazolam (48). (The PACC does not recommend intrathecal midazolam because of potential neurotoxicity.) The investigators classified patients according to their pain type with 18 (69% of subjects) having mixed nociceptive/neuropathic pain, six (23% of subjects) having predominantly radicular neuropathic pain and two (8% of subjects) having mixed radicular and peripheral neuropathic pain. The patients with mixed pain were trialed with continuous catheter infusion using an admixture of morphine and clonidine. The patients with neuropathic pain were trialed with an admixture of morphine and bupivacaine, and patients with radicular and peripheral neuropathic pain were trialed with an admixture of morphine, bupivacaine and clonidine. Midazolam was added to the regimen if pain was not sufficiently controlled. Patients were trialed for 3–10 days with a median duration of 7 days using a staged trial-to-implant approach and the IT catheter sited at T10 or above. Patients were not weaned off systemic opioids before the start of the trial. An external pump delivering 2 mL/day was used and the starting daily doses of the different medications were: morphine 0.5 mg/day, clonidine 0.015 mg/day, bupivacaine 0.5 mg/day, and midazolam 0.2 mg/day. Titration was carried out to achieve at least 50% pain relief by increasing the amount of morphine, and when the concentration of morphine was doubled so were the concentration(s) of adjuvant medications. Mean daily doses of morphine, bupivacaine, clonidine and midazolam at conclusion of the trial were 0.5 mg (\pm 0.3), 1.0 mg (\pm 0.4), 0.03 mg (\pm 0.015), and 0.4 mg (\pm 0.2), respectively. Systemic opioids were weaned during the trial and the first 2 weeks after implant such that “no patient received additional oral or parenteral drugs, besides antidepressants and minor tranquilizers.”

During the 24-month follow up period, pain scores remained under 50% of baseline, however, there was significant escalation in IT morphine dosages up to 5.2 mg/day (\pm 2.8; 26 patients). The doses for bupivacaine, clonidine, and midazolam at 24 months post-implant were 2.5 mg (\pm 1.5; 20 patients), 0.06 mg (\pm 0.03; 16 patients), and 0.8 mg (\pm 0.4; 10 patients) per day, respectively. The investigators had limited ability to manipulate concentrations for bupivacaine and clonidine; hence, patients had to come in for frequent refills (median 10/year; range five to 23). In spite of this, patient satisfaction was high and there was significant improvement in function, most notably in ambulation. Additionally, there was a “nearly complete reduction of supplemental oral or parenteral analgesics.” According to the authors, “morphine was combined with clonidine, bupivacaine and/or midazolam to achieve synergistic effects, to better treat neuropathic pain, and to reduce development of tolerance against morphine.”

A retrospective study by Hayek and colleagues reported on a cohort of 57 consecutive patients with a diagnosis of lumbar postlaminectomy syndrome and predominantly low back pain, who were trialed with an admixture of hydromorphone and bupivacaine and implanted with an IDDS delivering the same admixture (95). Patients

Table 9. Recommendations for Trialing Combination Medications by the Polyanalgesic Consensus Conference (PACC).

Statements	Evidence levels	Recommendation strength	Consensus strength
A combination trial may be administered in select patient populations.	II-3	B	strong
When combination therapy is used, continuous IT infusion with inpatient admission is recommended.	II-3	A	strong

were not weaned off opioids prior to trial or implant and received a combination of hydromorphone at a concentration of 5–50 mcg/mL and bupivacaine 0.5–0.625 mg/mL titrated up from 0.2 mL/hour to 0.8 mL/hour over 24 hours. The mean daily oral ME dose prior to trial was 56 ± 10 mg. There was significant sustained reduction in pain scores through the 24-month follow-up and marked reduction in oral opioid consumption to 15 ± 6 mg/day oral MEs. However, IT hydromorphone dosage escalated from 79 ± 6.8 mcg/day at implant to 487 ± 80 mcg at 24 months postimplant. Average IT bupivacaine dosage increased from 5.8 ± 0.3 mg/day at implant to 12.6 ± 0.9 mg/day at 24 months postimplant. Unfortunately, the authors did not comment on success rate of the trial or side effects encountered during trial.

Consensus Point 18. When patients are receiving an IT trial that includes bupivacaine or clonidine delivered continuously, the PACC recommends inpatient trial with frequent blood pressure and heart-rate monitoring (Table 9).

Consensus Point 19. For single-shot bolus IT trials with bupivacaine or clonidine, at least a 6-hour observation is required prior to discharge, in the absence of cardiopulmonary or neurologic complications.

