Interventional and Nonpharmacological Therapies for Neuropathic Pain

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Educational Objectives

1. To review the challenges of applying evidence to interventional therapies.
2. To describe current and emerging implantable therapies to treat chronic neuropathic pain.
3. To outline some nonpharmacological therapies to treat chronic neuropathic pain.

Interventional Therapies

Applying Evidence to Interventional Therapies

In recent years, interventional therapies to treat chronic pain have come under scrutiny owing to a lack of evidence supporting efficacy. This has led to the development of consensus guidelines based on the evidence as well as on expert consensus [35]. In 1990, the Institute of Medicine defined clinical guidelines as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" [18]. In 2011, this definition was revised as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [20]. The new definition acknowledged that, for many clinical domains, high-quality evidence is lacking or even nonexistent. Despite such constraints, guideline developers should still be able to produce trustworthy clinical practice guidelines.

Unlike the case for pharmaceuticals, there are obvious challenges in applying high levels of evidence to surgical or minimally invasive procedures. These challenges include ethical limitations of blinded surgical and sham procedures, prohibitive costs, and the need to recruit adequate numbers to complete a trial. In addition, there are wider variations in the definition of successful outcomes. For example, an American Academy of Neurology task force reported on the efficacy of epidural steroid injections (ESIs). They reviewed all of the literature on ESIs for lumbar radiculopathy and concluded that there is evidence that supports pain relief for up to 3 months; however, they could not recommend the routine use of ESIs for lumbar radiculopathy [2]. This conclusion is contrary to the general opinion that 3 months of pain relief from a single ESI is both clinically meaningful and cost-effective. A recent recommendations paper on interventional management of neuropathic pain from the IASP Special Interest Group on Neuropathic Pain (NeuPSIG) concluded that owing to the paucity of high-quality clinical trials, no strong recommendations can be made. However, on the basis of the available data, they recommended against using sympathetic blocks.
for postherpetic neuralgia or using radiofrequency lesions for radiculopathy [16].

Interventional treatment guidelines should serve two purposes: (1) to apply evidence-based medicine to improve patient selection and outcome and (2) to implement best clinical practices for techniques to improve outcome and safety. The latter point is important, and often overlooked, because as clinical experience evolves, risks emerge from interventions that have long been felt to be safe. An example is the transformaminal injection of particulate steroid, in which many reports of serious injury and death are emerging [43].

General Principles of Interventional Therapies for Neuropathic Pain

The application of interventional therapies for the treatment of neuropathic pain is quite different from that for nociceptive pain. In addition, the application will differ between noncancer and cancer pain. For example, with the exception of cryoablation, neuroablative therapies are rarely used to treat neuropathic pain because an additional insult/injury to the nervous system carries a high risk of increasing the pain from a preexisting nervous system injury. An exception to this rule is in the treatment of terminal cancer pain, given that the pain relief of the neurolytic procedure will outlast the life of the patient. In other words, the time it takes for the additional injury from the neurolytic to cause pain is longer than the life of the patient.

The location of interventional therapies in the pain treatment continuum will depend on the invasiveness of the therapy. Simple treatments such as epidural steroids (although controversial in the treatment of neuropathic pain) or sympathetic blockade might be used early on, whereas spinal cord stimulation (SCS) or intrathecal drug delivery systems (IDDS) would be used only after more conservative therapies have been tried. However, recent controversy has emerged with regard to the use of SCS over chronic opioid therapy for noncancer pain. With the increasing reports on the risks and limited value of opioids in chronic pain, SCS is being favored as a more conservative and safe therapy.

Although a number of interventional therapies are used in the management of chronic pain, this chapter will focus on implantable therapies used to treat neuropathic pain. NeuPSIG’s evidence-based guidelines for other interventional therapies were reviewed recently by Dworkin et al. [16].

Neural Stimulation

Electrical Basics

An understanding of basic electrical physics is critical for the application of SCS clinically. Ohm’s law is as follows: Voltage (V) = Current (I) × Resistance (R). We can control V and I, but not R. Patient factors that affect R include cerebrospinal fluid (CSF) depth, fluids (CSF, blood, injectates), dural thickness, epidural fat, and scar tissue. There are currently three systems on the market, with the main differences based on Ohm’s law: (1) single-source voltage-controlled, (2) single-source current-controlled, and (3) multisource current controlled. Although there are significant technologies behind these three systems, there are no controlled studies comparing efficacy. The stimulation pulse is the energy applied to the nerve and is characterized by the strength (amplitude) and duration (pulse width). Four parameters are controlled: (1) electrode polarity, (2) amplitude, (3) pulse width, and (4) frequency.

