Advanced Innovations for Pain

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Abstract

Chronic pain represents one of the most important public health problems in terms of both the number of patients afflicted and health care costs. Most patients with chronic pain are treated with medications as the mainstay of therapy, and yet most medically treated patients continue to report ongoing pain. Additionally, adverse effects from pain medications represent a major challenge for clinicians and patients. Spinal cord stimulation and intrathecal drug delivery systems have proven efficacy for a wide variety of intractable conditions and fewer adverse effects than systemic medical therapy in patients with refractory cancer-related pain. Spinal cord stimulation is cost-effective and provides improved pain control compared with medical therapy in patients with a variety of refractory pain conditions including complex regional pain syndrome, painful diabetic neuropathy, and chronic radiculopathy. Patients who have intractable pain that has not responded to reasonable attempts at conservative pain care measures should be referred to a qualified interventional pain specialist to determine candidacy for the procedures discussed in this article.

CME Activity

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Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. Mayo Clinic Proceedings aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

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Learning Objectives: On completion of this article, you should be able to (1) recognize that intrathecal analgesia via an intrathecal drug delivery device provides equivalent or superior analgesia and the advantage of fewer adverse cognitive and gastrointestinal adverse effects when compared with systemic opioid pain medication in patients with cancer-related pain; (2) give examples of pain syndromes or indications that are amenable to advanced interventional approaches such as spinal cord stimulation and intrathecal analgesia; and (3) list key patient selection criteria for patients being considered for treatment with spinal cord stimulation or intrathecal analgesia.

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Chronic pain, chronic low back pain, chronic neuropathic pain, and opioid use or misuse related to chronic pain represent important public health problems in the United States and abroad. Despite numerous advances in treatments, many patients with spine and/or limb pain do not have improvement with standard conservative medical therapy. A recent evidence-based review of medical therapy for neuropathic pain concluded that “existing pharmacologic treatments for [neuropathic] pain are limited, with no more than 40-60% of patients obtaining partial relief of their pain.” Put into practical terms, this means that roughly half of all patients who present to their physician with common painful conditions such as diabetic peripheral neuropathy (DPN), postherpetic neuralgia, complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS) with a neuropathic component, and chronic radiculopathy (sciatica) will not have sufficient improvement with conservative pain care measures.

Advanced pain care options should be considered for many, if not most, of these patients with refractory pain. Yet studies indicate that most clinicians are not familiar with these options. Accordingly, many patients who could benefit from such treatment are not referred to a pain specialist who can identify and implement the appropriate advanced interventional pain therapies (AIPTs). Because many of these chronic painful conditions are lifelong problems, failure to refer patients for appropriate therapy potentially subjects them to needless long-term suffering. Another important consideration regarding AIPT is that it offers an alternative to oral opioid therapy for patients with intractable or complex pain problems. Many patients with chronic pain are treated with long-term opioid therapy despite a paucity of evidence for long-term efficacy. Opioid-related adverse effects are common, and opioid misuse has reached epidemic proportions in the United States. In the past, AIPT was considered by many physicians to be a late-stage pain therapy, mainly because of the invasive nature of the therapy. More recently, because of the limited efficacy and the myriad problems associated with long-term opioid therapy, many pain specialists rightfully consider AIPT earlier in the treatment algorithm for patients with intractable pain. Unlike other interventions that may afford only temporary improvement in pain such as nerve blocks and injections, neuromodulation addresses chronic pain problems by continuous application of electrical stimulation or pharmacological treatment delivered to targeted nerves. In this review, we will discuss spinal cord stimulation (SCS) and intrathecal drug delivery systems (IDDSs), 2 advanced neuromodulation interventional therapies that have been proved to be effective treatments for patients with refractory chronic pain. Each of these techniques involves a surgically implanted pain-relieving device, as described in the subsequent sections.