As highlighted in a companion PACC 2016 publication (3), consideration for the site of service is required and is based on the patient's disease state, the IT medication given, previous opioid exposure, and risk stratification. The need for monitoring in the inpatient setting is required for continuous infusion and for bolus trials with long-acting opioids such as morphine. The need to admit a patient is less if the patient undergoes a single-shot trial with ziconotide or fentanyl. These trials are routinely performed in an outpatient setting with observation for at least 6 hours before discharge if the patient meets all discharge criteria.

Consensus Point 20. The patient should first undergo a trial with an FDA-approved medication if medically indicated.

Consensus Point 21. The patient should undergo trialing with an admixture only if it is medically indicated, and, in the opinion of the physician, the risks are outweighed by the benefit.

Consensus Point 22. The patient undergoing an admixture trial should be treated in accordance with the PACC algorithm for 2016 (3).

MEASURING THE SUCCESS OF A TRIAL

Pain Relief

Earlier we discussed the controversy regarding the need for a trial in all patients. If a trial is performed, it is critical to define what constitutes trial success. The trial serves multiple purposes and provides information to the pain care team, including the assessment of a change in pain based on VAS, improvement in function, presence and importance of side effects, appropriate starting doses, and consistency of response to the trial medication. Each of these variables

is measured and evaluated based on a patient's expectations. The pain relief endpoint of an IT trial is generally defined, in both research protocols and clinical practice, as a decrease in pain of $\geq 50\%$ (38). More recent trials with ziconotide have used $\geq 30\%$ pain relief as a valid endpoint in ziconotide trials (74,77), although others have used $>70\%$ (73). A trial measures pain relief using an accepted tool, such as the VAS, compared against baseline measurements to assess response.

Function

Many implanters also consider improvement of function as an important endpoint of a successful trial. This can be achieved by asking patients to take escorted walks during the observation period of the trial. Referral to a physical therapist during an IT trial is a reasonable approach. Expectations for function may vary based on the underlying disease and life expectancy. For example, for end-of-life care functional improvement may be less important than in the patient with non-life-threatening illness, and the focus may be on evaluating side effects. Functional assessment during an IT trial can be obtained by evaluating criteria such as VAS at rest, ODI and other functional objective measures, moving from supine to sitting position, sitting to standing, picking up objects from the floor, and ambulation (57). Perhaps an evaluation prior to trialing should be undertaken in an effort to establish a baseline on which improvement during the trial could be based. When a continuous trial is chosen, the systemic pain medication needs and changes may be useful indicators to assess efficacy of IT therapy. For bolus delivery, four outcomes are typically defined as endpoints (Table 10). Repeat trials or medication switches should be mindfully managed. Some authors recommend repeat IT trials to reduce the chance of placebo affect. It should be noted that, in the absence of blinded placebo-controlled trials with long-term follow-up, improvements in function reported during IT trials are short-term, may be subjective and subject to placebo effect, and may not predict long-term functional outcomes.

Consensus Point 23. Acceptable pain relief should be achieved during a trial. The amount of pain relief that is acceptable has varied

Table 10. Possible Outcomes of Bolus IT Trials.

Outcome	Consideration
Relief without side effects	Successful trial, medication and dose considered for chronic delivery
Relief with side effects	May be appropriate IT medication; consider reduction in medication dose for retrial or medication switch
No relief, side effects noted	Medication switch recommended for retrial
No relief, no side effects	Consider retrial with higher dose or medication switch

Table 11. Starting Infusion Trial Dosage Ranges for Single Medications Intended for Long-Term IT Delivery Recommended by the Polyanalgesic Consensus Conference (PACC).

Drug	Recommended starting dose*
Morphine	0.1–0.5 mg/day
Hydromorphone	0.01–0.15 mg/day
Ziconotide	0.5–2.4 mcg/day
Fentanyl	25–75 mcg/day
Bupivacaine	0.01–4 mg/day
Clonidine	20–100 mcg/day
Sufentanil	10–20 mcg/day

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

between 30% and 70% and no long-term prospective studies have defined the best practice percentage or reduction in systemic opioids. The PACC recommends an established goal of relief be discussed with the patient/caregivers before trialing.

Consensus Point 24. Consideration can be given to repeating the successful IT trial dose, as that may reduce the chance of placebo effect.

Consensus Point 25. A successful trial can be enhanced by an improvement in functional status. If functional improvement is a factor, pretrial benchmarks should be set.

Side Effects

Anderson and Burchiel conducted a retrospective study on 37 patients with chronic noncancer pain managed with IT hydromorphone after having failed IT morphine therapy (12). These patients were part of a larger group of 112 patients implanted with an IDDS over a 3-year period in the late 1990s at a tertiary care medical center. All patients were trialed with a continuous infusion of IT or epidural morphine for 1–2 days as inpatients, and those achieving $\geq 50\%$ pain relief proceeded to permanent implant. Three patients were switched during trial screening to a hydromorphone-based trial, having had intolerable morphine-related AEs, including nausea, vomiting and pruritus. Other patients were switched from IT morphine to hydromorphone after implant, with variable response on improving side effects of IT opioids over the long term.

