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Polyanalgesic Consensus Conference—2012: Recommendations on Trialing for Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel

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Introduction: Trialing for intrathecal pump placement is an essential part of the decision-making process in placing a permanent device. In both the United States and the international community, the proper method for trialing is ill defined.

Methods: The Polyanalgesic Consensus Conference (PACC) is a group of well-published experienced practitioners who meet to update the state of care for intrathecal therapies on the basis of current knowledge in the literature and clinical experience. An

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exhaustive search is performed to create a base of information that the panel considers when making recommendations for best clinical practices. This literature, coupled with clinical experience, is the basis for recommendations and for identification of gaps in the base of knowledge regarding trialing for intrathecal pump placement.

Results: The panel has made recommendations for the proper methods of trialing for long-term intrathecal drug delivery.

Conclusion: The use of intrathecal drug delivery is an important part of the treatment algorithm for moderate to severe chronic pain. It has become common practice to perform a temporary neuroaxial infusion before permanent device implantation. On the basis of current knowledge, the PACC has developed recommendations to improve care. The need to update these recommendations will be very important as new literature is published.

Keywords: Chronic pain, consensus, intrathecal, trialing

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INTRODUCTION

For more than 30 years, the use of intraspinal (intrathecal [IT]) infusion of analgesic medications to treat patients with chronic refractory pain has continuously increased. Trialing of such medications is often performed in patients for whom continuous delivery of IT therapy via an implanted pump has been identified as a potential option. Patient responses to trials of neuroaxial analgesic medications are assessed to determine whether pump implantation should proceed and to satisfy requirements for reimbursement defined by insurance companies and government payers. Despite the long-standing use of IT and epidural trials for determining proper use and dosing of IT therapy via implanted pumps, the most appropriate method of trialing remains undetermined on the basis of current clinical practice.

Several neuroaxial techniques are used for trialing of IT therapy. These protocols may involve administration of the medication in the IT or epidural spaces, by using bolus or continuous doses, and may involve various combinations of different doses, treatment durations, catheter/injection placement, and parameters for monitoring pain relief and trial success (1). Because the literature on trialing is limited, an optimal trialing protocol for each type of IT therapy has not been defined. The Polyanalgesic Consensus Conference (PACC), an expert panel composed of clinicians who are experienced in the use of IT analgesics for chronic pain management, convened to review the existing data on trialing of IT therapies and to recommend appropriate trialing protocols.

METHODS

A literature search was conducted to identify published clinical data on various trialing techniques used in candidates for continuous IT morphine (or other opioid), ziconotide, baclofen, or combination therapy delivered via implanted pump. MEDLINE®, BioMed Central®, Current Contents Connect®, EmbaseTM, International Pharmaceutical Abstracts®, and Web of Science® databases were searched. In addition, clinical experiences were evaluated and results from a survey of peers who are involved in trialing were reviewed. By analyzing common practices used for pretrialing medications, catheter placement, trial dosing and duration, and defining a successful trial, and by examining the long-term effects of continuous IT therapy after the completion of a successful trial, consensus opinions on trialing were formulated. Physician attitudes about implanted trialing were assessed by using a multinational survey. In May 2011, three detailed surveys on IT infusion use, safety, and reimbursement were sent by the PACC to more than 15,000 physicians and clinicians in the United States and internationally. Results of these surveys are provided in Appendix I.

Recommendations of the PACC

When making appropriate recommendations for trialing a patient who is suffering from moderate to severe pain, clinicians must consider several multifactorial issues. The patient's disease state, failure of conservative options, adherence to treatment, psychological

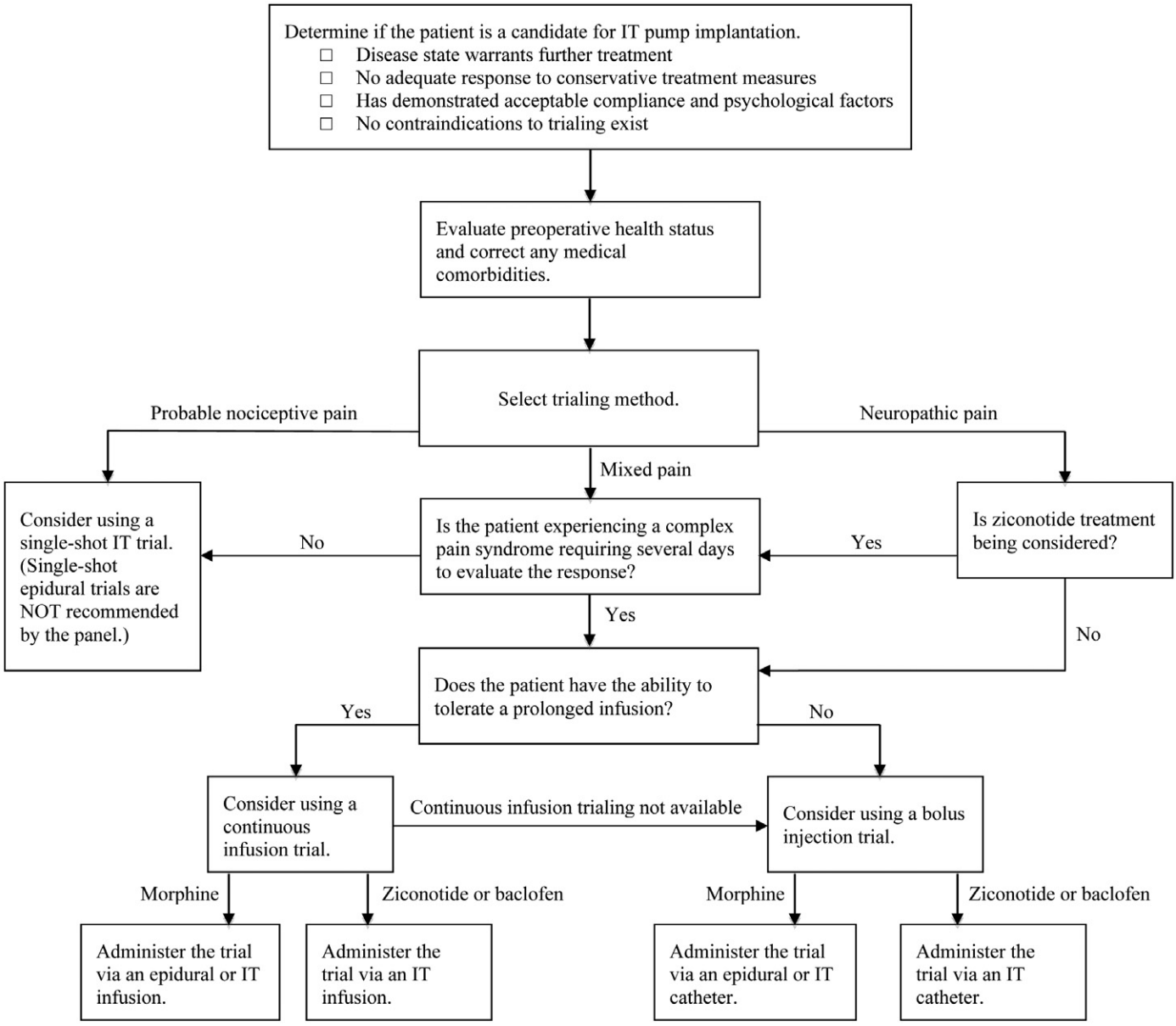

Figure 1. Trialing algorithm. IT, intrathecal.

state, and candidacy for the surgical procedure must be given appropriate consideration before proceeding with IT pump implantation. The recommended steps and the decision-making process for determining the appropriate type of trial are outlined in Figure 1.

Literature Review

Morphine Trialing Methods (Table 1)

Reports of trialing with morphine include four prospective studies involving bolus IT trials, four studies (including two prospective studies) involving continuous IT infusion trials, and two studies (including one prospective study) involving continuous epidural trials. Patients from these studies had a variety of pain types, including severe and chronic nonmalignant pain, refractory cancer pain, refractory pain resulting from vertebral fractures, low back pain, and bilateral leg pain.

Morphine: Bolus IT Trialing

Trials of bolus morphine were used in four prospective studies. In two studies by Kumar et al. patients received the trials in a double-blind, randomized controlled (2) or uncontrolled (3) fashion. Open-label bolus morphine trials were used by Anderson et al. in 18 patients from a randomized controlled (4) study and by Rauck et al. in an uncontrolled (5) study. In the Anderson et al. study, an additional 19 patients received a continuous epidural morphine trial; these results are described in the *Morphine: Continuous Epidural Infusion Trialing* section.

Pretrialing Medications. In all of the studies that used bolus morphine trials, patients were receiving systemic analgesics at baseline. The open-label randomized study by Anderson et al. required that all opioids and long-acting analgesics be discontinued for at least 12 hours before trial administration (4).

Table 1. Description of Trialing Parameters and Outcomes for Morphine Trials.

