

# Intrathecal Ziconotide: Dosing and Administration Strategies in Patients With Refractory Chronic Pain

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**Introduction:** Ziconotide is a non-opioid analgesic for intrathecal (IT) administration. The aim of this review is to provide a comprehensive and clinically relevant summary of the literature on dosing and administration with IT ziconotide in the management of refractory chronic pain, and to describe novel dosing strategies intended to improve clinical outcomes.

**Materials and Methods:** A Medline search was conducted for "ziconotide," supplemented by manual searching of published bibliographies and abstracts from conferences.

**Results:** Early experience with IT ziconotide in clinical trials combined with improved understanding of drug pharmacokinetics in the cerebrospinal fluid have led to a reappraisal of approaches to trialing and initiation of continuous-infusion therapy in an effort to improve tolerability. The traditional paradigm of trialing by inpatient continuous infusion may be shifting toward outpatient trialing by IT bolus, although definitions of success and specific protocols remain to be agreed upon. Expert consensus on IT continuous infusion with ziconotide suggests a starting dose of 0.5 to 1.2 mcg/day followed by dose titration of  $\leq 0.5$  mcg/day on a no more than weekly basis, according to individual patients' pain reductions and regimen tolerability.

**Discussion:** Newer modalities that include patient-controlled analgesia and nocturnal flex dosing have been shown to hold promise of further improvements in ziconotide efficacy and tolerability.

**Conclusions:** Clinical trials and experience confirm the feasibility and usefulness of IT ziconotide in the management of refractory chronic pain. Emerging evidence suggests that additional IT delivery options may further expand the usefulness and benefits of ziconotide.

**Keywords:** Chronic pain, drug delivery, intrathecal, refractory, ziconotide

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## INTRODUCTION

Chronic pain is a complex and multifaceted condition that affects at least 100 million adults in the United States and is a leading cause of disability worldwide (1,2). Refractory chronic pain poses special challenges to clinicians. In the context of evaluation for advanced pain management, Deer et al., in their article "A Definition of Refractory Pain to Help Determine Suitability for Device Implantation" (*Neuromodulation*, 2014, volume 17, page 714), defined pain as refractory "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" (3).

Intrathecal (IT) drug delivery is well-established as an effective treatment for chronic refractory pain (4–6). Clinical evidence shows that IT therapy can provide effective management of pain of cancer-related or noncancer-related etiology, including neuropathic pain and nociceptive pain (5,7,8). Only two pharmacologic agents, morphine and ziconotide, have been approved by the U.S. Food and

Drug Administration (FDA) for IT analgesia to date (7), and ziconotide is the only nonopioid analgesic agent approved for IT therapy in patients with refractory chronic pain (6,9). Specifically, ziconotide is approved for the management of severe chronic pain in patients for whom IT therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive

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therapies, or IT morphine (10). Nonopioid IT analgesia can be particularly useful for addressing unmet clinical needs in patients with refractory chronic pain for whom adverse effects associated with IT opioids, including peripheral edema, hormonal changes, respiratory depression, granuloma formation, opioid tolerance, and opioid-induced hyperalgesia, may be of concern (7,11). In the European Union, ziconotide is approved for the treatment of severe, chronic pain in adults who require IT analgesia (12). With respect to drug delivery, the FDA approved ziconotide for use with the Medtronic SynchroMed® II Infusion System (Minneapolis, MN, USA) or the CADD-Micro® Ambulatory Infusion Pump (Smiths Medical; St. Paul, MN, USA) (10). Ziconotide has also been used with the Prometra® Pump (Flowonix, Mt. Olive, NJ, USA) (13).

The efficacy of IT ziconotide in the treatment of patients with chronic refractory pain of cancer-related and noncancer-related etiology was established in randomized, placebo-controlled trials (14–16). A pooled analysis of these studies showed that ziconotide provided significant pain relief relative to placebo for a number of etiologies, including neuropathic, myelopathic, radiculopathic, and spinal pain, as well as failed back surgery syndrome (17,18). On the strength of these trials in the context of all available clinical evidence for this agent, the 2012 Polyanalgesic Consensus Conference (PACC) guidelines recommend ziconotide as first-line IT therapy for both neuropathic and nociceptive pain (7,9).

Ziconotide is commonly described as having a narrow therapeutic window, and its tolerability profile correlates more closely with the rate of dosage increase than with the actual dose administered (7,9,19,20). Therefore, careful selection of the initial ziconotide dose and titration with smaller increments relative to increments used with other agents are important in providing adequate efficacy while minimizing adverse effects (7,9,19). The aim of this review is to provide a comprehensive and clinically relevant summary of the dosing and administration of IT ziconotide in the management of refractory chronic pain and to describe novel dosing strategies that are intended to improve clinical outcomes.

## METHODS

The Medline database was searched for “ziconotide” in article titles and abstracts written in English (search conducted on April 13, 2015). This search returned 177 articles, of which 78 were identified for further evaluation on the basis of review of article abstracts for information about ziconotide dosing/administration in patients with chronic pain. Bibliographies from those articles were reviewed manually for additional relevant sources. Finally, abstracts from conferences focusing on pain management from 2012 through 2014 were also searched using the term “ziconotide.”

