

Managing Chronic Pain: Nine Informative Patient Presentations

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Case Report 1:

Spinal Cord Stimulation for Traumatic Peripheral Neuropathy

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A 49-year-old woman initially arrived for a consultation in August 2014. She presented with complaints of multiple foci of pain. Most of her pain was located in the lumbar region and bilateral lower extremities.

The patient had a devastating motor vehicle accident in 2011. She required multiple orthopedic surgeries for reconstruction of her ankles and left knee. She also suffered trauma to the lumbar region, which produced diskogenic and facet pain syndromes, especially in the lower lumbar spine (Figure).

She described her low back and lower extremity pain as a constant, spasmodic, dull ache present throughout the day. The pain was worse at night. She had intermittent bouts of sciatica with paresthesias and numbness in the legs and feet. The patient stated that the constant leg and knee pain caused difficulty walking. She had seen multiple physicians in an effort to provide any degree of pain relief. She was

employed and stated her desire to continue to work full time. We were subsequently consulted for possible interventional pain control for traumatic peripheral neuropathy.

Multiple injections were administered in the low back and lower extremities, with only temporary pain relief produced. We then discussed spinal cord stimulation (SCS), and she agreed to a trial of SCS.

Providing pain relief by paresthesia induced by a trial of percutaneous SCS over the low back and lower extremity region was necessary. Two cylindrical octrode leads were used. Access into the epidural space was performed with a 14-gauge Tuohy needle using the loss-of-resistance technique. The first octrode lead was placed in the physiologic midline at the T9-10 region of the epidural space. The second octrode lead was staggered with slight overlapping at the T11-12 region at the physiologic midline. The patient stated that she had good pain control over her low back and legs. The trial phase was uneventful. She returned to the clinic 3 days after the procedure for a follow-up appointment and lead removal. She stated that she had 70% overall pain relief from the SCS trial.

The patient had a permanent spinal cord stimulator placed 1 month after the SCS trial. A St. Jude Medical Penta paddle lead was placed at the T9-10 region of the epidural space. She initially had 50% pain relief after the procedure but required multiple bouts of reprogramming of the spinal cord stimulator every 3 to 4 months. She stated good pain relief was appreciated, but also noted that reprogramming was necessary because analgesia produced by a selected program would only last 1 to 2 months as analgesia diminished over time; thus, reprogramming was required every 4 months. Currently, the patient is enjoying 50% pain relief from her spinal cord stimulator. She is able to walk further and work longer, with decreased consumption of pain medication. She stated that the road to recovery was not easy but worth it.



Figure. Staggered both octrode leads at midline from T9 through T12.

No Antagonists for an Antagonist: One Pitfall of Chronic Oral Low-Dose Naltrexone

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A 48-year-old man was admitted to our center for management of a perforated duodenal ulcer with intraabdominal free air. For 10 years, he had chronic abdominal pain following an open repair of an abdominal aortic aneurysm, and was treated with “low-dose” naltrexone 1.5 mg per day for 3 years, with satisfactory efficacy.

Upon admission, the patient was administered IV opiates while a medical evaluation of the intraabdominal free air was performed. A duodenal ulcer was found, and the decision was made to manage the free air nonoperatively.

Despite dose escalation of IV fentanyl to 4,500 mcg per day and hydromorphone to 47 mg per day, his acute pain remained uncontrolled. We were surprised to observe that an opiate-naïve patient was refractory to the analgesic, sedative, or respiratory depressant effects of 2 IV opiates with liberal dose escalation. We hypothesize that the chronic oral naltrexone may have contributed to the lack of efficacy of the opiates, because the patient had previously responded to opiates at much lower doses during a prior hospitalization in the setting of a laparotomy.

Oral Naltrexone for Chronic Pain

In several small trials, naltrexone demonstrated efficacy in pain conditions including fibromyalgia and complex regional pain syndrome.^{1,2} Effectiveness in inflammatory conditions such as multiple sclerosis and Crohn’s disease suggests that low-dose naltrexone may act to inhibit inflammation, a mechanism potentially independent of its action on opioid receptors.^{3,4}

Somewhat paradoxically, low-dose naltrexone is both anti-inflammatory and analgesic, potentially via its ability to increase production of endogenous opioids or by decreasing glial cell activation.⁵ The role of glial cell activation in chronic pain continues to emerge, but microglial activation is known to contribute to both inflammation and pain sensitivity.⁶ Similarly, when microglial activity is suppressed, the production of neuroexcitatory reactive oxygen species is diminished.⁷

What Is ‘Low Dose’?

The target dose of naltrexone required to suppress microglial activity without antagonizing the μ -opioid receptor is unknown. To our knowledge, a dose-response curve for low-dose naltrexone has not been plotted, and it is unknown whether there is overlap between the anti-inflammatory dose-response curve and the opioid antagonist plot. We hypothesize that the analgesic “sweet spot” is heterogeneous in the general population, and the patient we encountered may have exceeded the anti-inflammatory dose and entered into an antagonist dose range.

The Challenge of Acute Pain Management

With a growing body of evidence supporting treating selected chronic pain conditions with low-dose naltrexone, we return to the question of caring for patients with acute pain who are treated with chronic oral naltrexone. Naltrexone has biphasic elimination: The initial elimination phase occurs 4 to 10 hours after the dose is administered, followed by the terminal elimination phase 24 hours later. The plasma half-life of naltrexone is 10 hours. Naltrexone’s major metabolite, 6 β -naltrexol, has a plasma half-life of 14 to 19 hours and contributes to the prolonged duration of action of the medication.⁸

Our attempt to overcome the presumed antagonist effect of naltrexone, first by escalating the dose and then later by changing to another opioid formulation, failed to provide meaningful analgesia. We hypothesize that the dose administered to this patient exceeded that required to suppress microglia, and entered into the dose that antagonized μ -opioid receptors.

While we are optimistic about the use of low-dose naltrexone as a potential novel analgesic option for

patients with chronic pain, we are reminded that currently, there is no antagonist for an antagonist. When unable to overcome the antagonistic effects of oral naltrexone with dose escalation, and while waiting through

the drug's washout period, the pain management specialist may be challenged to use adjunctive strategies such as regional or neuraxial analgesics to treat this unique subset of pain patients.

References

1. Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. *Pain Med.* 2009;10(4):663-672.
2. Younger J, Noor N, McCue R, et al. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis Rheum.* 2013;65(2):529-538.
3. Cree BA, Kornyeveva E, Goodin DS. Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Ann Neurol.* 2010;68(2):145-150.
4. Smith JP, Bingaman SI, Ruggiero F, et al. Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: a randomized placebo-controlled trial. *Dig Dis Sci.* 2011;56(7):2088-2097.
5. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol.* 2014;33(4):451-459.
6. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun.* 2007;21(2):153-160.
7. Liu B, Du L, Hong JS. Naloxone protects rat dopaminergic neurons against inflammatory damage through inhibition of microglia activation and superoxide generation. *J Pharmacol Exp Ther.* 2000;293(2):607-617.
8. Krishnan-Sarin S, O'Malley SS. Opioid antagonists for the treatment of nicotine dependence. In: George T, ed. *Medication Treatment for Nicotine Dependence.* Boca Raton, FL: Taylor & Francis Group; 2007.

Case Report 3:

Contrast Pattern Spread in Interlaminar ESI in Patients Who Have Had Previous Back Surgery:

A Prospective Observational Case Series of 10 Consecutive Patients

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Background

Spinal surgery for chronic back pain or lumbosacral radiculopathy is one of the most commonly performed procedures in the United States. It is estimated that each year over 200,000 individuals undergo spinal surgery for their chronic back pain,¹ with an uptrend in the number of cases of spinal fusion per year.²



Figure 1. Previous surgery (L3-4 discectomy). Had LESI L5-S1.

LESI, lumbar epidural steroid injection

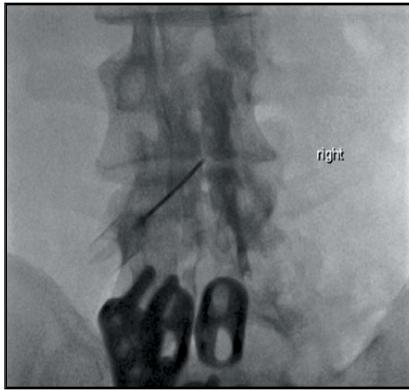


Figure 2. Previous surgery (L4-S1 fusion). Had LESI L3-4.