In a slow-titration study of continuous IT ziconotide infusion during trial with an externalized pump, four of the first 40 enrolled patients developed meningitis after the third week, prompting reduction of the titration phase to 1–2 weeks (79). In addition, cerebrospinal fluid (CSF) leakage with concomitant postdural puncture headache occurred in 10 patients (14.1%), and catheter-related complications in eight patients (11.3%). This study was undertaken, as slow IT titration of ziconotide has been shown to result in a lower incidence of AEs (63–65). Nonetheless, dizziness occurred in 31% of patients and nausea in 14% of patients. Only one serious AE related to IT ziconotide (asthenia/leg weakness) was reported (79).

Consensus Point 26. If side effects occur at the lowest reasonable dose of medication, the trial is a failure and a medication switch should be considered.

Pain Behavior

There are no studies outlining outcome differentials in pain behavior during trialing, but many clinicians use this period to determine patient compliance, functional improvements, and interaction

with the medical care team (see section below on behavioral evaluation).

Medication Selection

The previous PACC recommendations for trialing have been well cited in the medical literature, with 99 citations in peer-reviewed publications since 2012. Research, length of time available for clinical use, and regulatory labeling of IT preservative-free morphine have made it the most commonly used medication, but some physicians are hesitant to use this medication because of the potential of delayed respiratory depression in the outpatient setting. The PACC treatment algorithms published in 2016 determined that trial doses of morphine ranging from 0.075 to 0.15 mg were safe regarding respiratory depression (3). In a retrospective study, safe doses were determined to be 0.04 mg hydromorphone, 0.1 mg morphine (96), and 25 mcg fentanyl (97). Safety is well established in opiate-tolerant patients.

Many have used fentanyl as a trial medication for single-shot trialing because of the limited delayed risk of respiratory depression. Using fentanyl is helpful in evaluating the opioid response, but may not predict the response to long-term use of other opioids. The risks and benefits of an opioid medication are dependent on balancing many factors, as already discussed. IT ziconotide is approved for long-term infusion, but the manufacturer has not applied for a labeling for the trial phase. Nevertheless, IT ziconotide trialing is becoming a first-line trial method for many physicians (62).

In patients in whom admixtures are needed for pain care, a continuous infusion trial is most likely to yield information and facilitate titration. Trialing decision-making should follow the PACC 2016 algorithm when considering response, patient characteristics, and disease states (3).

Drug Titration and Dosing

The trial dose should be the lowest reasonable dose to achieve pain relief without intolerable side effects (Tables 11 and 12). Continuous short-term infusion over 3–5 days allows the medication volume and concentration to be adjusted. The adjustment should be based on pain response and side-effect assessment, with care to mimic the volume and rate of delivery of the available IT implantable devices. Monitoring should be based on the medication being infused. If a single-shot or bolus dose is used, the dose selection should be based on the acceptable lowest dose to achieve the desired response (Table 11). The decision to increase dose should be based on poor pain relief with either no or manageable side effects. Recommended starting doses for chronic permanent infusion are

Table 12. Doses Ranges for IT Bolus Trialing Recommended by the Polyanalgesic Consensus Conference (PACC).

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

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

suggested by the dosing achieved during the trial, but there is no formula for conversion of trial dose to infusion dose that has been shown to be safe and accurate. Because of this safety issue, the PACC recommends using a conservative approach to dosing permanent devices.

Consensus Point 27. The PACC recommends starting with the lowest reasonable dose possible when trialing medications. Upward titration should be slow and measured by response to pain relief, improved function and occurrence of side effects. (Recommended starting trialing doses are noted in Tables 11 and 12.)

Admixture Trialing

There are some data describing use of concurrent medications during IT catheter trials. Hayek et al. reported on a combination of hydromorphone (5–50 mcg/mL) and bupivacaine (0.5–0.625 mg/mL), initiated at a rate of 0.2–0.8 mL/hour for 24 hours, with monitoring of efficacy, side effects and AEs in 57 patients with the diagnosis of failed back surgery syndrome. Side effects, conversion rate, or duration of trial were not specifically reported (95).

Bolus vs. Continuous Spinal Infusion Delivery

IT drug delivery systems can be trialed by bolus injection using a single shot or intermittent injections with an indwelling catheter, or by continuous infusion for either a short or long term (2). The decision as to type of trial depends on many factors, including the patient's clinical status and diagnoses, reason for the trial, type of medication used, and physician preference/facility capabilities. Physicians engaged in IT therapy should have thorough knowledge of pharmacology and pharmacokinetics of intrathecally administered medications.

