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Review Article

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REVIEW ARTICLES

A Comprehensive Algorithm for Management of Neuropathic Pain

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Abstract

Background. The objective of this review was to merge current treatment guidelines and best practice recommendations for management of neuropathic pain into a comprehensive algorithm for primary physicians. The algorithm covers assessment, multidisciplinary conservative care, nonopioid pharmacological management, interventional therapies, neurostimulation, low-dose opioid treatment, and targeted drug delivery therapy. **Methods.** Available literature was identified through a search of the US National Library of Medicine's Medline database, PubMed.gov. References from identified published articles also were reviewed for relevant citations. **Results.** The algorithm provides a comprehensive treatment pathway from assessment to the provision of first- through sixth-line therapies for primary care physicians. Clear indicators for progression of therapy from firstline to sixth-line are provided. Multidisciplinary conservative care and nonopioid medications (tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, gabapentanoids, topicals, and transdermal substances) are recommended as firstline therapy; combination therapy (firstline medications) and tramadol and tapentadol are recommended as secondline; serotonin-specific reuptake inhibitors/anticonvulsants/NMDA antagonists and interventional therapies as third-line; neurostimulation as a fourth-line treatment; low-dose opioids (no greater than 90 morphine equivalent units) are fifth-line; and finally, targeted drug delivery is the last-line therapy for patients with refractory pain. **Conclusions.** The presented treatment algorithm provides clear-cut tools for the assessment and treatment of neuropathic pain based on international guidelines, published data, and best practice recommendations. It defines the benefits and limitations of the current treatments at our disposal. Additionally, it provides an easy-to-follow visual guide of the recommended steps in the algorithm for primary care and family practitioners to utilize.

Key Words: Spinal Cord Stimulation; Neuromodulation; Pharmacological Treatment; Neuropathic Pain; Targeted Drug Delivery

Introduction

Neuropathic pain has a significant impact on patients' quality of life, as well as social, economic, and psychological well-being [1]. Notably, it has an even larger economic burden on society as a whole when one considers the financial cost of managing it in the chronic setting [2,3]. Estimates of its prevalence in the general population vary from as little as 1% to as much as 7–8% [4,5]; however, when taking into account conditions such as diabetes (26%), herpes zoster/shingles (19%), and postsurgical pain (10%), the incidence is much higher [1]. There are a number of national and international guidelines/recommendations for the assessment and treatment of neuropathic pain, yet there remains to be a consensus or agreement on the positioning of pharmacologic management (specifically opioids), neurostimulation, or targeted drug delivery [1,2,6–18]. The purpose of this publication is to create a comprehensive algorithm for the treatment and management of chronic, noncancer neuropathic pain by merging the aforementioned guidelines/recommendations and integrating the currently available data from systemic reviews, randomized controlled trials (RCTs), and published case reports/series (Figure 1).

Methods

All guidelines focused on the assessment of neuropathic pain highlight the use of a comprehensive history and examination with reliance on clinical judgment in the interpretation of screening tools and investigations [1,6,7].

History

Neuropathic pain stems from a wide variety of causes that can be broadly organized into two basic categories: peripheral and central etiologies [19]. However, presentation may be variable both between peripheral and central etiologies and within individuals with the same etiology [20]. Common peripheral neuropathic conditions include diabetic peripheral polyneuropathy, chemotherapy-induced peripheral neuropathy, radicular pain (RP), and postsurgical chronic neuropathic pain (PSCP). Central conditions include multiple sclerosis, poststroke pain, spinal cord injury–related pain, postherpetic neuralgia (PHN), complex regional pain syndrome (CRPS), and trigeminal neuralgia (TN).

The clinical presentation of neuropathic pain commonly includes descriptions of burning, pins and needles (paresthesia), tingling, numbness, electric shocks/shooting, crawling (formication), itching, and intolerance to temperature. In more advanced cases, patients may describe pain arising from stimuli that are not usually painful (i.e., allodynia) or pain from normally painful stimuli that is out of proportion to what would be expected. (i.e., hyperalgesia) [6].