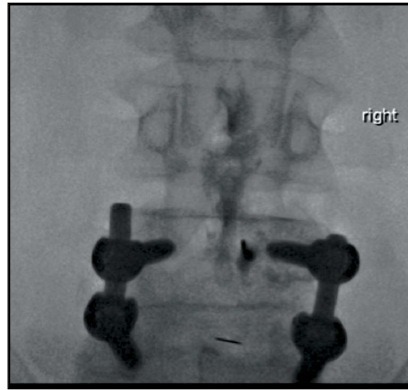


Figure 3. Previous surgery (L4-5 fusion). Had LESI L3-4.

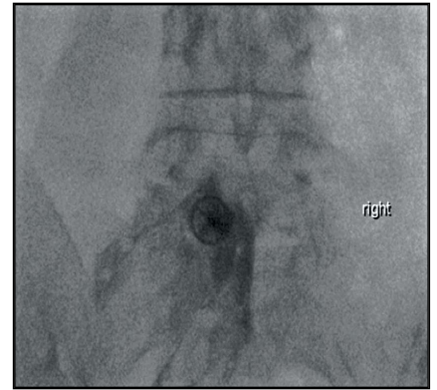


Figure 4. Previous surgery (L4-5 cyst excision). Had LESI L5-S1.



Figure 5. Previous surgery (L5 laminotomy). Had LESI L5-S1.

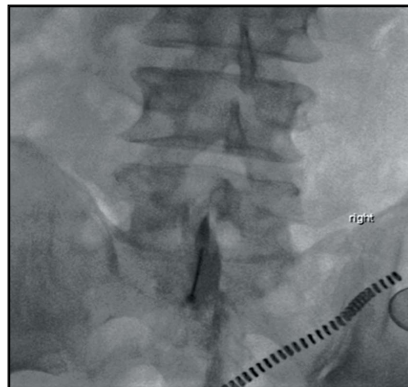


Figure 6. Previous surgery (L4-5 discectomy). Had LESI L5-S1.

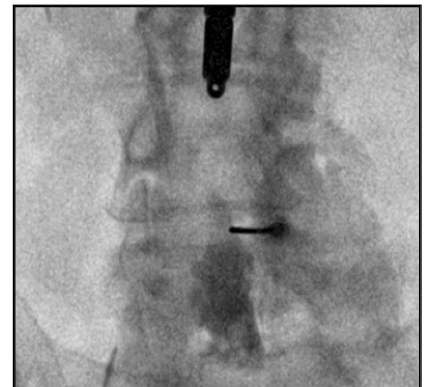


Figure 7. Previous surgery (T5-L3 fusion). Had LESI L4-5.

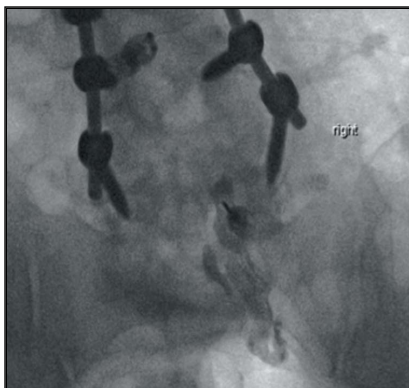


Figure 8. Previous surgery (L4-5 fusion). Had LESI L5-S1.



Figure 9. Previous surgery (L3-5 laminectomy with spinal fusion of L4-5). Had LESI L5-S1.

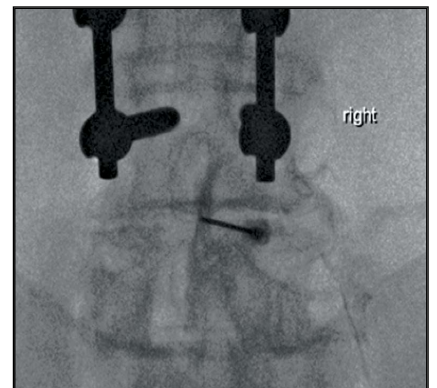


Figure 10. Previous surgery (L3-4 fusion). Had LESI L4-5.

LESI, lumbar epidural steroid injection

Surgical intervention for chronic back pain is generally warranted when the anatomical findings correlates with the patient's presentation, pharmacologic and nonpharmacologic options have been exhausted and persistent disabling symptoms are still present.

Common procedures include spinal fusion and laminectomy, which most patients tolerate well and find beneficial. However, as many as 40% of these patients continue to have back and leg pain of spinal origin after the surgery is completed,³ and a larger percentage develop recurrent disk herniations or adjacent segment disease. A small set continue to experience persistent pain or postlaminectomy syndrome especially at the site of surgery or the adjacent segment, which leads patients to seek further treatment such as epidural steroid injections (ESIs). Due to changes in anatomy (the removal of a portion of the lamina and the ligamentum flavum), the ESI is usually performed at the level of surgery, utilizing a transforaminal technique, or above or below the surgical site, using an interlaminar technique. The normal postsurgical processes of inflammation and wound healing can lead to the development of scar tissue at the surgical site, with rates of epidural fibrosis ranging from 5% to 33% for lumbar spinal surgery.⁴ This could lead to distortion of the local anatomy, and can potentially affect the spread of medication to the source of the patient's pain.

Our case demonstrates how having prior back surgery affects the spread of contrast to the surgical site in an interlaminar ESI. Of note, a contrast spread pattern does not correlate with clinical outcomes, and may expose a patient to excessive volume effect in stenotic or scarred areas. A transforaminal approach may produce improved contrast spread at the level of the surgery and potentially greater vascular, mechanical, and mass effect risk to the patient as a result of injecting into a scarred and neovascularized area.

Methods

We prospectively observed contrast spread patterns in 10 consecutive patients who had back surgery and were given an interlaminar ESI either above or below the surgical site at an academically affiliated outpatient pain management clinic.

The surgeries included spinal fusion, laminectomy, synovial cyst removal, and diskectomy. All ESIs were performed by the same practitioner, utilizing the same equipment and technique (loss of resistance [LOR] to air). After LOR to air was obtained, 2 ccs of myelographic contrast (iohexol [Omnipaque, GE Healthcare]) were given, and the fluoroscopic images were obtained. Another 2 ccs of contrast were then injected and further fluoroscopic images taken. Fluoroscopic images taken during ESI were reviewed and analyzed for the contrast spread patterns that were obtained. The literature on nonoperated backs generally demonstrates that contrast spread pattern favors greater spread toward the negative pressures in the thoracic spine; this mostly

produces a spread that is 2/3 cephalad and 1/3 caudad.

Results

Of the 10 patients, 5 had spinal fusions, 2 had laminectomies and diskectomies, 2 had laminectomies, and 1 had a synovial cyst removal. Two patients had midline or parasagittal ESIs above the level of their surgery. In these patients, the contrast spread in a cephalad fashion, with limited contrast penetrating the level of the surgical hardware or the area of the previous surgery.

The remaining 8 had ESIs below the level of their surgery with either midline or parasagittal needle placement. In these patients, the contrast spread in a caudal direction with limited spread above the inferior endplate of the vertebral level above, which had been the previous surgical site. All patients exhibited far greater contrast spread on the side of the needle placement.

Conclusion

Although many practitioners may consider a transforaminal epidural approach in operated backs, this technique poses distinct mechanical and vascular risks to patients while limiting the treatment to a single level per needle. The use of dexamethasone and particulate steroid with transforaminal ESIs is an area of active, unsettled discussion with respect to efficacy and safety. Perineural dexamethasone has been shown to be no more effective than IV dexamethasone.⁵ Furthermore, in an effort to have dexamethasone reach the efficacy of particulate steroids, even high doses of dexamethasone at 15 mg per level (which is equivalent to 75 mg triamcinolone or 75 mg methylprednisolone) have been associated with 6 times the number of patients needing up to 3 dexamethasone injections to achieve the desired effect; this potentially offsets any hypothetical benefits in favor of dexamethasone. This is in addition to the potential for time- and concentration-dependent dexamethasone-related neurotoxicity that is present in the literature. Do we need to inject perineural dexamethasone at all?

As expected, patients who had prior back surgery with subsequent ESIs at the level above or below the surgical site had most of their contrast spread above or below the surgical site performed with a 2- or 4-cc contrast injection. The therapeutic injectate volume would roughly double the total volume injected; this may be undesirable, but may enable the injectate to reach the surgical area.

Because many surgically fused backs develop adjacent segment disease and do not have an absolute indication for a transforaminal ESI, a parasagittal interlaminar injection above or below the surgical site would be able to concentrate the injectate at the desired adjacent segment.