## RESULTS

### Pharmacokinetics of Intrathecal Ziconotide

Familiarity with the pharmacokinetics of ziconotide following IT administration is important to understanding the implications for IT trialing and long-term continuous infusion with this agent. Flow dynamics of the cerebrospinal fluid (CSF) in the spinal column have been described as “heterogeneous” because of the number of influencing factors (4). Traditionally, bulk flow resulting from production of CSF by the choroid plexus and the consequent craniocaudal gradient of hydrostatic pressure were believed to be major drivers of CSF flow dynamics. Research with modern techniques has documented, however, that bulk flow accounts for no more than 1% of

CSF flow dynamics (4). Other forces, including arterial pulsations and respiratory intrathoracic pressures, are recognized as creating pulsatile flow with movement that is oscillatory, bidirectional, and cranio-caudal (4). This pulsatile-flow model suggests that intrathecally administered medications are dispersed within the CSF by oscillatory movement (4,21,22).

Within that context, distribution of an IT drug is further affected by the rate and volume of administration and by the physiochemical properties of the medication (23–25). Patterns of drug distribution in the CSF that are influenced by these factors may be expected to have clinical implications for the efficacy and safety of IT medications (24,25). Notably, ziconotide is a relatively large (25 amino acids with a molecular weight of approximately 2600 Da) hydrophilic peptide that would, therefore, be expected to have a longer time to onset of analgesia and a longer elimination half-life compared with smaller, lipid-soluble agents (10,25).

The pharmacokinetics of IT ziconotide have been explored in animal and clinical studies. Using an animal model with beagle dogs (with chronic IT lumbar injection and CSF sampling catheters), the pharmacokinetics of ziconotide were monitored during and following a single bolus IT injection (10 mcg in 1 mL) and continuous IT infusions (1 mcg/hour and then 5 mcg/hour at 100 mcL/hour, each for 48 hours) (25). After the single 10 mcg bolus dose, lumbar CSF sampling demonstrated an initial peak concentration (3 minutes) and biphasic clearance (0.14 and 1.68 hour, respectively). During chronic IT infusion with ziconotide 1 mcg/hour and 5 mcg/hour over sequential 48-hour intervals, lumbar CSF concentrations peaked by 8 hours, and remained stable at median values of 343 and 1380 ng/mL, respectively, to the end of the infusions. After 48 hours, the lumbar CSF:cisternal CSF:plasma ziconotide concentration ratio was 1:0.017:0.001 for a 1 mcg/hour infusion and 1:0.015:0.003 for a 5 mcg/hour infusion. Terminal elimination half-life after completion of the 5 mcg/hour infusion was 2.47 hours. Overall, the spinal kinetics of ziconotide in this animal model were linear and consistent with expectations for a large, hydrophilic molecule. In addition, the behavioral effects on arousal, muscle tone, and coordination were not altered following bolus IT administration at the dose levels studied, although they were transiently affected with continuous IT infusion.

The CSF pharmacokinetic profile of IT ziconotide and its relationship to ziconotide safety and efficacy were evaluated in a study of 22 adult patients with chronic noncancer-related pain (26). These patients received IT ziconotide at a dose of 1, 5, 7.5, or 10 mcg, with each dose administered as a single 1 mL bolus IT infusion more than 1 hour. The median half-life of ziconotide in CSF was reported as 4.5 hours across all dose groups, and the pharmacokinetics of this agent in CSF were dose proportional and linear across the dose range evaluated (26). In this study, the cumulative exposure to ziconotide in CSF, measured as CSF area under the concentration-time curve, was significantly predictive of pain relief. Findings were consistent with a delay between the administration of IT ziconotide and maximal analgesic response.

The apparent delay between bolus IT administration of ziconotide and its pharmacodynamic effects, particularly the onset and resolution of cognitive/neuropsychiatric adverse events, appears to reflect the slow penetration of this large, hydrophilic molecule to the site of action in the central nervous system (CNS) parenchyma (9,20,25–27). A key clinical implication of the pharmacokinetic/pharmacodynamic profile of ziconotide is that initial titration of the IT ziconotide dose should proceed at a pace that allows for distribution of drug within the CSF and penetration to the site of action. This suggests that titration from the initial dose, to be discussed in more detail below, should proceed with small dose increases that are made no more frequently than once every 24 hours to improve efficacy and safety

**Table 1.** Published Protocols for Trialing Intrathecal Ziconotide.

Route of IT trial	Duration/timing	Dose(s)	Criteria to define success
Continuous infusion (external pump) Caraway et al. (40)	3 days (may be extended for patients with inadequate analgesia and no significant adverse events)	Starting dose: 1.2 mcg/d, increased by 1.2 mcg/d every 12–24 hours, based on patient response*	Not reported
Stanton-Hicks et al. (42)	1–2 weeks	Starting dose: 0.5 mcg/d, increased by 0.5–1.0 mcg every 12–24 hours, based on patient response	Not reported
Bolus injection Mohammed et al. (30,35)	2–3 injections $\geq$ 1 week apart	Initial dose: 2.5 mcg Subsequent doses: 1.2, 2.5, or 3.75 mcg, based on patient response	$\geq$ 30% reduction in VAS pain rating with no significant side effects after 2 separate bolus doses
Pope & Deer (43)	2–5 injections $\sim$ 1 week apart	Initial dose: 2 mcg Subsequent doses: 1, 2, 4, 6, or 8 mcg, based on patient response	$\geq$ 75% pain reduction with no significant side effects after 2 boluses at the same dose

\*This rapid titration schedule has been associated with increased frequency and severity of adverse events.  
IT, intrathecal; VAS, visual analog scale.