The use of validated questionnaires is a simple means of identifying the presence of neuropathic pain and quantifying its impact on the patient: PainDetect, Douleur Neuropathique en 4 Questions (DN4), and the Leeds Assessment of Neuropathic Symptoms (LANSS). PainDetect relies solely on patient input without the need for a physical exam, with a sensitivity and specificity of 85% and 80%, respectively [21]. The DN4 and LANSS are both short measures of the presence of neuropathic pain [22,23]. The DN4 has seven pain discriminators and three examination findings: a score of 4+ indicates that neuropathic pain is likely, and its sensitivity and specificity are 83% and 90% [22]. The LANSS has five symptom descriptors and two examination findings. Its sensitivity and specificity are 82–91% and 80–94% [23]. The more conventionally known numeric rating scale (NRS) and/or the visual analog scale (VAS) can be used to measure pain intensity [24,25].

Quantifying the Consequences of Pain

Neuropathic pain can have a significant effect on mood and quality of life [26,27]. This impact can be measured using the PainDETECT Questionnaire [21], the Pain Disability Index [28], the Beck Depression Inventory [29], the Depression, Anxiety and Stress Test [30], the Hospital Anxiety and Depression Scale [31], and the Profile of Mood States (POMS) [32]. These questionnaires can be completed at an initial consult to detect if such an impact is present, and thereafter, a more formal assessment can be done by the allied health professional team. The psychologist plays an important role in quantifying the degree of catastrophizing, impact on mood and quality of life, coping strategies, and kinesophobia. This is typically performed utilizing a range of validated scales that include the Pain Catastrophizing Scale [33], Pain Coping Inventory [34], and the Tampa Scale of Kinesiophobia [35]. The Brief Pain Inventory [36] is used to assess condition-specific quality of life (QOL), and the EQ-5D [37] or SF-36 [38] assess overall health-related QOL.

Examination

No single sign or physical finding is diagnostic of neuropathic pain. Nearly 50% of patients with musculoskeletal pain use words that are commonly associated with neuropathic pain (e.g., "shooting" and "tingling") to describe their pain, and as much as 30% of patients with non-neuropathic pain will describe "burning," thus making it difficult to rely on patient history and descriptions alone [22,39]. Consequently, a thorough examination is crucial to determining the actual presence of neuropathic pain over more ambiguous symptoms or conditions.

The physical examination for neuropathic pain is straightforward and should include evaluation of tone, strength, reflexes, sensation, and vasomotor/sudomotor activity. It requires a paperclip or pin to test "pinprick" sensation, a cotton ball or fingers to test "light touch," a

