Clinical Uses of Intrathecal Therapy and Its Placement in the Pain Care Algorithm

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Abstract: Intrathecal drug delivery is an effective treatment option for patients with severe chronic pain who have not obtained adequate analgesia from more conservative therapies (eg, physical therapy, systemic opioids, nonsteroidal anti-inflammatory drugs, antidepressants, and anticonvulsants). This review focuses on, but is not limited to, the 2 agents currently approved by the U.S. Food and Drug Administration for intrathecal analgesia: preservative-free morphine and ziconotide (a nonopioid, selective N-type calcium channel blocker). We describe the appropriate use of intrathecal therapy in the management of severe chronic pain, based on current best practices. Topics addressed here include patient selection, trialing, dosing and titration, adverse event profiles, long-term management, intrathecal therapy for cancer-related pain, and the placement of intrathecal therapy in the pain care algorithm. In appropriately selected patients with chronic pain, intrathecal therapy can provide substantial pain relief with improved functioning and quality of life. Successful long-term management requires ongoing patient monitoring for changes in efficacy and the occurrence of adverse events, with subsequent changes in intrathecal dosing and titration, the addition of adjuvant intrathecal agents, and the use of concomitant oral medications to address side effects, as needed. Based on an infrequent but clinically concerning risk of overdose, granuloma, and other opioid-induced complications, nonopioid therapy with ziconotide may be preferred as a first-line intrathecal therapy in patients without a history of psychosis or allergy.

Key Words: intrathecal analgesia, chronic pain, nociceptive, neuropathic, mixed pain, cancer pain, refractory pain, algorithm, review

INTRODUCTION

Chronic pain affects at least 100 million adults in the United States, with associated annual economic costs of $560 to $635 billion, and is a leading cause of disability worldwide.1,2 Often, chronic pain is a complex, multifaceted medical condition affecting individuals not only physiologically, but mentally, emotionally, and interpersonally as well.3 Refractory pain has been defined as pain for which standard biomedical therapies (eg, physical therapy, systemic opioids, nonsteroidal anti-inflammatory drugs, antidepressants, and anticonvulsants) have proved inadequate and for which more advanced interventions (eg, spinal cord stimulation [SCS] and intrathecal [IT] therapies) may be indicated.4,5
Recently, the definition of “refractory” has been revisited to provide patients with improved pain management by moving advanced pain care therapies away from efforts of last resort. Deer et al. “propose the following definition of refractory pain for clinical use in evaluating whether a patient is an appropriate candidate for advanced pain management interventions, such as an implanted pain control device. Pain is defined as refractory, regardless of etiology, when (1) multiple evidence-based biomedical therapies used in a clinically appropriate and acceptable fashion have failed to reach treatment goals that may include adequate pain reduction and/or improvement in daily functioning or have resulted in intolerable adverse effects, and when (2) psychiatric disorders and psychosocial factors that could influence pain outcomes have been assessed and appropriately addressed.”

Intrathecal drug delivery is a strategy for pain control by which analgesic medication is delivered directly into the IT space, which allows direct access to spinal receptors and ion channels. Both chronic IT therapy and systemic opioid therapy have inherent risks and should be thoroughly compared in the context of individual patient characteristics. The long-term use of high-dose oral opioids is associated with notable risk (eg, overdose, fractures, addiction, intestinal blockages, and sedation) and should be limited to rare cases. Intrathecal therapy provides a viable method for reducing or eliminating oral opioids, thereby avoiding their well-known systemic side effects.

Advanced interventional IT and SCS therapies have demonstrated efficacy for providing pain relief to patients with chronic pain who have not responded to more conservative therapies. Robust evidence to guide treatment selection is currently lacking. As more novel SCS waveform options and more targeted neuromodulation strategies emerge, treatment selection will become increasingly complex. In an environment with so many advanced pain care modalities—including continuous IT infusion, IT bolus dosing/flex dosing/microdosing, opioid and nonopioid IT agents, traditional SCS therapy, dorsal root ganglion stimulation, and advanced waveform SCS—clinicians will need evidence-based guidance on how to choose among them. The SAFE principles (safety, appropriateness, fiscal neutrality, and efficacy) have been proposed as a model for evaluating the placement of interventional implantable technologies such as SCS and IT drug delivery in the pain care algorithm. This review is focused on the use of IT therapy for pain management; reviews of SCS are available elsewhere.