(9). Since maintaining patients on low doses of ziconotide at slow infusion rates may limit the onset of analgesic efficacy, clinicians need to balance patients' overall outcomes by adjusting the rate of upward dose titration to analgesic effect in relation to acceptable tolerability for individual patients (28).

### Trialing

Trialing continues to be a subject of discussion because of its potential to help improve clinical outcomes and guide appropriate use of healthcare resources for long-term continuous infusion in individual patients (28). Indeed, the PACC guidelines recommend a successful trial of IT therapy before implantation of an IT drug delivery system (IDDS) (29), and clinicians have developed a number of protocols featuring different modes of delivery (bolus or continuous infusion), site of drug administration (IT or epidural), and clinical setting (inpatient or outpatient) (28). However, the validity of trialing for predicting the efficacy of IT therapy has not been established (28,29). Investigators in one recent study (36 injections in 23 patients) commented that the predictive power of trialing with bolus IT ziconotide remains unclear; in their opinion, the low observed response rate, coupled with the pharmacological delays due to slow tissue penetration with this hydrophilic molecule, call into question the rationale for trialing with bolus IT ziconotide (30). Other clinicians have raised an issue that is a central challenge of trialing with IT ziconotide: the development of adverse effects with initial doses that may be too high and titration that may be too aggressive can lead to incorrect conclusions about the likelihood that patients will tolerate and benefit from long-term therapy that is trialed and initiated on a more gradual basis (29). In the absence of consensus, the value of trialing, previously considered a critical prerequisite to IT therapy, may now be viewed as "somewhat debatable" (7) and dispensable for certain patients, such as those with cancer-related pain and limited life expectancy, and those who require chronic anticoagulation (29,31).

Trialing with IT ziconotide has been conducted and studied by means of bolus (30,32–39) and continuous-infusion methods (40–43) (Table 1). The current literature does not support the use of one trialing method over the other (28,29). During the early experience with IT ziconotide, physicians surveyed indicated a preference for continuous-infusion trialing (29,44), which allows for a longer administration of the agent compared with bolus injection (29,31). However, this approach has multiple drawbacks, including increased cost, patient burden, and safety concerns (9,29). Findings from interim analysis of the ongoing Patient Registry of Intrathecal Ziconotide Management (PRIZM) registry suggest that preferences for ziconotide trialing may be shifting toward bolus injection: the majority of patients who received a trial of ziconotide (33 of 34 patients, 97%) received a single bolus injection administered on an outpatient basis (45).

Other recent publications provide additional insights into bolus trialing with ziconotide before implantation of a continuous-infusion pump. The bolus trial method described by Mohammed et al. involved 2 to 3 bolus doses of IT ziconotide, administered at least a week apart, with a starting dose of 2.5 mcg and subsequent sequential doses of 2.5 mcg, 1.2 mcg, or 3.75 mcg, depending on the patient's response to the initial dose (35). A successful trial was defined as one that provided a good analgesic response ( $\geq$ 30% reduction in visual analog scale [VAS] rating of pain, with no significant side effects) to two separate bolus doses (35). Overall, 55% of patients (11 of 20; 95% CI, 0.34–0.74) had a good analgesic response to the bolus injection trial. Patient reports on the VAS indicated a 43% reduction in pain from pre-treatment baseline (28 mm reduction, from 65 mm pre-injection to 37 mm post-injection; 95% CI, 22–34 mm). In another study, conducted by one of our authors (JEP), trialing involved an initial bolus 2 mcg dose of IT ziconotide injected with barbotage at L1-2, followed by 23 hours of observation (43). Patients who achieved  $\geq$ 75% pain reduction without adverse effects received a second IT bolus injection according to the same procedure and at the same dose. Successful trial, defined as similar

**Table 2.** Dosing of Intrathecal Ziconotide in Randomized Placebo-Controlled Trials and Open-Label Studies.

Study	Type of study	Patients	Dosing/titration	Key efficacy results	Adverse events
Staats et al. (14) (Study 95-001)	Short-term, randomized, double-blind, placebo-controlled trial	Refractory pain, cancer or AIDS n = 71 ziconotide n = 40 placebo	<p>Dosing/titration schedule</p> <ul style="list-style-type: none"> <li>• First 48 patients                             <ul style="list-style-type: none"> <li>- Starting dose: 5 ng/kg/hour</li> <li>- changed to 0.4 mcg/hour</li> <li>- Upward titration: once every 12 hours to maximum tolerated dose</li> </ul> </li> <li>• Subsequent 60 patients                             <ul style="list-style-type: none"> <li>- Starting dose: ≤0.1 mcg/hour</li> <li>- Upward titration: once every 24 hours to analgesic effect</li> <li>- Maximum dose allowed: 2.4 mcg/hour</li> </ul> </li> </ul> <p>Mean/median dose used: data not available</p>	<p>Mean VASPI scores improved by 53.1% in the ziconotide group; by 18.1% in the placebo group</p> <p>Opioid use decreased by 9.9% in the ziconotide group; increased by 5.1% in the placebo group</p>	<p>Rate of discontinuation due to AEs: 16.9% in the ziconotide group, 10.0% in the placebo group</p> <p>Most common AEs (≥10% of ziconotide patients and at least 2x placebo): dizziness, nystagmus, fever, postural hypotension, somnolence, confusion, urinary retention, abnormal gait</p> <p>Starting at lower ziconotide dose, using smaller dose increments, and increasing the interval between dose titrations tended to reduce incidence of AEs</p>
Wallace et al. (15) (Study 96-002)	Short-term, randomized, double-blind, placebo-controlled trial	Refractory pain, noncancer-related etiology n = 175 ziconotide n = 89 placebo	<p>Dosing/titration schedule</p> <ul style="list-style-type: none"> <li>• First 65 patients                             <ul style="list-style-type: none"> <li>- Starting dose: 0.4 mcg/hour</li> <li>- Upward titration: once every 24 hours to analgesic effect or intolerable AEs</li> <li>- Maximum dose allowed: 7.0 mcg/hour</li> </ul> </li> <li>• Subsequent 199 patients                             <ul style="list-style-type: none"> <li>- Starting dose: 0.1 mcg/hour</li> <li>- Upward titration: once every 24 hours to analgesic effect or intolerable AEs</li> <li>- Maximum dose allowed: 2.4 mcg/hour</li> </ul> </li> </ul> <p>Mean/median dose used: data not available</p>	<p>Mean percentage change in VASPI score from baseline to end of titration (day 6): 31.2% in the ziconotide group; 6.0% in the placebo group</p>	<p>Rate of discontinuation due to AEs (nondevice related): 14.1% in the ziconotide group, 0% in the placebo group</p> <p>Most common AEs (≥10% of ziconotide patients and at least 2x placebo): dizziness, nausea, nystagmus, abnormal gait, urinary retention, vomiting, somnolence, confusion, postural hypotension, amblyopia</p>