Polarity

For current to flow and nerve depolarization to occur, there must be at least one negative (cathode) and one positive (anode) electrode. Depolarization occurs under the cathode. An increased ratio of anodes to cathodes will increase the charge density under the cathode. A decreased ratio of anodes to cathodes will reduce the charge density under the cathode. This ratio controls the shape and density of the electrical field, which in turn will determine the nerve fibers in the spinal cord that are activated. More closely spaced electrodes will penetrate the current with more focus and depth, whereas more widely spaced electrodes will spread the current more widely and superficially. Multiple electrodes placed cephalad/caudad and medial/lateral over the spinal cord can be used to steer the current.

Amplitude

Defined as the strength of the stimulus measured in volts or milliamps, amplitude is the primary control over the intensity of the stimulus sensation. The higher the amplitude, the greater the size of the electrical field, resulting in the depolarization of nerves over a larger area. Higher amplitudes can result in painful sensations.

Pulse Width

Defined as the duration of the stimulation pulse, pulse width is typically measured in microseconds. Greater pulse width will cause the stimulation to stay on longer,
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resulting in depolarization of fibers with higher thresholds (sequential recruitment). Adjustment in pulse width can activate fibers that normally would require higher amplitudes, resulting in painful stimulation. Pulse width can be used in conjunction with amplitude adjustment to control the intensity of the stimulation pulse.

**Frequency**

Frequency is defined as the number of stimulation pulses delivered per second. Higher frequency increases the number of action potentials delivered by the nerve up to a point at which conduction block can occur. Changes in frequency result in changes in sensation. Low frequency results in a pulsing sensation, and high frequency results in a flutter sensation. Higher frequencies will increase the rate of battery depletion.

**Spinal Cord Stimulation**

**Conventional Paresthesia Stimulation**

Spinal cord stimulation (SCS) is indicated for the treatment of neuropathic pain. Neuropathic pain that is continuous and unchanging responds the best. SCS is not indicated for activity-related non-neuropathic pain. The goal of SCS is to apply sufficient electrical current over the dorsal columns to result in paresthesias that overlap the painful area while minimizing paresthesias in extraneous areas. The most common indication is failed back surgery syndrome with leg pain. Less common indications are peripheral nerve injury, complex regional pain syndrome (CRPS), and painful peripheral neuropathy [27]. In these three latter syndromes, overlapping paresthesias can be challenging, and it is more common for patients to report pain in spite of overlapping stimulation. The mechanism of action is thought to be based on the gate control theory of pain by selectively depolarizing large-fiber afferents in the dorsal column, thus closing the gate to small-fiber afferents that transmit pain into the spinal cord [37]. Animal studies also suggest that SCS may alter neurotransmitter release in the sympathetic nervous system and in GABAergic interneurons of the spinal cord. CSF concentrations of glutamate, glycine, and serotonin are affected by SCS. SCS does not appear to alter the μ-opioid receptor system [32].

The cost-effectiveness of SCS versus reoperation or versus conventional medical management for failed back surgery syndrome has been shown in randomized controlled trials [28,38]. However, these trials are from single sites, and there is a need for multicenter randomized controlled trials with larger numbers. An attempt was made to perform such a trial. However after over 2 years, the study was prematurely terminated due to difficulties in enrolling subjects. This failure stresses the challenges of performing high-quality studies on interventional therapies to treat pain.

**Burst Stimulation**

Burst spinal cord stimulation is an emerging technique that uses multiple bursts of stimulation that are paresthesia free. Traditional stimulation consists of a single higher-amplitude waveform. Burst stimulation uses multiple smaller-amplitude, higher-pulse-width waveforms in the same frequency range as traditional stimulation parameters. For example, a traditional waveform is 5 mA, 200 μs, and 40 Hz. A similar burst stimulation waveform is five 1-mA, 1000-μs bursts within a 40-Hz frequency. A typical burst stimulation parameter is five 1-μs bursts separated by 1-μs intervals in a 10-μs period, which results in a paresthesia-free stimulation. The lateral thalamic cells fire in a tonic pattern, and medial thalamic cells fire in a burst pattern. Therefore, the theory behind burst stimulation is that the medial thalamic cells are activated, resulting in a dissociation from the pain. These observations have been confirmed with studies showing that burst stimulation produces significantly more alpha activity in the dorsal anterior cingulate cortex (the medial pain system), which controls the affective/attentional component of the pain experience [15,22,25,34]. De Ridder et al. showed a statistically significant benefit of burst stimulation versus tonic for the general pain visual analogue scale. There was also a significant benefit of burst stimulation versus tonic stimulation with respect to attention to pain and attention to changes in pain. Further studies are currently in progress [14,15].