Authors and year	Trialing Study design	Trial type	Trial morphine dose*	Implantation/follow-up Initial morphine dose*	Follow-up morphine doses*	Adverse events	Efficacy
Kumar et al., 2001 (3)	Prospective, open-label, long-term study; trialing was double-blind; severe, chronic nonmalignant pain; 16 of 25 patients implanted after trialing; ≥50% reduction in VAS rated successful trial; ≥25% reduction in VAS defined long-term success; mean ± SD follow-up 29.14 ± 12.44 months	IT bolus followed by a continuous IT infusion trial in patients who were successful in the first trial	1 mg	1.11 ± 1.91 mg/d	3.1 ± 3.2 mg/d at 6 months; 7.4 ± 4.2 mg/d at last follow-up; >10 mg/d after >2 years	AEs in >50% of patients: dizziness, pruritus, disturbance of micturition, constipation, loss of appetite, sweating, fatigue; two patients had pumps explanted for intolerable side effects; two patients needed non-opioid medication to be added to IT morphine	Mean VAS score reduced 67.5% after 6 months and 57.5% at last follow-up; long-term, the VAS score was reduced 75% for deafferentation pain and 61% for mixed pain; 12 patients were successful at last follow-up; 10 patients were satisfied with the delivery system; 11 reported an improved quality of life
Rauck et al., 2003 (5)	Prospective, long-term, open-label; refractory cancer pain or uncontrollable side effects; 119 of 149 patients implanted after trialing; trial success rated by ≥50% reduction in NAS score at 2 of the 2-, 4-, or 6-hour posttrial measurements or a ≥50% reduction in systemic analgesic use within 12 hours after dosing; posttrial success rated by ≥50% reduction in one or more of the following: 1) NAS pain scores, 2) systemic opioid use, 3) opioid complication severity index scores	Single IT bolus injection	Approximately 1/100th or 1/200th of prestudy morphine sulfate equivalents†	Median dose, 1.8 mg/d	Median dose, 5.1 mg/d at 4 months	Seven device-related events included catheter kink, morphine leak, possible pump failure, catheter migration from the IT space, failed flow restrictor, inability to activate the device followed by surgical revision	Mean NAS score significantly reduced from 6.1 to 4.2 at 1 month ($p < 0.01$) and remained at this level until month 13 ($p < 0.05$); systemic opioid use was significantly decreased throughout the study ($p < 0.01$); significant reduction in opioid complication severity index was noted at all follow-up visits ($p < 0.01$); overall success in 91% of patients at 4 months
Anderson et al., 2003 (4)	Prospective, randomized open-label trial comparing IT to epidural drug delivery; chronic, nonmalignant, intractable pain; 67% of IT patients (12 of 18) and 79% of epidural patients (15 of 19) met the criterion for a successful trial; ≥50% reduction in two consecutive NAS reports rated successful trial; 3 and 6 months follow-up after implantation	Single IT injection or continuous epidural infusion	Most IT patients received a 1.0-mg dose; epidural patients received doses of 0.2–2 mg	0.87 mg/d	NA	Complications were mild; nausea, vomiting, diaphoresis, hypotension, urinary retention more frequent in IT patients than epidural patients; pruritus and constipation more common in epidural group; 24% patients had procedural complications; difficulty in accessing IT space by catheter (3 of 18 patients who underwent IT trialing); post–dural puncture headache (3 of 19 patients who underwent epidural trialing)	Cost for IT group was less than for epidural group; 60% and 64% of IT and epidural patients, respectively, had successful pain relief at last follow-up; differences between the IT and epidural groups in pain relief ($p = 0.32$) and functional responses were minimal
Kumar et al., 2002 (2)	Prospective, double-blind, randomized trial; 67 patients (23 patients underwent trialing and implantation, and 44 patients underwent conventional pain therapy); low back pain; ≥50% reduction in VAS rated successful trial; follow-up 5 years	IT bolus followed by a confirmatory IT infusion trial in patients who were successful in the first trial	NA	NA	NA	NA	Greater cost-effectiveness for IT group than for controls ($29,410 vs. $38,000); 27% improvement for IT patients vs. 12% for controls on ODI scores; 88% of patients were satisfied or very satisfied with the IT outcome
Grider et al., 2010 (6)	Case report; 62-year-old woman; chronic nonmalignant low back pain; systemic opioid pretreatment "holiday"; follow-up 2 years	Continuous IT infusion for 96 hours	0.025–0.150 mg/d	0.150 mg/d	0.258 mg/d at 2 years	No adverse events reported	NPS 8 out of 10 on day 1 of trialing, 5 of 10 on day 2, and 2 of 10 on day 3; NPS 3–5 after 1 year and 3 of 10 at 2 years; improved ADL
Grider et al., 2010 (6)	Case report; 52-year-old woman; complex regional pain syndrome type 2; no systemic opioid pretreatment; follow-up at 10 days and 2 years	Continuous IT infusion for 60 hours	0.025–0.30 mg/d	0.3 mg/d	0.41 mg/d at 2 years	No adverse events reported	NPS (at 8 out of 10 on presentation) decreased to 3 out of 10 at day 10 and to a range of 3–4 of 10 at 2 years
Kim et al., 2011 (1)	Retrospective hospital chart review in 2004–2007 of 35 patients with lumbar postlaminectomy pain; ≥50% reduction in baseline VAS score without side effects rated successful trial; no systemic opioids during trialing‡	Continuous IT infusion (as inpatients)	1.62 mg/d (range 0.036–6.912 mg/d)	15 mg/d	Median dose increase was 77% at 1 year	NA	At 1 year, mean VAS improvement of 26%; 57% patients switched to or added another analgesic; significant correlation at 1 year between less pain relief and higher IT trial opioid doses; older patients had more pain relief with smaller IT opioid dose escalation than younger patients had
Quattrone et al., 2007 (7)	Prospective, randomized trial; 42 patients; 21 with trialing vs. 21 patients without trialing; chronic cancer pain	Continuous IT infusion for 7 days or no trial	NA	NA	NA	Nausea and vomiting greater in trialing group than in patients implanted without trialing on day 1	Reduction in VAS significantly greater in trialing group at rest ($p = 0.01$) and while coughing ($p = 0.005$) than in patients implanted without trialing; opioid consumption lower in trialing group ($p = 0.001$)
Shaladi et al., 2007 (8)	Prospective, open-label; 24 patients; refractory pain due to vertebral fractures; ≥50% reduction in VAS rated successful trial; 1 year follow-up	Continuous IT infusion via external catheter for 6 days	11.28 mg/d	7.92 mg/d	16.32 mg/d at 1 year	Nausea, vomiting, itching; complications of wound infection, catheter dislocation, delayed healing	Significant pain relief (reduction in VAS scores [from level before screening test] of 58.6% and 78.2% [$p < 0.001$] after pump implantation and after 1 year, respectively); improvement in QDL parameters
Ruan et al., 2008 (12)	Case report; 64-year-old woman; chronic severe low back pain and bilateral leg pain	Continuous outpatient epidural infusion for 2 weeks	0.5 mg/mL delivered at 0.5 mL/hour	NA	NA	Bilateral leg edema	NPS score 8–9 out of 10 initially; 90% reduction in back and leg pain during trialing; discontinued oral opioids

*Doses are mean values unless otherwise noted.
†At 24 hours after an unsuccessful trial, patients received another bolus morphine trial at a dose that was increased by 100%; up to three trials were permitted.
‡91.4% of patients were trialed on morphine.
ADL, activities of daily life; AE, adverse event; IT, intrathecal; NA, not available; NAS, numeric analog scale; NPS, numeric pain scale; ODI, Oswestry Disability Index; QDL, quality of daily life; SD, standard deviation; VAS, visual analog scale.

Trial Dosing. Among studies for which it was reported, the typical dose of bolus morphine used was approximately 1.0 mg (3,4). Rauck et al. (5) noted that the bolus trialing dose was based on prestudy analgesic requirements, which were converted to morphine sulfate equivalents. Approximately 1/100th or 1/200th of the resulting conversion was used for the IT bolus trialing dose. At 24 hours after an unsuccessful trial, patients received another bolus morphine trial at a dose that was increased by 100%; up to three trials were permitted.

Definition of a Successful Trial. Typically, patients were considered to have completed a successful trial if they had a ≥50% reduction either in visual analog scale (VAS) pain score (2,3) or numeric analog scale (NAS) pain score (4,5) reports. Two consecutive posttrial NAS score measurements were required in the Anderson et al. study (4), whereas in the Rauck et al. study (5), an NAS score reduction observed at any of the two-, four-, or six-hour posttrial measurements was considered successful. Alternatively, patients in the latter study were also considered to have completed a successful trial if they had a ≥50% reduction in the need for systemic analgesics within 12 hours after dosing (5). In the two studies by Kumar et al. (2,3) patients who completed a successful bolus trial subsequently received an additional trial of morphine via a continuous delivery pump to confirm continued success and to assess side effects of the drug before proceeding with pump implantation.

Trialing Results. Across all studies that used bolus morphine trialing, 72% of patients (170 of 236) who underwent such trialing met the criteria for success and were implanted with an IT pump. The percentage of patients who completed a successful trial was highest (80%; 119 of 149) in the open-label uncontrolled study by Rauck et al. (5) and lowest (52%; 23 of 44) in the double-blind randomized Kumar et al. (2) study.

Some of the adverse events (i.e., nausea, vomiting, diaphoresis, hypotension, and urinary retention) that occurred during the trialing period of the Anderson et al. (4) study were more common in patients who received a bolus IT trial than in patients who received a continuous epidural trial, whereas pruritus and constipation were less common with bolus IT trialing than with continuous epidural trialing. These adverse events were mild and successfully treated with medications; however, catheterization was required in 10 of the 15 patients who developed urinary retention. Procedural complications were reported for six patients who underwent bolus IT trialing, but for only three patients who underwent continuous epidural trialing.

Long-Term Effects of Implanted Pumps. Overall, patients who completed a successful bolus morphine trial demonstrated favorable long-term responses to the therapy administered via implanted pump, as assessed by pain scale scores. In the uncontrolled study by Kumar et al. (3), long-term success was defined as a ≥25% reduction from baseline in VAS score and was classified according to pain type. At the final follow-up visit, long-term VAS score was reduced by 75% for deafferentation pain and by 61% for mixed pain at a mean of 29 months after implantation. Among patients who underwent an IT bolus trial in the Anderson et al. study with six months of follow-up, 60% experienced successful pain relief of ≥50% (4). The relationship of the dose of IT bolus required to obtain a successful trial and the baseline dose after one year does not appear to be correlated (3–5).

Improvements in quality of life measures and reductions in the use of concomitant systemic medications were also associated with bolus trialing success. Kumar et al. (2) reported in the randomized study that improvements in pretrial Oswestry Disability Index scores, assessed every six months and averaged over the course of five years of follow-up, were greater with IT morphine therapy (27%) than with conventional pain therapy (12%). In the uncontrolled study by Kumar et al. (3), 69% of implanted patients (11 of 16) reported an improvement in their quality of life. Compared with baseline systemic opioid use, systemic opioid use at the final follow-up visit in the Anderson et al. (4) study was 57% lower for all patients, and systemic opioid use in the Rauck et al. (5) study was decreased throughout 16 months of follow-up.