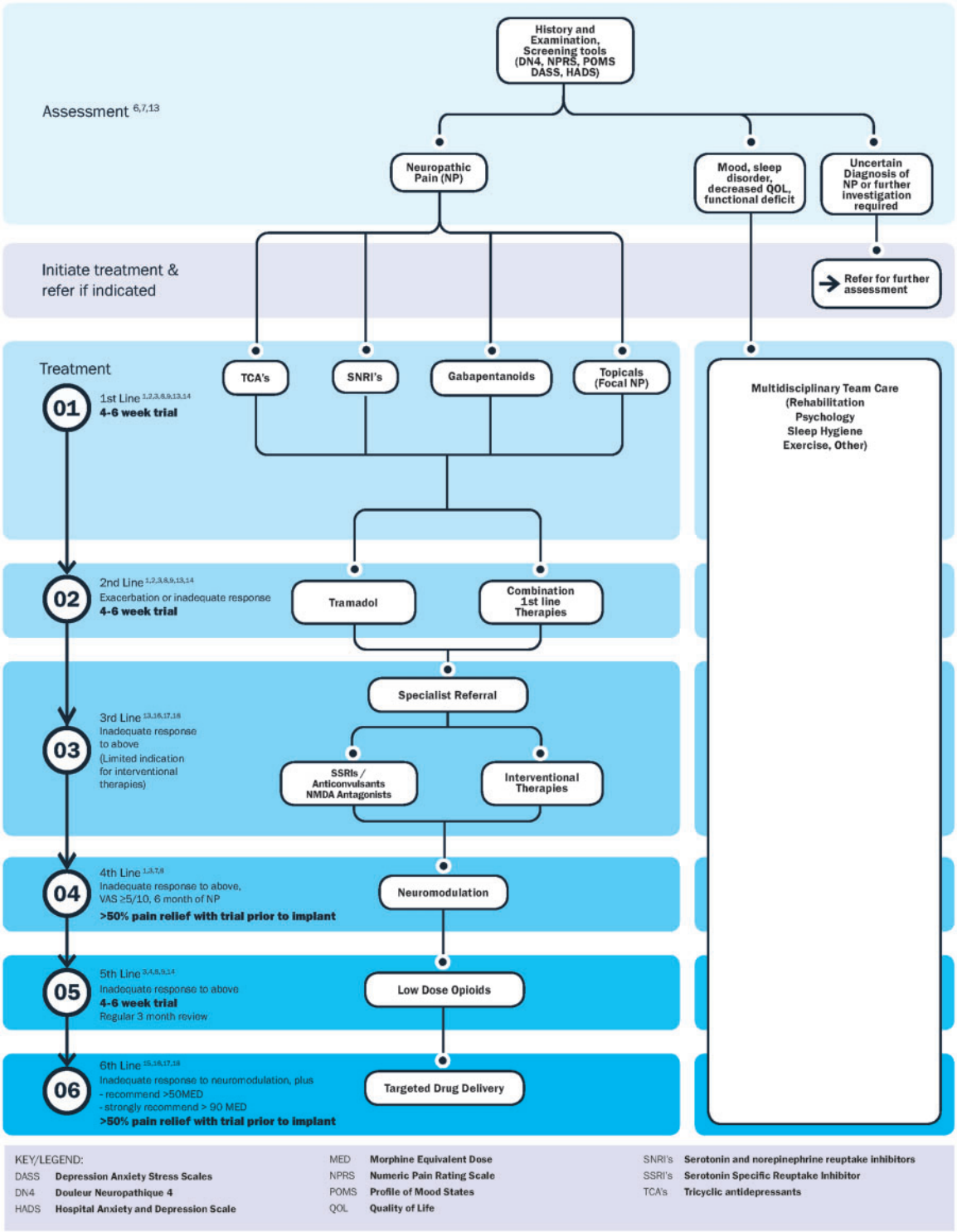

Figure 1. Comprehensive algorithm for the management of neuropathic pain.

reflex hammer cooled with tap water to test response to "cold," a tuning fork at 128 Hz for "vibration" sensation [40], and a thermometer to assess vasomotor responses [41]. Classically, a patient with neuropathic pain should have abnormal sensation in the area of maximal pain intensity [19]. Sensory changes should be rated as "increased," "decreased," or "normal"; a patient with neuropathic pain will commonly demonstrate decreased sensation to some sensory modalities and report pain in response to others [42]. The overall purpose of the examination should be to rule in, or out, the relevant neural pathways related to the patient's history.

If a neural lesion is suspected, an electroneuromyography (EMG) and nerve stimulation study (NCS) can be

performed to better define the region/area of defect and narrow the possibilities. If the examination fails to reveal a clear diagnosis but neuropathic pain is still suspected, referral to neurology or a more detailed investigation using quantitative sensory testing (QST) may be warranted in ambiguous cases. Referral to a pain physician also may be indicated for diagnostic nerve blocks to further narrow down the source of the pain. Lastly, magnetic resonance imaging (MRI) or skin biopsy can be used to identify central lesions or small fiber neuropathy, respectively.

Results

Firstline Treatment

Pain is more than just an unpleasant sensation. It can encompass emotional, social, and even spiritual suffering. Although all management strategies should strive for improvements in pain, the functional, sleep, mood, social, and spiritual consequences of pain must also be treated. It is these factors that drive much of our patients' quality of life [43].

