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# Intrathecal ziconotide for the treatment of chronic pain: a collection of clinical experiences and literature review

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**Abstract. – OBJECTIVE: Despite the wide use of ziconotide in the USA for treating refractory cancer- and noncancer-related pain, this agent is little used in Europe, even if licensed by the European Medicines Agency (EMA). The reason could be attributed to the high, fixed starting dose required for ziconotide, as stated in the EMA Summary of Product Characteristics (SmPC). This dosage recommendation is based on the results of pivotal clinical studies of ziconotide, which utilized aggressive titration schedules. Thus, a reappraisal of the available evidence, as well as a reflection on real-life clinical experiences, might be useful to identify practice adjustments to improve the clinical application of ziconotide in the European scenario. In line with this need, this paper reports some clinical experiences of patients with chronic pain treated with ziconotide intrathecal (IT) therapy in Italy, particularly focusing on long-term treatment to further characterize and improve the use of this agent in real practice. Moreover, a literature review of the available data on the effectiveness and safety of IT ziconotide is provided.**

**CASE SERIES: Collected clinical experiences suggested that the use of IT ziconotide represents a valuable option, particularly in cases where other treatments have been ineffective or poorly tolerated. Ziconotide was shown to not cause severe side effects in the long-term treatment, leading to a constant pain relief effect at stable doses, without adverse events that caused therapy interruption. The overall constant ziconotide dosages also suggest the absence of a tolerance effect. In parallel, the evidence in the literature aligns with real-world evidence and further supports the use of IT ziconotide as an important option for the management of chronic pain.**

**CONCLUSIONS: IT ziconotide represents a valuable addition to the armamentarium of pain management strategies, offering hope for improved quality of life for patients suffering from chronic, treatment-resistant pain. Continued research and clinical experience will further elucidate its optimal use and role in comprehensive pain care.**

*Key Words:*
Intrathecal therapy, Severe chronic pain, Ziconotide.

## Introduction

Intrathecal (IT) opioids are widely used for the management of chronic severe pain conditions resistant to other therapeutic modalities, with morphine as the most used agent thanks to its effectiveness, tolerability, and low cost[1]. However, up to 20% of patients experience pharmacological complications related to IT morphine administration, such as peripheral edema, nausea and vomiting, micturition disturbances, sedation, and decreased mental status, generally responding only to decreased opioid dose and, thus, limiting the therapeutic benefit of this agent[2]. In addition, many patients report decreased analgesic response with prolonged morphine exposure[3]. Consequently, the definition of alternative nonopioid analgesic strategies remains a focus of clinical research[4].

Ziconotide is a nonopioid analgesic, water-soluble cone snail venom-derived peptide approved for the management of severe chronic pain in the USA and the EU in December 2004 and February 2005, respectively[4-6]. Ziconotide selectively binds to N-type voltage-sensitive calcium channels on primary nociceptive afferent nerves in the dorsal horn of the spinal cord, allowing the release of analgesic neurotransmitters into the synaptic gap to block pain signal transmission. Ziconotide does not cross the blood-brain barrier, revealing its antinociceptive effect only after IT administration. Because of its narrow therapeutic window, careful dose titration and a lag time to allow for the onset (and offset) of analgesia and adverse effects are required[4].

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The Polyanalgesic Consensus Conference (PACC) guidelines emphasize that ziconotide should be the first drug selected for the management of chronic pain in non-cancer patients[7]. Indeed, in contrast to opioids, it does not cause tolerance, dependence, or respiratory depression. In addition, PACC guidelines indicate the use of ziconotide in patients who cannot receive morphine due to underlying conditions or opioid intolerance[7]. In line with this indication, data from the Patient Registry of Intrathecal Ziconotide Management (PRIZM) study[8] show that using ziconotide as first-line IT therapy might offer better pain relief and sustained efficacy, compared to using it subsequently to opioids.