Delivery of IT morphine via implanted pump was generally safe and tolerable in patients who completed a successful bolus morphine trial (3–5). Adverse events that occurred during pump implantation in these patients were generally mild (3–5) and included constipation, nausea, vomiting, pruritus, micturition, and sexual disturbances. Notably, in the randomized Anderson et al. study, nausea, vomiting, diaphoresis, and urinary hesitancy were more frequently reported in implanted patients who had received a bolus IT trial than in those who had received a continuous epidural trial (4). Most probably, fewer side effects occurred because continuous infusion trials give the physician a fairly accurate estimate of the starting daily dose after the implant, whereas the starting daily dose after the single bolus dose trial is generally a random estimate. However, this difference was not statistically significant, and the overall incidence of complications decreased over time. Complications associated with the pump implantation procedure (e.g., difficulty in accessing the IT space) (4) and with the IT pump device (e.g., catheter kink, morphine leak, pump failure, failed flow restrictor) (5) were reported in two studies.

Morphine: Continuous IT Infusion Trialing

Continuous IT morphine infusion trialing was used in four studies, including a retrospective review of medical records by Kim et al. (1), a series of two case reports (i.e., two women who were 52 and 62 years of age) by Grider et al. (6), and two prospective studies. In the prospective study by Quattrone et al. (7), half of the patients were randomly assigned to receive a continuous morphine infusion trial and the other half did not undergo trialing, whereas all patients from the Shaladi et al. (8) prospective study received the same trial. Additionally, one survey of clinical practice by Peng et al. (9) found that morphine was the single most common IT therapy used in six of the ten centers that were surveyed and that continuous IT infusion was the single most common trialing method used in five of the centers.

Pretrialing Medications. Reduction or discontinuation of pretrialing systemic medications occurred in all three studies for which information on pretrialing medications was available. The oral morphine dose was reduced by 50% before trial initiation in patients from the Shaladi et al. study (8), and it was gradually tapered to low doses as the trial dose increased until a VAS score reduction of ≥50% was achieved. In the retrospective Kim et al. study (1), pretrialing short-acting systemic opioids, sustained-release systemic opioids, and methadone were completely discontinued at 4, 12, and 24 hours before trial initiation, respectively. In the two patients from the Grider et al. case series, pretrialing opioids were completely discontinued at least six weeks before the continuous infusion trial (6).

Catheter Placement. Catheter placement was described for all patients who underwent continuous IT morphine infusion trials in the Kim et al. (1) and Grider et al. (6) studies. In 35 patients, IT catheters were placed under fluoroscopic guidance with confirmatory injection of Isovue-M® 300 contrast (1). Under strict aseptic conditions, with the patients receiving local anesthesia and intravenous

sedation, a low lumbar paramedian approach was used in the two patients from the Grider et al. case series (6). Temporary catheters were placed, were passed 4 to 5 cm into the lumbar IT space, and were tunneled subcutaneously to the lateral flank.

Trial Dosing and Duration. Continuous morphine infusion trials were administered for a period (6,7) that ranged from two to seven days, and the mean initial doses (6,8) ranged from 0.025 to 11.28 mg/d. In the Kim et al. study, the mean initial morphine doses used for continuous trialing in all patients were determined by calculating 1/300th of their equivalent or equianalgesic pretrial systemic morphine dose (1). Grider et al. suggested that the use of a low morphine dose (e.g., initial dose of 0.025 mg/d increased to a maximum dose of 0.3 mg/d during the trial), combined with the implementation of a systemic opioid holiday, is critical for the success of a continuous infusion trial (6).

Placebo Control. The use of a placebo arm is an attractive option for those undergoing pain treatment trials. The analysis of randomized controlled studies show the placebo arm is very important in establishing good data and advancing the field (10,11). The argument for using the placebo comparative arm is to evaluate those with a true response to the drug vs. a placebo responder. Despite this theory, the use of the randomized control trial in those being evaluated for an IT pump is controversial. The use of a control in a study has different goals than the use of this method in complex clinical settings. Several arguments against this method can be made. These include the importance of evaluating side effects during the administration of the proposed drug, and the possible inability to determine any problems in the placebo or treatment arm being related to confounding variables such as anesthesia, comorbidities, or adjuvant medications. The other major argument is the validity of calling a patient a placebo responder and thus a poor pump candidate when they respond in both the placebo and treatment arm. No study defines the best option for the treatment of this complex patient group. Based on these issues, the panel did not come to consensus on the use of placebo in pump trialing, although the majority of the panel does not use this method in its practice.

Definition of a Successful Trial. Similar to the definition of successful bolus morphine trialing, successful continuous morphine trialing typically involved a ≥50% reduction in VAS score (1,8). Patients in the Shaladi et al. (8) study were also required to have maintained this pain reduction at a consistent morphine dose for ≥3 days. In the study by Quattrone et al., the term *optimal IT dose* was used to describe the dose tested during successful trialing that provided both effective analgesia and minimal side effects (7). In addition to the ≥50% VAS score reduction requirement for a successful trial in the Kim et al. (1) trial, patients in this study were required to have an absence of adverse events. The two patients from the case series also had an absence of adverse events before undergoing IT pump implantation, in addition to achieving numeric pain scale (NPS) scores of ≤5 (out of 10 maximum) during trialing and experiencing functional improvement, all of which were confirmed during a 12- to 24-hour observation period after efficacy was reached (6).

Trialing Results. Trialing data from the case series and the two prospective studies suggest that continuous morphine infusion trials resulted in a high magnitude of pain reduction. Grider et al. (6) reported that the two patients had 75% to ~100% reductions in NPS score (pain scale highest possible score was 10), from 8 and 6 on the first day of the trial to 2 and nearly complete pain resolution, respectively, on the third day of the trial. In the Shaladi et al. study, the mean VAS score decreased by 59% over the course of the trial (8). Quattrone et al. reported that reductions in VAS score were significantly greater, at rest ($p = 0.01$) and while coughing ($p = 0.005$), in patients who received a continuous infusion trial than in patients who did not receive a trial before implantation (7). In addition, opioid consumption by these patients was reduced during this period.

The trials were generally well tolerated in these studies. Patients in the Quattrone et al. and Shaladi et al. studies experienced continuous morphine infusion trialing-associated nausea, vomiting, and itching (7,8); however, the vomiting and itching were reported to be resolved after treatment with antiemetic and antihistaminic medications (8). No adverse events occurred in the two case reports (6).

Long-Term Effects of Implanted Pumps. Pain reductions demonstrated during continuous infusion morphine trials were generally sustained after pump implantation; however, the magnitude of long-term changes in VAS score varied. The two patients from the case series (6) experienced continued pain reductions after one and two years; one patient had a 63% NPS score reduction from day of the trial to two years, and the other patient had a 67% reduction from day of the trial to one and two years. In two other studies, VAS score reductions were greater at one year after implantation than at the pretrialing assessments; Shaladi et al. (8) reported a 78% mean reduction in 24 patients, whereas Kim et al. (1) reported a 26% reduction in 35 patients. In the Kim et al. study, higher trialing IT morphine doses were correlated with less pain relief (i.e., smaller reductions in VAS score; $p = 0.012$) at one year, and older patients were shown to experience greater pain relief (i.e., greater reductions in VAS score; $p = 0.038$) (1). However, baseline VAS scores were not correlated with percentage changes in VAS score at one year (1).

Long-term improvements in quality of daily life (QDL) (8) and reduced or minimal use of concomitant systemic medications (1,6,8) were also predicted by continuous infusion trialing success. In the Shaladi et al. study (8), QDL was improved by 36% at one year, and no patients required additional systemic analgesic medications. For patients from the retrospective Kim et al. (1) study and the Grider et al. (6) case series, in which patients were required to take an opioid holiday before undergoing continuous morphine infusion trialing, minimal increases in IT morphine doses used during trialing were needed to maintain pain relief during the one- to two-year follow-up periods after implantation.

In the Grider et al. and Shaladi et al. studies, IT morphine was safe and tolerable in patients who underwent IT pump implantation after the completion of a successful continuous morphine infusion trial (6,8). At one year after IT pump implantation in one patient from the Grider et al. case series, no side effects were reported (6). Three of the 24 patients in the Shaladi et al. study experienced nausea, and four patients developed complications such as wound infection, delayed healing, and catheter dislocation (8).

Morphine: Continuous Epidural Infusion Trialing

Trials of continuous epidural morphine infusion were used in a 64-year-old woman from a case report by Ruan et al. (12) and in 19 patients from the prospective, open-label randomized Anderson et al. (4) study. In the Anderson et al. study, an additional 18 patients received a bolus IT morphine trial; these results are described in the *Morphine: Bolus Intrathecal Trialing* section.

Pretrialing Medications. In both studies that used continuous epidural infusion trials, patients were receiving systemic analgesics at baseline. In the Anderson et al. study, patients discontinued all opioids and long-acting analgesics for at least 12 hours before trial administration (4), whereas in the Ruan et al. case report, after catheter placement, the patient was gradually weaned off the oral methadone medication she had been receiving for more than three months (12).

Catheter Placement. Catheter placement was described for the case report: the (epidural) catheter was placed under fluoroscopic guidance at L2-L3 and tunneled subcutaneously to T12 (12).

Trial Dosing and Duration. Continuous epidural morphine infusion trials were administered at durations of 36 to 48 hours (4) to two weeks (12). The 64-year-old woman received the same 6.3-mg/d dose throughout the entire two-week trialing period; on-demand bolus doses of 0.2 mL (0.5 mg/mL) with a 60-min lockout interval were permitted. In the Anderson et al. study (4), typical initial doses of 4.8 mg/d, which were based on each patient's opioid treatment history, were titrated up to 48 mg/d on the basis of NAS scores or pharmacologic complications.