**High-Frequency Stimulation**

High-frequency stimulation uses frequencies up to 10 kHz, pulse width up to 1000 ms, and amplitude up to 15 mA, which results in paresthesia-free stimulation. The exact mechanism of pain relief is unclear, but preclinical studies have shown that a high-frequency alternating-current sinusoidal waveform applied to a nerve will result in a reversible block of activity [3]. This block occurs in three phases: an onset response, a period of asynchronous firing, and a steady state of complete or
partial block. This technology is currently available in Europe and Australia, with clinical trials ongoing in the United States. Due to the high frequencies used, energy consumption is high, thus requiring a rechargeable battery. This method is used primarily to treat back pain, with some effect on lower-extremity pain. Intraoperative paresthesia mapping is not necessary, and leads are placed anatomically over T9 in the midline, thus shortening procedure time. A U.S. pilot study in 24 patients with back and leg pain demonstrated a significant reduction in back and leg pain [49]. A European study conducted in 83 patients with primarily low back pain was successful in 72 patients. Long-term follow-up to 12 months showed a significant reduction in both back and leg pain. There was also a significant improvement in the Average Oswestry Disability Index Score. Sleep disturbance was improved, and patient satisfaction was high [50]. Perruchoud et al. performed a blinded, sham-controlled study interspersing high-frequency and sham stimulation between conventional stimulation periods. They demonstrated no difference between high-frequency and sham stimulation. However, they placed the leads for conventional stimulation with frequencies of 5 kHz [41]. The current system approved in Europe uses 10 kHz with all leads placed a specific location, which may explain the results.

**Dorsal Root Ganglion Stimulation**

The dorsal root ganglion (DRG) has an important role in the development and maintenance of chronic neuropathic pain. In addition, CRPS, distal leg and foot pain, inguinal pain, and truncal pain have been difficult areas to target with conventional paresthesia stimulation. Therefore, the DRG is a reasonable target for stimulation to treat these challenging pain syndromes. The predictable location of the DRG in the epidural space and the lack of overlying CSF allows for increased energy efficiency and lower energy consumption than traditional and high-frequency spinal cord stimulation. Leads are placed into the epidural space and steered out of the target neural foramen to overlay the DRG. Advancing the lead into the epidural space creates retaining loops that reduce lead migration. A prospective study was performed in 32 patients with chronic pain of the limbs and/or trunk. At 6 months after implant, more than half of the participants reported 50% or greater pain relief, with the proportions experiencing 50% or more reduction in pain specific to back, leg, and foot regions being 57%, 70% and 89% respectively. They concluded that areas hard to treat with SCS (such as the feet and trunk) may be more amenable to DRG stimulation [31].

**Peripheral Nerve Stimulation**

Peripheral nerve stimulation (PNS) was first used over 40 years ago, but it fell out of favor because of the need for an invasive cut-down for lead placement [52]. SCS came into favor owing to its success and the ease of lead placement. However, with recent advances and new techniques, there is renewed interest in PNS to treat chronic neuropathic pain, partly because SCS is not as effective in the treatment of peripheral nerve injuries. There are several ongoing clinical trials with DRG stimulation for the treatment of traumatic nerve injury and CRPS. The mechanism of PNS is unclear, but some suggest that it changes the neurotransmitter milieu of the peripheral nerve to relieve pain. The classic gate control theory has also been suggested [6,51].

Indications for PNS include pain in the distribution of an accessible peripheral nerve. The most common nerves to be treated are the supraorbital, infraorbital, greater occipital, ulnar, median, suprascapular, intercostal, ilioinguinal, iliohypogastric, genitofemoral, lateral femoral cutaneous, saphenous, sciatic, posterior tibial, superficial peroneal, and sural nerves. With the use of ultrasound, the percutaneous placement of leads is becoming more common, at least in trials. The same concepts of electrical physics described for SCS also apply to PNS [44].

There are few studies on the long-term outcomes of PNS. Deer et al. published a recent study showing relief from a device that does not require an implantable pulse generator. They are currently conducting a multicenter trial. Hassenbusch and Stanton-Hicks published a study evaluating PNS for CRPS. The success rate was more than 60% with devices that would now be considered antiquated. There are also favorable studies evaluating PNS to treat migraine (with occipital nerve stimulation), facial pain, and axial spine pain [8].

