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Interventional procedures for refractory neuropathic pain

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Abstract

Neuropathic pain is an increasingly common disease affecting millions of individuals worldwide. Refractory pain poses a significant impact on patients' quality of life, financial and economic stability, and social interaction. Numerous effective modalities for treatment of refractory neuropathic pain are presently available. Currently, many options provide symptomatic treatment but are associated with an unfavorable side effect profile and increased risk of addiction. The present investigation reviews current medical management for refractory neuropathic pain including the use of antidepressants, anticonvulsants, gabapentinoids and opioid therapy, as well as interventional pain procedures such as spinal cord stimulation (SCS) and intrathecal targeted drug delivery. While multidisciplinary management with lifestyle modification and pharmacologic regimens remains at the forefront of treating many of these patients, interventional modalities are growing in popularity and have been demonstrated to be highly efficacious. In this regard, continued understanding of the pathophysiology surrounding refractory neuropathic pain has led to the development of interventional procedures and better outcomes for patients suffering from refractory neuropathic pain. When and if patients fail conservative therapy, interventional techniques are desirable alternatives for pain management. SCS and intrathecal targeted drug delivery are important tools for the treatment of refractory neuropathic pain. In summary, treatment modalities for refractory neuropathic pain are evolving with demonstrated efficacy. This review aims to outline the efficacy of various interventional procedures for refractory neuropathic pain in comparison to traditional drug therapies.

Keywords

Spinal cord stimulation, neuromodulation, pharmacological treatment, neuropathic pain, targeted drug delivery

Introduction

Neuropathic pain stems from lesions in the somatosensory system, including both peripheral fibers and central neurons [1]. Nervous system injury leads to progressive and detrimental sensory loss and the development of unfavorable sensory symptoms [1]. Imbalance in excitatory and inhibitory neural pathways, alterations in ion channel behavior, and variability in activation of the central nervous system (CNS) all play a significant role in chronic pain development [2]. Notable symptoms patients experience are related to hyperactivity and increased sensitivity of nociceptors, which present as hypersensitivity, paresthesia, shooting or shock-like pain, decreased sensitivity to touch, vibration, or proprioception, and reflex changes [2]. These symptoms are growing in prevalence as neuropathic pain affects 7–10% of the global population and is increasing in number as there is a growing incidence of comorbid conditions such as diabetes mellitus and cancer, as well as increasing age of our population [1, 3]. As the incidence of neuropathic pain grows, treatment of these patients has escalated in complexity. The burden of neuropathic pain is not limited to physical symptoms but is highly evident with regard to financial and social burdens, limiting mobility, mood, and sleep. Those suffering from refractory pain undergo more physician visits and take more medications, often in a futile attempt to control the pain. When and if patients fail conservative and traditional therapy, interventional techniques are a highly desirable alternative for pain management. Newer interventional pain modalities such as spinal cord stimulation (SCS), radiofrequency ablation (RFA), targeted drug delivery, and neurostimulation are promising strategies for the management of refractory pain [3]. Despite challenges, progress in the understanding of the pathophysiology of neuropathic pain has resulted in the development of new diagnostic procedures and personalized interventions [1]. With a low side effect profile and minimal risk of dependence, these techniques are at the forefront of a multidisciplinary approach to the management of neuropathic pain.

Medical management of neuropathic pain

Neuropathic pain may be caused by a variety of mechanisms, most of which have been identified by experimental animal models. Among these mechanisms are both peripheral and central sensitization of nerve fibers. Other mechanisms include invasion of activated macrophages and release of pro-inflammatory cytokines, disinhibition of central neuronal regulation, uncontrolled modulation brought on by decreased inhibitory neurotransmitters [gamma-aminobutyric acid (GABA), glycine], several gene alterations [e.g., sodium voltage-gated channel alpha subunit 9 (*SCN9A*) gene], activation of microglial cells, and somatosensory cortex abnormalities, amongst others. Though there are many unique treatment modalities for neuropathic pain; the most common pharmacologic therapies will be briefly reviewed. The most efficient pharmacologic treatments are tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, tramadol, lidocaine, and capsaicin.