Given the uncertainty over the optimal injectate in transforaminal injections, for those patients who previously underwent laminotomy and diskectomy who have developed a recurrent disk herniation, an

ipsilateral interlaminar epidural injection above or below the surgical site also is an option to get the medication to the intended target before a transforaminal is undertaken.

In summary, for those patients who have had spine surgery who develop adjacent segment disease or a recurrent disk herniation, interlaminar ESIs remain a viable option.

References

1. Anderson GB. Epidemiological features of chronic low-back pain. *Lancet*. 1999;354(9178):581-585.
2. Weinstein JN, Lurie JD, Olson PR, et al. United States' trends and regional variations in lumbar spine surgery: 1992-2003. *Spine*. 2006;31(23):2707-2714.
3. Shapiro CM. The failed back surgery syndrome: pitfalls surrounding evaluation and treatment. *Phys Med Rehabil Clin N Am*. 2014;25(2):319-340.
4. Masopust V, Häckel M, Netuka D, et al. Postoperative epidural fibrosis. *Clin J Pain*. 2009;25(7):600-606.
5. Martinez V, Fletcher D. Dexamethasone and peripheral nerve blocks: on the nerve or intravenous? *Br J Anaesthesia*. 2014;113(3):338-340.
6. Kennedy DJ, Plastaras C, Casey E, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective, randomized, double-blind trial. *Pain Med*. 2014;15(4):548-555.

Case Report 4:

Spontaneous Intracranial Hypotension Treated by Cervical Epidural Blood Patch

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A 40-year-old woman without significant medical history presented with newly onset headache that began approximately 1 month before presentation. She had no known trauma or precipitating event leading up to the onset of headache. She described the headache as bilateral in the occipital region without radiation. The pain is a continuous, dull pain that worsens to a sharp stabbing pain at times. She denies light or sound sensitivity.

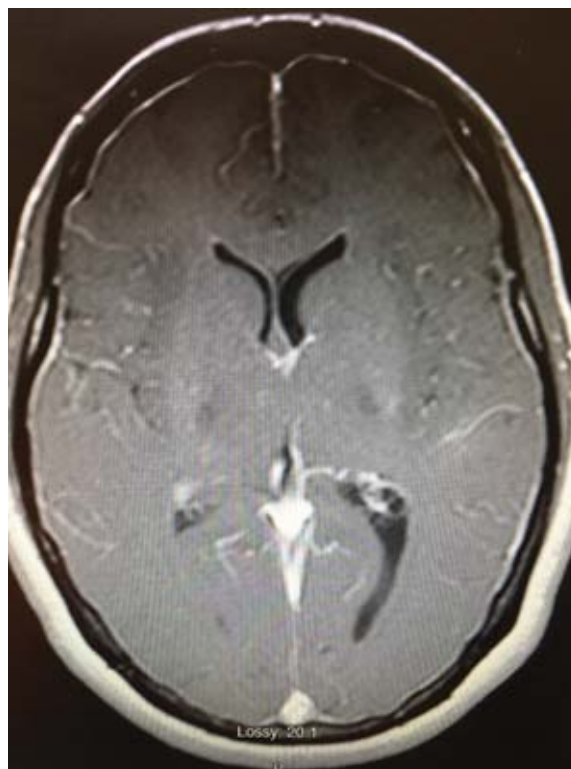


Figure 1. Magnetic resonance image of the brain.

The patient reported that when she would lay down the headache would improve, almost completely. However, when she would sit upright, after several minutes she would develop worsening headache, become off-balance, and develop nausea.

A magnetic resonance image of the brain with contrast was obtained (Figure 1), which revealed diffuse pachymeningeal enhancement. A diagnosis of spontaneous intracranial hypotension was made, and a lumbar epidural blood patch was recommended. After administration of the lumbar epidural blood patch, the patient noticed a modest improvement in her symptoms for several weeks, but the symptoms returned and were as disabling as before the procedure.

Due to the persistence of her symptoms, a myelogram of the spine (Figure 2) was obtained. It showed cerebrospinal fluid (CSF) signal intensity within the epidural space between C7 and T6, with a site of

communication at the level of C7-T1. With a suspected CSF leak at the cervicothoracic junction, the patient was referred to pain anesthesiology for a blood patch targeted at that level.

An epidural blood patch was administered at the T1-2 interspace. The patient tolerated the procedure well without complications. She had immediate relief of headache after the procedure. One month later a repeat MRI of the brain was performed, which showed resolution of the previously seen meningeal enhancement. At 3 months' follow-up, she has continued to do well without any significant symptoms.

Conclusion

Patients presenting with positional headache that worsens when upright should be evaluated for intracranial hypotension. If a lumbar epidural blood patch fails to alleviate symptoms, further testing should be performed to identify a potential site of a CSF leak, which if identified can serve as a target for a repeated blood patch.

Suggested Reading

1. Amoozegar F, Guglielmin D, Hu W, et al. Spontaneous intracranial hypotension: recommendations for management. *Can J Neurol Sci.* 2013;40(2):144-157.
2. Chazen JL, Talbott JF, Lantos JE, et al. MR myelography for identification of spinal CSF leak in spontaneous intracranial hypotension. *AJNR Am J Neuroradiol.* 2014;35(10):2007-2012.
3. Mokri B. Spontaneous intracranial hypotension. *Continuum.* 2015;21(4 Headache):1086-1108.
4. Smith KA. Spontaneous intracranial hypotension: targeted or blind blood patch. *J Clin Neurosci.* 2015 Oct 9. doi: 10.1016/j.jocn.2015.07.009. [Epub ahead of print].
5. Steenerson K, Halker R. A practical approach to the diagnosis of spontaneous intracranial hypotension. *Curr Pain Headache Rep.* 2015;19(8):35.

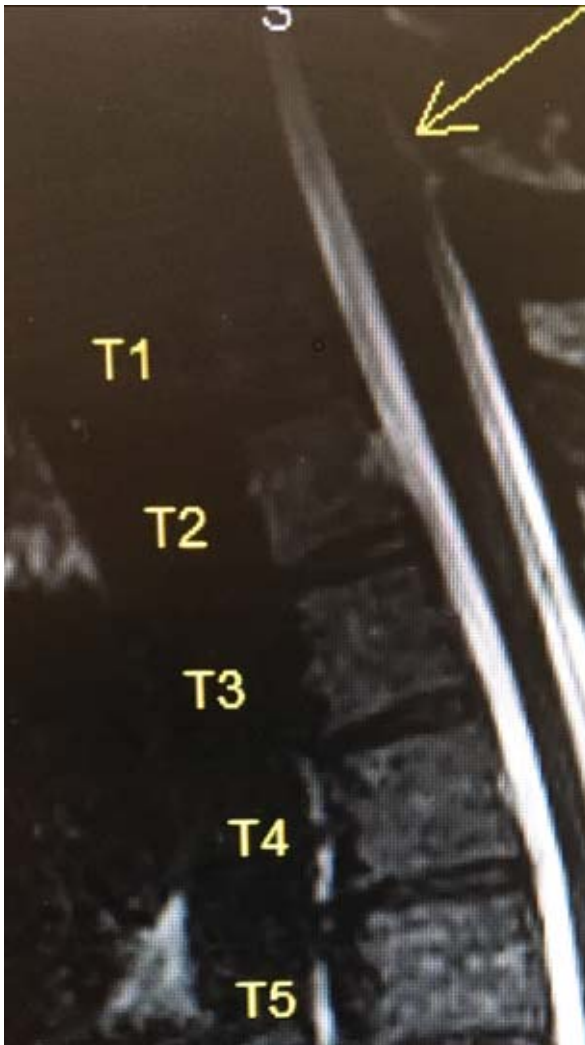


Figure 2. Myelogram of the spine.

Sensing in Spinal Cord Stimulation: Pacing the Dorsal Columns

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Dr. Deer has consulted in the past 2 years for Axonics, Bioness, Globus, Medtronic, Nevro, Spinal Modulation, and St. Jude Medical; holds minor stock options in Axonics, Bioness, Saluda, and Vertos; and previously held stock options in Nevro and Spinal Modulation.

Dr. Pope is a consultant for Flowonix, Jazz Pharmaceuticals, Mallinckrodt Pharmaceuticals, Medtronic, and St. Jude Medical.