There are various advantages and disadvantages with the different trialing modalities (84). A single-bolus injection with a needle potentially allows for a quicker trial, fewer confounders when detecting side effects compared to an indwelling catheter, less infection risk, and viability in an outpatient setting. However, patients may need to have repeat injections (8,51). Single-bolus IT injections, titrated to effect on separate days, have been used in trialing morphine, ziconotide, and baclofen. Single-bolus IT trials that are performed outpatient require clear communication of potential side effects with the patient and family.

Continuous catheter trials allow for dose titration targeting a particular dermatome, and direct observation of the patients who are typically admitted to hospital for the trial. Continuous catheter trials have been accomplished using the epidural or IT route (12,48,57,98,99). Compared to the epidural approach, and over longer term duration than typical pump screening trials, the IT route may have fewer AEs and result in superior pain relief (100). There is no proof that a continuous infusion trial with an IT catheter better mimics what would occur at implant, since most external pumps used for continuous infusion deliver the medication at rates that are typically ≥ 20 times faster than those of implanted IDDSs. While there are two models of external pumps that are capable of delivering low rates of infusion similar to implanted IDDSs, adoption has been limited due to logistic and safety concerns with keeping an externalized IT catheter for prolonged periods while slowly titrating the IT infusion in noncancer pain patients (79,101). Continuous catheter infusion allows for combination IT medication trials. In some cases, such as in anticoagulated patients and in patients admitted with cancer pain, a staged IT trial may be desired. The process involves placing a potentially permanent IT catheter, securing it to the fascia, and tunneling an externalized extension catheter for a

short-duration inpatient trial with an external pump. On completion of the trial, the patient would proceed to implantation in case of successful trial or explanation of the catheter if the screening trial was unsuccessful. The physician should be assured of operating room time at the end of the trial.

The pharmacokinetics of IT continuous infusions are understandably different from the pharmacokinetics of bolus injection. It should be noted that in both cases, factors such as drug amount, volume, rate of delivery, and lipophilicity play important roles in drug distribution and uptake. Ummenhofer and colleagues studied IT pharmacokinetics of morphine, alfentanil, fentanyl, and sufentanil in a pig model (102). IT catheters were placed at the L4-L5 space with the catheter tip at the level of the L3 spinous process, and equal amounts of radiolabeled opioid (0.013 μ M; morphine, alfentanil, fentanyl, and sufentanil) in a volume of 0.1 mL over 2 min were injected. Sampling was then performed by means of microdialysis probes placed at L2-L3, T11, T7, and T3, and a model of IT opioid distribution was developed based on the collected data.

Morphine, the least lipid-soluble opioid, was found to have the highest spinal cord concentration and also the highest rostral spread. This is likely due to morphine's limited volume of distribution in the spinal cord and limited uptake into the systemic circulation. While alfentanil redistributed quickly to the spinal cord, it was cleared very rapidly to the systemic circulation. The highly lipid-soluble fentanyl and sufentanil have the most limited rostral spread; however, they also display low integral exposure in the extracellular fluid of the spinal cord. Indeed, much of the sufentanil in the spinal cord is thought to sequester in the myelin sheath and very little is believed to reach opioid receptors in the extracellular space of the gray matter. Fentanyl is believed to sequester predominantly in the epidural fat, as more of fentanyl is in an ionized fraction compared to sufentanil. Work by Bernards (103,104) and Yaksh (105) has shed doubt on longstanding concepts about IT drug distribution. The CSF flow appears to be limited and pulsatile following cardiovascular physiologic changes in CSF flow (106), and regional intermixing exists with uneven spread. Thus, the spread of drug based on lipophilicity may have less impact on the patient outcome than previously thought, as CSF flow patterns are more limited than previously assumed.

Compared to slow IT infusion, bolus dosing may result in more widespread distribution of injected substances within the IT space (107). This may be due to imparting kinetic energy during the injection process. However, most externalized infusion pumps deliver much faster rates (on the order of 20 times or more) than the standard IDDS rates, resulting in overall better dissemination of IT injectates when delivered through IDDS after implant (104).

There may be a need for congruency between trialing methodology and long-term delivery strategy (i.e., trial bolus to IDDS bolus vs. trial continuous infusion via external pump with IT catheter to continuous infusion from an IDDS with IT catheter)—taking into consideration the limitations just discussed. Peer-reviewed evidence has not shown this to be true at this time. Systemic redistribution to venous circulation of intraspinal medications is the likely culprit for supratentorial side effects (108).

SETTING AND MONITORING DURING TRIALING

Placement of an IT catheter is typically performed with local anesthesia, either under sedation or, in special circumstances, under general anesthesia. The operational setting for the trial depends largely

Table 13. Psychological Considerations in a Trial of IT Drug Delivery.