TCAs

TCAs, such as amitriptyline and nortriptyline, have been the most frequently studied and used medication class for the management of neuropathic pain. Although TCAs have numerous mechanisms of action, these medications function by inhibiting serotonin and norepinephrine reuptake within the presynaptic terminals, resulting in elevated concentrations of these neurotransmitters within the synaptic cleft [4]. Their side effect profile can be attributed to their blockage of sodium, acetylcholine, histamine, and adrenaline channels [5, 6]. Common adverse effects can include constipation, dizziness, blurred vision, xerostomia, urinary retention, and tachycardia. TCA-induced histamine blockade (H1) may lead to sedation, increased appetite, weight gain, and confusion in patients. TCAs may also induce cardiovascular complications, including arrhythmias such as heart rate corrected QT interval (QTc) prolongation, ventricular fibrillation, and sudden cardiac death, particularly in individuals with preexisting ischemic heart disease [4]. Therefore, assessing a patient's cardiac health is important before prescribing TCAs. Both amitriptyline and nortriptyline are available in oral formulations and can be started at a dose of 10–25 mg nightly with a maximum dose of 150 mg/day, however, it is important to consider cardiac risk before prescribing [3]. Use caution when prescribing these drugs, as their narrow therapeutic index increases the

risk of toxicity in some patients [4]. While TCAs have minimal impact on radiculopathy, human immunodeficiency virus (HIV), and chemotherapy-induced peripheral neuropathy, they are successful in treating peripheral neuropathy, post-herpetic neuralgia (PHN), and neuropathic pain, especially involving spinal cord etiology [7–12].

SNRIs

Many widely used and respected guidelines list SNRIs as the first-line therapeutic regimen for the management of neuropathic pain. As the name suggests, they act by preventing serotonin and norepinephrine reuptake in the synapse. The absence of affinity for muscarinic, histaminic and alpha1-adrenergic receptors and the absence of action on monoamine oxidase limits their adverse effects and allows them to be better tolerated than TCAs [13]. Two of the most commonly prescribed drugs for chronic pain are venlafaxine and duloxetine, both of which are SNRIs [7–12]. Recommended starting dosages for duloxetine and venlafaxine are 30 mg and 37.5 mg per day with maximum up to 60 mg and 225 mg daily, respectively [3]. Due to patient tolerance for these medications, they can also be prescribed for long-term treatment and in high doses, making them ideal solutions for chronic pain [13]. They have been demonstrated to be successful in treating painful peripheral neuropathy, peripheral diabetic neuropathy, and moreover, centrally mediated neuropathic pain brought on by multiple sclerosis [8, 9, 11, 14]. In addition to neuropathic pain, SNRIs have also been proven to be helpful for depression, osteoarthritis, fibromyalgia, and persistent low back pain. A systematic evaluation of 14 randomized clinical trials (RCTs) found a combined number needed to treat (NNT) of 6.4 (5.2–8.4) and a number needed to harm (NNH) of 11.8 (9.5–15.2) for duloxetine and venlafaxine, respectively [12].

Gabapentinoids

Another class of medication commonly used for refractory pain includes gabapentin and pregabalin. They belong to a class of anticonvulsants that function by preventing presynaptic alpha-2-delta calcium channels from opening in the dorsal horn and thus do not allow the release of neurotransmitters [11]. Its original use was as a muscle relaxer and anti-spasmodic medication, but later its potential as anticonvulsive medication and as an adjunct to more potent anticonvulsants came to light. It also has an off-label use for neuropathic pain, fibromyalgia, bipolar disorder, essential tremors, anxiety, resistant depressant, and mood disorders [15]. Gabapentin may take days to weeks to exert its maximum effects and needs to be slowly titrated to up to 600 mg three times a day with a maximum daily dose of 3,600 mg; however, caution is recommended in renally impaired patients. Pregabalin, has a quick onset of action; can be started at 150 mg twice or thrice daily with a maximum daily limit of 600 mg [3]. Both gabapentin and pregabalin have been demonstrated to be efficient treatments for diabetic peripheral neuropathy (DPN) and post-herpetic neuropathic pain [15–17]. An important benefit of gabapentin is that there is no interaction with other seizure medications including valproate, lithium, and carbamazepine. The minor side effects of pregabalin and gabapentin make them ideal for refractory pain control [18].