**Table 2.** *Continued*

Study	Type of study	Patients	Dosing/titration	Key efficacy results	Adverse events
Rauck et al. (16) (Study ZIC-301)	Short-term, randomized, double-blind, placebo-controlled trial	Refractory pain, any etiology n = 112 ziconotide n = 108 placebo	<u>Dosing/titration schedule</u> <ul style="list-style-type: none"> <li>Starting dose: 0.1 mcg/hour</li> <li>Upward titration: 0.05–0.10 mcg/hour increments at ≥24-hour intervals to analgesic effect or intolerable AEs</li> <li>Downward titration allowed at any time to improve tolerability</li> <li>Maximum dose allowed: 0.9 mcg/hour</li> </ul> <u>Mean/median dose used</u> <ul style="list-style-type: none"> <li>Mean dose at week 3: 0.29 mcg/hour</li> <li>Maximum dose used: 0.8 mcg/hour</li> </ul>	Mean percentage improvement in VASPI scores from baseline to week 3: 14.7% in the ziconotide group; 7.2% in the placebo group	Rate of discontinuation due to AEs: 5.4% in the ziconotide group, 4.6% in the placebo group AEs significantly more common in ziconotide vs. placebo group: dizziness, confusion, ataxia, abnormal gait, memory impairment
Ellis et al. (47) (Study 95-002)	Long-term, open-label extension to Studies 95-001 and 96-002	Responders to IT ziconotide in a previous RCT N = 155	<u>Dosing/titration schedule</u> <ul style="list-style-type: none"> <li>Patients initially maintained on their previously established effective dose for 30 days, if analgesic effect and AEs were acceptable</li> <li>Upward or downward titration based on analgesic effect and AEs</li> <li>Maximum 2-fold increase permitted per 12-hour period</li> </ul> <u>Mean/median dose used</u> <ul style="list-style-type: none"> <li>Mean dose through month 12: 0.3–0.6 mcg/hour</li> <li>Dose requirements generally stable over time</li> </ul>	Mean percentage improvement in VASPI scores from baseline: 31.8–45.8% during months 1–12; 36.9% at last available observation	Rate of discontinuation due to AEs: 39.4% Most common AEs (≥ 15% of patients): confusion, dizziness, nystagmus, memory impairment, abnormal gait, myasthenia, impaired verbal expression

**Table 2.** Continued

Study	Type of study	Patients	Dosing/titration	Key efficacy results	Adverse events
Wallace et al. (48) (Study 98-022)	Long-term, open-label study	Severe chronic pain from cancer, AIDS, or their treatment or pain of noncancer-related etiology with a demonstrable neurological basis N = 644	<u>Dosing/titration schedule</u> <ul style="list-style-type: none"> <li>Starting dose: <math>\leq 2.4</math> mcg/day</li> <li>Dose increases: <math>\leq 2.4</math> mg/day, not more than once every 24 hours</li> <li>No maximum dose defined</li> </ul> <u>Mean/median dose used</u> <ul style="list-style-type: none"> <li>Mean dose at last infusion: 8.4 mcg/day (range: 0.048–240.0 mcg/day)</li> </ul>	Among patients with VASPI baseline scores $\geq 50$ mm who completed 1 month of therapy: 129/394 patients (32.7%) had $\geq 30\%$ improvement in VASPI score at month 1	Rate of discontinuation due to AEs: 48.9% Most common AEs ( $\geq 25\%$ of patients): nausea, dizziness, headache, confusion, pain, somnolence, memory impairment
Webster et al. (49) (Study 351)	Long-term, open-label extension to Studies 95-002 and 98-022	Completers of a previous long-term study N = 78	<u>Dosing/titration schedule</u> <ul style="list-style-type: none"> <li>Patients initially maintained on their previously established effective dose</li> <li>Dose adjustment based on analgesic effect and AEs</li> <li>Upward titration: <math>\leq 2.4</math> mg/d, not more than once every 24 hours</li> <li>Downward titration allowed at any time</li> <li>No maximum dose defined</li> </ul> <u>Mean/median dose used</u> <ul style="list-style-type: none"> <li>Median dose across study visits: 5.52–7.20 mcg/day</li> </ul>	For patients who had a VASPI score available at the initial visit and $\geq 1$ subsequent visit (n = 72): mean VASPI scores were 55.6 $\pm$ 28.7 mm at the initial visit; 58.9 $\pm$ 27.30 mm at the termination visit	Rate of discontinuation due to AEs: 5.1% Most common AEs ( $\geq 5\%$ of patients) considered related to ziconotide: memory impairment, dizziness, nystagmus, speech disorder, nervousness, somnolence, abnormal gait
Raffaelli et al. (50)	Long-term, retrospective observational study	Refractory chronic pain of cancer-related or noncancer-related etiology N = 104	<u>Dosing/titration schedule</u> : not available <u>Mean (SD) initial ziconotide dose</u> : 1.41 (0.61) mcg/day	Apparent relationship between efficacy and dose: for patients with pain intensity reduction of $\geq 10\%$ , $\geq 20\%$ , $\geq 30\%$ , $\geq 40\%$ , and $\geq 50\%$ , mean daily dose was 3.50, 3.99, 4.36, 4.85, and 4.98 mcg/day, respectively	Most common ziconotide-related AEs ( $> 10\%$ of patients): psychomotor disorders, asthenia, balance disorders, sensory impairments, altered muscle tone, and motor coordination disorders