Practical considerations related to psychological assessment	<ol style="list-style-type: none"> 1. Should a psychological evaluation be performed? 2. If it should be performed, when is the best time? 3. Who should perform the psychological evaluation? 4. What are the best practice guidelines for this evaluation?
Functions of psychological assessment	<ol style="list-style-type: none"> 1. Identification of psychological states and traits that will negatively impact the outcome of an IT trial and long-term management 2. Provision for the development of an individualized treatment plan 3. Education of the patient and family about the realistic appraisal of the neuromodulation process and long-term management of the pain 4. Opportunity for the inclusion of mental health interventions such as cognitive behavioral and insight-oriented therapy, as well as behavioral training such as biofeedback and meditation 5. Addressing of negative behaviors and psychological responses that may preclude the patient from engaging in the IT therapy process (Ranjan R. <i>Psychosocial Interventions for Chronic Pain: In Search of Evidence</i>. New York: Springer; 2008.)
Cancer vs. noncancer-related pain	<p>Patients with significantly compromised life expectancy: Psychological evaluation should be considered optional.</p> <p>Patients whose disease process has been arrested but there is a significant probability of reoccurrence: Psychological evaluation is encouraged.</p> <p>Patients whose cancer has been eradicated by appropriate therapies and continue to manifest chronic pain secondary to medical treatment/anatomical/disease-related damage, but wherein life expectancy is only minimally compromised: Can be considered in the same context as the approach to chronic noncancer pain patients.</p>

on the risk assessment and benefit of each potential site of service. For infusion trials the PACC recommends inpatient trialing (48,95). For other types of trials, the site of service is dependent on several factors involving patient risk, including patient obesity, decreased pulmonary function, concurrent use of sedative/soporific medications, especially benzodiazepines and barbiturates, sleep apnea, cardiac disease, as well as lack of tolerance to systemic opioids. The American Society of Anesthesiologists published guidelines for the use of neuraxial-delivered opioids in 2009 (109). The neuraxial delivery of opioid recommendations was for postoperative pain relief, but there is some applicability to IT trialing and IDD. They concluded that the literature was insufficient to recommend noninvasive positive pressure ventilation to prevent opioid-induced respiratory depression. There was also no evidence that monitoring with pulse oximetry or electrocardiography reduced the risk of sequelae to respiratory depression. There was no evidence that neuraxial-delivered opioids increased the risk of respiratory depression compared to other routes of administration. There was a consensus that higher doses of IT opioids increased the risk of respiratory depression and that hydrophilic opioids, such as morphine and hydromorphone, increased the risk compared to IT fentanyl and sufentanil. There was no agreement as to whether pulse oximetry was more likely to detect respiratory depression than clinical signs, although the PACC recommends pulse oximetry in the monitoring phase of recovery after trial and implant. The recommendations for postoperative IT opioid use were that monitoring was needed at least once an hour for the first 12 hours, every 2 hours for the next 12 hours, and then once every 4 hours for a minimum of 48 hours. The decision to discharge a patient after trialing centers around the half-life of the drug delivered and the risk status of the patient undergoing IT postoperative pain management.

The literature is inconclusive regarding the place of service for IT trialing. Anderson and Burchiel (12) did not report respiratory depression with either continuous epidural or single-shot IT trials. Coffey et al. (24) reported that mortality risk was increased in the

first 3 days after implantation if larger doses (>0.75 mg) of IT morphine were used. A dose of 0.75 mg resulted in the death of an obese patient who was on oral opioids and other central nervous system depressants. These data suggest the need to reduce the recommended allowable dose for those who undergo a single-shot trial, particularly an outpatient trial. The recommended dose for an outpatient single-shot trial is 0.15 mg morphine, 0.04 mg hydromorphone, or 25 mcg fentanyl. Extrapolated to the perioperative setting and with a definition of respiratory depression of <10 breaths per minute, one of approximately 1500 patients was identified as risking respiratory depression (110).

As stated in the main PACC 2016 publication (3), risk stratification is necessary, and conservative dosing is always recommended. If outpatient trialing is performed, observation for at least 6–8 hours is highly recommended and patient compliance is a necessity. Patients and physicians should pay strict attention to optimizing comorbidities, and there should be strict abstinence from sedating medications (e.g., concomitant use of benzodiazepines, especially in patients with obstructive sleep apnea or significant pulmonary compromise) before the trial. If ziconotide is used, an observation period may be needed to monitor blood pressure and watch for psychotic side effects. This period is probably on the order of 6–12 hours, with overnight stay recommended if the patient lives alone, lacks social support, or has side effects that do not resolve during the observation period. No matter the setting, the goals of an IT trial include pain relief, improvement of function, and determining potential side effects. The trial must be performed in a manner that allows these goals to be documented with the safest techniques and setting possible.