**Intrathecal Drug Delivery**

Intrathecal drug delivery (IDD) is considered an invasive and labor-intensive therapy. Therefore, appropriate patient selection and failure of more conservative therapies are essential. Indications for IDD include: (1) somatic/nociceptive pain, (2) neuropathic pain that has
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failed to respond to spinal cord stimulation (if indicated), (3) multiple pain sites with truncal/axial pain, and (4) static or changing pain. Table I summarizes selection criteria for IDD [55].

### Table I

**Patient selection for intrathecal therapy**

**Malignant Pain**  
- Life expectancy greater than 3 months  
- Inadequate pain relief and/or intolerable side effects from systemic agents  
- Favorable response to screening trial

**Nonmalignant Pain**  
- Objective evidence of pathology  
- Inadequate pain relief and/or intolerable side effects from systemic agents  
- Lack of drug-seeking behavior  
- Favorable response to screening trial

Patients with a psychological profile deemed appropriate for IDD therapy have better outcomes than those deemed inappropriate; therefore, psychological clearance is important to success. Psychological exclusion criteria include: (1) active psychosis, (2) active suicidality, (3) active homicidality, (4) major uncontrolled depression or other mood disorders, (5) somatization or other somatoform disorders, (6) alcohol or drug dependency, (7) compensation or litigation resolution, (8) lack of appropriate social support, and (9) neurobehavioral or cognitive deficits [4]. The choice of screening technique for IDD remains controversial. Both continuous infusion and bolus dosing have been used. A recent polyanalgesic consensus panel published the first recommendations for IDD (Table II) [9].

### Table II

**Recommended doses for intrathecal drug bolus trialing**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended i.t. Bolus Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.2–1.0 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.04–0.2 mg</td>
</tr>
<tr>
<td>Ziconotide</td>
<td>1–5 μg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25–75 μg</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.5–2.5 mg</td>
</tr>
<tr>
<td>Clonidine</td>
<td>5–20 μg</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>5–20 μg</td>
</tr>
</tbody>
</table>

Even more controversial is whether to withdraw systemic opioids prior to trying IDD. Advantages include: (1) reversal of tolerance, (2) identification of patients with strong physical dependence, (3) possible identification of patients with psychological dependence and addiction, and (4) possible reduction of total IDD dose over time. Disadvantages include increasing pain and suffering while the patient is off the opioids and delays in initiation of IDD. Guidelines have been published for the management of both cancer and noncancer pain (Tables III–VI) [10,11].

### Drugs Used for IDD

#### Opioids

Agonism of pre- and postsynaptic µ-opioid receptors in the dorsal horn reduces presynaptic neurotransmitter release and hyperpolarizes the postsynaptic membrane. Morphine is the gold standard and the only opioid with U.S. Food and Drug Administration (FDA) approval for IDD. Other commonly used opioids include hydromorphone, fentanyl, and sufentanil. Side effects include respiratory depression with overdose, nausea, urinary retention, pruritus, and peripheral edema [24,39,40].

#### Ziconotide

Ziconotide is the first nonopioid approved for IDD to treat chronic pain. Its mechanism is through presynaptic N-type calcium channel blockade in the dorsal horn to reduce presynaptic neurotransmitter release. Ziconotide is indicated for the management of severe chronic pain in patients for whom IDD is warranted, and who are intolerant of or refractory to other treatments such as systemic analgesics, adjunctive therapies, or IDD morphine. Two fast-titration trials (one for malignant and one for nonmalignant pain) and one slow-titration trial led to FDA approval. The malignant and nonmalignant pain study showed a 53.1% vs. 18.1% and 31.2% vs. 6% reduction in pain (ziconotide vs. placebo), respectively; however, there was a high dropout rate due to side effects [48,53]. A follow-up 3-week slow-titration trial in chronic pain patients with preexisting implanted IDD pumps showed a
14.7% vs. 7.2% reduction in pain (ziconotide vs. placebo) at 3 weeks ($P = 0.36$). Side effects were much less severe, and the dropout rate did not differ between the ziconotide and placebo group [42]. Although ziconotide has a high incidence of cognitive side effects, there is a wide margin of safety in overdose. Cognitive side effects are reduced with slow titration. There is no acute drug withdrawal syndrome upon cessation of the ziconotide. Ziconotide can be used in combination with other drugs, but there is some loss of potency when it is mixed with morphine [54].