SPINAL CORD STIMULATION

SCS Devices

For most patients, the placement of an SCS device is a 2-stage process: stage 1 is a trial or temporary implant, and stage 2 is the implantation of the long-term unit. The use of the trial procedure imparts a substantial advantage for SCS over many other invasive or interventional spinal procedures in that it allows both the patient and the medical team to assess the likelihood that SCS will be helpful for the patient’s painful condition. The trial involves placing short-term or temporary SCS leads into the epidural space. It is a minimally invasive outpatient surgical procedure. In most cases, an incision is not required because the leads are placed via epidural needles. Once the leads are successfully placed, the needles are removed and the leads are steriley taped and secured to the skin surface and then connected to an external battery or generator. The patient is instructed in the proper use of the SCS trial generator and is then dismissed and allowed to assess the amount of relief over the course of the trial period, which usually lasts from 3 to 10 days. At the end of the trial period, the temporary SCS leads are removed, and a decision is made regarding the success of the SCS trial. In most cases, if the patient experiences 50% or greater pain relief as well as notable functional improvement, the decision will be made to implant a long-term SCS system.

There are 2 main components to an implanted SCS system, the generator and the leads (Figure 1). The lead or leads are placed...
into the dorsal epidural space, usually via a minimally invasive outpatient surgical procedure performed under local anesthesia and intravenous sedation. There are many different lead types and configurations, and the lead selection depends on several factors including the patient’s anatomy, the pain diagnosis, and the pain location. From the spine, the leads are tunneled under the skin to connect to a generator or battery (similar to a pacemaker generator). The generator is surgically placed just under the skin, usually in the buttock, flank, or abdomen. The patient has some control over the device via a portable handheld remote control that can turn the device on and off as well as perform some programming functions. These devices are most commonly rechargeable, allowing the device to deliver more energy with a longer battery life. The physician team managing the patient includes a programmer trained in sophisticated programming. The device then delivers electrical impulses to the dorsal spinal cord. In most cases, the patient experiences a mild and pleasant paresthesia, usually in the distribution of the underlying pain pattern. The US Food and Drug Administration (FDA) has approved a new paresthesia-free SCS system that may be advantageous for patients who do not like the sensation produced by the paresthesia. Additional paresthesia-free subthreshold waveforms are currently under investigation in multicenter prospective trials.

In recent years, the use of dorsal root ganglion (DRG) spinal stimulation has been approved in Europe and Australia and is under study in the United States. This approach involves using the epidural route to place a novel, small arch-shaped lead around the DRG in the spinal canal. This method also involves a generator but requires about 5% of the energy of the normal device; thus, it does not need to be recharged in normal use.

Indications and Mechanism of Action

The first spinal cord stimulator trial was performed in 1967, and the procedure has been FDA approved since 1989 to treat intractable (neuropathic) pain of the trunk and/or limbs. In the United States, the most common indications for SCS include new or persistent back and leg pain after spine surgery (FBSS), CRPS, and chronic radiculopathy, but it may be used to treat many other refractory neuropathic pain conditions. Several recent trials have reported substantial benefit for patients with painful diabetic neuropathy, and recent studies have examined causalgia and traumatic nerve injury of the lower extremities and groin.

The mechanisms by which SCS relieves pain, although still uncertain, have been studied extensively. The electrical signals are thought to exert pain-relieving effects by one or more of several mechanisms. There is evidence that SCS increases the levels of several dorsal horn neurotransmitters that are known to modulate pain including serotonin, norepinephrine, γ-aminobutyric acid, and acetylcholine. Spinal cord stimulation has been found to suppress or modulate hyperexcitable or sensitized dorsal horn wide dynamic range neurons that are implicated in many neuropathic pain states. The procedure may also antidiromically stimulate the peripheral release of vasodilatory neurotransmitters including calcitonin gene-related peptide and nitric oxide. These mechanisms are all congruent with the observed clinical pain-relieving effects of SCS. The effect of SCS on pain from ischemia may be from a different mechanism, with the most commonly
accepted pathway being that of sympathetic nervous system alteration. The mechanism of action for DRG spinal stimulation appears to be a direct action on the abnormal primary cell bodies in the DRG.8