AE, adverse event; AIDS, acquired immune deficiency syndrome; RCT, randomized controlled trial; SD, standard deviation; VASPI, visual analog scale of pain intensity.

**Table 3.** Recommendations for Dosing of Intrathecal Ziconotide Continuous Infusion.

Ziconotide prescribing information (10)	Starting dose: $\leq 2.4$ mcg/day Upward titration: $\leq 2.4$ mcg/day, no more than 2–3 times per week Maximum dose: 19.2 mcg/day
Expert consensus (51,52)	Starting dose: $\leq 0.5$ mcg/day Upward titration: $\leq 0.5$ mcg/day, no more than once per week
PACC guidelines (7)	Starting dose: 0.5–2.4 mcg/day Maximum dose: 19.2 mcg/day
PACC, Polyanalgesic Consensus Conference.	

favorable responses ( $\geq 75\%$  pain reduction without adverse effects) to both trial doses of ziconotide, identified patients as appropriate candidates for implantation of an IDDS. All of the 16 consecutive patients who met the criteria for trialing had successful trialing with IT ziconotide and received an implantable device, with IT ziconotide monotherapy initiated at the successful trial dose (i.e., 2 mcg/day) (43). Notably, these studies were consistent with the PACC guidelines recommendation of an IT ziconotide dose in the range of 1 to 5 mcg for bolus trialing (7).

### Dosing of Intrathecal Ziconotide via Continuous Infusion

As with approaches to trialing, IT ziconotide therapy approaches continue to develop. Ziconotide solution for IT administration is available in concentrations of 25 mcg/mL and 100 mcg/mL for use in delivering IT therapy (10). The 25 mcg/mL solution should be used undiluted for the initial pump fill, with adjustment of the pump flow rate to achieve the desired ziconotide dose according to the individual patient's analgesic response and the tolerability of the regimen. The 100 mcg/mL formulation may then be used diluted until patients' appropriate doses have been established or undiluted after those doses have been determined (10). Using aseptic procedures, dilution should be performed with 0.9% sodium chloride injection, USP (preservative free), before loading the solution into the microinfusion pump. The pump-refill interval is shortened when using diluted solution (40 days) vs. undiluted solution (84 days) because ziconotide stability is decreased when the solution is diluted (10,46).

The registration trials of IT ziconotide provide guidance on dosing and refinement according to patients' responses (Table 2) (14–16,47–50). In the first two randomized controlled trials of IT ziconotide (Study 95-001, Study 96-002), the starting dose and the titration schedule were modified during the course of the studies because of tolerability issues (14,15). In these trials, the initial dose of IT ziconotide was decreased from 9.6 to 2.4 mcg/day, and the interval between dose increases was lengthened from 12 to 24 hours; the titration period remained constant at five to six days (14,15). A lower starting dose (2.4 mcg/day) and a slower titration schedule (at least a 24-hour interval between dose increases across a three-week titration period) were used in the third randomized controlled trial (Study ZIC-301) (16). In long-term extensions of these randomized controlled trials and in other open-label studies (Table 2) (14–16,45,47–50), dosing was individualized according to patient response (analgesic effect and occurrence of adverse effects). Substantial interpatient variability in actual dose delivered was observed, although mean daily doses after titration were generally within the range of 7 to 14 mcg.

Current recommendations for ziconotide continuous infusion dosing appear in the product prescribing information, as well as in the Expert Consensus and the PACC guidelines (Table 3) (7,10,51,52). The ziconotide prescribing information states that the starting dose should be no more than 2.4 mcg/day (0.1 mcg/hour), with upward titration in increments of no more than 2.4 mcg/day at intervals of no more than two to three times per week; the maximum recommended dose is 19.2 mcg/day (10). Expert consensus among some experienced pain medicine practitioners and clinical investigators recommends a more gradual approach, with a starting dose of no more than 0.5 mcg/day followed by titration in increments of no more than 0.5 mcg/day made no more often than once a week (51,52). The PACC guidelines recommend a starting dose of 0.5 to 2.4 mcg/day for IT ziconotide and a maximum dose of 19.2 mcg/day (7).