Definition of a Successful Trial. In both studies, definitions of a successful continuous epidural morphine trial were based on reductions in NAS score. As previously described in the *Morphine: Bolus Intrathecal Trialing* section, patients in the Anderson et al. study were considered to have completed a successful trial if they had a ≥50% reduction in two consecutive posttrial NAS score reports (4). In the case study, adverse events and reductions in the use of systemic opioids were also considered in assessing the success of trialing (12).

Trialing Results. Among patients who underwent continuous epidural trialing in the randomized Anderson et al. (4) study, 79% (15 of 19) met the criteria for success and were implanted with an IT pump. In the case report, the patient experienced a 90% pain reduction during the epidural trial and was able to discontinue her oral opioid medication; however, the patient developed progressively worsening bilateral leg edema during the trial. In the randomized study, pruritus and constipation were more common with continuous epidural trialing than with bolus IT trialing, whereas nausea, vomiting, diaphoresis, hypotension, and urinary retention were less common with continuous epidural trialing. Post–dural puncture headache, reported in 16% of patients who underwent epidural trialing, was the only procedural complication of this type of trial.

Long-Term Effects of Implanted Pumps. Among patients from the Anderson et al. study who received a continuous epidural trial, 64% experienced successful ≥50% pain relief at the final six-month follow-up after IT pump implantation (4). Additionally, no significant differences in pain relief or function were noted between patients who underwent continuous epidural trialing and patients who underwent bolus IT trialing. Pump implantation and long-term follow-up after implantation were not discussed in the case report (12).

The incidences of complications at three and six months after pump implantation were lower in patients who initially underwent continuous epidural trialing than in patients who underwent bolus IT trialing; however, this difference was not statistically significant. The overall incidence of complications decreased over time, as expected with increased duration of therapy (4).

Morphine Combination Therapy Trialing Method

Morphine plus several other medications (i.e., a local anesthetic, an alpha$_2$-adrenergic agonist, or a benzodiazepine) were used during trialing and after pump implantation in a study that involved continuous IT infusion trialing of the drug combination (13). Patients in this study had chronic back and leg pain due to degenerative lumbar spinal disease. Moreover, a survey of clinical practice by Peng et al (9) found that combination therapy is used by seven of the ten centers that were surveyed.

Morphine Combination Therapy: Continuous IT Infusion Trialing

A prospective study by Rainov et al. (13) evaluated 26 patients who underwent trials of morphine combination therapy via continuous IT infusion.

Pretrialing Medications. Patients who had continuous IT infusion trials of morphine combination therapy were receiving systemic analgesics (e.g., morphine sulfate, diclofenac, metamizol) at baseline that were gradually tapered after initiation of the trialing (13). Pretrial doses were continued for three days after trial initiation, in order to minimize breakthrough pain, and were completely tapered after seven to ten days.

Catheter Placement. Catheter placement for patients who underwent continuous infusion trials of morphine combination therapy involved displacement of a 2- to 3-cm portion of skin during needle puncture. The IT catheter tip was then placed in close proximity to the uppermost pain dermatome, but not below Th10 (13). Subsequently, the 2- to 3-cm portion of skin was returned to its original position, which helped to preserve the sterility of a subcutaneous portion of the catheter.

Trial Dosing and Duration. The typical starting dose of morphine during trialing was 0.5 mg/d, which was titrated upward over the course of the three- to ten-day trialing period until patients demonstrated a pain response (13); the mean morphine dose during the trial was 0.5 mg/d and the median trial duration was seven days. If the starting dose of morphine had been doubled during titration, the other IT medications were titrated to improve analgesic effects. Morphine was further titrated only if doses of all other adjuvant IT drugs had been doubled.

Definition of a Successful Trial. Successful continuous morphine combination therapy trialing was defined as a ≥50% reduction in VAS scores for both pain intensity and unpleasantness (13). Subjective patient reports of satisfaction were also considered.

Trialing Results. All 26 patients completed a successful trial (13). Both pain intensity and unpleasantness were significantly reduced from approximately 8.4 and 7.0 out of 10, respectively, on the first day of trialing to 3.2 and 2.2 on the eighth day of trialing ($p < 0.01$). Adverse events and complications during trialing were not reported. Subsequently, patients underwent implantation of a permanent IT pump.

Long-Term Effects of Implanted Pumps. Patients who had trialing success generally experienced long-term postimplantation efficacy of morphine combination therapy, which was evaluated during a follow-up period that lasted for a mean duration of 27 months (13). At 24 months after implantation, 77% of patients (20 of 26) were receiving both IT morphine and a local anesthetic, 62% of patients (16 of 26) were receiving both IT morphine and an alpha$_2$-adrenergic agonist, and 38% of patients (10 of 26) were receiving both IT morphine and a benzodiazepine. Although VAS score reductions varied over the course of the follow-up period, patients consistently experienced ≥50% reductions from the preimplantation scores. Patients also experienced long-term improvements in walking ability and distance, sleep duration and quality, and urinary bladder control, in addition to reductions in the need for systemic analgesic medications and reductions in motor and sensory disturbances. Moreover, 73% of patients (19 of 26) rated long-term efficacy as excellent or good. Morphine was administered during the follow-up period at a mean dose of 6.2 mg/d, which was moderately greater than the doses used during the initial trial.

IT morphine combination therapy was safe and tolerable in patients who underwent IT pump implantation after the completion of a successful continuous infusion trial. No major adverse events occurred, and only 3 of 26 patients experienced complications, which included catheter leakage or occlusion and a leaky reservoir septum.

Other Opioid Trialing Method

Reports of trialing with opioids other than morphine included one study of patients with refractory cancer pain (14). These patients received either bolus IT trialing or bolus epidural trialing; however, only patients who underwent bolus IT trialing were considered for IT pump implantation.

Other Opioids: Bolus IT Trialing

In a retrospective review of medical records, Burton et al. (14) evaluated 61 patients who underwent trials of opioid medications via single-shot IT injection. Of these patients, 24 received nonmorphine opioid medications. Pretrialing medications, trialing doses, and the definition of a successful trial were not reported.

Trialing Results. Among 61 patients who underwent bolus IT opioid trialing, 92% (56 patients) met the criteria for success; however, the percentage of these patients who received nonmorphine IT opioid medications was not provided. Of the patients who completed a successful trial, 95% (53 of 56) were implanted with an IT pump; the remaining 5% (3 of 56) received IT analgesia via an external pump.

Long-Term Effects of Implanted Pumps. In this retrospective study, bolus IT trialing success may suggest long-term postimplantation efficacy of opioids (other than morphine) (14). At eight weeks after IT or epidural treatment initiation, the mean proportion of patients with severe pain decreased from 86% to 17% ($p < 0.001$), mean numeric rating scale scores decreased from 7.9 to 4.1 ($p < 0.001$), and morphine equivalent daily dose decreased from 588 mg/d to 294 mg/d ($p < 0.001$). Although efficacy results were not specifically reported for only those patients who received nonmorphine IT opioid medications via an implanted pump, it was noted that there were no significant differences between patients who underwent IT therapy and those who underwent epidural therapy ($p < 0.15$). IT therapy-related neurologic sequelae or complications were not reported in patients with implanted pumps.

Ziconotide Trialing Methods (Table 2)

Burton et al. reviewed several methods of ziconotide trialing by identifying published and unpublished data that involved the use of such trials (15). Trialing methods were identified in four studies (including three prospective studies) that used bolus IT trials, three studies (including one prospective study) with continuous IT infusion trials, one study involving limited-duration IT trials, and one study that used limited-duration epidural trials. Patients from these studies had a variety of pain types, including severe chronic nonmalignant pain, postthoracotomy pain, central thalamic poststroke pain, postmastectomy pain, pudendal neuralgia, chronic neuropathic pain, complex regional pain syndrome, myofascial pain syndrome, and low back pain.

Ziconotide: Bolus IT Trialing

Trials of bolus ziconotide were used in three prospective studies and a retrospective study by Baumgartl (16) of four patients (15). In two prospective single-center studies, Grigsby and McGlothlen (17) evaluated 42 patients, and Okano et al. (18) evaluated 11 patients. Six additional patients received bolus IT ziconotide trials in a randomized, double-blind, placebo-controlled study by Rosenblum (19). No specific pretrialing treatments or procedures were discussed. However, some patients from the Grigsby and McGlothlen study (17) and the Okano et al. (18) study had received previous medication via IT pumps.

Trial Dosing. Typical doses used during bolus IT ziconotide trialing in the reviewed studies ranged from 1 to 5 μg; however, Baumgartl (16) reported that the four patients who were retrospectively evaluated received relatively high ziconotide doses of 5, 40, and 50 μg (15). In the largest study, conducted by Grigsby and McGlothlen (17), 42 patients received a bolus ziconotide dose of 1 μg; if this trial was unsuccessful, patients had the option to receive up to two additional injections of the drug at 3- and 5-μg doses (15).

Definition of a Successful Trial. Across three studies, patients were considered to have completed a successful bolus trial of IT ziconotide if they had a ≥50% pain reduction (15,17–19). Additional outcomes that were defined included a lack of serious adverse events in the Grigsby and McGlothlen study and a >30% reduction in VAS score in the Rosenblum study.

Trialing Results. Across three of the studies that used bolus ziconotide trialing, 70% of patients (40 of 57) met the criteria for success, and 51% (29 of 57) initiated or were scheduled to initiate continuous IT ziconotide treatment (16–18). Seventy-five percent of patients (3 of 4) in the Baumgartl (16) study, who received relatively high ziconotide doses up to 50 μg, had an NPS score reduction of approximately 2 out of 10 to 5 out of 10. In the Rosenblum (19) study, where patients received ziconotide doses of 0 (i.e., placebo), 2, 4, and 8 μg, a dose-dependent increase was apparent in the proportion of patients who reported a >50% reduction in VAS score (15). The proportion of patients who reported a >30% reduction in VAS score was higher with placebo than with the 2-μg dose, but increased in a dose-dependent manner for the 4- and 8-μg doses. Adverse events that occurred during these trialing studies included nausea, vomiting, dizziness, ataxia, and dysphoria; urinary retention, motor weakness, and hallucinations were also reported as serious adverse events (15,18,20).