Transdermal substances

For those who cannot tolerate medications orally and/or experience adverse effects from oral regimens, topical patches, ointments, or creams can serve as an efficacious alternative. Administration involves placing a small amount of medicated ointment or patch over area designated by physical for optimal pain relief. Topical medications are applied externally and are taken up through the skin. They exert their effects close to the site of application, and there is no substantial systemic uptake or distribution. This compares with transdermal application, where the medication is applied externally and is taken up through the skin, but relies on systemic distribution for its effect [19]. Their use for refractory neuropathic pain is growing in popularity due to ease of use and patient satisfaction.

Lidocaine

As with other local anesthetics, the site of action of lidocaine is at sodium ion channels on the internal surface of nerve cell membranes. The uncharged form diffuses through neural sheaths into the axoplasm

before ionizing by combining with hydrogen ions. The resulting cation binds reversibly to sodium channels from the inside, locking them in the open state and preventing nerve depolarization, thus decreasing pain [20]. It can be distributed as a topical cream or transdermal patch to desired area. For the management of focal neuropathic pain, such as PHN, it is prescribed as either a first- or second-line medication. In five RCTs, a 5% lidocaine patch was found to be noninferior to pregabalin and to be more tolerable in the treatment of PHN with brush allodynia [3, 8, 21]. Although uncommon, side effects of topical and transdermal lidocaine are possible in high doses including slurred speech, tinnitus, circumoral paresthesia, and dizziness. Severe reactions include seizures or loss of consciousness [20].

Capsaicin

Capsaicin is currently distributed as an 8% adhesive patch (QUTENZA®) containing a high concentration of synthetic capsaicin, a selective agonist of transient receptor potential vanilloid 1 channel [22]. Initially, capsaicin binding opens ion channels, causing depolarization and the production of action potentials, which are usually perceived as itching, pricking or burning sensations. Repeated applications or high concentrations of capsaicin give rise to a long-lasting effect, probably owing to a number of different effects that together overwhelm the cell's normal functions, and can lead to reversible degeneration of nerve terminals [19]. It is approved for treatment of peripheral neuropathic pain in adults in Europe and the United States [22]. Adverse events from capsaicin are mainly at the application site (burning, stinging, erythema), and usually attenuate with time and repeated applications [19]. According to the ASCEND trial (NCT01737294) which used capsaicin 8% patch treatment in an open-label study, patients who received the first application saw a mean numeric pain rating scale (NPRS) score reduction of 26.6% [95% confidence interval (CI): 23.6–29.62; n = 412] from week 0 to weeks 2 and weeks 8 [23]. Equivalent effects on neuropathic back pain, post-operative and traumatic neuropathic pain, PHN amongst others were also seen [23].

Opioids

Combination therapy for neuropathic pain showed that gabapentin and opioids are more effective in relieving pain than either drug alone, however, this was accompanied by an increase in side effects. The NNH was determined to be 10 (6.5–25), and the NNT was 9.5 (5.0–86), further suggesting that the combination will be beneficial to only approximately 10% of the patients [24]. Duloxetine 60 mg and pregabalin 300 mg together performed no better than monotherapy in a significant international trial to treat pain in DPN [25]. However, it was discovered that nortriptyline with pregabalin reduced pain more effectively than monotherapy in DPN. Likewise, the TCA imipramine and pregabalin combination reduced pain levels by at least two points (31%) on the NPRS [26]. In most guidelines, tramadol is regarded as a second- or third-line option but is considered first-line for acute neuropathic pain, neuropathic pain associated with cancer, and intermittent neuropathic pain exacerbations. Tramadol has a number of different modes of action, but its main effects are as a μ-opioid receptor agonist and a serotonin and norepinephrine reuptake inhibitor [8, 9, 12, 27]. Another weak μ-receptor agonist and norepinephrine reuptake inhibitor is tapentadol. Due to its stronger effects compared to tramadol, it is regarded as a third- or fourth-line therapy [27]. Its mode of action differs slightly from tramadol's in that it has a higher suppression of noradrenaline reuptake and almost little effect on serotonin reuptake [28]. Anticonvulsants such as lamotrigine, carbamazepine, topiramate, and sodium valproate; and *N*-methyl-*D*-aspartate (NMDA) antagonists are several other classes of drugs which has proven to be beneficial in treating refractory neuropathic pain, however, their use is limited [3].