The PACC allows for an exception to this recommendation. The exception would be in those patients who may be nearing end-of-life where trial could be performed in a home setting in the presence of a health care infusion nurse to monitor the patient. Single-dose IT ziconotide bolus trialing is often performed in the outpatient setting. The PACC does recommend an observation

period sufficient to determine stability of blood pressure and absence of psychotic side effects.

Consensus Point 28. The setting of a trial is based on the method of medication administration, the patient disease and health characteristics, and the facilities where trialing is performed.

Consensus Point 29. In most cases a continuous trial should be performed in the inpatient setting. In long-term infusions in patients with end-of-life disease, a home setting may be necessary.

PSYCHOLOGICAL EVALUATION DURING THE SCREENING AND TRIALING PROCESS

The experience of pain is complex and dynamic, with both sensory and emotional components (111). The experience of pain may actually rely on psychic phenomena for conscious awareness of the pain to occur (112). Pain, especially in the chronic form, is not a single, unified or static event, but an ongoing and variable process (113,114). It follows that neuromodulation interventions, including IT therapies, must include an assessment of psychological factors when determining patient suitability. This practice is consistent with the general approach to the pain patient (115). Technically adequate implantations do not assure successful long-term outcomes (18). Assessment of the psychological context of a patient's pain experience will improve patient care (116).

Given the data substantiating psychological factors in the perception of pain and psychiatric comorbidity with chronic pain, best practice guidelines should require a preimplant psychological assessment. It is incontrovertible that chronic pain patients have high levels of mental pain and suffering. These experiences are due to many factors—including adverse childhood events leading to chronic psychic trauma, biological vulnerabilities to mood and thought disorders, and the trauma of the chronic pain situation in and of itself, with its accompanying loss of identity and social role (117). In addition, third-party payers often mandate this screening process for authorization of the procedure.

Alteration of the route of administration of analgesics from the oral/transdermal to IDDS, and the sole focus on the subjective experience of pain during the trialing procedure will not address premorbid, negative psychological phenomena. These are more complex phenomena that require specialized assessment. While clinical experience by physicians and psychologists has affirmed this approach, there are a limited number of systematic and controlled studies with good evidence for the fact. Although the literature describes various assessment approaches for obtaining the patient history, performing the mental status examination, and administering standardized psychological testing, there are no standardized procedures (43,45,118).

A review of the published literature from 1998 through 2010 regarding IT therapy reveals that a psychological evaluation was an aspect of this intervention in only a minority of cases (119). Furthermore, there appear to be few, if any, systematic studies with sufficient follow-up to determine a positive or negative contribution of psychological evaluation to outcomes. There has also been criticism of reliance on psychological assessment as a component of the selection criteria (120). There is, however, a continuing emphasis on the identification of predictive characteristics for success or failure of IT therapy. Identification of patient states or traits that would predict outcome is not scientifically valid. A more reliable approach is to assess for psychological symptoms (e.g., depression) and/or psychiatric diagnoses (e.g., post-traumatic stress disorder), which would negatively impact on a positive outcome.

Chronic pain in and of itself can compromise a patient's quality of life—thus, it would not be a negative predictor. The emphasis of the psychological assessment should be on developing a description of the patient to determine if there is a need for a mental health intervention. For example, coping skills training could be implemented prior to the trial, during the trial, and/or during the long-term maintenance phase.

Behavioral observations by the physician can contribute to the clinical impression as to whether the patient is a good candidate for IT therapy, especially during the trial. Although there are elements of classically described pain behaviors (121), these observations emphasize the concept of functionality. The evidence suggests that a reduction in pain is not always accompanied by improvement in functioning (122,123). Similarly, one can have improvement in functioning/quality of life without concomitant reduction in pain ratings (124,125). Having the patient identify reasonable functional goals that are testable during a trial, such as increased up time, increased sitting tolerance, increased walking tolerance, etc., would provide useful information. The patient's psychological response to a change in functioning is also meaningful.

Behavioral observations during the trial and at the implantation may change. These include changes in posturing/bracing/guarding, increased activity/exercise tolerance, reported reduction in numerical pain rating, and observations by significant others. Patients' response to having a catheter and external device, reaction to reduction in analgesics, and the degree of attention demanded of the staff can all be observed, suggesting that the patient may manifest significant dependency needs. A reported or observed reduction in negative mood states, such as depression and anxiety, in response to subjective pain relief reinforces the interpretation of these mood states as being associated with the pain. Patients demand for continued oral medications may reflect a psychological or physiological dependence and/or the presence of a substance use disorder. Hesitancy to engage in increased functioning, where it is considered appropriate based on anatomical anomalies, would suggest significant deconditioning as well as tendencies toward activity avoidance and anticipatory pain, which may have to be addressed.