Long-Term Effects of Implanted Pumps. In patients from the Okano et al. (18) study with six months of follow-up and in the Baumgartl (16) study at a ziconotide dose of 2.4 μg/d, a successful trial suggested that patients would have successful responses to continuous infusion in 73% of patients (8 of 11) (15). After 2, 4, 13, and 26 weeks of follow-up in the study by Grigsby and McGlothen, 27% of patients (4 of 15), 42% (5 of 12), 71% (5 of 7), and 40% (2 of 5), respectively, experienced reductions in VAS score; the mean dose of ziconotide at the time of last assessment was 1.19 μg/d and ranged from 0.60 to 5.0 μg/d (17). Mild adverse events, including cognitive changes that led to treatment discontinuation in one patient, as well as dysphoria in another patient, were reported with continuous ziconotide infusions (16,17).

Ziconotide: Continuous IT Infusion Trialing

Continuous IT infusion was assessed for ziconotide trialing in one open-label study by Ver Donck et al. (21), in one retrospective review of medical records by Ting et al. (22), and in a 54-year-old patient from a case series (23) by Wermeling and Berger (15).

Pretrialing Medications. Patients received prophylactic antibiotics before catheter placement (21,22). In the Ver Donck et al. study (21), the antibiotics were administered within one hour before placement and for 72 hours after placement. At baseline, almost all patients

Table 2. Description of Trialing Parameters and Outcomes for Ziconotide Trials.

Authors and year	Trialing Study design	Trial type	Trial ziconotide dose	Implantation/follow-up Initial ziconotide dose	Follow-up ziconotide doses	Adverse events	Efficacy
Okano et al., 2008; and Shah and Akbik, 2009 (18,20)	Prospective, single-center study of 11 patients; 73% of patients completed a successful trial; ≥50% reduction in pretrialing pain was defined as a successful trial	IT bolus	1.2, 2.4, and 5 μg	NA	NA	Urinary retention and motor weakness were experienced with the 5-μg dose, hallucination was experienced with one of the lower doses	88% patients continued to experience pain relief at 6 months after ziconotide was added to the IT pump
Rosenblum, 2008 (19)	Prospective, double-blind, randomized, placebo-controlled study of six patients with severe chronic pain; proportions of patients who completed a successful trial were 25% (0 μg), 17% (2 μg), 50% (4 μg), and 67% (8 μg); >30% or >50% reduction in VAS rated successful trial	IT bolus	0, 2, 4, and 8 μg	NA*	NA*	Nausea, vomiting, ataxia all occurred with the 8-μg dose; nausea also occurred with the 4-μg dose	NA
Grigsby and McGlothlen, 2008 (17)	Prospective, single-center ongoing study of 42 patients with chronic pain; 67% of patients completed a successful trial and received or were scheduled to receive continuous ziconotide infusion at the time of reporting; ≥50% reduction from baseline in VAS score was defined as a successful trial	IT bolus	1 μg and up to two additional injections of 3 and 5 μg if a ≥50% pain reduction was not achieved	1 μg*	1.2 μg/d*	Well tolerated by most patients; nausea and vomiting were experienced with the 1- and 3-μg doses; one patient discontinued continuous ziconotide infusion because of cognitive changes	27%, 42%, 71%, and 40% of patients who experienced effectiveness with the trial or who were satisfied with the trial continued to experience pain relief after 2 weeks, 1 month, 3 months, and 6 months, respectively
Baumgartl, 2006 (16)	Retrospective study of four patients; 75% patients had NPS score reductions of approximately 2 out of 10 points to 5 of 10 points	IT bolus	5, 40, and 50 μg	NA*	Progressive doses of 0.6 to 7.2 μg/d*	Dysphoria was experienced with the 5-μg dose; nausea and positional dizziness were experienced with the 50-μg dose	One patient had a 5-point reduction in pain after a 50-μg bolus dose but not with continuous infusion; one patient had no reduction in pain after 40- and 50-μg bolus doses or with continuous infusion; one patient had a 25% reduction in pain after her bolus dose and with continuous infusion
Ting et al., 2008 (22)	Retrospective study of seven patients with chronic malignant or nonmalignant pain; 71% of patients completed a successful trial, 43% of whom were implanted with an IT pump; ≥3-point reduction from baseline in Pain Now score or a >50% improvement in self-reported pain was defined as a successful trial	Continuous IT infusion	Initial dose, 1.2 or 2.4 μg/d; maximum dose, 2.5 or 5.6 μg/d, respectively	NA	NA	Post-dural puncture headache, catheter dislodgement, deep vein thrombosis	NA
Ver Donck et al., 2008 (21)	Prospective open-label study of 71 patients with severe chronic pain; 61% of patients implanted after trialing; VAS, CPRS, and CGI scales were used to assess a successful trial	Continuous IT infusion for a period of 3 or 4 weeks, which was later reduced to 1 or 2 weeks	Initial dose, 2.4 μg/d; subsequent doses, 3.4–4.1 μg/d	NA	NA	Nausea, dizziness, asthenia, vertigo, headache, leg weakness, meningitis, device failure, CSF leakage, lumbar puncture headache, catheter-related complications	Continuous IT trialing of ziconotide may be sufficient for the assessment of patient response
Wermeling and Berger, 2006 (23)	Case report of a 54-year-old man with severe peripheral neuropathy; VAS scale and patient-reported results on the Pain Relief scale were used to assess a successful trial	Continuous IT infusion	0.3–100 ng/kg/h	20 ng/kg/h	5–12 ng/kg/h	Confusion, double vision, memory impairment, sedation, slurred speech, altered sense of smell, feeling of an out-of-body experience, anxiety, personality change, tiredness	Pain relief was assessed as significant by the patient at 2 months
Wermeling et al., 2003 (24)	Open-label study of 22 patients with chronic pain; VAS and CPRS scales were used to assess a successful trial	Limited-duration IT infusion for 1 hour	1, 5, 7.5, or 10 μg	NA*	NA*	Primarily mild to moderate in severity; severe myasthenia, dizziness, and headache were reported with the use of the 10-μg dose	NA
Wermeling and Berger, 2006 (23)	Case series of two 47-year-old women with severe pain; both patients experienced success with the trial; VAS and CPRS scales were used to assess a successful trial	Limited-duration epidural infusion for 1 hour	5 or 10 μg	NA*	NA*	Mild headache, somnolence, light-headedness, itchiness, nausea, hypotension	NA

*Some patients may have received continuous IT ziconotide therapy via externalized infusion pump.
CGI, Clinical Global Impression; CPRS, Categorical Pain Relief Scale; CSF, cerebrospinal fluid; IT, intrathecal; NA, not available; NPS, numeric pain scale; VAS, visual analog scale.

were receiving other medications (e.g., 53 out of 71 patients were receiving systemic opioids), which were continued during the trials.

Catheter Placement. Catheter placement was described in the study by Ver Donck et al. (21) in which the IT catheter tips were typically placed from T11 or T12 to L1 or L2 under fluoroscopic guidance. The catheters were then connected and anchored internally. In the case study, an IT catheter was placed at the lumbar space and tunneled subcutaneously to the abdomen.

Trial Dosing and Duration. In the largest study of patients who underwent continuous IT ziconotide trials (71 patients) (21), a three-

or four-week trialing period was chosen, but this was later reduced to one or two weeks because of four cases of meningitis that occurred between two and three weeks; a mean initial dose of 2.3 μg/d was used, followed by doses ranging from 3.4 to 4.1 μg/d. Patients from the retrospective study by Ting et al. (22) received an initial dose of 1.2 or 2.4 μg/d and a mean maximum dose of 2.5 or 5.6 μg/d for approximately two weeks. The patient from the case report received various doses from 0.3 to 100 ng/kg/h over the course of the trial (23).

Definition of a Successful Trial. Continuous IT ziconotide trialing success was assessed in two studies by using the VAS (15,21,23). In the retrospective Ting et al. (22) study, adequate analgesia was specifically defined as a ≥3-point reduction in Pain Now score or a >50% improvement in patient-reported pain. Patient-reported results on a pain relief scale were also used in the case report (23). In addition to VAS scores, Ver Donck et al. (21) assessed the effectiveness of pain relief by using the Categorical Pain Relief Scale (CPRS) and the Clinical Global Impression (CGI) scale.

Trialing Results. After undergoing a continuous IT trial of ziconotide, the majority of patients elected to receive long-term ziconotide therapy via implanted pump (21,22). Significant improvements from baseline in VAS score were experienced by 11.0%, 32.6%, 31.0%, and 23.5% of patients from the Ver Donck et al. (21) study after one, two, three, and four weeks of continuous IT ziconotide trialing, respectively ($p < 0.005$). More than 50% of patients reported improvements in CPRS and CGI scale scores at the end of the study. In the study by Ting et al. (22) adequate analgesia was achieved by 71.4% of the patients. The patient from the Wermeling and Berger study had a >70% reduction in pain intensity at five days after trial initiation (23).

Although no adverse events that occurred during trialing in the Ting et al. (22) study were related to ziconotide therapy, treatment-related dizziness, nausea, asthenia, vertigo, and headache occurred in the Ver Donck et al. (21) study and are consistent with ziconotide-related adverse events reported in other studies (15). Serious adverse events, including one case of treatment-related leg weakness, were reported by 27% of patients (21). The patient from the case report experienced several adverse events (i.e., confusion, double vision, memory impairment, sedation, and slurred speech) after six days, all of which resolved after temporary discontinuation of ziconotide for 24 hours (23).