These dosing recommendations and especially the rate of dose increases are important considerations for improving tolerability with IT ziconotide. As noted above, the incidence of adverse effects with IT ziconotide has been correlated with the rate of dose increases, rather than with the absolute dose delivered (7,9,20). With respect to other aspects of overall tolerability and safety profile, clinicians should note that nonopioid ziconotide does not present the concerns about adverse effects of morphine, which include respiratory depression, granulomas, tolerance, dependence, and hyperalgesia (53). Even after massive accidental overdoses of IT ziconotide caused by programming or dilution errors, adverse effects typically resolved in 24 hours after discontinuing the infusion, with no permanent sequelae (51,54,55). In addition, discontinuation of ziconotide therapy, including abrupt discontinuation, does not produce withdrawal symptoms (10,20).

More aggressive IT dosing and titration schedules may be appropriate, if tolerable, in patients deemed to be short-term survivors (i.e., life expectancy  $\leq 1$  year) in order to address escalating pain and maintain quality of life (56). High doses of ziconotide have been well tolerated by some patients, although the patient characteristics that may be related to this effect are unknown (27,57,58).

In summary, it is recommended that continuous infusion with IT ziconotide be initiated at a dose of 0.5 to 1.2 mcg/day and increased in increments of  $\leq 0.5$  mcg/day on a weekly basis based on analgesia and tolerability (51,52). In light of the marked interpatient variations in dosing observed in longer-term studies, individualized dosing regimens are important when using IT ziconotide.

### Use of Patient-Controlled Analgesia With Intrathecal Ziconotide

In addition to the continuous infusion of IT ziconotide described in the product prescribing information, other approaches for ziconotide dosing have been developed (Table 4). One of these is patient-controlled analgesia (PCA), which is widely used in the intravenous administration of opioids and other analgesics, particularly for managing postoperative pain (59) and cancer pain (60,61). The Personal Therapy Manager (PTM) is an external activating device for use with the implanted SynchroMed Infusion System that enables patients to trigger on-demand bolus PCA doses of IT analgesia, within preset limits of individual bolus dose, frequency, and total allowable daily bolus dose set by the prescriber, in addition to the baseline continuous infusion (62–64). The PTM prescribing information states that use of ziconotide with this device is contraindicated because ziconotide has a defined titration schedule (64). However, the rationale for employing PTM administration of IT ziconotide is supported by clinical experience and research data, notably: bolus dosing is routinely used in trialing ziconotide (35,43); ziconotide has been used with

**Table 4.** Novel Dosing Paradigms for Intrathecal Ziconotide.

<p>Patient-controlled analgesia via PTM</p> <ul style="list-style-type: none"> <li>• Background continuous infusion of IT ziconotide</li> <li>• Patient administers additional doses via PTM; bolus dose, dosing interval, and maximum number programmed by the clinician                     <ul style="list-style-type: none"> <li>– Each bolus dose is ~10% of continuous dose</li> <li>– Dose adjustment as necessary to improve efficacy and minimize AEs</li> </ul> </li> <li>• May be used with ziconotide monotherapy or in combination with other IT medications</li> </ul> <p>AEs, adverse events; IT, intrathecal; PTM, Personal Therapy Manager.</p>	<p>Bolus flex dosing</p> <ul style="list-style-type: none"> <li>• No continuous infusion of ziconotide</li> <li>• Pump delivers daily bolus dose of IT ziconotide as programmed by the clinician                     <ul style="list-style-type: none"> <li>– Initial dose (1–3 mcg/day) based on trialing</li> <li>– Upward titration by tenths of micrograms</li> <li>– Dose adjustment as necessary to improve efficacy and minimize AEs</li> </ul> </li> <li>• May be used as IT monotherapy or in combination with other IT medications</li> </ul>
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the PTM system clinically in case series (65); and, in contrast to opioid medications, ziconotide overdose does not lead to respiratory depression or death (53).

One of our authors (GCM) developed a strategy for use of the PTM device by patients receiving continuous infusion of ziconotide and evaluated its clinical performance in a case series (Table 5) (65,66). Fourteen patients with cancer-related or noncancer-related pain who received continuous infusion of IT ziconotide (monotherapy in three patients, combination therapy with hydromorphone in 11 patients) had PCA access via the PTM to bolus ziconotide doses equivalent to approximately 10% of the daily continuous dose (dose range for PTM ziconotide bolus was 0.15–0.25 mcg). The programmed dose of ziconotide/hydromorphone was calculated on the basis of the ziconotide infusion dose and limited to prevent excessive dosing of the opioid. The interval for administration of PTM doses was every four to six hours in patients with pain of noncancer-related origin and every one to two hours in patients with cancer pain. This new approach allowed for greater individualization of therapy and more aggressive management of challenging cancer-related pain.