The Polyanalgesic Consensus Conference (PACC) convened a panel of experts to review the literature and provide recommendations regarding many aspects of IT therapy for pain management, including patient selection, trialing, selection of IT agents, and risk reduction. Using these recommendations and case-based examples, this review will summarize how IT therapy can be used successfully to treat patients with chronic pain. The therapeutic approach outlined here is based on the published literature and also our best practices in providing advanced pain care. This review will focus primarily on the 2 agents currently approved by the U.S. Food and Drug Administration (FDA) for IT analgesia: morphine (Infumorph®; West-Ward Pharmaceutical Corp., Eatontown, NJ, U.S.A.) and ziconotide (Prialt®; Jazz Pharmaceuticals, Palo Alto, CA, U.S.A.), a nonopioid, selective N-type calcium channel blocker.

**CASE PRESENTATION**

Nearly 8 years ago, a 59-year-old woman with a history of previous discectomy and 2-level fusion at L3–4 and L4–5 presented to a pain clinician with poorly controlled axial and bilateral lower extremity pain. She had pain that was progressive and predictively worsened when lying supine, standing, and walking. She had trialed and failed controlled diagnostic facetogenic interventions and epidural steroid injections performed under fluoroscopy. Her systemic regimen of medication included methadone 10 mg 3 times a day, duloxetine 20 mg once daily, and hydrocodone/acetaminophen 10 mg/325 mg 4 times a day as needed. She reported that aqua-therapy was helpful while in the pool, and she developed erythema ab igne on her back from extensive exposure to her heating pad. She reported that in the past she had spinal cord stimulation trialed by 1 provider and implanted by another, with mixed results. The device was subsequently explanted 3 years ago.

After discussions regarding therapies for advanced pain care, she was trialed with IT therapy with ziconotide, using a bolus, dual-trialing strategy (2 mcg in 1 mL) at T12–L1 or L1–L2, under fluoroscopy and as described in a recent publication. After the trials, she received 75% and 85% relief for 9 and 13 consecutive hours, respectively. She underwent placement of an IT drug delivery device, employing a nocturnal flex dosing strategy of low-dose continuous infusion (0.24 mcg/day) and a 2 mcg bolus dose at 11:00 PM, with a
concentration of 5 mcg/mL, yielding a total daily dose of 2.3000 mcg/day. The lowest available volume delivered continuously to allow for additional programming of the SynchroMed II pump is 0.048 mL/day. Titration of 0.1 mcg of the bolus dose was performed in serial weeks to a dose of 2.6002 mcg/day, and has been stable as IT monotherapy for nearly 7 months. She has reduced her systemic oral medications to ibuprofen as needed.

**PATIENT SELECTION**

Patients who present to pain specialists have typically received treatment by 1 or more physicians and have had several pharmacologic and nonpharmacologic therapies fail. Among advanced pain care modalities, IT therapy is often considered when SCS fails to provide adequate analgesia, but it is also appropriate as an alternative to SCS in select patients (eg, patients with non-neuropathic pain or diffuse cancer-related pain). Proper screening and patient selection are paramount and increase the likelihood of success with IT therapy, although no trialing strategy demonstrates high predictive values of success during or after the conversion to chronic IT drug delivery.\(^{23,24}\) First, it is important to confirm that the patient’s diagnosis is correct and that there is a clear etiology of pain indicating the appropriateness of IT therapy. IT therapy has been used successfully to treat a wide array of pain etiologies, with efficacy demonstrated in clinical studies of pain classified as nociceptive, neuropathic, or mixed, and for both cancer-related and non-cancer-related pain.\(^{3,14,25–30}\) Whereas the classic teaching has been to use ziconotide in the treatment of neuropathic pain, peer-reviewed literature has demonstrated efficacy for ziconotide in the treatment of nociceptive pain, positioning it, along with IT opioids, as a first-line choice for both types of pain. This opinion was reflected in the PACC guidelines in 2012.\(^{14,31}\)

As in the case presentation, consideration of patients as strong candidates for an IT approach depends on the potential to provide regional coverage with IT delivery of medicine at active sites in the spinal cord and the indwelling receptors. On the other hand, patients with general, non-cancer-related, whole-body pain are considered as less appropriate candidates for IT therapy in most settings. Characteristics of patients with non-cancer-related pain who are suitable candidates for IT therapy, along with related contraindications and concerns, are summarized in Table 1.

A clinical concern in selecting appropriate patients for IT therapy is the ability to place the IT catheter in a location that will deliver the infusion to an anatomically appropriate site. The oscillatory movement of cerebrospinal fluid (CSF), with locomotives of cardiac and pulmonary origin,\(^{32,33}\) produces limited net movement of the CSF and thereby restricts the rostral spread of drugs administered intrathecally.\(^{34–37}\) Consequently, administering the IT infusion at a spinal level that corresponds to the primary location of pain origin may enhance analgesic efficacy, although some variability exists based on the lipophilic nature of the infused medication.