**Local Anesthetics**

Local anesthetics are widely used in IDD. They work through blockade of pre- and postsynaptic sodium channels. They are most commonly used in combination with other IDD agents. Bupivacaine is most commonly used. It has few side effects with minimal sensory and motor disturbances at doses <20 mg/day [55].

**Clonidine**

Clonidine works through agonism of pre- and postsynaptic adrenergic $\alpha_2$ receptors, resulting in a reduction in presynaptic neurotransmitter release and hyperpolarization of the postsynaptic membrane. It is FDA approved for epidural use in cancer pain only; however, it is widely used in IDD therapy. Side effects include hypotension, bradycardia, and sedation. It is often used in combination with other IDD agents [55].

**Baclofen**

Baclofen is a GABA$_B$ agonist with antispasmodic effects through decrease release of excitatory neurotransmitters from IA, IB, and A-α afferents in the spinal cord. Analgesic effects may be due to effects on voltage-sensitive calcium channels. It is FDA approved as an antispasmodic [55].

**IDD Systems**

There are currently two FDA-approved systems on the market used to treat chronic pain. The Medtronic Synchromed II comes in 20- and 40-mL reservoir volumes. It uses a programmable peristaltic rotor system for variable rate delivery. A patient-controlled bolus dosing allows for treatment of breakthrough pain. It has a 5-year battery life and is FDA approved for morphine, baclofen, and ziconotide. The Flowonix Prometra pump uses a pressurized gas chamber as
the driving force with a programmable flow-metering valve for variable rate delivery, resulting in much lower energy requirements and thus longer battery life (10 years) [19].

**Morbidity Related to IDD**

The most common cause of morbidity relates to catheter problems. The track record for drug delivery by the system is quite good, with rare reports of system over- or under-infusion. Occasionally, the system can shut down if the rotor stalls, resulting in acute drug withdrawal. Filling of the pump pocket with high drug concentrations, filling errors, and programming errors have been reported and can be life threatening. Increasing reports of catheter tip granuloma formation were thought to be the result of high drug concentrations. The exact drug concentration that will predispose to granuloma formation is unknown [7,12,13,23,57].

**Efficacy of IDD for Chronic Pain**

There is only one prospective randomized controlled trial on IDD, in which 202 cancer patients with uncontrolled pain were randomized to either IDD or comprehensive medical management (CMM). Clinical success was defined as at least 20% reduction in visual analogue scale (VAS) scores or equal scores with at least 20% reduction in toxicity. More IDD patients achieved success (84.5% vs. 70.8%; \( P = 0.05 \)). More IDD patients achieved at least 20% reduction in both pain VAS and toxicity. There was a nonsignificant change in mean VAS between groups (IDD 52%, CMM 39%). IDD patients had a significantly greater change in toxicity scores (52% vs. 17%; \( P = 0.004 \)). There was no difference in survival between the groups [45].

**Nonpharmacological Treatments**

**Hypnosis**

Hypnosis has been used for centuries to treat pain by generating a state of highly focused attention that results in a dissociation from the pain [46,47]. It can reduce pain and anxiety related to pain in both adults and children [5,29].

**Acupuncture**

Acupuncture originated in China over 4000 years ago. Its traditional basis hinges on the existence of acupuncture points; however, studies have found a greater than 70% correlation between myofascial trigger points, motor points, and acupuncture points [33,36]. In addition, the traditional meridians in the extremities highly resemble the distribution of peripheral nerves. The mechanism is not clear, but acupuncture appears to work peripherally by stimulating A\(\delta\) afferents and centrally through the endorphin system [17,30]. There is also evidence of a neurohumoral effect [26]. One animal study suggested a long-term effect on neuroplasticity in rats with neuropathic pain [56]. There are two clinical trials showing benefits of acupuncture in painful diabetic peripheral neuropathy [1,21].

**Transcutaneous Electrical Nerve Stimulation**

TENS is a widely used treatment for chronic pain. An estimated 250,000 units are prescribed annually in the United States. There are two main stimulation patterns: (1) a low-frequency, 1–4-Hz, long-pulse-width, high-intensity stimulation that causes muscle contraction; (2) a high-frequency 50–120-Hz, low-intensity stimulation. The low-frequency pattern mimics acupuncture, whereas the high frequency uses the gate control theory. The evidence is poor in supporting the efficacy of TENS.

**References**


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