Although this use of the PTM with IT ziconotide had not yet been evaluated in controlled clinical trials, this case series provided preliminary evidence of an association between PTM ziconotide and improved pain relief and/or improved functioning, greater patient satisfaction, and acceptable tolerability in all eight evaluable patients. A few patients experienced nausea or dizziness with PTM ziconotide doses that exceeded 60% of the continuous-infusion

**Table 5.** Case Series of Personal Therapy Manager Use With Intrathecal Ziconotide (65).

Chronic pain condition	Continuous infusion dose	PTM dose	Outcome
Intrathecal ziconotide monotherapy*			
Arachnoiditis (66)	Ziconotide 16.4 mcg/day	Ziconotide 0.25 mcg q 4 hours	Pain 4/10, maintains active lifestyle
Rheumatoid arthritis and osteoarthritis	Ziconotide 4.8 mcg/day	Ziconotide 0.20 mcg q 3 hours	Plus (oral) oxycodone extended release 5 mg q 12 hours, pain 4–5/10, more functional
Chronic pancreatitis (failed spinal cord stimulator)	Ziconotide 1.5 mcg/day	Ziconotide 0.15 mcg q 2 hours	Pain 5/10, functional
Combination intrathecal therapy: ziconotide + hydromorphone†			
Metastatic breast cancer with lumbar spine metastases	Ziconotide 6.701 mcg/day + hydromorphone 6.7 mg/day	Ziconotide 0.25 mcg + hydromorphone 0.25 mg q 8 hours	Pain 6/10, now fully ambulatory and more active
Metastatic breast cancer with metastases in thoracic/lumbar spine and bilateral femurs; extensive pelvis metastases with fractures	Ziconotide 14.408 mcg/day + hydromorphone 3.0 mg/day	Ziconotide 0.10 mcg + hydromorphone 0.02 mg q 3 hours	Pain remains high, but patient is functional despite continued tumor spread
Metastatic pancreatic cancer with L5 metastasis	Ziconotide 1.0 mcg/day + hydromorphone 1.5 mg/day	Ziconotide 0.10 mcg + hydromorphone 0.15 mg q 8 hours	Pain 1/10 within 1 month, rare PTM use, doses reduced by 5%
Lumbar postlaminectomy syndrome (failed spinal cord stimulator)	Ziconotide 3.994 mcg/day + hydromorphone 1.33 mg/day	Ziconotide 0.20 mcg + hydromorphone 0.067 mg q 3 hours	Pain 4–5/10, young patient remains active
Diabetic peripheral neuropathy	Ziconotide 6.0 mcg/day + hydromorphone 1.2 mg/day	Ziconotide 0.25 mcg + hydromorphone 0.05 mg q 3 hours	Patient more active, less neuropathy pain, less frequent anxiety flares

PTM, Personal Therapy Manager.

\*Pain flares controlled by adding PTM without increasing the continuous dose.

†PTM dose calculated on basis of ziconotide infusion dose, limited to prevent excessive dosing of the opioid.



**Table 6.** Case Series of Bolus Flex Dosing With Intrathecal Ziconotide (43).

Chronic pain condition	Flex dose (mcg/day)	Treatment duration (months)	Outcome
Lumbar radiculopathy	3.9719	10	NPRS pain rating from 10 to 2
Lumbar radiculopathy	2.5000	3	Discontinued due to hallucinations, global dysesthesia; switched to IT morphine
Lumbar FBSS	2.6002	9	NPRS pain rating from 9 to 2
CRPS (upper extremity)	5.9990	4	Discontinued due to urinary retention; switched to IT hydromorphone
Lumbar radiculopathy	2.2370	7	NPRS pain rating from 9 to 2
Lumbar radiculopathy	2.6998	8	NPRS pain rating from 10 to 3
Lumbar radiculopathy	3.5002	4	Discontinued due to urinary retention; switched to IT morphine
Lumbar radiculopathy	3.3013	6	Discontinued due to urinary retention; switched to IT morphine
Lumbar FBSS	2.9986	7	NPRS pain rating from 9 to 2
Lumbar radiculopathy	2.2007	6	NPRS pain rating from 9 to 0
Lumbar radiculopathy	3.2056	5	NPRS pain rating from 10 to 4
Lumbar FBSS	2.4341	4	NPRS pain rating from 8 to 0
Lumbar radiculopathy	2.0000	4	NPRS pain rating from 10 to 3
Lumbar spondylosis	3.0767	4	NPRS pain rating from 10 to 2
Lumbar radiculopathy	3.7936	3	NPRS pain rating from 7 to 2
Lumbar radiculopathy	2.0355	3	NPRS pain rating from 8 to 0

CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome; NPRS, Numeric Pain Rating Scale.  
 Adapted with permission from Pope JE, et al. *Neuromodulation*. 2015, International Neuromodulation Society. © 2015 International Neuromodulation Society.

dose of that agent, but no severe adverse effects were reported. One patient in this series, a 23-year-old woman with arachnoiditis and severe pain despite long-term therapy with high-dose oral opioids, underwent trial with a bolus injection of ziconotide and received implantation of an IDDS with PTM technology (66). A slow titration regimen with ziconotide reduced the mean pain score from 7/10 on oral opioids to 4/10 with PTM ziconotide, with the patient able to maintain an active lifestyle (66). A separate report of two patients who received IT ziconotide infusion for pain related to sickle cell disease showed that PTM ziconotide was effective for aborting pain flares and reducing the number of emergency room visits in both patients (67). In addition, the PTM approach was useful during the titration period for finding the optimal ziconotide dose in these patients. In a third case presentation, PTM ziconotide was added to continuous infusion of ziconotide to provide additional control of episodic neuropathic pain in a patient with a spinal cord injury secondary to a gunshot wound (68). The patient underwent a successful trial with IT ziconotide, had a pump placed for long-term PTM delivery of ziconotide, and achieved sufficient pain reduction with ziconotide to discontinue therapy and have the pump removed; the patient's pain was reported as stable at 12 months (68). Clearly, formal study is needed to further define dosing parameters for PTM administration of ziconotide and to assess its efficacy, safety, and tolerability.