Interventional modalities for refractory neuropathic pain

Pharmacologic therapy tends to be the first and second line of treatment for refractory pain with medications such as TCAs, serotonin reuptake inhibitors, gabapentin, tramadol, lidocaine, and capsaicin. However, these medications often come with several adverse effects which warrant a review approximately one month into treatment to assess efficacy in controlling the patients' pain as well as seeing if there are

any adverse effects present [3]. If these treatments fail to control the pain for the patient, then interventional treatments are considered. Interventional treatments often come second line after failed pharmaceutical therapy due to the invasive nature and the associated risks of adverse effects. These risks include common risks among all invasive procedures such as infections, bleeding, thrombosis, and in the setting of intrathecal medication delivery there can be reactions to medication administered [3].

Epidural injection

Treatments such as epidural injections may be recommended for some conditions such as disc herniation or radiculitis but may not be as effective for radiculopathy due to herniated lumbar discs [29, 30]. The American Pain Society (APS) provided a weak recommendation for epidural steroid injection in cases of persistent radiculopathy caused by herniated lumbar discs [3, 30], while the American Society for Interventional Pain Physicians (ASIPP) concluded that there is good evidence for the use of epidural injections for disc herniation or radiculitis, with or without steroids [3, 29]. The Neuropathic Pain Special Interest Group (NeuPSIG) recommends considering epidural injections in patients who have not fully responded to other therapies [31, 32]. Common formulations for epidural injections include methylprednisolone, triamcinolone, betamethasone, or dexamethasone [32]. Non particulate (such as dexamethasone) formulations are considered first line as severe complications have been observed only with particulate formulations [3, 33]. The effectiveness of epidural corticosteroid injection in treating painful radiculopathy remains a topic of debate, with differing recommendations and evidence of moderate quality. For refractory pain due to PHN there was moderate evidence for epidural injections as a treatment [3]. Additionally, epidural injections using the transforaminal approach are more likely to produce a positive outcome as opposed to interlaminar techniques for radiculopathy [31]. These epidural steroid injections were shown to provide relief in short-term periods.

Neuromodulation options: RFA

Neuromodulation is another efficacious treatment for refractory pain. Although these treatments usually involve more invasive procedures, they have been shown to provide effective pain control in patients with chronic neuropathic pain. Additionally, these procedures tend to provide relief for more extended amounts of time as compared to modalities such as injections and peripheral nerve blocks. These treatments include pulsed radiofrequency (PRF) as a nondestructive technique that passes an electrical field across the nerve to change its synaptic transmission producing a neuromodulator effect [3]. This procedure is nondestructive in the sense that it delivers PRF followed by a 480-ms heat dissipation interval which inhibits the temperature from exceeding 42°C [34]. This mechanism is different compared to continuous RFA in that this procedure does not inhibit signal transduction but is elicited by electrical field effects. This characteristic allows the radiofrequency to be repeatedly applied without causing nerve tissue damage. PRF has been shown to provide relief for the treatment of PHN for out up to 3 months [35]. Whereas in a different study, PRF provided a significant reduction in pain in the treatment of cervical radicular pain for up to 6 months [36]. PRF for neuropathic pain can be considered before moving to more invasive options or when trying to control exacerbation of pain [3]. Contrarily, RFA is the use of radiofrequency current passed through an electrode targeted to a specific pain pathway to cause tissue destruction resulting in the modulation of pain sensation. RFA has become a widely used interventional technique for refractory neuropathic pain [37]. This procedure inhibits pain transmission by producing heat by friction and vibration which leads to denaturation, thermocoagulation, and necrosis of target tissue [34]. Extensive research has been conducted on the clinical efficacy of RFA in treating various types of refractory neuropathic pain. A recent meta-analysis of 16 clinical trials of RFA for sacroiliac joint pain indicated a clinical benefit in 15 out of 16 trials [38]. However, there is still mixed evidence on the generalizable effectiveness of RFA for all patients, when compared to other modalities, such as intra-articular injections, for treating refractory neuropathic pain [38].

Sympathetic blockade

Sympathetic blocks refer to the administration of medication, such as bupivacaine, ethanol, or botulinum toxin, through ultrasound or fluoroscopic guidance directly to a bundle of sympathetic nerves to disrupt the sympathetic nerve supply to specific target areas [39]. Lumbar sympathetic blocks are commonly used to treat lower extremity pain, while cervical sympathetic blocks via the stellate ganglion are used for treating upper extremity and neck pain, and thoracic paravertebral blockade is used for thoracic pain associated with neuropathic conditions [39–41]. Clinical efficacy of thoracic sympathetic block for treating thoracic pain was demonstrated, as 11 out of 12 patients experienced an immediate and significant reduction in Numerical Rating Scale (NRS) pain score [40]. Complications of sympathetic block include those common to any injection, such as bleeding, bruising, swelling, weakness, visceral injury, or infection [39]. More significant complications are determined by the location of the targeted injection. Overall, sympathetic blocks have been shown to have efficacy and are a useful option for interventional treatment of refractory neuropathic pain.