Long-Term Effects of Implanted Pumps. Ver Donck et al. concluded that a continuous IT trial of ziconotide may be sufficient for the assessment of patient response (21). However, neither this study nor the Ting et al. study evaluated the long-term effects in patients who continued to receive this therapy (21,22). In the case study, pain relief during the second month of follow-up was significant, as evaluated by the patient; however, he continued to experience adverse events that required reduced dosing (23).

Ziconotide: Limited-Duration IT Infusion Trialing

Trialing of ziconotide via limited-duration IT infusion was used by Wermeling et al. in an open-label uncontrolled study of 22 patients (15,24).

Pretrialing Medications. Patients who received treatment with epidural medications were excluded from the study (24). Additionally, although patients were required to discontinue their pretrialing IT opioids before the study, they were permitted to continue receiving their oral analgesic medications until the limited-duration IT ziconotide trial began (24).

Catheter Placement. Entry sites for the IT catheters were between L2 and L5 (24). In patients who had already been implanted with IT pumps, catheter tips were generally placed between T10 and T12. Temporary IT catheter tips were placed between L3 and L5.

Trial Dosing and Duration. Patients received an IT infusion trial of ziconotide at a dose of 1, 5, 7.5, or 10 μg for a limited duration of one hour (15,24).

Definition of a Successful Trial. The definition of a successful trial was based on improvements in both VAS and CPRS scores (15,24).

Trialing Results. Improvements from baseline in mean VAS and CPRS scores were reported over the course of the first 48 hours of the limited-duration trials (15,24). The mean maximum VAS score was lowest with the 1-μg ziconotide dose, highest for the 7.5-μg dose, and was comparable between the 5-μg and 10-μg doses. Although most adverse events were mild to moderate in severity, severe adverse events of myasthenia, dizziness, and headache were reported by patients who received a 10-μg dose.

Long-Term Effects of Implanted Pumps. The long-term effects of IT ziconotide therapy after limited-duration IT trialing were not reported (24).

Ziconotide: Limited-Duration Epidural Infusion Trialing

Limited-duration epidural infusion was used for trialing ziconotide by Wermeling and Berger in a series of two 47-year-old women (15,23). No specific pretrialing treatments or procedures were discussed.

Catheter Placement. Epidural catheters were placed between L2 and L3 or between L3 and L4 (23).

Trial Dosing and Duration. The one-hour epidural ziconotide trials were administered at doses of 5 or 10 μg (15,23).

Definition of a Successful Trial. Trial effectiveness was evaluated by using both VAS and CPRS scores (15,23).

Trialing Results. Effectiveness of the limited-duration epidural trials was demonstrated in both patients (15,23). The first patient experienced substantial analgesia for more than seven hours. From a pretrialing value of 68 out of 100, her VAS score fell to 0 during the periods between 1 and 3 hours and 5 and 20 hours after trial initiation. The pretrialing VAS score of the second patient was 85 out of 100, and during the first seven hours after the beginning of the trial, the VAS score decreased to less than 20. The trials were generally well tolerated by both patients and were associated with adverse events of only mild severity. These adverse events included headache, somnolence, light-headedness, itchiness, nausea, and hypotension and resolved within several hours.

Long-Term Effects of Implanted Pumps. The long-term effects of continued ziconotide therapy after limited-duration epidural infusion ziconotide trials were not evaluated (23).

Baclofen Trialing Method

Trialing of IT baclofen was used in a single study of patients with neuropathic pain who had an inadequate response to spinal cord stimulation (SCS) (25).

Baclofen: Bolus Trialing

Bolus injections were used for trialing of IT baclofen in a prospective study by Lind et al. of 48 patients (25). An IT catheter was initially used to administer the trials; however, this technique resulted in problems with cerebrospinal fluid (CSF) leakage. As such, the technique was switched to daily fine-needle lumbar IT injection.

Trial Dosing. Although information on pretrialing medications was not reported, the bolus trials of baclofen were administered at daily incremental doses of 25, 50, 75, and 100 μg/d (25). Placebo was randomly administered during the trialing period, and patients were blinded to the doses received.

Definition of a Successful Trial. Pain relief was assessed at baseline and every half hour; SCS was initiated after 1.5 hours. Regardless of trial duration, patients who had a ≥50% reduction in VAS score were considered to have completed a successful trial.

Trialing Results. Among patients who underwent bolus IT baclofen trialing, 42% of patients (20 of 48) met the criteria for success (25). Pump implantation for continuous IT baclofen administration occurred in 23% of the patients (11 of 48) who underwent bolus baclofen trialing. Of these 11 patients, 7 received adjunctive SCS and 4 received IT baclofen alone.

Long-Term Effects of Implanted Pumps. At the first follow-up of the 11 implanted patients, which occurred an average of 32 months after implantation, the mean VAS score was reduced by 57% from baseline (25). However, the average baclofen dose increased from 69 μg/d at baseline to 171 μg/d at 32 months in the patients who received continuous IT baclofen alone. Additionally, IT pumps were explanted from two patients because of reduced efficacy and subjective local irritation. At the follow-up of the remaining nine patients that occurred at an average of 67 months after implantation, the mean VAS score reduction was sustained, and the average dose of baclofen was further increased by 30% in most patients. Adverse events after both 32 and 67 months of follow-up included diarrhea, weight gain, numbness and heaviness of the feet, and sexual disturbances.

DISCUSSIONS OF THE CONSENSUS PANEL

Overview

Although trialing is generally recommended, there are currently no well-designed studies to address this recommendation, and therefore, no convincing data or solid basis to support the clinical decision to refute or adopt preimplantation trials. Moreover, panel members noted several aspects of trialing on which there is no general agreement. First, no consensus has been reached with regard to the outcome (e.g., extent of pain alleviation, improvement in function), drug, or drug combination that should be used to judge the efficacy of a trial. In addition, no studies have been conducted to evaluate patients who have "failed" the test but are nevertheless implanted with a definitive system. As such, the fate of the "screened out" patients and the significance (i.e., sensitivity and specificity) of the procedure in these patients are unknown. Results from an early study of SCS for the treatment of pain have shown that 21% of patients who failed the screening test but were implanted with a stimulator had good outcomes (26). The panel believes that a similar study of IT drug therapy may be warranted. Although trialing may not completely predict the long-term success of IT therapy, long-term opioid responsiveness at two years was shown to be loosely correlated with the initial dose needed for pain control (27); the magnitude of morphine dose escalation was higher in patients who required high initial doses than in patients who required low initial doses. There is also general disagreement on which technique should be used for trialing.

Trialing may not be suitable for all patients and may be omitted for the consideration of whether IT pump implantation should proceed in some patients. Socioeconomic factors may be involved in some decisions to forgo trialing. Patients with cancer-related pain almost always experience greater success with IT therapy than with systemic therapies. Trialing can be valuable to obviate severe pain, and the trial catheter may be tunneled and left in place until the permanent IT pump can be implanted (28–30).

There are also nonmalignant conditions in which trialing may be unnecessary or even detrimental. In patients who require chronic anticoagulation after having had a stroke, one could debate the need for trialing and the need to remove the patient from life-sustaining prophylaxis on more than a single occasion. The patient would need to remain off anticoagulation medication until the trial catheter is removed. This can be accomplished with bridging of heparin or with removal of the drugs, if appropriate. Some implanters have opted to not perform trials in these patients before proceeding with permanent implant placement; however, this practice is controversial. In patients with cerebral palsy, the response to baclofen has a high success rate, and many physicians believe that trialing is unnecessary if the patient has tolerated oral baclofen. In similar cases, the need for trialing IT morphine has been debated for patients with multilevel spinal instrumentation because of the potential requirement for an open surgical approach with catheter placement; avoiding the IT trial allows for only a single spinal intervention. Long-term outcomes in patients for whom IT therapy trialing was not used have not been closely studied; however, these outcomes may be unaffected by the use of a trial. Further studies are needed to determine the value of IT trialing.

Goals of Trialing

Trialing of IT therapy is performed to achieve goals that vary across patients with different disease states. Several factors were noted to be important considerations in trialing, including goals for pain relief and functional improvement, reduction in systemic opioid use, management of adverse events and complications, and potential mental status changes. Because complete pain relief is rarely achieved, encouraging patients to define their own specific personal and quantifiable pain reduction goals (e.g., stand for 30 min, sit on the floor to play with grandchildren) before trialing begins is important. Encouraging patients to avoid general goals (e.g., less pain) also helps in managing expectations and promoting long-term patient satisfaction. In order to achieve patient-defined goals during trials of medications administered at reasonable doses, while ensuring that no unacceptable or unmanageable adverse events occur, physicians should advise patients on tolerance issues and the management of breakthrough pain. Objective goals should also be defined by using patient-reported functional outcomes (i.e., CGI of change, ease of function) and measures of patient global satisfaction. The panel also noted that a potential placebo effect of trialing should be considered as a caveat in determining the success of a trial.

Pretrialing Treatment and Assessment

Before initiating trials of IT therapy, IV hydration with normal saline is generally recommended to avoid a hypovolemic response and subsequent hypotension. This problem has been seen most commonly

in trialing with ziconotide. Optimal medical care for IT therapy trialing involves the establishment of IV access, and the optimization of fluid status. Ideally, endocrine status should also be tested to establish baselines for essential hormones such as testosterone; however, the procedure is expensive and may not be feasible in all patients.