Spinal cord stimulation (SCS) has traditionally operated in open-loop mode, with the only information about the effect of the stimulation coming from patients' verbal feedback. Measurement or sensing has gradually become an important part of other stimulation therapies: Cardiac rhythm management devices sense activity to automatically adjust the rate of cardiac pacing, or sense fibrillation to deliver a defibrillator shock; cochlear implants use sensing technology to aid device programming, particularly in infants; vagal nerve stimulators use a heart rate-based epileptic seizure detector to control stimulation¹; and new deep brain and cortical stimulation devices are able to sense electrical activity in the brain to determine when to stimulate for conditions such as Parkinson's disease and epilepsy.¹ With the recent advancements in the neuromodulation space,²⁻⁵ the pace of neuromodulation and the "next big thing" are already in development.^{6,7}

Case Report

A 54-year-old man presented to the clinic with low back and leg pain after surgery that was managed for approximately 18 months with traditional SCS. The patient had excellent therapeutic coverage, although he was very sensitive to uncomfortable positional-ity, despite multiple reprogramming attempts. To that end, the patient was interested in removal of the device and enrolled in a study testing a new closed-loop technology. The application of this novel strategy was able to improve the positionality challenges, and the patient continues to have regained excellent pain relief.

Discussion

Spinal cord stimulation is now incorporating new sensing technologies, such as accelerometer-based position sensing,⁸ and epidural recording of evoked compound action potential (ECAP).⁹ The spinal cord moves relative to the stimulating electrodes with

patient movement, so that the distance to the neural target in the spinal cord changes. Therefore, with tonic SCS systems, the stimulation delivered to the spinal cord is always changing between nontherapeutic understimulation, therapeutic stimulation, and potentially overstimulation—which can cause uncomfortable side effects. To maintain stimulation in this therapeutic window, the SCS system must automatically adjust the stimulation for changes with movement.

Accelerometer-based position sensing SCS systems determine when the patient is in 1 of 6 postures and automatically adjust the stimulation amplitude or stimulation electrodes to pre-programmed settings. Although these systems have been reported to show improved pain relief and convenience compared with traditional tonic stimulation, they do not represent a feedback mechanism, but simply a movement sensor with programming.⁸

Spinal cord stimulation systems that measure ECAP have been used to confirm the activation of dorsal

column A β fibers^{9,10} based on the conduction velocity measured from ECAP propagating along the spinal cord (Figure 1). The amplitude of the ECAP increases

linearly with increasing current, and this has been shown to correlate with the extent of paresthesia felt by the patient.⁹ To maintain paresthesia in a therapeutic range, minimizing uncomfortable overstimulation, a closed loop or feedback loop has been applied in patients with chronic pain (Figure 2). The SCS system measures the ECAP amplitude and automatically adjusts the stimulation current to maintain constant target amplitude. The ECAP amplitude signal in Figure 2 shows that with tonic stimulation, normal activities may result in overstimulation or low-level stimulation that provides little or no therapy. With feedback, however, the ECAP is maintained in the therapeutic range for the patient. Closed-loop stimulation has been demonstrated effective in a study of patients undergoing an extended trial of up to 20 days with crossover periods with and without feedback.¹¹ Figure 3 shows that ECAP sampled throughout the day demonstrates a marked variation in amplitude with feedback off, but is relatively constant with feedback on.

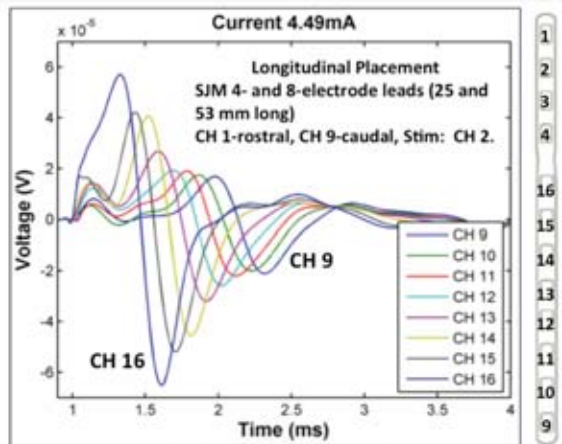


Figure 1. ECAP propagating antidromically from stimulation on 4-electrode paddle lead to 8-electrode paddle lead in humans with chronic pain. Conduction velocities averaged 50 m/s in this study.¹²

ECAP, evoked compound action potential

Conclusion

Although it may reasonably be assumed that such a closed-loop feedback system may reduce unwanted paresthesia strength effects, it is currently under research whether additional benefits may accrue from this approach. The possibility exists that such feedback loop-controlled paresthesia may become less obvious and intrusive to patients, and potentially that there may be incremental analgesic response from more constant therapeutic window activity. Certainly in other fields of neuromodulation, such sensing has proved to be a useful advance over open-loop delivery.

References

1. Sun FT, Morrell MJ. Closed-loop neurostimulation: the clinical experience. *Neurotherapeutics*. 2014;11(3):553-563.
2. Liem L, Russo M, Huygen FJ, et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation*. 2015;18(1):41-49.
3. De Vos CC, Bom MJ, Vanneste S, et al. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. *Neuromodulation*. 2014;17(2):152-159.
4. Kapural L, Yu C, Doust MW, et al. Novel 10-kHz high-frequency therapy (HF10 Therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. *Anesthesiology*. 2015;123(4):851-860.
5. Rosen SM, Bromberg TA, Padda G, et al. Intrathecal administration of Infumorph[®] vs compounded morphine for treatment of intractable pain using the Prometra[®] programmable pump. *Pain Med*. 2013;14(6):865-873.
6. Pope JE, Falowski S, Deer TR. Advanced waveforms and frequency with spinal cord stimulation: burst and high frequency energy delivery. *Expert Rev Med Devices*. 2015;12(4):431-437.
7. Deer TR, Krames E, Mekhail N, et al. The appropriate use of neurostimulation: new and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. *Neuromodulation*. 2014;17(6):599-615.
8. Schultz DM, Webster L, Kosek P, et al. Sensor-driven position-adaptive spinal cord stimulation for chronic pain. *Pain Physician*. 2012;15(1):1-12.
9. Parker JL, Karantonis DM, Single PS, et al. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain*. 2012;153(3):593-601.
10. Parker JL, Karantonis DM, Single PS, et al. Electrically evoked compound action potentials recorded from the sheep spinal cord. *Neuromodulation*. 2013;16(4):295-303.
11. Obradovic M, Shariati NH, Gorman RB, et al. Acute feasibility study: initial results from a randomized double-blinded crossover study examining the effectiveness of closed-loop control in spinal cord stimulation. Presented at: 22nd Annual Napa Pain Conference; August 27-29, 2015; Napa, California.
12. Obradovic M, Cameron T, Gorman RB, et al. Evoked compound action potentials recorded from paddle leads during intraoperative testing. Presented at: Neuromodulation Society of Australia and New Zealand 10th Annual Scientific Meeting; March 15, 2015; Hobart, Australia.
13. Shariati N, Cameron T, Obradovic M, et al. Evaluating spinal cord stimulation incorporating feedback control using evoked compound action potential. Presented at: North American Neuromodulation Society 18th Annual Meeting; December 11-14, 2014; Las Vegas, Nevada.
14. Kapural L. Potential of closed loop feedback in SCS. Presented at: 22nd Annual Napa Pain Conference; August 27-29, 2015; Napa, California.