The practical considerations related to psychological assessment for IT interventions are summarized in Table 13. Based on the psychological comorbidity of pain and psychological distress and suffering, as well as clinical observations by health care practitioners, it is essential that a psychological evaluation be provided to every non-cancer patient undergoing analgesic IT therapies. The approach to the patient with cancer-related pain is somewhat more flexible. Preferably, the evaluation should be done prior to the trial and ideally when the patient will be cared for in long-term management. This approach lessens the confounding influence of the patient presenting in an unrealistic manner in the hope of being given a trial.

The psychological evaluation should involve an interview with the patient (obtaining of history and mental status examination), as well as the utilization of appropriate and validated personality assessment measures that are applied consistently (126). The use of computer administered and interpreted assessment conducted in the absence of an in-person clinical examination/interview is discouraged and does not fulfill the recommendation for a psychological evaluation. It should be noted that the level of evidence in support of the above recommendations is level III with the strength of recommendation being I.

Psychological evaluation can serve several functions. Historically, the presence of major psychiatric disorders such as severe depression, psychoses, poor compliance and/or insufficient acceptance and understanding of the procedure, lack of social support,

Table 14. Management of Oral/Systemic Opioids in Patients With IDDS Implants During Trialing by the Polyanalgesic Consensus Conference (PACC).

Statements	Evidence levels	Recommendation strength	Consensus level
Oral/systemic opioid reduction and/or elimination is desirable before proceeding with an IDDS trial, and should be a goal for therapy after implantation.	II	B	strong

significant substance abuse/addiction, and significant cognitive disruption have been set forth as contraindications for neuromodulation. The evidence for these exclusionary criteria has emerged as a result of clinical practice and consensus statements. They await validation via systematic study.

Consensus Point 30. The presence of psychological factors related to chronic pain may impact the outcome. The PACC recommends a psychological evaluation by a properly trained mental healthcare professional as a part of the trialing process.

Consensus Point 31. The PACC recommends that any evaluation concern found by the psychological expert should be addressed in the preoperative education period.

MANAGEMENT OF ORAL/SYSTEMIC OPIOIDS DURING TRIALING

Virtually all patients being considered for IDD are currently taking or have previously taken oral/systemic opioids. In most cases, consideration of IT therapy is undertaken in those a) not achieving acceptable relief with oral/systemic opioids, b) developing tolerance/hyperalgesia to systemic opioids, c) achieving efficacy but experiencing intolerable opioid-related side effects or having neuropathic pain component that is not controlled with other conservative measures. Initially, chronic IT morphine infusion was approved as an alternative route of delivery with the assumption that systemic opiates were eliminated (127). Over time, IDD gradually became an adjuvant therapy. During the past 15 years reduction or elimination of oral opioids in those trialing IDD has become increasingly common. The last PACC noted that for all methods of trialing (IT bolus, IT continuous, and epidural continuous) systemic opioid reduction or elimination during the trial period was a stated goal of the authors (38). In keeping with these concepts, there are four possible scenarios for managing oral/systemic opioids during and after the IDD trial: 1) the subject remains on systemic opioids throughout trial/implant; 2) systemic opioids are eliminated prior to trial/implant; 3) systemic opioids are reduced during trial/implant; or 4) systemic opioids are reduced during trial and eliminated after implantation.

Given the potential safety concerns recently raised regarding subjects receiving IDD while concomitantly taking oral opioids, dose reduction or elimination should be a goal for clinicians managing patients on IDD (24,128; Table 14). However, in the absence of patient-controlled analgesia for breakthrough pain this goal may be difficult to achieve. In the setting of IT ziconotide, low-dose intermittent opioid rescue doses may be reasonable.

Several small studies and case series reported tapering systemic opioids at (or within 24 hours of) the IDD trial (9,12,129). These studies suggest reasonable analgesia is possible using this method of managing systemic opioids. Both the case report and retrospective case series by Grider et al. reported sustained analgesia at 1 year at low IT dosing using a pretrial opioid-free period lasting 6 weeks

(57,130). Additionally, in that series pretrial VAS before opioid taper and 6 weeks following opioid taper were nearly identical, suggesting opioid tolerance in that study population. Hamza and colleagues also reported opioid reduction/elimination prior to the IDD trial, with complete elimination of systemic opioids prior to implantation (51). This study also resulted in stable analgesia over a 3-year period at relatively low IT doses.