**Outcomes of SCS Therapy**

Several randomized controlled trials (RCTs) and systematic reviews have documented the effectiveness of SCS in chronic pain states (Table 1). Spinal cord stimulation with physical therapy was superior to physical therapy alone in a prospective RCT that measured pain scores and global perceived effect over 2 years in patients with refractory CRPS.28 Another study reported better outcomes with SCS than with redo lumbar spine surgery in patients with FBSS.29 Greater than 50% pain relief was achieved long-term in 47% of patients randomized to SCS vs 12% randomized to reoperation. Furthermore, 14 of 26 patients randomized to reoperation elected to cross over to the SCS arm vs 5 of 24 patients randomized to SCS who crossed over to reoperation. In an RCT of 100 patients, Kumar et al30 found that SCS plus medical therapy was far superior to medical management alone for the treatment of intractable neuropathic pain in the setting of failed lumbar spine surgery. In that study, only 5% of patients receiving medical management achieved greater than 50% relief of pain at 1 year vs 45% of patients treated with SCS. The SCS group also experienced significant improvements in function and quality of life (QOL) compared with the medical therapy group. A recently completed RCT comparing 2 different types of SCS for patients with chronic back and leg pain reported that 65% of patients treated with 10,000-hertz SCS experienced significant pain relief at 18-month follow-up, a result that was statistically superior to conventional tonic SCS.7 Several recent trials including 2 RCTs have found SCS to be effective for the treatment of intractable pain related to diabetic neuropathy.15,17,31,32 A recent multicenter RCT comparing SCS to “best conventional medical practice” in patients with painful DPN reported no improvement in patients who received medical therapy, whereas SCS-treated patients experienced significant improvement in pain and QOL.15 Spinal cord stimulation has been documented to provide significant pain reduction in patients with painful vaso- spastic diseases.16,33 Patients with refractory chest pain from coronary vasospasm or small-vessel disease that is not amenable to stenting or bypass can have significant improvement in pain, QOL, and reduced physician or emergency department visits following treatment with SCS.34-37 The procedure has shown promise in a number of other difficult to treat chronic neuropathic pain states including postherpetic neuralgia, postamputation pain, and limb pain secondary to peripheral vascular disease.

Recently, the results of a prospective randomized multicenter study comparing SCS to DRG spinal stimulation were presented at the 3-month efficacy end point.38 The results showed a statistically superior outcome in the DRG group for neuropathic pain involving the groin or lower extremity. Safety data was similar in each group, and 2-year follow-up is planned.

In the past, it has been argued that SCS is costly and should only be used as a last resort. Several recent studies have reported that SCS is not only less costly but also cost-effective and represents value-based therapy for many patients with intractable pain.5,39-41 This finding should not be surprising given the high costs of multiple rounds of medications, physician and emergency department visits, and other therapies such as injections and nerve blocks that patients with chronic pain often require over a period of years. Two recent studies found that SCS plus medical management was cost-effective compared with medical management alone for several chronic neuropathic pain conditions including FBSS and CRPS. The study by Kumar and Rizvi15 documented an incremental cost-effectiveness ratio (ICER) well below most commonly accepted willingness-to-pay per quality-adjusted life-year thresholds. In their study, the ICER for FBSS was $9293 (Canadian dollars), and the ICER for CRPS was $11,216.

It is well understood that the longer a patient with chronic pain remains debilitated,
the more treatment-refractory that pain becomes. This issue has led to a reappraisal of SCS being used as a late-stage or last resort therapy for intractable pain. Recent studies have found that earlier intervention with SCS leads to much better outcomes.\textsuperscript{3,4,14,42-44}

Knowing that chronic neuropathic pain is notoriously resistant to medical therapy and that SCS therapy provides cost-effective pain relief and improved QOL when compared with conventional medical management has led many pain specialists to place SCS therapy much earlier in the chronic pain treatment algorithm. A corollary is that patients with refractory chronic pain should be referred to a pain specialist earlier rather than later.

### Adverse Events

Because SCS is an interventional and surgical procedure, consideration should be given to possible adverse events and outcomes. The most common adverse events are listed in Table 2. The risk of a serious adverse event can be minimized or mitigated with experience and by adhering to good surgical technique and published guidelines.\textsuperscript{45,46} The risk or likelihood of a severe neurologic injury such as spinal cord injury or nerve root injury is very low. In the 2 largest series, Mekhail et al\textsuperscript{47} reported no permanent neurologic injuries in a review of over 1200 lead placements, and Cameron\textsuperscript{48} reported one case of paralysis due to infection and epidural abscess in a series of nearly 3000 patients. The most feared SCS complication is epidural hematoma from lead placement. This is a rare complication, and the likelihood of it occurring depends on many factors including the selection of lead type. Levy et al\textsuperscript{49} reviewed over 44,000 cases of surgically placed paddle-type leads and identified 83 cases of epidural hematoma (0.19%), with 51% of these patients having persistent residual impairment.