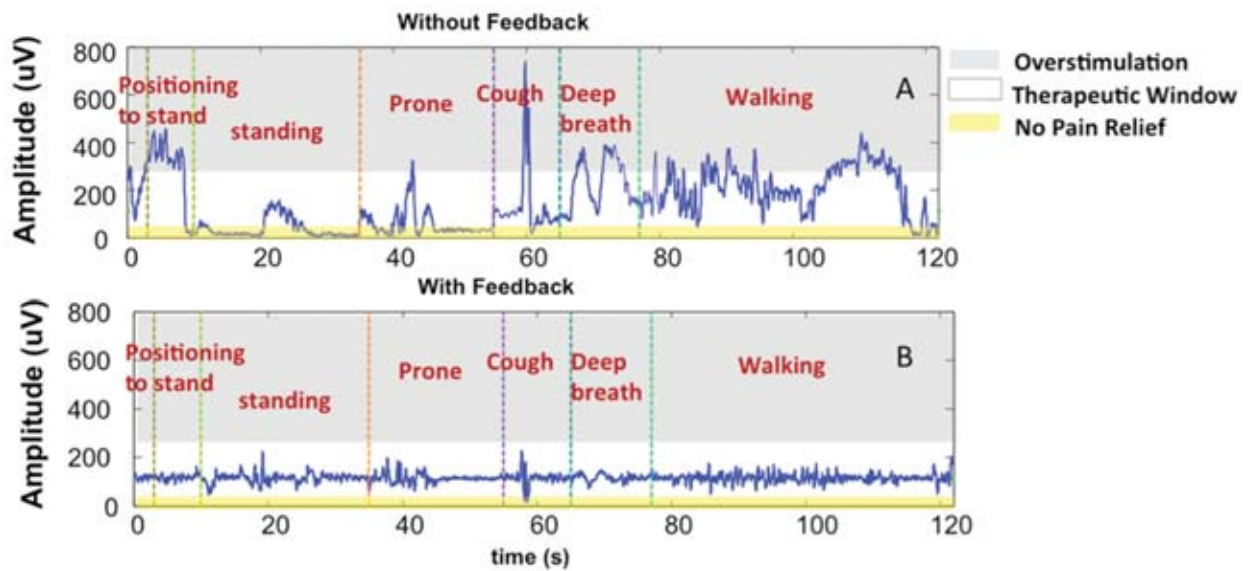


Figure 2. ECAP amplitude measured without feedback (A) and with feedback (B) in humans with chronic pain.¹³

ECAP, evoked compound action potential

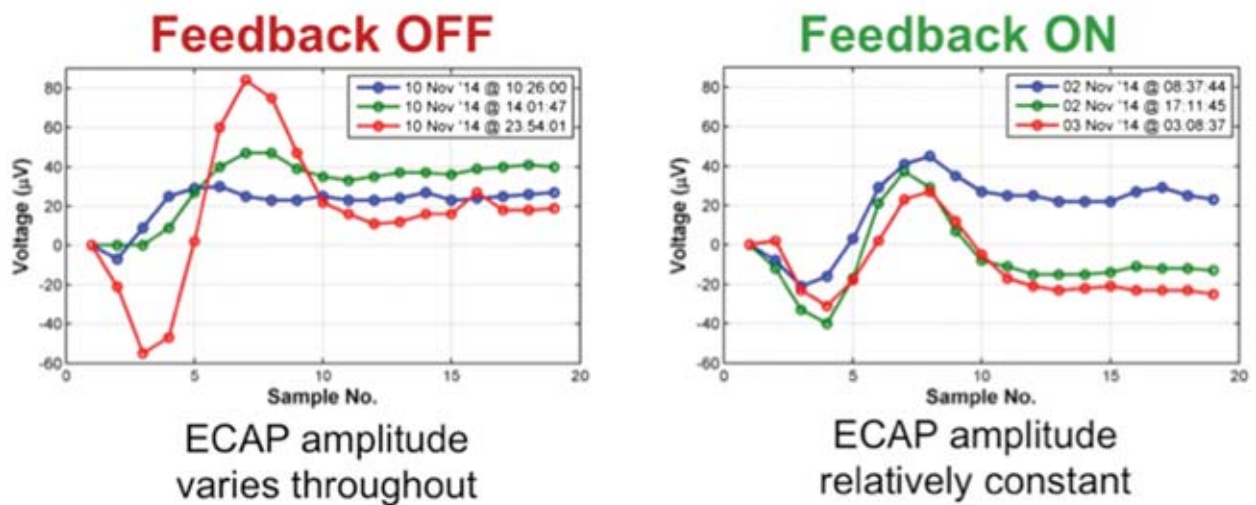


Figure 3. ECAP measured morning, afternoon, and night with an external trial stimulator.¹⁴ With feedback, the ECAP amplitude remained relatively constant, whereas without feedback the ECAP amplitude varied throughout the day.

ECAP, evoked compound action potential

Dorsal Column Stimulation Using Novel Burst Waveform for the Treatment of Neuropathic Foot Pain

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Spinal cord stimulation (SCS) has been in use since the initial implantation by Shealy et al in 1967,¹ based on the gate control theory by Melzack and Wall in 1965.² Over the last 4 decades, there have been innovations in the implantation technology, especially in the area of SCS hardware. We have always been after paresthesia stimulation to achieve pain relief, and this has been challenged with new waveforms. Burst is one such new waveform; it has enabled patients to achieve pain relief without paresthesia. Bursting, or burst firing, is a phenomenon of the activation patterns in the central nervous system, including the spinal cord.

Case Report

A 51-year-old man medically retired from the British army in 1991. He was seen in 2010 with refractory peripheral neuropathic pain. The source of the neuropathic pain was thought to be related to diabetes and possible chemical burns received during the Gulf War. A nerve conduction study showed bilateral reduced sural nerve thresholds suggestive of a mild sensory predominance axonal peripheral neuropathy.

The patient's main clinical symptoms were a painful sensation that he described as a "feeling of walking on glass"; this symptom was at its worst in the morning. He was confined to a wheelchair due to this peripheral neuropathic pain. He had a traditional SCS device implanted in 2010. This helped control his pain, although the implantable pulse generator depleted in 2014. His revision implantable pulse generator contained a new-generation device using a burst modality chip, which was activated immediately after implantation.

The burst modality not only eradicated the patient's paresthesia, but also had a positive effect on the pain within the first 2 hours of activation. The patient no longer felt the sensation of walking on glass, and experienced improvement in his mobility. The patient stated that the pain relief was greater with this new burst modality compared with the old system.

As this patient was used to paresthesia, he was initially overstimulated, leading to an unpleasant feeling related to the stimulation. Education, along with reduction in thresholds lower than paresthesia, resulted in significant improvement.

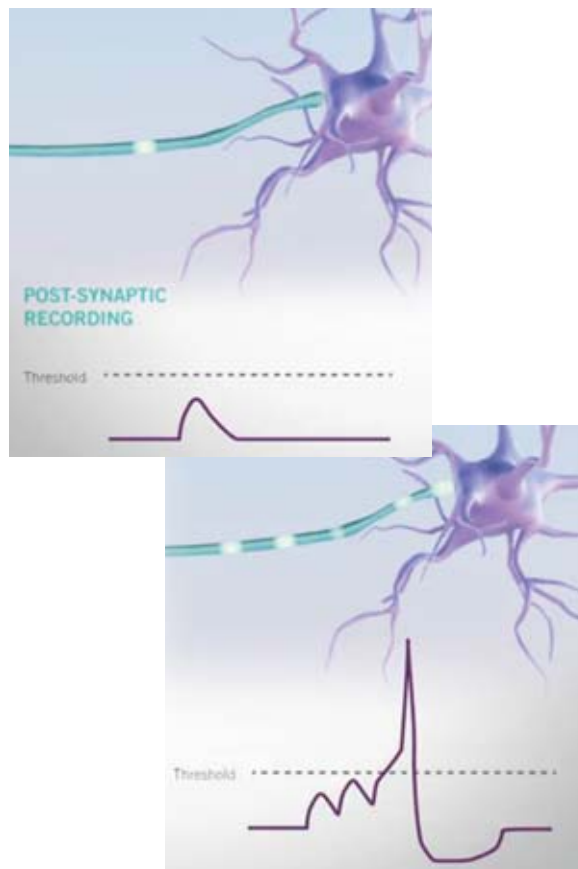


Figure. The burst waveform.

Discussion

Burst stimulation involves stimulating the spinal cord with a uniquely shaped waveform that produces 5 bursts of 1-millisecond impulses with a 1-millisecond gap between pulses, 40 times per second (500 Hz delivered for 10 milliseconds, 40 times per second). In most patients, therapeutic doses have been shown to be delivered at subthreshold electrical delivery levels (figure).

In vitro studies have shown that the thalamic cells can fire in tonic and burst mode,³ and that burst stimulation was better in activating the cortex than tonic stimulation.⁴ The clinical application of burst stimulation was first reported by De Ridder et al in 2010.⁵ A further study by the same group found that burst SCS provided better analgesia with no paresthesia compared with placebo. There was medial pathway activation in the anterior cingulate cortex as evidenced by electroencephalographic changes. This area is involved in the emotional experience of pain.

References

1. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. *Anesth Analg*. 1967;46(4):489-491.
2. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150(3699):971-979.
3. Jahnsen H, Llinás R. Voltage-dependent burst-to-tonic switching of thalamic cell activity: an in vitro study. *Arch Ital Biol*. 1984;122(1):73-82.
4. Swadlow HA, Gusev AG. The impact of "bursting" thalamic impulses at a neocortical synapse. *Nature Neurosci*. 2001;4:402-408.
5. De Ridder D, Vanneste S, Plazier M, et al. Burst spinal cord stimulation: toward paresthesia-free pain suppression. *Neurosurgery*. 2010;66(5):986-990.