Despite this evidence and the wide use of ziconotide in the USA for treating refractory cancer- and noncancer-related pain, this agent is little used in Europe, even if licensed by the European Medicines Agency (EMA)[9]. The reason could lie in the high, fixed starting dose required for ziconotide according to EMA Summary of Product Characteristics (SmPC), which is based on the results of the pivotal clinical studies of ziconotide, which used aggressive titration schedules[10-12]. Thus, a reappraisal of the available evidence, as well as a reflection on real-life clinical experiences, might be useful to identify practice adjustments to improve the clinical application of ziconotide in the European scenario. In line with this need, this paper reports some clinical experiences of patients with chronic pain treated with ziconotide IT therapy in Italy, particularly focusing on long-term treatment to further characterize and improve the use of this agent in real practice. Moreover, a literature review of the available data on the effectiveness and safety of IT ziconotide is provided.

## Cases Presentation

The authors retrospectively selected and reported three clinical cases related to patients with chronic pain treated with IT ziconotide, highlighting the features of prolonged treatment. Patients were treated at the AUSL Modena (Emilia Romagna Region Hub Centre, Italy) and "S. Anna & S. Sebastiano" Hospital of Caserta (Italy). Inclusion criteria included being 18 years or older and having a clinical need for ziconotide treatment based on physician judgment. Ziconotide was administered IT using implanted infusion systems or an external SynchroMed™ II infusion pump (Medtronic, Dublin, Ireland). Ziconotide was formulated in an aqueous isotonic solution containing 100 μg/mL of ziconotide (calculated as free-base). The treatment was prescribed as monotherapy or in addition to other concomitant therapeutic regimens and was administered according to the doses and modalities defined in the SmPC. Because of the retrospective description of this case series, treatment regimens and patient education were not standardized. The study was conducted following the ethical principles of the revised version of the Declaration of Helsinki and notified to the Ethics Committee of each participating center. Participants signed an informed consent form for publication of the details of the medical case and any accompanying images.

### *Case 1: Low-Dose Ziconotide n the Treatment of Persistent Spinal Pain Syndrome Type 2*

A 78-year-old female patient presented in December 2010 with persistent spinal pain syndrome type 2 (PSPS II), with anamnesis of T7 vertebral fracture treated with vertebral stabilization, multiple degenerative disk disease, and widespread osteoarthritis. After exhausting conservative therapeutic options and following a failed spinal cord stimulation (SCS) trial, it was decided to initiate treatment with an IT pump with a tip catheter at T7, initially using hydromorphone as the primary drug at a dosage of 0.3 mg/day. After a few months of relative well-being, the painful symptoms increased again. The hydromorphone dosage was then increased to 0.5 mg/day. In the follow-up after 1 month, the patient reported a modest reduction in painful symptoms with an increase in side effects, such as sedation and mental clarity impairment. Due to side effects, the patient refused an increase in the dosage of hydromorphone. Ziconotide was then introduced as a secondary drug into the pump with an initial dosage of 1 μg/day with a concurrent reduction of hydromorphone dosage to 0.3 mg/day. After 4 weeks, the patient reported a slight improvement in painful symptoms. During the pump refill, the ziconotide dosage was increased to 1.8 μg/day while keeping the hydromorphone dosage unchanged. Further slight increases in the ziconotide dosage occurred at each refill, approximately every 4 weeks, until reaching a dosage of 3.4 μg/day in 6 months. This dosage, along with the initial hydromorphone dosage, remained stable for about 5 years. During the combined treatment, the patient's quality of life was optimal, engaging in all normal activities

of daily living. During the 6th year following the pump implantation, the painful condition showed a notable increase, necessitating an increase in the ziconotide dose to 4.8 μg/day while keeping the hydromorphone dosage stable. No further change in the intrathecal medication dosage was required up to the patient passed away, at the age of 87 years, due to sepsis.

### Case 2: Ziconotide for the Management of Cancer-Related Pain

A 49-year-old female patient presented in February 2021 reporting a long-course pain in the right iliac wing with gait deficit, consequent to bone metastases of breast cancer diagnosed in 2003, treated with surgery followed by both radiotherapy and chemotherapy. At X-ray exam, she reported metastases in the right hemipelvis (ischio-pubis branch, sacrum, cox-femoral join), sternum, 3rd posterior arch rib and vertebra (D12, L2, L4), invading spinal cord. The objective examination reported significant pain in the right hemipelvis, which was constant, with peaks following exertion or remaining in an upright position. The patient was immediately treated with methadone, a fentanyl patch (100 μg/h every 72 h) and rapid-onset opioid (ROO). Despite the gradual increase in medication, the pain did not improve. In June 2021, an intrathecal catheter connected to an electronic pump (40 ml reservoir) was implanted for the infusion of an analgesic mixture of ziconotide (0.5 μg/day), morphine (0.3 mg/day) and levobupivacaine (0.6 mg/day) at a rate of 1 ml/day. The patient was discharged after 4 days with pain equal to 0 on the numeric rating scale (NRS).