Neurostimulation

Neurostimulation techniques are effective in managing chronic neuropathic pain, particularly in cases of paraplegia and above-knee amputation [42]. Neurostimulation for pain is categorized into peripheral and CNS modulation, as well as invasive and non-invasive types. Devices with electrodes are applied to the brain, spinal cord, or peripheral nerves [42, 43]. Epidural motor cortex stimulation (EMCS) is a safe and effective therapeutic option for chronic neuropathic and drug-resistant pain [42, 44]. In case of failure of SCS in pain management or central pain, clinicians switch to deep brain stimulation (DBS) or motor cortex stimulation (MCS) [42]. Peripheral nerve stimulation (PNS) has also been proven helpful in treating several chronic pain conditions, including peripheral nerve dysfunctions, complex regional pain syndrome, and cranial neuralgias [42].

SCS

SCS is another procedure of neuromodulation where stimulation is applied to the dorsal columns within the epidural space to decrease pain transmission from the small nociceptive pain fibers in the dorsal horn. Specifically, the implanted electrodes are paired with a remote, and various stimulation parameter such as tonic stimulation (30–80 Hz), high-frequency stimulation (1–10 kHz), high-frequency burst stimulation (40 Hz with 5 closely spaced pulses at 500 Hz), and dorsal root ganglion stimulations. Low-frequency SCS has been suggested for the treatment of heat hyperalgesia due to C-fiber neuropathy. High-frequency SCS may be better for the modulation of mechanical allodynia due to A-fiber neuropathy [45]. This can suppress central neuronal hyperexcitability with an impressive reduction of pain intensity scores [42]. This technique has been found exceptionally useful for patients with failed back surgery syndrome [46]. Additionally, other indications for SCS include truncal PHN, drug-refractory painful diabetic neuropathy, and complex regional pain syndrome [32, 47]. Although SCS has shown moderate efficacy results, some limitations have been reported during clinical applications. Some limitations include contamination of implanted leads or pulse generator, the pain caused by the pressure of the implanted leads on the nervous system, or discomfort caused by the implanted pulse generator device. These limitations are being investigated to try to find an acceptable balance between the advantages and disadvantages of SCS [45].

Targeted drug therapy

Finally, targeted drug delivery is an interventional technique to deliver pharmacologic agents directly to the site of action at the dorsal horn of the spinal cord. This method bypasses first pass metabolism and greatly increases potency which allows less of the drug to be administered but still achieves the therapeutic effect [3]. This technique also decreases the time of onset for the analgesic medications to work. Currently, only morphine and ziconotide are applicable in intrathecal pain therapy for the treatment of different types of neuropathic pain [32]. One method of targeted drug delivery is intrathecal pumps. These pain pumps deliver medication directly to the thecal space instead of epidurally which prevents the need for the medication to diffuse past the dura to elicit its effect. Intrathecal drug delivery systems consist of both a

pump, which acts as a drug reservoir, and a catheter. The pump is placed under subcutaneous skin in the abdominal region and the catheter tip is placed at the level of the spinal cord that innervates the body region causing the pain [48]. For this treatment to be most effective, it is imperative physicians are carefully selective of patients who are candidates for this treatment. Due to the limited spread of drugs in the cerebrospinal fluid, a patient who has localized pain is more likely to best respond to targeted drug delivery as compared to those with diffuse pain [3]. While some patients may benefit from targeted drug delivery, neurostimulation has a higher safety profile and should be considered before initiating targeted drug delivery. Likewise, due to ziconotide's high safety profile, it may be considered before oral opioids but in most cases targeted drug delivery should not be considered until after low-dose oral opioids have failed to control the chronic pain (Table 1) [3].