In addition, it is important to obtain a psychological assessment as part of the patient evaluation process for any implantable therapy, with only rare exceptions (ie, cancer patients with limited life expectancy), to determine the patient’s ability to understand and comply with the requirements of IT therapy, as well as to identify potential contraindications to intrathecal drug delivery system (IDDS) implantation or exposure to specific IT agents. Psychiatric conditions—particularly anxiety and depressive disorders—are common in patients with chronic pain\(^{38–43}\) and often require ongoing treatment. Psychological assessment should also evaluate for personality disorders and cognitive functioning\(^3\) to identify issues that may interfere with the success of IT therapy. It

| Table 1. Characteristics of Good Potential Candidates for Intrathecal Therapy and Concerns or Contraindications |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **IT Therapy Type** | **Characteristics of Good Potential Candidates** | **Concerns/Contraindications** |
| General | Nociceptive or neuropathic pain | Widespread pain |
| | Cancer-related or non-cancer-related etiology | Headaches, facial pain |
| | Clear diagnosis, well-localized pain | Inability to place catheter near site of pain origin |
| | | Ischemic heart disease, heart failure, or cerebrovascular disease |
| | | Inadequate caregiver support, transportation to appointments |
| | | Cancer with life expectancy < 3 mo |
| | | Refractory to systemic opioids |
| Morphine | Responsive to systemic opioids | Substance abuse |
| | | Pulmonary disease |
| | | Obstructive sleep apnea |
| | | History of psychosis |
| Ziconotide | Neuropathic pain | |
| | Visceral pain | |
| | Complex regional pain syndrome | |
| | Concerns related to opioid use | |

IT, intrathecal.
is important that psychiatric disorders and psychosocial factors be addressed before trialing and concurrently during IT therapy when indicated. Ziconotide deserves special mention in considering psychological comorbidity because it is contraindicated in patients with a preexisting history of psychosis. Intrathecal opioids may still have a role in pain management for such patients. Other issues to be considered include smoking status and poor nutrition (due to the potential issues around wound healing) and the patient’s social situation (eg, adequate autonomy, caregiver support, and available transportation for follow-up appointments).

**SELECTING INTRATHECAL AGENTS**

Currently, the only FDA-labeled agents for IT analgesia are morphine and ziconotide. In patients who do not respond to these agents, it is acceptable to use off-label medications. Based on analysis of safety and efficacy, other recommended first-line IT agents in the PACC guidelines are morphine plus bupivacaine for neuropathic pain, and hydromorphone or fentanyl for nociceptive pain.

It is important to evaluate the patient’s experience with systemic opioids, including the development of tolerance, side effects, presentation of opioid-induced sequelae, or opioid-induced hyperalgesia. Changing the route of morphine administration from systemic to IT is essentially a dose escalation, because the potency of the medication is dramatically enhanced by IT delivery. Therefore, we consider patients in whom high-dose systemic opioid medications have failed to provide adequate pain relief to be less suitable candidates for IT opioid therapy; instead, we would initiate IT therapy with ziconotide for these patients. For example, for a patient with active cancer progression who does not respond to rapid escalation of systemic opioid therapy, IT therapy with ziconotide rather than an opioid should be considered first line.

Other medical conditions that may lead the clinician to carefully evaluate IT opioids include peripheral edema, uncontrolled central or obstructive sleep apnea, pulmonary disease, and hormonal imbalances. In addition, nonopioid therapy may be preferred for younger patients (18 to 50 years) because of the potential for dose escalation of the monotherapy IT opioid throughout the lifetime of the therapy, and for older patients (> 65 years) because of the increased risk of negative consequences from adverse events, particularly respiratory depression.

The possibility of an overdose (from a pump malfunction, dosing, or administration error) is a serious concern with IT opioids, due to the risk for potentially fatal respiratory depression. Particular care is warranted when first initiating IT opioid therapy and when restarting IT opioids after an interruption in therapy. When reducing the dose or discontinuing IT opioid therapy, it is important to monitor for and address symptoms of opioid withdrawal. Device-related complications that reduce or obstruct the IT flow may also precipitate withdrawal symptoms. It is suggested that the clinician consider a catheter evaluation when taking over the management of an existing pump if the patient is having a less than optimal result, although the risk vs. benefit should be considered.

The following medical conditions have been observed in patients receiving IT ziconotide: cognitive and neuropsychiatric adverse reactions, meningitis and other infections, reduced level of consciousness, and elevation of serum creatine kinase. As described previously, a history of psychosis is a contraindication to ziconotide use, which highlights the importance of a partnership with a psychiatrist or psychologist to evaluate candidates for advanced pain care therapies. Further, morphine may be an excellent choice for patients with a history of psychosis if they meet other selection criteria.