In the following months, the patient reported the resumption of pain because of an L4 vertebra fracture. The dose of ziconotide was then titrated by 0.5 μg/day each month for 1.5 years to a dose of 9 μg/day, again in combination with morphine (2.4 mg/day at last control) and bupivacaine (0.875 mg/day at last control). The patient passed away in December 2022.

During the period of treatment with ziconotide, the patient showed no tolerance to the drug, no resistance to treatment, and good control of pain.

### Case 3: Importance of Ziconotide Dosing in the Management of Non-Cancer Chronic Pain

An 80-year-old male patient presented in January 2010 with chronic low back pain due to spinal canal stenosis, inoperable scoliosis, and degenerative osteoarthritis in the zigoapofisary, hip, and knee joints. Every conservative approach failed due to inefficacy or adverse effects. In May 2010, an intrathecal catheter connected to a mechanical pump was implanted, beginning with a slow infusion of ziconotide until to 4.25 μg/day and bupivacaine 1.5 mg/day (reservoir 20 ml, infusion rate 0.5 ml/day). Refill was performed every 35-40 days and allowed good pain control with the same dosage for about 13 years (NRS 0-5). Meanwhile, the patient had a right hemicolectomy due to a cancer diagnosis (2012), gastric blending treatment (2015), prosthesis on his right hip (2016) and his right knee (2017), and the infusion of ziconotide and bupivacaine was continued at the same dosage. In July 2020, the patient appeared underweight and was in a wheelchair due to reduced mobility. The patient's daughter, with the patient's agreement, requested a reduction in the drug infusion. Consequently, the amount of bupivacaine was halved to 0.75 mg/day, while the dosage of ziconotide remained the same (4.25 μg/day). The following month, the dose of ziconotide was also halved to 2.12 μg/day, while the bupivacaine dosage was maintained at 0.75 mg/day. After 15 days of ziconotide reduction, the patient reported increased persistent pain (NRS 7-8). It was therefore decided to gradually increase the dose of ziconotide to 4.25 μg/day (dosage of ziconotide at the beginning) again, with a good recovery of analgesic activity for the last 17 months of his life. He died at 92 years old. In this patient, the decrease in dosage created discomfort that resolved when the stable dosage was restored. No drug resistance occurred when the initial infusion concentration was restored. There was no correlation between the age of the patient and the dose of the drug.

## Discussion

### Literature Review

A narrative review on the effectiveness and safety of ziconotide was conducted through a bibliographic search on PubMed using the following keywords: "ziconotide", "ziconotide" AND "clinical trials", "ziconotide" AND "safety". The research was restricted to clinical studies conducted on humans in the last 15 years. Only papers written in English were examined.

Five studies[13-17] were retrieved with regard to the effectiveness of ziconotide. A retrospective Italian cohort study reported data on the safety and effectiveness of long-term ziconotide IT infu-

sion for the management of cancer or non-cancer intractable chronic pain[13]. Overall, 104 patients were included, and among them, 55 patients received ziconotide as the first IT drug[13]. In 72 patients, at least a 30% pain intensity reduction was reported (mean ziconotide dose: 4.36 μg/day)[13]. Moreover, a sustained analgesic effect of the ziconotide IT therapy was observed for up to 6 months in a group of 45 patients without treatment interruptions and with relatively stable doses. In total, 66 patients reported at least one side effect related to ziconotide. However, adverse events have not always been decisive for treatment interruptions[13].

In a cohort study[14] involving 20 patients with pain related to spinal cord injury, a decrease in pain scores of more than 40% was observed in 14 patients treated with long-term IT ziconotide therapy. Of them, only 11 (55%) were implanted with permanent pumps due to side effects and patient choice. These patients were followed up for a mean of 3.6 (±1.9) years, and in eight patients, the decrease in pain scores was maintained with an average dose of 7.2 μg/day of ziconotide. No significant long-term side effects of the molecule were reported[14].