Table 1. Interventional modalities for refractory neuropathic pain

Interventional modality	Description	Clinical efficacy	Complications	Limitations
Epidural injections [11–16]	Injection of corticosteroids directly into the epidural space	Differing recommendations and moderate quality evidence	Complications rare, severe complications observed only with particulate formulations	Effectiveness for treating painful radiculopathy is a topic of debate with varying recommendations; relief provided by epidural corticosteroid injections is often short-term
RFA [3, 5, 17, 18]	Use of radiofrequency current passed through an electrode targeted to a specific pain pathway to cause tissue destruction resulting in the modulation of pain sensation	Mixed evidence on generalizable effectiveness when compared to other modalities	Complications rare, potential nerve damage	Mixed evidence on the generalizable effectiveness of RFA for all patients
Sympathetic blocks [19–21]	Administration of medication through ultrasound or fluoroscopic guidance directly to a bundle of sympathetic nerves to disrupt the sympathetic nerve supply to specific target areas	Efficacy demonstrated, useful option for interventional treatment	Common injection complications, more significant complications dependent on location of targeted injection	Potential complications include bleeding, bruising, swelling, weakness, visceral injury, or infection; more severe complications vary depending on the location of the targeted injection
Neurostimulation techniques [22–24]	Categorized into peripheral and CNS modulation, as well as invasive and non-invasive types. Devices with electrodes are applied to the brain, spinal cord, or peripheral nerves	Effective in managing chronic neuropathic pain, particularly in cases of paraplegia and above-knee amputation	Complications rare, potential for infection or device malfunction	Mixed evidence for effectiveness for all patients
SCS [3, 7–9]	Stimulation applied to the dorsal columns within the epidural space to decrease pain transmission from the small nociceptive pain fibers in the dorsal horn	Exceptionally useful for patients with failed back surgery syndrome, also used for truncal PHN, drug-refractory painful diabetic neuropathy, and complex regional pain syndrome	Complications rare, potential for infection or device malfunction	Primarily used for specific conditions such as failed back surgery syndrome and certain neuropathic conditions; effectiveness varies among all patients
Targeted drug therapy [1, 9, 10]	Intrathecal delivery of pharmacologic agents directly to the site of action at the dorsal horn of the spinal cord	Effective for neuropathic pain, only morphine and ziconotide are applicable in intrathecal pain therapy	Complications rare, potential for infection or catheter migration	Limited options for intrathecal drug therapy; not all patients may be suitable candidates for intrathecal drug delivery; typically considered after other treatments have failed

Risks of interventional treatment modalities

Despite advances in non-pharmacologic interventional treatment modalities for the treatment of refractory neuropathic pain, these modalities are invasive procedures and are not without their risks. Specifically, these invasive procedures have the same risks as with any surgical procedure, including infection, bleeding,

and irreversible damage to surrounding neurovascular structures. Additionally, invasive modalities involving implantation of devices, such as SCS or neurostimulation, have risks associated with device implantation, hardware failure, and continued pain despite adequate implantation [3].

Conclusions

Refractory neuropathic pain is a condition with life-changing implications. The burden of neuropathic pain is not limited to its physical symptoms but is evident in the consequences of employment, mental health, and social interactions. Chronic pain can become refractory to pharmacologic methods over time, leaving patients with poor symptom control and quality of life. Despite challenges, progress in the understanding of the pathophysiology of neuropathic pain is encouraging the development of new diagnostic procedures and patient-tailored interventions [1]. When and if patients fail conservative and traditional therapy, interventional techniques are desirable alternatives for pain management. The innovative practice of interventional modalities such as neurostimulation and targeted drug delivery are promising in the management of refractory pain [3]. With a low side effect profile and minimal risk of addiction, these novel techniques are at the forefront of a multidisciplinary approach to the management of neuropathic pain.

Abbreviations

CNS: central nervous system

DPN: diabetic peripheral neuropathy

PHN: post-herpetic neuralgia

PRF: pulsed radiofrequency

RFA: radiofrequency ablation

SCS: spinal cord stimulation

SNRIs: serotonin norepinephrine reuptake inhibitors

TCAs: tricyclic antidepressants

Declarations

Author contributions

HGM, SK, NJS, and CCO: Conceptualization, Formal analysis, Writing—original draft. SB: Formal analysis, Writing—review & editing. SA, SS, and ADK: Conceptualization, Formal analysis, Writing—review & editing. All authors listed have made a direct and intellectual contribution to the work and have been approved for publication.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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