Ziconotide may be appropriate for patients with moderate to severe nociceptive and/or neuropathic pain, especially those with severe refractory neuropathic pain, complex regional pain syndromes, and certain refractory visceral pain states. In addition, patients who are not ideal candidates for IT opioid therapy due to factors such as poor systemic opioid response, obstructive sleep apnea, pulmonary disease, or history of catheter-tip granuloma may benefit from IT ziconotide (Table 1). Interestingly, data from an interim analysis of the ongoing, prospective Patient Registry of Intrathecal Ziconotide Management (PRIZM) study suggested better treatment response with first-line use of IT ziconotide compared to use of ziconotide after prior IT therapy. A retrospective study of patients who received IT opioid therapy found that coadministration of IT bupivacaine during the initial titration of IT opioids reduced IT opioid dose escalation during the first year after implant. Efficacy implications of the initial IT medication selection suggest the need for a thoughtful trialing strategy.
TRIALING

The primary objective of trialing is to identify patients who are likely to benefit from IT therapy. However, the literature on trialing is limited and the predictive validity of trialing has not been established in randomized studies. Nonetheless, a successful trial may be required by insurance payers before implanting an IT device.

The mechanics of trialing and the philosophy behind it are heavily debated. Issues related to the use of a bolus IT trialing procedure for predicting response to long-term continuous IT infusion is central to this discussion. Although some clinicians suggest that trialing lacks clinical utility, as there is poor translatable evidence of successful conversions to chronic IT therapy with any trialing method, employing a trial may ultimately improve patient success and outcomes and may provide some important clinical insights. First, the trial offers an initial indication of the efficacy of IT therapy, and as chronic IT dosing strategies begin to mimic trialing methods, the gap may lessen. Setting appropriate patient expectations regarding quantifiable goals for pain reduction and/or improved functioning is helpful for obtaining clinically useful information from trialing. Second, the trial can identify problematic adverse events from the chosen IT agent. Third, trialing affords another important opportunity for psychological assessment of patient response to the IT route of administration. In cancer patients with limited life expectancy, after careful consideration of psychological/spiritual status, disease progression, pain etiology (eg, tumor mass effect, visceral, bone pain), and response to other strategies (eg, radiation and/or neurodestructive techniques), some clinicians forego trialing and proceed directly to the implantation of an IDDS. A risk–benefit analysis of employing an IT trial and implant in patients on anticoagulant medications is important to reduce the risks associated with a long interruption in therapy. Figure 1 depicts our algorithm for patient selection and trialing.

The debate surrounding trialing extends to the methods employed. Risks and benefits of bolus vs. continuous infusion trialing need to be assessed for each patient. It has become increasingly popular to employ IT bolus trialing methods. Although continuous infusion trialing allows for a longer administration of the agent under consideration and is mechanistically closer to the method by which the drug will ultimately be administered, it has multiple drawbacks, including increased cost, patient burden, and potential infection risks. Because of ziconotide’s relatively longer CSF clearance time and duration of effect relative to morphine, bolus trialing may be particularly appropriate for evaluating the effects of IT ziconotide.

Similar strategies for bolus trialing of IT ziconotide are described in a study by Mohammed et al. and a more recent publication by 2 of our authors (JEP and TRD); success with bolus ziconotide dosing was demonstrated prior to IDDS implant. The difference between the 2 approaches lies more in the strategy for chronic delivery of IT medication than in the trialing methods. Bolus delivery, or weighted delivery, may ultimately prove to be more efficacious and sustainable for IT ziconotide than continuous delivery. During bolus IT trialing, the patient is placed in the prone position under sterile conditions, using fluoroscopy to confirm needle or catheter position, and thoracic and lumbar myelogram to detect filling defects. A bolus injection is administered with barbotage into the IT space in the lumbar spine. The required number of single shot boluses is based on physician judgment. In some settings, a single bolus may be appropriate; in those settings in which more than 1 bolus is administered, we recommend a separation of ≥72 hours, with escalating medication doses as needed to evaluate efficacy. The therapeutic target is a demonstration of analgesic efficacy with minimal to no reported adverse events or side effects in 1 or more trials. Pain reduction >70% to 80% on a Visual Analog Scale and/or ≥4 points on an 11-point Numeric Pain Rating Scale (NPRS) are deemed promising indicators of efficacy. One of our authors (SF) uses and encourages IT bolus trialing, but also works in a multidisciplinary team with physicians who trial with continuous infusion. It is the authors’ opinion that bolus trialing provides information similar to what is gleaned from continuous trialing, but with less overall cost, decreased patient burden, and less risk (particularly a lower risk of infection). Randomized controlled trials are needed to confirm this assessment.