Conclusion

Burst stimulation has been used in Europe and Australia for more than a year, with case reports and small randomized studies showing promise in managing patients without paresthesia. The case presented here suggests that electrical dosing may be the key to further understanding the best methods of delivery of neuromodulation going forward. In the United States, the SUNBURST study, an FDA-monitored investigational device exemption study, is currently being completed, with planned data presentation at the North American Neuromodulation Society Meeting in Las Vegas, Nevada, in December 2015. The results of that comparative efficacy study will help determine future uses of this novel waveform. Additional studies are recommended for other indications.

Case Report 7.*

Dorsal Root Ganglion Stimulation for The Treatment of Neuropathic Foot And Hand Pain

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The successful treatment of neuropathic limb pain can be challenging. The origin of these problems can be from trauma, postsurgical scarring, or neuropathy from disease. In many cases, the pain is refractory to oral medications, nerve blocks, and surgical interventions. Spinal cord stimulation (SCS) often is used for neuropathic limb pain as part of the pain care algorithm. Although this has led to success in some settings, there are cases in both the upper and lower limb in which the lack of specificity of stimulation results in less than optimal outcomes. Secondary to this limitation, an effort was made over the last decade to search for new novel targets, that improve specificity and patient satisfaction by developing a new method of neuromodulation, of which a novel lead targets the dorsal root ganglion (DRG) to achieve more specific stimulation patterns and improve outcomes.¹⁻³

Case Reports

CASE 1

The patient was a 50-year-old man who underwent a traumatic amputation of his second toe after a hunting accident. Postoperatively, he developed a causalgia in the area of the surgery. The patient failed treatment with the conventional medical management algorithm. He then underwent a series of sympathetic blocks without any improvement. After considering neuromodulation options, the physician determined that due to the specific nature of the pain, the patient's failure rate with conventional stimulation would be unacceptable over time. At this time, a unilateral DRG lead was placed at L5. The patient had a successful trial with 90% pain relief at a subthreshold energy level. A permanent device was placed with unilateral leads at L4 and L5. At 6 months, the patient had reduction on the visual analog scale from a baseline of 90 to 10 mm. His activity had normalized and he was not taking any adjuvant medications (Figure 1).

CASE 2

The patient is a 36-year-old man who had suffered a traumatic injury to the radial nerve. He underwent surgical repair of the nerve that worsened the pain. After 6 months, he was treated with multiple medications, stellate ganglion blocks, and ongoing physical medicine. A conventional SCS device was used and failed to provide relief in the area of the pain distribution. A DRG spinal stimulation system was then trialed with excellent coverage of the pain, with 2 leads placed unilaterally at C6 and C7. The device was placed in a 2-stage fashion, and

after 14 days the lead was internalized to a permanent generator. At 1 year, the patient has had an optimal outcome (Figure 2).

Discussion

The DRG is an intraspinal structure within the epidural space that serves as the processing center for all input entering the central nervous system. With chronic pain, the DRG becomes hypersensitive, and the neurotransmitters create an abnormal state that leads to aberrant neural firing. The DRG has an intricate communication system, in which there are divergent and convergent pathways that allow for modulation of these signals at different levels in order to change primary cell body firing. Standard leads used for conventional stimulation of the dorsal columns are too large, improperly shaped, and potentially dangerous in the area of the DRG.⁴ This led to the development of a novel lead with a new design placed in the normal manner of spinal stimulation with an epidural approach. A sheath is used to deliver the lead to the target. The system allows for 4 leads to be placed, which has allowed for the successful treatment of bilateral pain syndromes, such as neuropathy, in both Europe and Australia. Dorsal root ganglion spinal stimulation is approved and used widely in Europe and Australia.³ The cases presented here are typical of current patients treated in those continents.

Dorsal root ganglion spinal stimulation has been studied in the United States in a prospective, randomized fashion in a comparative efficacy model with conventional SCS. The 3-month efficacy data have been presented at the 2015 International Neuromodulation

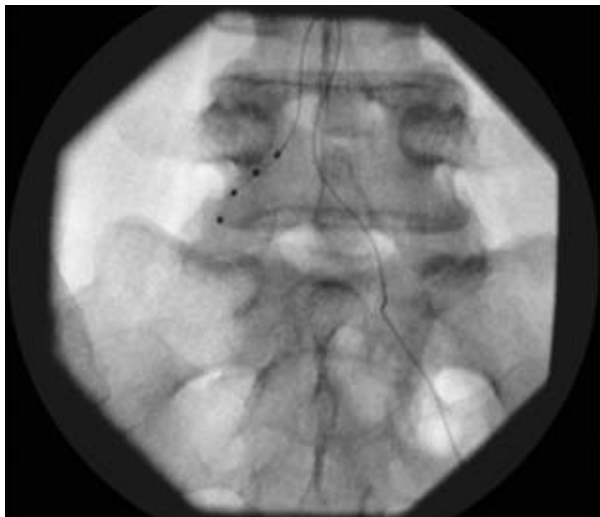


Figure 1. Dorsal root ganglion (DRG) spinal stimulation at the left L5 DRG with the novel lead system deployed.



Figure 2. Cervical placement of the dorsal root ganglion spinal stimulation leads on the right at C6 and C7.

Society World Congress. Dorsal root ganglion spinal stimulation was superior to conventional SCS when considering the primary end point of greater than 50% pain relief and a lack of neurologic safety problems with neuromodulation activation.⁵ The 1-year data have been completed and are under review with the FDA. The current use of DRG spinal stimulation in the United States is experimental, and the authors would recommend consulting with the country of practice regarding local governmental approvals.

European, Australian, and US Studies

The acute DRG study was published and established the proof of concept. This was followed up by a prospective European and Australian study

that showed favorable outcomes at 1 year.¹ A number of papers were then published showing a number of conditions that were successfully treated with the DRG spinal stimulation approach.²⁻⁴ The US IDE study has reached the 1-year mark. Results are pending, and FDA approval will be requested on the basis of those findings.

Conclusion

Dorsal root ganglion spinal stimulation has shown great success in the countries in which it has been widely used. Recent studies have been encouraging, and additional studies are planned for DRG of the cervical and thoracic spine and new waveforms and frequencies on the DRG target.

References

1. Liem L, Russo M, Huygen FJ, et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation*. 2015;18(1):41-48.
2. Deer T, Pope J, Hayek S, et al. Neurostimulation for the treatment of axial back pain: a review of mechanisms, techniques, outcomes, and future advances. *Neuromodulation*. 2014;17(suppl 2):52-68.
3. Pope J, Deer T, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. *Pain Med*. 2013;14(10):1477-1496.
4. Deer T, Grigsby E, Weiner R, et al. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation*. 2013;16(1):67-71; discussion 71-72.
5. Deer TR, Levy R. Safety and efficacy of the axium neurostimulator system for the treatment of chronic lower limb pain associated with complex regional pain syndrome (CRPS) or peripheral causalgia. Presented at: International Neuromodulation Society 12th World Congress; June 6-11, 2015; Montreal, Quebec, Canada.

Disclosure: Dorsal root ganglion stimulation is currently under an investigational device exemption study in the United States. The device and procedure are experimental and not approved for clinical use unless as part of an FDA-monitored study. The cases in this manuscript are based on patients in the European Union. All privacy information has been protected.

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Case Report 8:*

Ziconotide Delivered in a Novel Intrathecal Drug Delivery System

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Intrathecal therapy continues to evolve concurrently with our understanding of the intrathecal space. Evidence suggests that it is a necessary and viable component of pain care.^{1,2} The historical methodology of the chronic delivery of intraspinal medicine was weighted toward low-volume, slow, continuous delivery. Advancement was seemingly tied to finding a new intrathecal medication, with goals of mitigating dose escalation and improving safety.^{3,4}

Tied to the historical placement of a pump as a salvage therapy, and with the added complexity of FDA mandates with existing technologies, a limited number of advanced pain physicians seem to be interested in adoption of the therapy.⁵ Unfortunately, there has been little innovation in the development pipeline of intrathecal medicine, exclusive of ziconotide (Prialt, Jazz, Figure 1).⁶ However, there is some innovation in the space. New infusion strategies are becoming more prominently adopted. New catheters and software advancements are being realized. A new pump recently entered into the market, which may offer new technology to address concerns regarding intrathecal therapy and potentially make it an alternative to spinal cord stimulation in appropriate patients.