**Flex Dosing of Intrathecal Ziconotide**

A second alternative approach to the traditional use of continuous infusion of IT ziconotide has been published by one of our authors (JEP) (43). This approach uses the flex-mode feature of the SynchroMed II infusion pump to program delivery of IT medication at varying rates throughout the day or enable administration of scheduled bolus doses (Table 4) (69). This feature has a defined clinical role in the management of spasticity with IT

baclofen (70,71). Research using animal models suggests that bolus dosing of IT medications may produce greater drug distribution compared with slow IT infusion and may, therefore, have potential for improving the efficacy of IT therapy (72,73). Several clinical trials of IT ziconotide indicate that a single bolus dose may provide pain relief for up to 24 hours (33,34). Failure of IT therapy after a successful bolus trial may be related to differences in the pharmacokinetics of ziconotide when administered via continuous infusion vs. bolus dosing (43).

A novel flex-dosing approach developed by one of our authors (JEP) for IT ziconotide may help overcome this obstacle (43,74). This approach was evaluated in a prospective case series of 16 patients with noncancer-related pain who had a successful bolus trial, had an IDDS implanted, and were treated with IT ziconotide (Table 6) (43). Success of the bolus trial was defined as completion of two injections, at least a week apart, with each injection providing  $\geq 75\%$  pain reduction approximately 24 hours post-injection without side effects (43,74). After pump implantation in patients with a successful trial, the initial nocturnal flex bolus dose was determined on the basis of the trial dose. In addition to low-dose continuous infusion of IT ziconotide (flow rate of 0.48 mL/day with drug concentration of 5 mcg/mL), a bolus dose was administered starting at 11:00 PM over the course of 30 to 45 min, with solution concentrations of 5 mcg/mL or 10 mcg/mL of ziconotide. The nocturnal flex dose was then titrated upward by tenths of micrograms every 7 days until a therapeutic dose was reached. At baseline, patients had diagnoses of lumbar radiculopathy ( $n = 11$ ), lumbar failed back surgery syndrome ( $n = 3$ ), lumbar spondylosis ( $n = 1$ ), or complex regional pain syndrome ( $n = 1$ ). Before patients entered the study, their mean pain duration was 153 months (range: 15–444 months) and almost all patients (15/16) had failed to obtain adequate pain relief from spinal cord stimulation (either a trial or an implant); only one patient had a prior history of IT therapy. Analysis of the primary study endpoint,

tolerability of ziconotide at three months, showed that all (16/16) patients achieved this endpoint; 75% of patients completed four months of therapy; and 70% completed six months of therapy. The longest duration of therapy was ten months. Analysis of the ziconotide dose delivered showed that all patients (16/16) received their initial flex dose at 2 mcg/day and their mean final daily dose was 3.03 mcg (range, 2.000–5.999). Scores on the Numeric Pain Rating Scale (NPRS) showed that pain decreased from a mean of 9.1 at baseline to a mean of 1.8 at completion, and opioid consumption decreased by an average of 91.5% from baseline doses that ranged up to 405 morphine equivalents. Four patients (25%) discontinued treatment because of adverse events of urinary retention ( $n = 3$ ) after four to six months of ziconotide therapy at final doses of 3.5002 to 5.999 mcg/day or hallucinations/global dysesthesia ( $n = 1$ ) after three months of ziconotide therapy at a final dose of 2.5000 mcg/day. Larger investigations are needed to confirm the results of this proof-of-concept study and to determine the optimal times and intervals for administration of ziconotide bolus doses.

## CONCLUSION

Research study findings and clinical experience confirm the feasibility and usefulness of IT ziconotide in the management of refractory chronic pain. Recent research has provided insights into ziconotide pharmacokinetics and helped to explain the now-recognized delay in distribution and uptake at its site of action in the CNS following IT administration. This delay has clinical implications in that it supports IT trialing with low doses and transition to continuous infusion at low initial doses followed by titration in small, upward increments to balance patients' need for pain relief with tolerability in support of long-term therapy.

Currently, several issues pertaining to IT trialing remain open. These include the relative merits of trialing by means of bolus injection vs. continuous infusion and the choice of inpatient vs. outpatient setting. Although inpatient trialing with continuous infusion has been the traditional technique, this paradigm may be shifting, as indicated by an interim finding from the PRIZM registry that 97% of patients received a single bolus injection for trialing on an outpatient basis (45). With regard to dosing for continuous-infusion ziconotide therapy, a low starting dose (0.5 to 1.2 mcg/day) of ziconotide followed by small titration increments ( $\leq 0.5$  mcg/day) once weekly, according to individual patients' pain reduction and ability to tolerate the regimen, is recommended (51,52).

Evidence is emerging to suggest that delivery options for ziconotide could expand to include other dosing regimens beyond the traditional low volume/slow continuous infusion approach, such as PCA with the PTM system or bolus nocturnal flex dosing. Additional supportive research is needed to establish the usefulness and the benefits of these modalities and, if successful, could open new opportunities for further improving the management of chronic refractory pain with IT ziconotide.

## Authorship Statements

Drs. McDowell and Pope have developed protocols for dose titration and have each presented or published their work. They both actively participated in the development, writing, and review of this manuscript. Both authors approved of the final version to be published.

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## COMMENTS

This manuscript provides an in-depth summary of the available studies of intrathecal ziconotide trials. It authors provide a well-balanced discussion about various techniques and offer practical suggestions. This document is a welcomed tool for those entering the field of IT ziconotide therapy.

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