The initial dose for a trial of IT morphine is based on the patient’s current systemic opioid dose, reduced to account for the change in route of administration. The PACC recommendations comprise a wide dose range for a bolus morphine trial (0.2 to 1.0 mg) (Table 2). For IT opioid-naïve patients, dosing should be conservative (near 0.1 to 0.2 mg). Typically, we do not wean patients off systemic opioids before an IT morphine trial, and the oral opioid dose remains unchanged until IT pump implantation. Adequate monitoring of patient safety is
an important aspect of IT morphine trialing, and we typically employ a 23-hour outpatient observation period, consistent with the PACC guidelines. Some clinicians contend that trialing at the opioid doses described is very unlikely to contribute to opioid overdose and do not recommend the 23-hour observation period, referencing a study by Coffey et al. as justification. Inspection of the Coffey et al. data indicates that much larger opioid doses had been used when overdose resulted in mortal events. We recommend the clinician consider the patient’s medical and opioid history when making these critical decisions.

Cardiopulmonary monitoring requirements are less vital when trialing IT ziconotide, because of the low risk of cardiac, pulmonary, or respiratory complications. We consider weaning of systemic opioids to be optional before trialing IT ziconotide. Discharge after a single injection may be reasonable within 6 to 12 hours if no adverse events are reported.

**INITIATING INTRATHECAL THERAPY**

For patients with a successful IT trial, practical considerations must be addressed before IDDS implantation. First, there are pragmatic issues with regard to insurance coverage and other financing of the IDDS and the medications. In addition, successful IT therapy necessitates preventing and managing procedural and device-related issues including infection risk, pocket fills, programming errors, and device malfunction.

Studies on drug distribution in the CSF suggest that the catheter tip should be placed in close proximity to the suspected site of pain origin if clinically appropriate and known with certainty. Every effort should be made to position the IT catheter tip near the primary pain generator, although achieving this goal may be limited by the patient’s spinal anatomy and pathology.

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**Figure 1.** Patient selection and trialing algorithm for intrathecal therapy. Solid arrows: yes or desired outcome achieved. Dashed arrows: no or failure. AE, adverse event; IDDS, intrathecal drug delivery; IT, intrathecal; PNfS, peripheral nerve field stimulation; PNS, peripheral nerve stimulation; PTM, Personal Therapy Manager; SCS, spinal cord stimulation. Reprinted with permission from Pope and Deer.
The recommended starting dose of IT morphine continuous infusion is 0.1 to 1.0 mg/day in patients without tolerance to opioids and variable dosing in those with a tolerance to high doses of oral agents. There is unquestionably a direct relationship between the starting dose of morphine and the incidence of severe side effects. In chronic infusions, the maximum dose of IT morphine recommended in the PACC guidelines is 15 mg/day (Table 2). It is useful with ziconotide to initiate IT therapy at low doses and titrate upward slowly to achieve sufficient efficacy and tolerability, as higher starting doses and rapid titration of IT ziconotide are associated with treatment-limiting adverse effects. The ziconotide prescribing information states that the starting dose should be no more than 2.4 µg/day, with upward titration of no more than 2.4 µg/day at intervals of no more than 2 to 3 times per week. However, experienced pain medicine practitioners and clinical investigators have recommended a lower dosing and titration protocol for ziconotide. We adhere to the recommendation of a low starting dose and slow titration for ziconotide with some variation among our standard procedures, with an initial continuous infusion of IT ziconotide ranging from 0.5 to 1.2 µg/day and upward titration of 0.2 to 1.0 µg/week in patients with non-cancer pain (for dosing/titration in patients with cancer pain, see the section on “Intrathecal Therapy for Pain Related to Cancer” below). Preclinical data suggest that bolus administration may provide more widespread drug distribution in the CSF and spinal cord relative to slow IT infusion. A combination dosing option is to administer low-dose infusion throughout the day, with potential flex bolus dosing at night to improve efficacy and tolerability.

Patient-controlled administration of IT medications is available via the Medtronic Personal Therapy Manager (PTM) accessory to the SynchroMed II Infusion System, with another patient-controlled bolus strategy via the Prometra II system (Flowonix, Mt. Olive, NJ, U.S.A.) recently approved by the FDA. The PTM has been used for delivery of IT morphine and IT ziconotide in patients with chronic pain, although ziconotide is not approved for use with PTM, and the manufacturer of the SynchroMed pump indicates that PTM administration of ziconotide is contraindicated because ziconotide has a defined titration scheme. If PTM administration of IT ziconotide is to be used in conjunction with a continuous infusion, it is important to first titrate to a stable infusion dose of ziconotide and then calculate the bolus dose and dosing interval for the PTM. There are projects underway to look specifically at bolus-only IT therapy and patient-controlled delivery without continuous infusion.