Managing Comorbidities

Patients with comorbid conditions such as diabetes, sleep apnea, a history of infections, or immunosuppression should receive appropriate therapy throughout the duration of IT therapy trialing. Generally, patients may receive the same concomitant medications at the same doses throughout the trial. The use of different antibiotics may be warranted for patients with conditions that are associated with immunosuppression (e.g., vancomycin) and in nonimmunocompromised patients (e.g., cephalosporin). Appropriate management of bleeding disorders is also important; however, discontinuation of anticoagulant treatments is required within days before trialing. Treatment with clopidogrel (Plavix®; Bristol-Myers Squibb and Sanofi-Aventis) should be stopped by 7 to 14 days before trialing, whereas cessation of direct thrombin inhibition therapy should occur by ten days before a trial. At 5 to 7 days before a trial, warfarin treatment should be stopped, and international normalized ratios should be normalized (less than 1.5), just before the procedure. If necessary, patients can be switched to enoxaparin treatment; enoxaparin treatment may continue to be administered up to 24 hours before trial initiation. The panel also suggested that coagulation factor inhibitors may be used to offset other bleeding risks. The American Society of Regional Anesthesia and Pain Medicine (ASRA) has created guidelines for spinal injections and catheters. Many individuals have debated the applicability of these guidelines to implantable devices; however, after considering these arguments in addition to current evidence, the PACC believes that the ASRA guidelines should be followed in all cases except for those in which a patient presents with an unusual clinical situation (31).

Managing Pretrialing Systemic Analgesics

Changes in concomitant opioid doses may be warranted to help ensure that the trial correctly predicts whether the IT therapy will be effective, safe, and tolerable. Three pretrialing algorithms for tapering systemic opioid doses should be considered: complete weaning, partial weaning using the lowest possible dose, or no weaning (i.e., systemic opioid doses remain consistent).

Panel members noted that full weaning may help to reveal whether opioid-induced hyperalgesia (OIH) is responsible for the severity of the pain. In patients who tolerate weaning of medications, the presence of OIH can be evaluated. If hyperalgesia is suspected, concomitant administration of systemic and IT opioids is not advisable. Complete tapering of pretrialing systemic opioids by six weeks before IT opioid trialing may reduce the risk of developing hyperalgesia, while providing sustained analgesia during IT therapy. Pump implantation may not be needed in some patients, if weaning them from systemic opioids has eliminated OIH. In patients who are still responding to systemic opioids, partial or no tapering of the opioid doses may be warranted before trialing. Key considerations involve whether the opioid is providing any pain relief and whether pain is worsened when a dose of medication is missed or weaned.

Pre–Ziconotide Trialing Treatment

When patients with neuropathic pain are not responding to pretrialing systemic opioids, a trial of ziconotide should be considered after tapering. Although some clinicians provide prophylactic administration of meclizine for dizziness before an IT ziconotide trial, insufficient evidence supports the use of this pretrialing medication. Furthermore, evidence suggests that pretrialing medications to prevent urinary retention during ziconotide trialing are not necessary, provided that microdosing is used to administer the ziconotide treatment.

Table 3. Psychological Aspects of Trialing Checklist.

- ● Behavioral expectations during trialing
- ○ Realistic expectations of the procedure and outcome of the trial, as well as of IT efficacy
- ○ Credible and consistent response to trial medication infusion as assessed by improvement in VAS score
- ○ Minimal requests for discomfort-related pain medications during the trial procedure
- ○ Stable mental status
- ■ Minimal negative symptoms (i.e., depression, anxiety)
- ■ Minimally altered mental status (i.e., confusion, cognitive impairment, psychosis)
- ■ Minimal or absent anger and victimization
- ○ Adequate stress management and coping skills
- ○ Minimal conflict with the implanting physician and cooperative with staff in the surgery center
- ○ Adequate social support present and involved with the trial

IT, intrathecal; VAS, visual analog scale.

Table 4. Psychological Comorbidities in Chronic Pain.

- Mood disorders (i.e., depression with possible suicidal ideation)
- Anxiety disorders (i.e., anxiety, panic, OCD, phobias)
- Anger and hostility (i.e., dangerousness)
- Psychosis or dissociation
- Eating disorders (i.e., uncontrolled anorexia or bulimia)
- Substance dependence disorders (i.e., medication abuse, alcohol or street drug use)
- Cognitive impairment (i.e., medication-related loss of brain function, pain, mental disorders, underlying brain disease)
- Sleep cycle disturbances (i.e., poor sleep because of a primary sleep disorder)
- Personality disorders (i.e., inability to function because of excessive emotionality, avoidance, mistrust of others, unusual habits, and lifestyle)
- Factitious disorders (i.e., unconscious feigning of illness) or malingering (i.e., conscious feigning of illness)

OCD, obsessive compulsive disorder.

Pretrialing Evaluation of Psychiatric and Neurocognitive Status (Table 3)

Pretrialing evaluation and optimization of mental status and cognition are also important. Many patients with chronic pain disorders have comorbid psychological disorders (Table 4). Therefore, assessment of these conditions in the context of medical decision making for IT therapies is essential for determining whether they have the potential to interfere with the outcome of IT therapy.

Trialing Methods

Overall, both epidural and IT sites of trialing delivery as well as both bolus and continuous infusion trialing are viable trialing techniques. Acute tests with single epidural or subarachnoid injections or "long-term" (i.e., days to weeks) IT or epidural trials involving the place-

ment of percutaneous catheters have all been used. On the basis of the limited amount of published data on trialing, no method can be considered superior. A study by Dominguez et al. (27) showed that outcomes of trialing were not associated with long-term effects of IT therapy, regardless of the trialing method used. Additionally, another study showed that the long-term failure rate of IT drug delivery is approximately 40% (at 3.2 years), irrespective of the trialing technique used (32). The trialing technique and the definition of a positive trial outcome remain largely controversial and may depend on the clinical context.

Site of Trialing Drug Delivery (epidural vs. IT)

The use of epidural or IT trialing may depend on the pain sensitivity of patients in response to certain factors. The two sites of delivery will produce different responses in patients who may be highly sensitive to a particular IT drug. For pain that is sensitive to the spinal action of the drug, any trialing method may be appropriate.

Mode of Trialing Drug Delivery (bolus vs. continuous)

Several factors are typically considered in determining the use of bolus or continuous delivery for IT therapy trials. Well-documented recommendations published by the British Pain Society provide the best clinical practice guidelines for the use of IT drug delivery to treat pain and spasticity (33). The panel concluded that either bolus or continuous injection trials should always be performed before implantation of a drug delivery system. The primary advantages of bolus trialing are convenience, cost, and safety. It was noted, however, that compared with continuous infusion trials, bolus trials may be less informative in accurately representing the long-term effects of IT opioid therapy because of the relatively short duration of effect of this medication. Because the duration of effect is longer with baclofen and ziconotide than with opioids, bolus trialing of IT baclofen and ziconotide may be suitable for representing the longer term effects.

Some implanters use an IT catheter for trialing because they believe this method is most representative of the pharmacokinetic and pharmacodynamic effects of the eventual implanted IT therapy system. However, this assumption cannot be supported by current controlled data or by the limited amount of existing literature on the topic. Although costs are greater with the use of a catheter than with other trialing methods (4), the most recent data from the United States (34) and Canada (9) revealed that 45% of implanters perform IT catheter trials over the course of at least two days. These data also revealed a 26% incidence of epidural catheter use and a 27% incidence of single or multiple IT injection use. The panel discussed the need for updates to current US Medicare regulations, which recommend the use of an IT catheter during trialing. Although this trialing method of drug delivery may be considered the "gold standard" in patients for whom continuous IT therapy is the ultimate goal, medical literature does not provide any evidence to support that it leads to improved outcomes; it also may be impractical, inappropriate, or even unsafe for some patients. Patients who receive continuous infusion trialing are required to undergo close monitoring in a hospital, thereby raising the cost of trialing. Moreover, this trialing technique is associated with an increased risk of infection and spinal cord injury resulting from the relatively large needle size and from catheter placement procedures. The use of external, long-term implanted catheters may be warranted for trialing in patients who require an extended duration of administration. Such patients may include those with complex socioeconomic issues such as litigation or worker's compensation adversarial conflicts. No data in the peer-reviewed literature currently suggests that longer trialing provides added predictability of long-term outcomes with the use of an IT pump. However, an IT catheter trial may provide adequate time for the assessment of functional improvement, which would be much more important and meaningful than the assessment of VAS scores.

Trial Setting

Although costs are lower and convenience is greater in an outpatient setting than in an inpatient setting, panel members strongly agreed that most patients who undergo trialing should be monitored for at least 24 hours, regardless of whether this monitoring occurs in an inpatient setting or in another appropriate environment. On the basis of information reported by Coffey et al. (35,36) overnight observation after trialing initiation is strongly recommended. Patients should generally be hospitalized throughout trialing if a tunneled catheter is being used, because of the risk for catheter breakage or CSF leakage; an inpatient setting in such circumstances allows for appropriate monitoring and rapid titration. An inpatient setting throughout the duration of trialing is warranted for patients with cancer-related pain who have higher life expectancies and for all patients with non-cancer-related pain who receive opioid trials. Panel members noted that 24-hour hospitalization is likely sufficient for bolus trialing of short-acting IT opioids or in opioid-naive patients.

Overnight observation after trialing initiation can be relinquished in certain circumstances. Published evidence suggests that hospital discharge is appropriate in patients with normal neurological function at 12 hours after a single-shot ziconotide trial. Additionally, there are only minimal risks of cardiac, pulmonary, or respiratory complications with the use of such trials in a medical office or ambulatory surgery center. As such, an outpatient setting is feasible for bolus trialing of IT ziconotide in patients with non-cancer-related pain. Patients who receive bolus IT opioid trialing should not be treated as outpatients and should be monitored overnight to reduce morbidity and mortality. An outpatient setting for patients with cancer-related pain who require the use of a catheter may only be appropriate in patients who have a short life expectancy. This type of trialing can be performed at home, and a permanent implant can be placed if necessitated by the clinical situation.

Trialing Medications

Opioids

Methods for trialing of IT opioids are inconsistent and therefore controversial; however, lower opioid doses are generally preferred.

Ziconotide

The primary challenge of IT ziconotide trialing is the association of side effects with the administration of incremental doses at a fast rate. As such, results from bolus trialing may wrongfully suggest that a patient will not tolerate the therapy at the trialing dose used. Because of the high cost of this therapy, insurance authorization of a second ziconotide trial at a different dose would be unlikely. The alternative of using an external catheter for an extended trialing period involving smaller dosing increments may also be impractical and associated with other safety and tolerability concerns.