The most frequent adverse events are equipment related including discomfort around the hardware and movement of the leads. The frequency of these issues has been reduced considerably in the past 5 years with improvements in equipment and surgical techniques.\textsuperscript{35,50} Recently, the International Neuromodulation Society provided guidance in a large consensus project on best practices to reduce the rate and severity of complications of SCS.\textsuperscript{45}

### INTRATHECAL DRUG DELIVERY SYSTEMS

#### IDDS Devices

There are 2 main components to IDDS devices, the pump component and the catheter that carries the drug(s) from the pump to the cerebrospinal fluid within the spinal canal (Figure 2). These devices are surgically placed in a fashion similar to that for the SCS systems. The IDDS device placement can be performed as an outpatient procedure, but most patients are hospitalized for the procedure, observed overnight, and dismissed the next day. The pump is filled with the desired analgesic medication, and the pump delivers the medication via the catheter to the cerebrospinal fluid. The amount of drug that the patient receives can be regulated by controlling the concentration of the drug in the pump and/or by varying the rate of the infusion. Most pumps that are currently in use are fully programmable via an external programmer controlled by the management team. This feature allows dose adjustments to be made noninvasively as the patient’s clinical condition changes. Additionally, patients may be equipped with a remote device whereby they can self-administer a bolus on an as-needed basis; the dose, lockout interval, and maximum doses per day are preset by the clinician. The pump must be refilled periodically, for most patients every 1 to 3 months, in a sterile procedure performed in the clinic or through a home visiting nurse service. The pump has an access port (much like a subcutaneous intravenous port) that can be accessed by a special needle and kit. After sterile preparation of the skin, the needle

#### TABLE 2. Adverse Events Associated With Spinal Cord Stimulation

<table>
<thead>
<tr>
<th>Hardware or device related</th>
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<tbody>
<tr>
<td>Pain over the generator site or stimulator leads</td>
</tr>
<tr>
<td>Lead migration causing loss of therapy</td>
</tr>
<tr>
<td>Lead fracture</td>
</tr>
<tr>
<td>Generator depletion</td>
</tr>
<tr>
<td>Painful stimulation</td>
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<tr>
<td>Surgery related</td>
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<tr>
<td>Infection (surgical site infection)</td>
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<tr>
<td>Neurologic injury</td>
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<tr>
<td>Accidental dural puncture with associated headache</td>
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<tr>
<td>Epidural hematoma</td>
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is advanced through the skin and through the access port into the drug reservoir. The medication is delivered, the needle is removed, and the pump is reprogrammed.

**Indications and Mechanisms of Action**

Wang and colleagues from the Mayo Clinic reported the first use of intrathecal opioids in humans in 1979. The first programmable intrathecal catheter and pump implant was placed in 1982. Over the ensuing years, spinal analgesia via an implantable IDDS has become mainstream treatment for intractable pain and spasticity. There are 3 main clinical scenarios in which IDDS devices can be extremely beneficial:

1. Intrathecal baclofen can be very effective in managing intractable spasticity in the setting of brain and/or spinal cord pathology from a number of causes including multiple sclerosis, cerebral palsy, spinal cord injury, and stroke.
2. Intrathecal delivery of pain medications is effective for patients with intractable cancer-related pain and has been found to provide improved pain control and QOL with substantially fewer adverse effects (such as constipation and sedation) compared with systemic analgesics.
3. The third scenario is the use of IDDSs for the management of many chronic painful conditions that have failed to respond adequately to more conservative pain care measures (eg, physical therapy, oral medications, nerve blocks, cognitive behavioral therapy).