The multicenter observational PRIZM study by Deer et al[7] and McDowell et al[15] prospectively examined the long-term effectiveness, safety, and tolerability of the low and slow administration of IT ziconotide for the management of severe chronic pain in adult patients in clinical practice[7,15]. Ziconotide was initiated as the single agent in the pump; however, other intrathecal medications were permitted. The pain was assessed using an NRS and Patient Global Impression of Change scores[7,15]. A total of 93 patients were included and treated for 3 months (74 patients) and 18 months (28 patients). Overall, IT ziconotide was effective in reducing neuropathic pain at this dose[7,15]. Moreover, greater improvements were observed when ziconotide was initiated as first-line intrathecal therapy *vs.* not the first intrathecal agent in the pump. The adverse event profile was consistent with the ziconotide prescribing information, with nausea (25.8%), confusional state (22.6%), and dizziness (20.4%) as the most reported events.

A recent prospective study[16] elucidated the positive effects of IT ziconotide on decreasing patients' disability, decreasing pain catastrophizing, and improving emotional well-being in patients with neuropathic pain. Overall, 11 patients completed the long-term follow-up (mean ± standard error: 10.9±0.7 months), and, among them, there were seven responders based on NRS minimum clinically important difference, suggesting that ziconotide is able to improve pain as well as emotional components and function[16].

A recent systematic review[17] of randomized controlled trials reported that the most common reported side effects of ziconotide monotherapy were dizziness (42%), nausea (30%), nystagmus (23%), confused state (25%), gait abnormality (16%), and memory impairment (31%). The recent PRIZIM study by McDowell et al[15] reported decreased side effects with slower titrations and doses specifically for dizziness (20%), gait abnormality (8%), and memory impairment (14%)[15]. Respiratory depression is seen in 60-100% of patients receiving IT morphine, whereas no respiratory depression, even at the maximum dose, occurs with ziconotide[18].

## Conclusions

The standard treatment for neuropathic pain is represented by oral anti-convulsant medications, such as gabapentin or pregabalin, with the addition of tricyclic antidepressant or SNRI medications as adjuvant therapy[19]. However, these drugs present relevant side effects that outweigh their benefits and often make patients refractory to first-line treatments[2,3].

IT drug delivery is a valuable therapeutic alternative for patients suffering from refractory chronic pain. Only two drugs are approved by the FDA and EMA for IT administration for chronic pain: morphine and ziconotide as monotherapy[20]. In particular, the stability of ziconotide can be positively influenced by coadministration with morphine[21]. Therefore, despite IT multidrug regimens representing off-label usage, a combination regimen is frequently considered.

Collected clinical experiences suggested that the use of IT ziconotide represents a valuable option, particularly in cases where other treatments have been ineffective or poorly tolerated. Ziconotide was shown to not cause severe side effects in the long-term treatment, leading to a constant pain relief effect at stable doses, without adverse events that caused therapy interruption. This suggests that once the early side effects were overcome, the responsive patients were not exposed to long-term risks. The overall constant ziconotide dosages also suggest the absence of a tolerance effect. Therefore, it is advisable to consider that adding low-dose ziconotide to the

IT opioid allows achieving a synergistic effect without an increase in side effects while ensuring adequate analgesia. In parallel, literature evidence aligns with real-world evidence and further supports the use of IT ziconotide as an important option for the management of chronic pain.

In conclusion, IT ziconotide therapy stands as a valuable option for managing chronic pain, especially neuropathic pain refractory to conventional treatments. Thus, IT ziconotide represents a valuable addition to the armamentarium of pain management strategies, offering hope for improved quality of life for patients suffering from chronic, treatment-resistant pain. Continued research and clinical experience will further elucidate its optimal use and role in comprehensive pain care.

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### Availability of Data and Materials
All data generated or analyzed in this case series are included in this article. Further inquiries can be directed to the corresponding author.

### Ethics Approval
The review of patients' data was conducted following the ethical principles of the revised version of the Declaration of Helsinki and was notified to the Ethics Committee of each participating center. A formal approval is not required in accordance with local/national guidelines.

### Informed Consent
Participants signed an informed consent form for publication of the details of the medical case and any accompanying images.

### Authors' Contributions
Both authors contributed to the definition and contextualization of the paper's contents, critically edited the manuscript, and approved its final version for submission. Both named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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