As was noted by the previous PACC, the presence of opioid-induced hyperalgesia/tolerance (OIH-T) could impact the IDD trial (38). Therefore, if OIH-T is suspected, elimination of systemic opioids would be necessary for evaluating the efficacy of IT therapy, with the caveat that elimination of opioids may in and of itself improve pain response and re-establish systemic oral opioid effectiveness (128). Subjects still having partial opioid responsiveness would need to be closely evaluated for confounding effects during the trial to distinguish the true effect of IDD from the oral opioid effect. At least two studies have evaluated the role of pretrial systemic opioids on postimplant analgesia (128). Neither of those studies found a correlation between the systemic opioid dose and analgesia after implantation at 1 and 2 years, respectively (9,131). Taken together the evidence in favor of systemic opioid reduction is supported with case studies, one prospective study eliminating systemic opioids at trial (12), another prospective study reporting significant dose reduction prior to trial with elimination of oral opioids prior to implantation (129), and one moderate-sized retrospective study reporting effective results with pretrial systemic opioid elimination (9). The duration of the opiate-free or opiate-reduced period has not been firmly established. Opiate reduction appears to be a reasonably tolerated maneuver in most patients.

Consensus Point 32. Oral and other systemic opioid reduction and or elimination are desirable in the period of IT trialing, and after the IDDS implant.

Consensus Point 33. Based on the current literature, it is unclear which method of systemic opioid management produces the best results.

FUTURE RESEARCH RECOMMENDATIONS ON TRIALING

There are many variables to consider in trialing patients with chronic pain, hence, one strategy may not fit all patients or caregivers. Psychological factors notwithstanding, important patient considerations include whether:

1. pain is related to a terminal process with limited survival, or non-cancer related with normal life expectancy (132)
2. pain is localized to one or few adjacent dermatomes or diffuse (133–135)
3. patient is an older or younger person (8,136)

4. pain is neuropathic, nociceptive, or mixed neuropathic/nociceptive (131)
5. patient has significant comorbidities or is relatively otherwise healthy (137,138)
6. site of service for implementation of therapy.

Considering these variables, decisions may be made as to what medication(s) to choose for trial and what route of administration is most appropriate. The PACC recommends prospective longitudinal studies in patient cohorts of similar relevant clinical characteristics with long-term follow-up of outcomes.

CONCLUSIONS

The practice of trialing for IT drug infusions systems remains an area of continued evaluation and transition. To the extent that IT therapy focuses on proper patient selection, improved function, curtailing/elimination of oral opioids, use of the smallest dose possible, and use within a multidisciplinary setting, IT therapy can minimize a number of the concerns expressed by the Centers for Disease Control guideline for prescribing systemic opioids for chronic pain (139). That document addressed the primary care physician treating chronic pain in the outpatient setting, detailing the literature related to various complications, hazards, and side effects associated with using oral or transdermal opioids. These include the use of systemic opioids for nonmedical purposes, diversion, inadequate security resulting in use by someone other than the intended patient (especially adolescents), accidental/unintentional overdose, and unsanctioned dose escalation. IT therapy is not appropriate for every patient with chronic pain. But it does provide an alternative, and a potentially safer option, to the use of "high-dose" oral/transdermal opioids, in the properly selected and managed patient.

The PACC holds two points of view/recommendations regarding trialing that may be accepted by reasonable physicians.

A Trial Is Required

This position is supported by the following clinical scenarios:

1. The patient is being trialed with ziconotide as a first-line chronic infusion choice to assess response and side effects.
2. The patient is being trialed with opioid and has increased risk of respiratory depression, such as the patient with sleep apnea, chronic obstructive pulmonary disease, pulmonary fibrosis, morbid obesity, severe edema/venous insufficiency, smoking, or the patient is opioid naïve.
3. The patient is being trialed with baclofen to assess response and side effects.
4. The patient is being trialed with an infusion of a drug combination, such as an opioid with local anesthetic or clonidine.
5. The patient is being assessed for functional improvement or behavior during an extended period of time.

A Trial Is Not Required

This position is supported by the following clinical scenarios:

1. The patient has advanced disease with limited survival time (such as some cancer-related pain) and is a high risk for procedures. If the patient has been shown to tolerate opioids by other routes, a trial is not required. Cancer pain patients in full remission may be trialed.
2. The patient has the risk of bleeding or has an infection that makes the trial a high risk, and the patient demographics suggest

a high likelihood of trial success (e.g., older person, localized pain, on no- or low-dose systemic opioids pretrial). Considering recent studies showing success of greater than 95% regardless of trialing method, this approach should be considered when medically indicated.

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Authorship Statement

Dr. Deer served as primary author, project organizer and editor; Drs. Hayek, Pope, Lamer, Hamza, and Grider assessed evidence; Drs. Huntoon, Mekhail, and Krames served as senior editors; all authors acquired or interpreted data, wrote sections of the manuscript, and provided critical reviews and editing.

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