The FDA has approved 2 medications for pain and 1 for spasticity. Baclofen is a very effective FDA-approved agent for management of intractable and refractory spasticity. Currently, no off-label drugs have been found to be clinically acceptable for the treatment of spasticity or movement disorders when delivered intrathecally. Morphine and ziconotide are the 2 FDA-approved pain medications currently available for use in IDDS devices.

Morphine exerts a very potent analgesic effect in the spinal canal. Pain signals are moderated by morphine binding to opioid receptors in the dorsal horn of the spinal cord. As an example of the potency, a typical daily oral morphine dose for a patient with chronic or cancer-related pain is 100 mg per 24-hour period. An approximate equivalent intrathecal 24-hour dose is 0.5 to 1.0 mg.

Ziconotide, a nonopioid analgesic, is a 25–amino acid conotoxin (derived from cone snails) that blocks N-type calcium channels in the brain and spinal cord. This process in turn interferes with the release of neurotransmitters involved in pain modulation and transmission in the spinal cord. Ziconotide may be a very potent analgesic in some patients, but it requires careful dose titration because of its very narrow therapeutic window, as discussed subsequently.

In past analysis, it appears that only 20% to 25% of patients are successfully treated with these 2 initial drugs. Because of the high failure rate of these medications due to either lack of efficacy or adverse effects, most patients are treated with medications or combinations that are not labeled for initial use. In addition, of those receiving the 2 drugs initially labeled by the FDA, most are treated with compounded formulations to address concentration needs; therefore, a minority of patients are treated on-label. The safe and efficacious use of these medications...

**FIGURE 2.** Intrathecal drug delivery device. The catheter is inserted into the intrathecal space. From there it is tunneled subcutaneously to the pump, which contains the drug reservoir.
has been outlined by an expert consensus group.\textsuperscript{56-62} The Polyanalgesic Consensus Conference group has met intermittently over the past several years to establish the best practices for this therapy.\textsuperscript{58} Table 3 lists the most commonly used medications. Off-label medications that are commonly used, depending on the type and location of the pain, include bupivacaine, clonidine, hydromorphone, and fentanyl.\textsuperscript{57,58,61} Combinations of medications are used in many patients, and all combination therapies represent off-label use. That being said, in 3629 of 5478 SynchroMed II intrathecal pain pumps (Medtronic) enrolled in the manufacturer’s Implantable Systems Product Registry, off-label drug or admixture was used, and this number is most likely much higher considering that any compounded drug is by definition off-label, including morphine.\textsuperscript{63}

A challenge that is faced when drug combinations are used in the pump is that the pump has a single drug chamber. All medicines being used are combined into a single mixture, and the pump chamber is then filled with the drug mixture. Therefore, when a combination drug mixture is used, individual drug dosage changes cannot be made unless the pump is refilled with a new drug mixture. As an example, when a single drug such as morphine is used, the dose can be changed by simply reprogramming the pump with a telemetry-based programmer. When a pump containing a drug mixture such as morphine and bupivacaine is programmed to change the dose, the doses of both drugs are affected. The only way to change the dose of one drug and keep the other drug dose constant is to refill the pump with a new drug solution. The use of intrathecal drug combinations requires very careful and thoughtful dose adjustments by an experienced team in order to optimize therapy and minimize adverse events.

There are 2 important advantages of the use of an IDDS in refractory pain states. The first is that when an opioid is used, the dosage required is at least 50 to 100 times less than an equianalgesic oral systemic dose. The clinical advantage is that the 3 most troublesome adverse effects of opioid therapy—constipation, sedation, and cognitive dysfunction—are almost always decreased with IDDS therapy compared with systemic therapy. The second advantage is that multiple medications are available for intrathecal use that are not available for systemic pain therapy, thus increasing treatment options.