**LONG-TERM INTRATHECAL THERAPY**

Long-term maintenance of efficacy and safety is an important consideration during IT therapy yet the research literature provides limited evidence regarding optimal long-term management. Options for managing inadequate efficacy of IT therapy during long-term treatment include dose escalation, altering the dosing schedule, opioid rotation, and combination IT therapy. Dose escalation is typically the first strategy in patients with insufficient pain reduction after the initial titration of IT therapy (Figure 2), with consideration of the propensity for rapid escalation to result in granuloma formation (for opioid medications) or device integrity failure. The upper limits of IT dose escalation are determined by medication safety and tolerability. The PACC guidelines recommend a maximum daily dose of 15 mg IT morphine and 19.2 µg IT ziconotide (Table 2). If there is no analgesic efficacy after successive dose escalation of IT opioids approaching 50% of the PACC maximum limit or after ziconotide titration to a dose of ≥ 6 µg/day, the provider should evaluate the integrity of the catheter/device.

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**Table 2. Polyanalgesic Consensus Conference Dosing Recommendations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>IT Bolus Trialing Dose</th>
<th>Starting dosage</th>
<th>Maximum Concentration</th>
<th>Maximum dose per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.2 to 1.0 mg</td>
<td>0.1 to 0.5 mg/day</td>
<td>20 mg/mL</td>
<td>15 mg</td>
</tr>
<tr>
<td>Ziconotide</td>
<td>1 to 5 µg</td>
<td>0.5 to 2.4 µg/day</td>
<td>100 µg/mL</td>
<td>19.2 µg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.04 to 0.2 mg</td>
<td>0.02 to 0.5 mg/day</td>
<td>15 mg/mL</td>
<td>10 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25 to 75 µg</td>
<td>25 to 75 µg/day</td>
<td>10 mg/mL</td>
<td>No known upper limit</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.5 to 2.5 mg</td>
<td>1 to 4 mg/day</td>
<td>30 mg/mL</td>
<td>10 mg</td>
</tr>
<tr>
<td>Clonidine</td>
<td>5 to 20 µg</td>
<td>40 to 100 µg/day</td>
<td>1,000 µg/mL</td>
<td>40 to 600 µg</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>5 to 20 µg</td>
<td>10 to 20 µg/day</td>
<td>5 mg/mL</td>
<td>No known upper limit</td>
</tr>
</tbody>
</table>

IT, intrathecal. Adapted with permission from Deer et al.
As an alternative to dose escalation, changing to another IT agent with a different mechanism of action, adding adjuvant therapy, or switching medication within the class should be considered. The use of combination IT therapy has been evaluated primarily in small, uncontrolled studies that support the efficacy of IT therapy with ziconotide and morphine,74–77 morphine (or other opioids) and bupivacaine,54,78,79 and morphine and clonidine.80 Numerous other IT combinations are used in clinical practice,81,82 some of which are recommended by the PACC guidelines for nociceptive, neuropathic pain, or both as Tier 2 and below.14 Careful selection of a compounding pharmacy helps to ensure the safe preparation of admixtures using aseptic procedures.3 In addition, the stability of the compound admixtures is important, as IT ziconotide stability is reduced in some combination IT solutions, which may alter the pump refill interval.83–90

Effective long-term IT therapy requires ongoing management of side effects. IT morphine may cause respiratory depression, IT granuloma, peripheral edema, hypogonadism, and opioid tolerance.14,47,58,91–94 Some adverse events may develop during the course of long-term therapy,92,94,95 which highlight the importance of ongoing monitoring for signs and symptoms. Monitoring for catheter-tip granulomas promotes early detection and may allow noninvasive remediation (eg, removal or replacement of the catheter, change to nonopioid medication); however, surgical removal is necessary in very rare cases.58,96–99 Adverse events of concern with IT ziconotide include central nervous system (CNS)-related effects such as dizziness, confusion, somnolence, memory impairment, and psychosis, as well as nausea and urinary retention.59–61 Concomitant or recent use of antidepressants, anticonvulsants, or other medications with CNS-depressant effects is common in patients receiving IT therapy, and may worsen the CNS-related adverse reactions to IT ziconotide.18 Further, monitoring of creatine kinase (CK) levels is recommended in patients receiving ziconotide, although elevations of 2 to 3 times the upper limit of normal have been reported without incident. Symptoms and signs such as cramping or high serum CK levels may warrant dose reduction or discontinuation of ziconotide. If a reduction in dose leads to a normalization of CK levels and the pain control is maintained, it is acceptable to continue monotherapy ziconotide.