Case Report

A 65-year-old woman presented with a history of severe back and leg pain despite having surgery 2 years previously. The axial component of her pain was markedly greater than her leg pain. She had undergone numerous epidural injections, with transient relief lasting 6 to 8 weeks, and failed to respond to opioid therapy at a dose of 300 mg of morphine equivalents per day. She reported a previously unsuccessful trial of conventional

tonic spinal cord stimulation, which did not significantly reduce her pain despite adequate paresthesia. The trial leads were discontinued, and the patient was asked to return for further assessment 2 weeks later. Intrathecal therapy was introduced at that time as an option and a trial of intrathecal ziconotide was performed. The patient underwent 2 controlled trials with ziconotide at a dose of 2 mcg. The patient reported significant improvement with both trials of greater than 70% relief and was then implanted with a novel implantable pump (Prometra II, Flowonix Medical). The pump was initiated with a bolus-only dosing strategy using a planned bolus with 1 dose every 24 hours at 2 mcg, delivered in 23 minutes with a basal infusion of 0 mcg. Weekly titration of 0.1 mcg was performed, and the patient is now on a dose of 2.3 mcg per day with sustained pain relief at 6 months after implantation.

Discussion

We present a case utilizing a novel dosing strategy with a new intrathecal pain pump. Currently, there are 2 FDA-approved medications to treat pain intrathecally: morphine and ziconotide. Of those, ziconotide is only indicated for use with the Medtronic SynchroMed II and the Smiths Medical CADD Micro infusion pumps.⁷ Recent insights have highlighted that sustained use is achievable with low-dose, slow titration, employing mindful dosing and infusion therapies.^{1,6,8-11} It is important to highlight these differences.

The SynchroMed II device requires a volume of 0.048 cc per day to be delivered for the availability of additional programming features, including flexed dosing or patient-controlled bloused dosing. As described in a recent article, this dosing strategy was investigated in a pilot study.¹²

The Prometra II programmable pump by Flowonix is an implantable, programmable pump that uses a valve-gated bellow delivery mechanism. It has a flow gate valve that is activated by the presence of a magnetic field, requiring removal of the intrathecal medication from the reservoir and reprogramming after MRI is performed, similar to the needed interrogation following MRIs with other pumps available.

In addition, data suggest that the pump is extremely accurate ($\geq 97.1\%$; 90% CI, 96.2%-98.0%).¹³⁻¹⁵ Of note, the Prometra II system allows for zero flow in between doses, allowing for accommodation of our recent insights with the pharmacokinetics of intrathecal therapy.

Conclusion

Ziconotide is the only nonopioid intrathecal agent that is FDA approved for pain management. Its mechanism of action centers on presynaptic calcium channel blockade on the dorsal horn of the spinal cord.¹⁶ It is an n-type calcium channel blocker, as demonstrated in animal models.

It is used for nociceptive and neuropathic pain,¹⁷ and with recent interest in bolus-only strategies,¹⁸ delivery

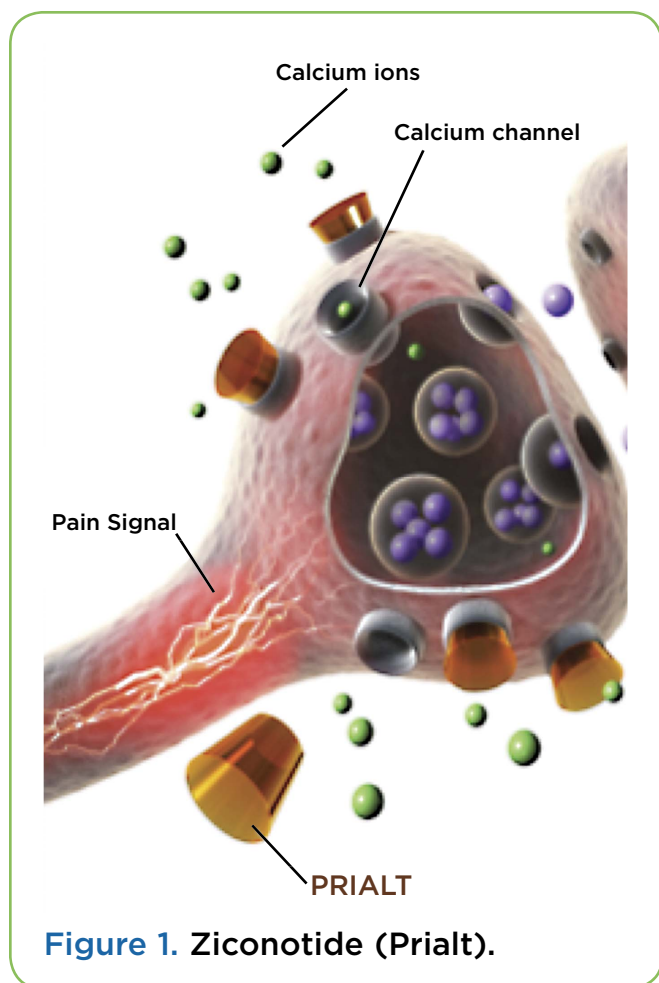


Figure 1. Ziconotide (Prialt).

via a Prometra II system, which has been shown to be very accurate in dose delivery,¹⁴ allows for zero flow, and may improve sustainability of ziconotide monotherapy—specifically when dosing is in micrograms and

titration is in tenths of micrograms. Further prospective studies are needed to confirm this theory, but from an engineering standpoint the dosing characteristics are very favorable.

References

1. Pope JE, Deer TR, McRoberts W. Intrathecal therapy: the burden of being positioned as a salvage therapy. *Pain Med*. 2015;16(10):2036-2038.
2. Hayek SM, Deer TR, Pope JE, et al. Intrathecal therapy for cancer and non-cancer pain. *Pain Physician*. 2011;14(3):219-248.
3. Veixi IE, Hayek SM, Narouze S, et al. Combination of intrathecal opioids with bupivacaine attenuates opioid dose escalation in chronic noncancer pain patients. *Pain Med*. 2011;12(10):1481-1489.
4. Coffey RJ, Owens ML, Broste SK, et al. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. *Anesthesiology*. 2009;111(4):881-891.
5. Pope JE, Deer TR. Intrathecal drug delivery for pain: a clinical guide and future directions. *Pain Manag*. 2015;5(3):175-183.
6. Deer TR, Pope JE. Factors to consider in the choice of intrathecal drug in the treatment of neuropathic pain. *Expert Rev Clin Pharmacol*. 2015;8(5):507-510.
7. Pope JE, Deer TR. Ziconotide: a clinical update and pharmacologic review. *Expert Opin Pharmacother*. 2013;14(7):957-966.
8. Mohammed SI, Eldabe S, Simpson KH, et al. Bolus intrathecal injection of ziconotide to evaluate the option of continuous administration via an implanted intrathecal drug delivery system: a pilot study. *Neuromodulation*. 2013;16(6):576-581.
9. Backryd E, Sorensen J, Gerdle B. Ziconotide trialing by intrathecal bolus injections: an open-label non-randomized clinical trial in postoperative/posttraumatic neuropathic pain patients refractory to conventional treatment. *Neuromodulation*. 2015;18(5):404-412.
10. Hayek S, Hanes MC, Wang C, et al. Ziconotide combination intrathecal therapy for noncancer pain is limited secondary to delayed adverse effects: a case series with a 24-month follow-up. *Neuromodulation*. 2015;18(5):397-403.
11. Toilapi L, Bondi F, De Carolis G, et al. Ziconotide use in the Prometra Programmable Infusion Pump: initial results. Presented at: North American Neuromodulation Society World Congress; December 6-9, 2012; Las Vegas, Nevada.
12. Pope JE, McRoberts P, Deer TR. Randomized, prospective study to assess the safety of a novel intrathecal bolus-only delivery strategy as compared to traditional simple slow continuous delivery. Presented at: North American Neuromodulation Society World Congress; December 11-14, 2014; Las Vegas, Nevada.
13. Rauck R, Deer T, Rosen S, et al. Accuracy and efficacy of intrathecal administration of morphine sulfate for treatment of intractable pain using the Prometra Programmable Pump. *Neuromodulation*. 2010;13(2):102-108.
14. Rauck R, Deer T, Rosen S. Long-term follow-up of a novel implantable programmable infusion pump. *Neuromodulation*. 2013;16(2):163-167.
15. Rosen SM, Bromberg TA, Padua G, et al. Intrathecal administration of Infumorph® vs compounded morphine for treatment of intractable pain using the Prometra® programmable pump. *Pain Med*. 2013;14(6):865-873.
16. Prialt [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2013.
17. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinous) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation*. 2012;15(5):436-464; discussion 464-466.
18. Pope JE, Deer TR. Intrathecal pharmacology update: novel dosing strategy for intrathecal monotherapy ziconotide on efficacy and sustainability. *Neuromodulation*. 2015;18(5):414-420.