**Outcomes of IDDS Therapy**

Intrathecal analgesia has been documented in multiple trials, including a multicenter randomized controlled trial, to provide equal or superior analgesia with fewer adverse effects compared with systemic analgesics in patients with severe cancer-related pain.\textsuperscript{64,65} Intrathecal analgesia should be strongly considered in patients with advanced disease who have severe cancer-related pain that is suboptimally managed with systemic medications and in those who are experiencing severe pain medicine toxicity (usually constipation and/or cognitive dysfunction). In this setting, implementation of intrathecal analgesia with an IDDS will allow a substantial reduction in the dose of systemic pain medication(s) and almost always leads to improved pain control and improvement in systemic pain medication-induced bowel and/or cognitive dysfunction.\textsuperscript{60,64-66}

The use of an IDDS may also be considered for patients with nonterminal disease who have refractory pain. Patients who may be good candidates include those with severe back pain, severe pain accompanied by spasticity (eg, multiple sclerosis), and CRPS.\textsuperscript{56,60,62,67,68} Conversely, patients with diffuse or widespread pain (eg, fibromyalgia) or poorly defined pain problems in which the pathoanatomic or pathophysiologic basis is unknown typically do not do well with IDDSs and are not typically considered candidates for this therapy.

**Adverse Events**

Adverse events related to IDDS therapy can be divided into medication-related adverse effects,
device-related events, surgical procedure–related events, and human error (Table 4). Although intrathecal opioids have a lower incidence of the 3 most troublesome opioid-related adverse effects (sedation, cognitive dysfunction, and constipation) than systemic opioids, adverse effects can occur and require monitoring. The most common adverse effects are readily manageable and include pruritus, nausea, lower extremity edema, urinary hesitancy, and opioid-related endocrinopathies.\(^{67,69}\) Opioid-related hypogonadism due to suppression of the hypothalamic-pituitary-gonadal axis occurs commonly with both oral and intrathecal opioid therapy. This complication can be monitored by checking testosterone, follicle-stimulating hormone, and luteinizing hormone levels and treating deficiencies appropriately. Additionally, sterile growths of macrophages, monocytes, and neutrophils can occur at meninges surrounding the intrathecal catheter tip in patients receiving morphine or hydromorphone. This phenomenon, called a granuloma or inflammatory mass, can lead to progressive neurologic disease.\(^{70}\) With the recent identification of this issue being directly related to morphine or hydromorphone concentration, the incidence of granuloma appears to be declining.

The most common device-related adverse events include catheter leaks or obstruction, pump malfunction, catheter migration out of the intrathecal space, and pump refill–related complications.

The most common surgical- and procedure-related adverse events include surgical site infections and persistent spinal fluid leak related to puncture of the dural sac during catheter placement. Rarely, nerve or spinal cord injury related to needle or catheter placement into the dural sac can occur. This complication may be mitigated by performing this part of the procedure with the patient under conscious sedation, although the risk benefit must be considered in those who have severe pain in the surgical position.

Errors that may occur during the refilling and/or reprogramming of the pump represent the most serious and life-threatening adverse events and also the most preventable. Errors that lead to unrecognized medication underdosing can cause acute withdrawal syndromes, which can be serious and in the case of baclofen, life-threatening. Errors in programming or refilling that lead to an unrecognized overdose can be fatal. These errors are preventable by having systems and procedures in place that follow published guidelines and refill protocols. Most IDDS-related adverse events will require management or comanagement with the patient’s pain management team. When a primary care physician or non–pain specialist is caring for these patients, the most clinically important situations to be aware of are opioid-induced hypogonadism, sudden loss of pain relief in a patient who was previously doing well, new back pain, and new neurologic symptoms. Symptoms of hypogonadism should be assessed regularly and endocrine work-up obtained if symptoms occur. Opioid-induced hypogonadism is treatable with appropriate hormone replacement therapy.

As with systemic pain medications, tolerance to the pain-relieving effects often occurs over time with IDDS therapy. This problem can usually be managed by dose adjustments or alternative medications. Conversely, a sudden loss of pain relief should signal the need for an immediate and systematic evaluation. The most common causes of a sudden loss