Routine patient monitoring for adverse events is of paramount importance, along with a commitment to adjusting dosing and titration schedules on a patient-specific basis until an acceptable balance is achieved between efficacy and tolerability. Assuming that IT therapy has provided some degree of pain relief, opioid-related adverse events may be mitigated by a 10% dose reduction or a 20% reduction along with the addition of IT bupivacaine. Another option is to employ nocturnal flex dosing (in addition to low-dose continuous infusion) to manage adverse effects such as opioid-associated gastrointestinal or genitourinary symptoms. The management of ziconotide-related adverse events depends upon their severity. For mild adverse events, we typically stop upward dose titration until the adverse events resolve. For symptoms such as ataxia, memory impairment, dizziness, and nausea, the ziconotide dose is typically reduced by 10% to 20% with a reassessment after 5 days. For severe neuropsychiatric adverse events (eg, paranoia or hallucinations), the ziconotide dose may be reduced by 50%, or to a minimal infusion rate, with slower upward titration after the adverse events resolve. The use of concomitant medications to manage...
adverse effects of IT therapy (eg, nausea, urinary retention, or opioid-induced constipation) is summarized in detail elsewhere \(^5\),\(^8\),\(^1,\(^0\),\(^0\); concomitant medications targeting specific symptoms (eg, bethanechol for urinary retention or hydroxyzine for pruritus) are used in conjunction with dosing or titration adjustments, particularly in patients for whom dose reduction results in decreased pain relief. Antipsychotic agents may be used to treat adverse psychiatric effects of ziconotide, although this approach is not based on empirical data. When it is necessary to switch to an IT agent with a different mechanism of action, clinicians should be alert to the possibility of withdrawal symptoms, which may occur during dose reduction or discontinuation of IT morphine but are not observed with IT ziconotide.

**INTRATHECAL THERAPY FOR PAIN RELATED TO CANCER**

Pain related to cancer encompasses many different clinical situations, including patients confronting end-of-life issues, those with chronic cancer pain (eg, from a slow growing tumor or bone metastasis), chronic treatment-related pain (such as that due to surgery or chemotherapy), or chronic pain unrelated to cancer treatment or disease burden (eg, low back pain due to degenerative disk disease).\(^1\)\(^0\) The treatment algorithm for each of these patient groups is different, some being more aggressive than others. IT therapy can provide significant benefit to patients with pain related to cancer,\(^2\)\(^8\),\(^1,\(^0\),\(^2\)\(^3\) and there is no robust evidence to suggest that certain types of cancer-related pain are more amenable to IT therapy than others.\(^2\)\(^5\) Intrathecal therapy is effective in patients undergoing chemotherapy or radiation\(^1\)\(^3\); however, low white blood cell count (\(\leq 2 \times 10^9/L\)) and low absolute neutrophil count (\(\leq 1,000/\mu L\)) may be contraindications for IT device implantation\(^1\)\(^0\) and warrant consultation with the patient’s oncologist.\(^2\)\(^5\) If IDDS therapy is appropriate, the device should be placed outside the radiation field.\(^2\)\(^5\) The presence of epidural metastases tends to reduce the efficacy and increase the risk of complications with IT therapy.\(^2\)\(^5\)

Psychological evaluations to assess the suitability of an IT device are considered optional in cancer patients with limited life expectancy, although psychotherapy might be helpful for addressing end-of-life issues. In the interest of more rapidly providing pain relief to patients with cancer and because of the reduced need for treatment sustainability in patients with limited life expectancy, physicians may consider bypassing an IT trial.\(^1\)\(^5\),\(^2\)\(^5\)

The IT therapy starting dose and titration schedule depend on disease progression. If the disease is rapidly progressive, moving quickly through the tiers of the PACC guidelines with more rapid dose escalation and/or earlier consideration of combination IT therapy may be necessary to provide adequate pain control. However, a slow-titration protocol using IT ziconotide has also been used successfully in treating patients with refractory cancer pain.\(^1\)\(^0\) Patient-controlled supplemental doses of IT opioids may also be useful for managing cancer pain. A prospective observational study found that combination IT therapy with ziconotide and morphine was an effective treatment option for patients with refractory cancer pain.\(^1\)\(^0\)\(^5\) If the disease is in chronic remission, dosing and titration should follow chronic pain guidelines. As cancer survivorship increases, more patients are making the transition from cancer-related pain to non-cancer-related pain and oftentimes require treatment bridging.