Considerations for Replacing Intrathecal Pumps at the End of a Device's Life

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Intrathecal therapy is a vital component to the pain care algorithm.¹ Management of the devices has undergone changes, with a growing appreciation for the pharmacokinetics of the intrathecal space.² Because these devices have been in use for over 20 years, management of patients at end of the generator's life is becoming increasingly commonplace. Further, cost-effectiveness is an essential part of any health care plan, with intrathecal therapy being no exception. We discuss the troubleshooting associated with intrathecal therapy at end of device life and cost concerns.

Case Report

The patient is a 58-year-old man with axial back pain who has been managed for approximately 5 years with intrathecal therapy: bupivacaine and morphine at 1.5 mg per day with no bolus delivery. He came to the clinic for continued management of his device, having recently relocated from out of state. He reported no challenges with the device, but with his previous intrathecal therapy, he reported the need for a catheter revision because "there was a kink in it." Examination of the device's elective replacement indicator showed it was at 3 months, signaling the impending end of the device's life. He reported that over the last few months, he noted a difference in his typical analgesia. An x-ray was performed that revealed a continuous catheter. A catheter examination under fluoroscopy demonstrated a catheter that was unaspirable. The patient was prepped and draped in the lateral decubitus position, in order to gain surgical access to the catheter and the pump. The abdominal incision where the pump was placed was opened; the pump was disconnected; and after 2 attempts using a 10-cc syringe, cerebrospinal fluid was obtained from the catheter.

The new SynchroMed II intrathecal infusion pump (Medtronic) was prepared, 20 mL of the aforementioned solution were placed in the pump's reservoir, and the catheter was reconnected. The pump was then placed within the previous pocket after copious irrigation and the incision was closed. Dressings were applied and the rest of the surgery proceeded uneventfully. In

recovery, the length of the catheter was then bolused, and the patient was again reprogrammed with the previous simple continuous rate. A patient therapy manager was ordered for patient-controlled bolus initiation the following week. He was observed overnight and discharged in the morning.

Discussion

End of device life is an important component and consideration in pain care utilizing advanced pain care therapies. As employment of these therapies broadens with new advancements and expanding indications,³⁻⁶ so too does the increased probability of clinicians confronting the scenario described above. Intrathecal therapy has multiple variables that need to be considered collectively for successful implementation: patient selection, location and etiology of pain, catheter position, medication employed, integrity of the delivery system, and method of chronic intrathecal delivery.^{7,8}

In scenarios in which intrathecal therapy enters into a practice, understanding the aforementioned variables is necessary. Our patient has had excellent relief with the medication delivery strategy and doses, as recommended by the Polyanalgesic Consensus Conference.⁹ The patient reported a history of a complication with the integrity of the system, which necessitated a catheter revision. The factors for loss of efficacy of intrathecal therapy include granuloma, medication compromise (based on the length of refill or medication degradation), or system compromise (catheter or

pump malfunction). When the catheter or the pump are in questionable condition, a catheter evaluation is typically suggested. This procedure is performed under fluoroscopy where the side port is accessed, and once aspirated (to clear the contents of the catheter) contrast is injected. Most importantly, if the clinician cannot aspirate the catheter, it should not be bolused, as this could conceivably deliver the contents of the catheter length into the patient.

In the case of an unaspirable catheter, delivery of the medicine into the intrathecal space is not guaranteed. An unaspirable catheter could be functional for drug delivery within the intrathecal space, or could be a sign that there is a problem within the catheter system or its final placement. For patients in our practice, evaluation of the device might show a need for a catheter revision or replacement, with possibly replacement of the intrathecal pump. At the time of pump replacement, the physician can directly visualize the backflow of the cerebrospinal fluid if it is a patent system, or consider total system revision, proximal revision only, or distal revision with catheter splicing.

Medtronic states that 97.6% of their pumps employing on-label medications have an average survivability of 6.5 years.¹⁰ The pump is designed to have longevity of 4 to 7 years, based on flow rate, with a shutoff at 7 years (the elective replacement indicator on the SynchroMed II intrathecal infusion pump).¹¹ The purpose for the shutoff is to “ensure safe therapy transition by avoiding unpredictable failures that could occur as the pump’s mechanical components age.”¹¹

In terms of the cost-effectiveness of intrathecal therapy, the break-even point with conservative therapy occurs at around 28 months.¹² This is paramount, as a recent article suggests cost-effectiveness is contingent

on device longevity within the patient, which is based on a retrospective review from 1998 to 2012 using the 2013 Centers for Medicare & Medicaid Services fee schedule.¹² Median system longevity in clinical practice at the Cleveland Clinic was 5.4 years, with end of battery life occurring at 5.9 years.¹² The median cost per day was \$10.46, with the cost at the end of the battery’s life estimated at \$9.26 per day.¹² As one can appreciate, if the pump is explanted prematurely from end of battery life, costs can increase to as much as \$44.59 per day. If one could increase the longevity of the intrathecal pump, cost-effectiveness would also be improved.

New novel intrathecal delivery devices have been approved for use in the United States and European Union. One such device, the Prometra II intrathecal infusion system (Flowonix, Medical) has a projected longevity of 10 years,¹³ reducing the cost per day—based on the aforementioned fee schedule—to \$5.69 per day. Theoretically, accommodating the break-even point at 28 months, the new system is cost-effective for the remaining 7.66 years of the device. There is no evidence that the use of adjuvant medications that are within the normal standard of care will diminish the longevity of this device. Going forward, the need for comparative cost-effectiveness of devices will be important, in order to determine best practices in a health care system affected by costs.

Conclusion

The influence of end-of-life device management and battery longevity is important in the description of sustainability and access of the pain care space. Assembling a differential for end-of-pump life considerations will call for sustainable therapy, a necessity for every pain care practice.

References

1. Pope JE, Deer TR. Intrathecal drug delivery for pain: a clinical guide and future directions. *Pain Manag.* 2015;5(3):175-183.
2. Bernards CM. Cerebrospinal fluid and spinal cord distribution of baclofen and bupivacaine during slow intrathecal infusion in pigs. *Anesthesiology.* 2006;105(1):169-178.
3. Pope JE, Falowski S, Deer TR. Advanced waveforms and frequency with spinal cord stimulation: burst and high frequency energy delivery. *Expert Rev Med Devices.* 2015;12(4):431-437.
4. Liem L, Russo M, Huygen FJ, et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation.* 2015;18(1):41-49.
5. De Vos CC, Bom MJ, Vanneste S, et al. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. *Neuromodulation.* 2014;17(2):152-159.
6. Kapural K, Yu C, Doust MW, et al. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. *Anesthesiology.* 2015;123(4):851-860.
7. Pope JE, Deer TR. Intrathecal drug delivery for pain: a clinical guide and future directions. *Pain Manag.* 2015;5(3):175-183.
8. Deer TR, Pope JE. Factors to consider in the choice of intrathecal drug in the treatment of neuropathic pain. *Expert Rev Clin Pharmacol.* 2015;8(5):507-510.
9. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation.* 2012;15(5):436-464; discussion 464-436.
10. Medtronic Neuromodulation Product Performance Report. 2012. <http://professional.medtronic.com/pt/neuro/idd/prod/synchromed-ii/features-specifications/#.VkkcXaKBIZF>. Accessed November 17, 2015.
11. Kumar K, Hunter G, Demeria DD. Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost effectiveness analysis. *J Neurosurg.* 2002;97(4):803-810.
12. Bolash R, Udeh B, Saweris Y. Longevity and cost of implantable intrathecal drug delivery systems for chronic pain management: a retrospective analysis of 365 patients. *Neuromodulation.* 2015;18(2):150-155; discussion 155-156.
13. Flowonix website. www.flowonix.com/healthcare-provider/resources/faqs. Accessed November 17, 2015.

* This case contains treatment and information that is not labeled for approved use in the United States and is investigational. Please consult with your country of practice for regulatory guidance. The authors do not recommend use outside of investigational studies.