### Table 4. Adverse Events Associated With IDDS Therapy

<table>
<thead>
<tr>
<th>Hardware or device related</th>
<th>Surgery related</th>
<th>Medication adverse effects (different for each medication)</th>
<th>Human error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pump malfunction</td>
<td>Infection (surgical site infection)</td>
<td>Sedation (opioids, clonidine, ziconotide)</td>
<td>Pump programming error</td>
</tr>
<tr>
<td>Catheter breakage, obstruction, or migration</td>
<td>Neurologic injury</td>
<td>Endocrine dysfunction, especially hypogonadism (opioids)</td>
<td>Pump refill error</td>
</tr>
<tr>
<td>Pain/discomfort from the pump</td>
<td>Spinal fluid leak from dural puncture (spinal headache)</td>
<td>Urinary retention (opioids, local anesthetic, ziconotide)</td>
<td>Pharmacy drug concentration error</td>
</tr>
<tr>
<td>Granuloma (mass) formation at catheter tip</td>
<td>Hypotension (local anesthetic, clonidine)</td>
<td>Hypogonadism (opioids)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor weakness (local anesthetic)</td>
<td>Urinary retention (opioids, local anesthetic, ziconotide)</td>
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</tr>
<tr>
<td></td>
<td>Cognitive dysfunction (ziconotide)</td>
<td>Hypotension (local anesthetic, clonidine)</td>
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<tr>
<td></td>
<td>Psychiatric symptoms (ziconotide)</td>
<td>Motor weakness (local anesthetic)</td>
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<tr>
<td></td>
<td>Edema (opioids)</td>
<td>Cognitive dysfunction (ziconotide)</td>
<td></td>
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<tr>
<td></td>
<td>Pruritus (opioids)</td>
<td>Psychiatric symptoms (ziconotide)</td>
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</table>

IDDS = intrathecal drug delivery system.
of pain relief are a new pain problem, pump or catheter system malfunction, and the development of a granuloma around the tip of the intrathecal catheter. The lattermost situation is a medical emergency because catheter tip granulomas can compress the adjacent spinal cord and if not recognized and treated promptly, can lead to permanent neurologic injury including paralysis. The most common clinical presentations of a catheter tip granuloma are the loss of pain relief with or without new back pain and/or new neurologic symptoms such as radiating trunk or leg pain, gait changes, and a change in bowel or bladder function.

PATIENT SELECTION FOR AIPT

Many RCTs have found that SCS is superior to medical management in patients with severe, painful neuropathic conditions including CRPS, FBSS, and painful DPN. It is also clear that implementing SCS earlier in the treatment algorithm rather than as a last resort leads to better outcomes. Accordingly, patients with chronic pain in whom reasonable attempts at conservative care have failed should be referred to an experienced interventional pain specialist for consideration of AIPT. For most patients with neuropathic pain, a reasonable attempt at conservative care would include the following: (1) a trial of 2 or 3 first-line neuropathic pain medications. Examples include topical lidocaine, gabapentin, duloxetine, and amitriptyline, depending on the patient and the pain problem. Too often patients experience years of multiple failed medication trials, leading to hopelessness, frustration, and wasted time and resources; (2) a good physical medicine program including a concerted effort of therapeutic exercise and the use of adjunctive physical modalities (eg, heat, ice, surface electrical stimulation); and (3) cognitive behavioral therapies. Concomitant management modalities that have proved useful in a particular patient in conjunction with neuromodulation may offer the best option for achieving satisfactory pain relief.

Many pain specialists and pain centers have a formal psychological screening process as a component of the patient evaluation process. This process includes screening for untreated or suboptimally treated anxiety, depression, and personality and substance abuse disorders that could negatively affect the outcome of interventional therapies. A patient’s medical and emotional conditions should be optimized before implantation of an SCS or IDDS device. Because these devices involve surgery of the spine, coagulation status must be normal, blood sugar control should be optimized in diabetic patients, and clinically important chronic disease states should be stable and optimally managed. Table 5 lists the most important contraindications to IDDS and SCS therapy.

OTHER STIMULATION TECHNIQUES

Spinal cord stimulation and IDDS are the 2 advanced interventional techniques currently approved by the FDA. Many other stimulation techniques that have off-label uses have been found to be useful in certain pain situations. Occipital nerve stimulation is a procedure involving the placement of stimulation electrodes just under the skin in the occipital region in order to electrically stimulate the occipital nerves. It has been used for almost 20 years to treat refractory headache syndromes. Sphenopalatine ganglion stimulation is a relatively new procedure that has shown promise in treating refractory head and face pain syndromes. Deep brain stimulation and motor cortex stimulation can be useful in carefully selected patients with refractory pain syndromes including head, face, and poststroke pain. Noninvasive stimulation techniques may also be used in the future. Transcranial magnetic stimulation and direct current