Although we acknowledge that prognostication is difficult, cancer patients with a life expectancy of at least 3 to 6 months are considered as candidates for IDDS implantation, and we do not place external infusion delivery devices. Data suggest that life expectancy may be increased in patients with cancer who receive IT therapy compared with those who receive non-IT comprehensive medical management (Figure 3).\(^1\)\(^0\)\(^3\) In terminally ill patients, the available resources of local hospice programs may affect the decision to initiate IT therapy.

**PLACEMENT OF INTRATHECAL THERAPY IN THE PAIN CARE ALGORITHM**

Historically, IT therapy was thought of as salvage therapy. However, with improved IT management strategies and appropriate patient selection, this is no longer the case, and placement of IT therapy within the treatment algorithm for chronic pain continues to evolve.\(^2\)\(^4\) Based on the available research, it appears that the use of IT medications follows the principles of safety, appropriateness, fiscal neutrality, and efficacy.

The number and type of therapies that should be undertaken before considering IT therapy vary based on pain etiology, pain distribution, patient characteristics, and patient entry within the pain care algorithm. Advocacy for placement of advanced therapies within 2 years of pain onset is based on improved outcomes...
and greater cost effectiveness compared to conventional medical management after 2 to 2.5 years of SCS and greater cost effectiveness 22 to 28 months after implant for IT therapy.12,106–110 We support earlier placement of advanced techniques in the treatment algorithm for several reasons: poor tolerability to systemic opioids, poor control of neuropathic pain by opioids, the known benefits of earlier intervention with advanced therapies, and the known risks with little benefit acquired from increased systemic opioid use. With proper patient selection it has been established that there are significantly higher success rates with interventional pain therapies, with lower use of opioids.108

Therapeutic options in SCS continue to progress, and newer techniques, including high frequency, burst, and dorsal root ganglion stimulation, show promising efficacy.111–117 With the advent of changing technology and waveform strategies, SCS is an evolving treatment paradigm. It is important to recognize that IT therapy candidates and traditional SCS candidates are not always one and the same, and fewer overlaps will be appreciated. Specifically, we most often use SCS in patients with regional neuropathic pain of either cancer-related or non-cancer-related origin. We generally do not use SCS for patients with non-neuropathic pain or widespread cancer pain (ie, bone pain, axial spine pain, visceral pain), but instead consider IT therapy for these patients. Intrathecal ziconotide may be an alternative to SCS for select patients, and may also prove to be helpful in those for whom SCS failed.21

As shown in Figure 1 and Table 1, we consider using IDDS in selected patients with chronic pain classified as neuropathic, nociceptive, or mixed, and of cancer-related or non-cancer-related etiology. For patients with neuropathic pain, implantation of an SCS device is an alternative to IDDS. In clinical practice, we employ both techniques and do not require a failure of SCS before initiating IT therapy. We increasingly use ziconotide as first-line IT therapy in patients without a history of psychosis, because we have found that IT ziconotide provides effective pain relief with less overall risk than IT opioids and with no development of tolerance. The use of ziconotide as first-line IT therapy is supported by the results from an interim analysis of the ongoing Patient Registry of Intrathecal Ziconotide Management (PRIZM), which indicated that adult patients with severe chronic pain who initiated ziconotide as their first IT therapy exhibited a larger treatment response than patients who had received prior IT medications.53 Successful long-term therapy with ziconotide requires addressing issues related to its narrow therapeutic index and putative problems with sustainability. With routine patient monitoring for changes in efficacy and adverse events and adjustment of ziconotide dosing and titration schedules—particularly the use of nocturnal flex dosing—effective long-term pain control may be possible. More studies are needed on this subject.

**CONCLUSION**

Intrathecal therapy is a valuable option for the management of severe chronic pain and can be used successfully in a wide range of patients. Optimizing the use of IT therapy with regard to patient selection, trialing, treatment initiation, and long-term management is vital in patient success.

**DISCLOSURES**

Dr. Pope has served as a consultant for Medtronic, St Jude Medical, Jazz Pharmaceuticals, Mallinckrodt Pharmaceuticals, and Flowonix. Dr. Deer has served as a consultant for Axonics, Bioness, St. Jude Medical, Nevro, Flowonix, Jazz Pharmaceuticals, Greatbatch, and Medtronic, and is a minor stock option holder in Axonics and Bioness. Dr. Bruel has served as a consultant for Medtronic, Boston Scientific, and Mallinckrodt and has received research support from
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Note

Flex mode is a programming option of the SynchroMed Programmable Infusion System that permits variation in the continuous infusion rate (eg, by day or time of day) and the administration of bolus doses of IT medication.22

REFERENCES