Switching From IT Opioids to IT Ziconotide

When making the transition from IT opioid to IT ziconotide therapy, the IT opioid must be weaned and replaced with oral opioid therapy (37). Infusion and bolus trials are the two methods that have been studied for temporary trialing of ziconotide efficacy in patients with existing IT pumps. One group of authors described a three-week IT

opioid weaning period followed by a one-week stabilization period during which systemic opioids were administered (37). Subsequently, patients began to receive a 2.4 μg/d continuous IT infusion of ziconotide via their existing pumps. The ziconotide dose was titrated upward by 1.2 to 2.4 μg/d until efficacy was achieved or until patients could no longer tolerate the therapy; a minimum of 24 hours was required between upward titrations. Compared with patients randomly assigned to receive a placebo infusion, patients in the ziconotide group began to experience an improvement in VAS score at one week after ziconotide initiation; this benefit was statistically significant at three weeks (ziconotide, 14.7%; placebo, 7.2%; $p = 0.036$).

Bolus trialing of ziconotide efficacy has also been evaluated in two studies of patients with existing IT pumps. In one study, patients received a 1-μg injection of IT ziconotide for which efficacy was evaluated over the course of 24 hours, as measured by VAS and patient satisfaction scores. Seventeen additional 3- and 5-μg injections were permitted in patients who did not experience effectiveness or adverse events. Of the 27 patients who received a 1-μg IT ziconotide injection, 18.5% achieved effectiveness and 11.1% reported adverse events. In another study of 11 patients with existing IT pumps who underwent bolus IT ziconotide trialing (1.2, 2.4, or 5.0 μg), 72.7% achieved effectiveness (i.e., >50% pain relief) and 27.3% reported adverse events (18).

Baclofen

Bolus trialing doses of 25, 50, and 75 μg IT baclofen, as well as a 100-μg dose for some patients, were used in the study by Lind et al. (25) of patients with neuropathic pain resulting from peripheral nerve lesions. The use of these IT baclofen doses is well established in patients with spasticity, as measured by the Ashworth scale and spasm frequency scores (38–41).

Managing Complications of Trialing

Post–dural puncture headache (PDPH), the most common complication that occurs during trialing, is typically well managed by advising the patient on supine posture and hydration and by the use of combination treatment involving caffeine intake, theophylline, intravenous dexamethasone, and/or analgesics. If necessary, these management techniques can be followed by an epidural blood patch. In rare circumstances, open repair may subsequently be required. Because of interference of PDPH with proper assessment of trialing success, the panel recommends aggressive treatment. In patients who develop urinary retention, management methods involve catheterization, bethanechol treatment, and/or the use of an alternative IT opioid drug. In patients who develop orthostatic hypotension during trialing, appropriate hydration and monitoring are recommended.

Although catheter dislodgment is relatively rare during trialing, efforts to prevent or manage this complication are important. Catheter dislodgment is unlikely to occur after a placement procedure involving a low entry site in the lumbar region, positioning the anchor over the sacrum, because there is minimal or no movement of the spine at this level. Such placement prevents the occurrence of dislodgment in the absence of applied force.

Meningitis, another relatively rare complication of trialing, can be prevented by using proper sterility techniques during catheter placement, tunneling the catheter, and limiting the trial duration time (i.e., ≤3 days); appropriate aseptic conditions must be maintained. This complication can be managed by consulting with a clinician who is experienced in treating infectious diseases. Removing the catheter after using it to administer a bolus of gentamicin or other antibiotic can result in dramatic improvement in a patient who has developed meningitis.

Retrialing

The decision of whether to retrial in a patient who has previously received IT therapy involves medical and psychological considerations. The PACC recommends assessment of the reason for the initial lack of trialing success in the patient. If the patient did not respond to the drug but did not experience any side effects, a retrial should be considered. If a single drug was used without success, the team should consider retrialing with the use of an alternative drug. If fluoroscopy was not used during catheter placement, the panel strongly believes that trialing should be repeated with a proper imaging study and contrast to confirm epidural or IT spread of the agent.

Patient Education and Training

A patient's psychological readiness for and response to trialing should be evaluated. It is important that the patient's expectations regarding trialing and IT therapy are realistic. Additionally, the patient should have a stable mental status and an adequate social support network. Education should involve discussions about the procedure and the cosmetic changes resulting from a device under the skin. The patient should learn about the need to keep appointments for refills and about the signs of withdrawal. Patients should also be educated about how to contact the health-care team, who to call with problems, and what information to tell other members of the health-care team. Psychological education should occur during the psychological evaluation, which is accomplished by testing, by proper interviewing conducted by a well-credentialed professional, and by an in-depth assessment of the patient's understanding of the procedure, goals, and complications.

Noncancer patients should be assessed psychologically and, at end of life, patients should receive counseling on death and coping with family dynamics during this complex time of change. After the pump is implanted, the continued use of psychological professionals should be considered if the patient has ongoing psychological issues regarding chronic pain, disability, and changes in the patient's life.

Initiation of IT Drug Delivery After Successful Trial

A trial is performed to create a situation in which the patient and health-care team members can evaluate the potential for a possible permanent implant. Trialing is intended to create a situation that is similar to that of having a permanent implant, but the fact that these situations are not identical should be considered by the implanting team at the time of implantation. The implanter should not attempt to match the dosing of the trial, especially if an epidural trial is being used to predict the outcome of a permanent IT implant, because of potential changes in the patient's clinical status. Clinicians should err on the side of conservative dosing by using the lowest possible reasonable dose at the time of implantation. Careful monitoring should occur postoperatively in order to ensure that the selected dose does not cause respiratory depression.

CONCLUSION

Trialing is important in assessing the appropriateness of IT drug delivery. Although trials have been performed for more than a

decade, the art of the trial has not been defined by data and the science of trialing. Further studies of proper trialing are needed with regard to the route of delivery, assessment tools for patient response, and long-term impact on outcomes.

APPENDIX I

Survey Results on Trialing

Physician attitudes about trialing were assessed by a multinational survey of implanting doctors. The results are provided in this appendix.

In May 2011, the PACC sent three detailed surveys on IT infusion use, safety, and reimbursement to more than 15,000 physicians and clinicians in the United States and internationally. Approximately 55% of respondents were licensed anesthesiologists, 8% were physical medicine and rehabilitation physicians, and 7% were neurosurgeons. The largest category of respondents (47.5%) were in private practice, 11% worked in private hospital systems, and 18% were in academic institutions. More than 55% of respondents had been working in pain management for longer than ten years, with 75% of respondents dedicating at least 75% of their time to pain management in patient populations evenly distributed between neuropathic and nociceptive pain pathologies.

With respect to trialing in patients with nonmalignant pain, preference was greater for continuous infusion trials (45%) than for single-shot (28%) or externalized trials (10%). For trialing patients with malignant pain, 35% of respondents preferred continuous infusion trials, 28% preferred single-shot trials, 10% preferred externalized trials, and 10% of respondents indicated that they do not perform a trial in patients with malignant pain.

Many respondents (40%) indicated that they significantly reduced oral and systemic opioids during an IT therapy continuous infusion trial, whereas 22% indicated that oral and systemic opioids were discontinued entirely. Only 15% of respondents indicated that patients were weaned off all oral and systemic opiates immediately or up to two weeks before a trial. However, 33% of respondents indicated that dosages of oral and systemic opiates were unchanged before a trial.

With respect to continuous flow vs. bolus dosing, 70% of respondents indicated that they used bolus dosing capability via either a programming option, patient-controlled analgesia, or a personal therapy management system. Interestingly, however, the therapy most often programmed for bolus dosing was morphine (51%); less than 1% of respondents indicated that they would program ziconotide for a bolus dose. Patients with cancer pain were most often identified as the population for whom bolus dosing would be prescribed (40%). It was also noted that bolus dosing needed to be used with extreme caution in elderly patients.

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COMMENTS

The purpose of the trial is to predict as accurately as possible the long-term effectiveness of a device before its definitive implantation. It should therefore mimic closely the conditions of an intrathecal infusion as provided by an implanted pump. However, no single method described in the literature, either continuous infusion or bolus injection into the epidural or intrathecal space meets all the criteria of an ideal trial. Currently, the trial addresses only the pharmacodynamic part of the problem, namely whether the tested drug is effective for the pain condition presented by the patient and the side effects are tolerable. Pharmacokinetic questions remain unanswered such as drug distribution in the intrathecal space during slow infusion. Yet the failures encountered in intrathecal therapies are more frequently pharmacokinetic than pharmacodynamic failures (1,2).

Since no method can be considered superior in predicting the long-term failures, the trial should remain safe, cheap, and convenient for the patient and the physician and the risks it may cause should not exceed the uncertain benefits it provides. Indeed its efficacy has not been demonstrated so far by randomized placebo-controlled studies and long-term failures in the literature range up to 39%, regardless of the trialing method used (3). Many of the publications on intrathecal trials are either anecdotal, case series or case reports and do not involve RCT's. This present report provides an objective and complete summary of the current literature but the quality of the studies are inconstant with important methodological problems: studied populations are heterogeneous, suffering from different types of pain, tested with non standardized procedures and measured with different outcomes. Moreover, many data are missing, making the results of a systematic review inconclusive. The realization of randomized controlled trials with standardized outcomes is therefore mandatory to determine the usefulness of a trial. Defining a successful trial is also required. Still, it may be difficult to predict definitely the long-term efficacy of a therapy for a more or less rapidly progressive disease.

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Intrathecal therapy is a viable option for patients with nonmalignant and malignant pain alike. Keys to success center on diligent patient selection and safe trailing practices. The Polyanalgesic Consensus Panel's recommendations for intrathecal trailing for chronic neuroaxial infusion has established a patient centric approach to mitigate patient morbidity and mortality and improve implantable device outcomes.

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