<table>
<thead>
<tr>
<th>TABLE 5. Contraindications to SCS and IDDS Therapy</th>
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<tr>
<td>Widespread pain without a defined cause</td>
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<tr>
<td>Active coagulopathy</td>
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<tr>
<td>Active systemic infection</td>
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<tr>
<td>Poorly controlled diabetes</td>
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<tr>
<td>Immune dysfunction</td>
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<tr>
<td>Spinal anatomy that precludes device placement</td>
</tr>
<tr>
<td>Suboptimally treated psychiatric disease</td>
</tr>
<tr>
<td>Active substance abuse disorder</td>
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</tbody>
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IDDS = intrathecal drug delivery system; SCS = spinal cord stimulation.
stimulation are being studied to treat a number of neurologic symptoms, and some studies have found benefit in patients with chronic pain.87-90

THE FUTURE OF SCS AND IDDS THERAPIES
The past 25 years have seen remarkable advancements in the field of advanced interventional pain-relieving devices. Outcomes are improving because of continuing advancements in equipment and surgical implant techniques. Indications are expanding as evidenced by several recent trials documenting the efficacy of SCS for patients with painful DPN and chronic chest pain. Recently approved novel neuromodulation systems, and more to come, will add to our armamentarium. A new paresthesia-less SCS system has been found to be very effective in treating patients with persistent pain following back surgery, and a recently approved DRG stimulation system looks promising for treatment of some of the most challenging painful conditions. It is likely that some of the off-label techniques described in this article may become FDA-approved therapies in the future, pending the results of additional clinical trials.

CONCLUSION
Chronic pain represents one of the most important public health problems in terms of the number of patients afflicted and health care costs. Most patients with chronic pain are treated with medications as the mainstay of therapy, and yet most medically treated patients continue to report ongoing pain. Additionally, adverse effects from pain-related medications represent a considerable challenge for clinicians and patients. Spinal cord stimulation and IDDS therapy are well-established techniques that have been utilized for over 25 years. Intrathecal drug delivery systems have proven efficacy for a wide variety of intractable pain conditions and substantially fewer adverse effects than systemic medical therapy in patients with refractory cancer-related pain. Spinal cord stimulation is cost-effective and provides improved pain control compared with medical therapy in patients with a variety of refractory pain conditions including CRPS, painful diabetic neuropathy, and FBSS. Patients with intractable pain that has not responded to reasonable conservative pain care measures should be referred to a qualified interventional pain specialist to determine candidacy for the procedures discussed in this article.

Abbreviations and Acronyms: AIP = advanced interventional pain therapy; CRPS = complex regional pain syndrome; DPN = diabetic peripheral neuropathy; DRG = dorsal root ganglion; FBSS = failed back surgery syndrome; FDA = Food and Drug Administration; IDDS = intrathecal drug delivery system; ICER = incremental cost-effectiveness ratio; QOL = quality of life; RCT = randomized controlled trial; SCS = spinal cord stimulation

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Dr Deer is a consultant for Bioness Inc, Nevro Corp, St. Jude Medical, Inc, Medtronic, Flowonix Medical Inc, Jazz Pharmaceuticals, Saluda Medical, Axonics Modulation Technologies, Vertos Medical Inc, and Nuveerta Corporation; has minority shares in Axonics Modulation Technologies, Bioness Inc, and Nevro Corp; was previously a shareholder in Spinal Modulation Inc; and receives research funding from St. Jude Medical, Inc, and Nevro Corp.

Dr Hayek serves as a consultant or medical advisory board member for Boston Scientific Corporation’s Neuro modulation Division, Neuron Medical Inc, and Flowonix Medical Inc; is a consultant for Nuveerta Corporation, Globus Medical, Inc, and Micro Systems Engineering, Inc; receives research funding from Boston Scientific Corporation; has applied for research funding from Medtronic, Boston Scientific Corporation, Medtronic, and St. Jude Medical, Inc; and receives support from University Hospitals’ fellowship program for pain medicine, where he serves as program director.

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The Symposium on Pain Medicine will continue in an upcoming issue.

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