Multidisciplinary Team Care

Multidisciplinary care is highlighted as a key component of the management of neuropathic pain by a number of guidelines [1,13,42,44]. Nonpharmacological and noninterventional therapies such as psychology, physiotherapy, exercise, and massage should be initiated early to address issues such as depression, anxiety, pain catastrophizing, sleep disturbance, or deconditioning, to name but a few.

Multidisciplinary care in chronic neuropathic pain has been shown to statistically significantly decrease pain and improve function, mood, catastrophizing, and pain acceptance [45]. Clinically significant changes of greater than two points on a VAS scale were seen immediately post-treatment, but only 49% of patients maintained this level of pain reduction at three-month follow-up. The average pain relief at this time was 1.3 on a 10-point numeric pain scale. Similarly, early gains in depression were lost by three months, whereas the significant gains in catastrophizing and pain acceptance were maintained [45].

If trialed alone without pharmacological or interventional strategies, it is recommended that these are limited to a duration of six to eight weeks. If adequate pain relief is not achieved within this time, firstline medications should be initiated. Neuropathic pain and its physical, psychological, and social consequences for the patient are variable throughout the course of the condition. At any point in the treatment protocol, the above conservative measures should be utilized to manage any ongoing concerns or new issues arising secondary to the pain.

Pharmacological Management

Medications form the basis of first- and second-line therapy for neuropathic pain (Table 1). Tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentanoids, tramadol, lidocaine, and capsaicin are the most effective options [1–3,8,9,13,14]. Most of these first- and second-line options come with considerable potential for side effects. Depending on the medication, a three- to eight-week trial is recommended with review midway and at the end of the trial to assess effectiveness. If the patient does not receive significant relief or has adverse effects from a medication, then dosing should be adjusted, an alternative medication or combination therapy should be tried, or the patient should be considered for a trial of neurostimulation.

Tricyclic Antidepressants. TCAs are one of the most studied antidepressants for the treatment of neuropathic pain. Their use as a firstline therapy is supported across multiple guidelines [1–3,8,9,13,14]. They have been shown to be effective in the treatment of peripheral neuropathy, post-herpetic neuralgia, and neuropathic pain post–spinal cord injury and of limited effect in radiculopathy, HIV, and chemotherapy-induced peripheral neuropathy [8,46].

TCAs have multiple modes of action, with the most important pain-relieving effect likely being via inhibition of serotonin and norardrenaline re-uptake [47]. However, they also block histamine, adrenalin, acetylcholine, and sodium channels, accounting for their broad side effect profile [48]. Their pain-relieving effect is independent of their antidepressant effect, occurring at 20–30% of the effective antidepressant dose [9].

In a Cochrane review of 61 RCTs, it was found that TCAs had a number needed to treat (NNT) of 3.6 for the achievement of moderate pain relief and a number needed to harm (NNH) for adverse effects, defined as an event leading to withdrawal from a study, of 28. For minor adverse effects, the NNH was 9 [46]. In a separate randomized, double-blind trial of antidepressants in neuropathic pain in spinal cord injury, it was found that the NNT for TCAs at a high dose (150 mg) was 7.6, whereas the number needed to harm (NNH) was 9.2 [49]. When trialing TCAs, it is recommended that it be done over a four- to eight-week period [13]. Failure to gain adequate pain relief should result in progression to another firstline medication or combination therapy. Caution is required in the use of TCAs in the elderly and frail to avoid potential adverse effects such as falls, cardiac arrhythmias, orthostasis, urinary retention, and dry mouth.

Serotonin and Norepinephrine Reuptake Inhibitors. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are considered firstline treatment in multiple international guidelines [1–3,8,9,13,14]. The most commonly studied are duloxetine and venlafaxine. They facilitate descending inhibition by blocking serotonin and

Table 1. First- and second-line medications for neuropathic pain

Firstline Medications			
Drug Class	Drug	Recommendations	Cautions
Gabapentinoids	Gabapentin	Slow titration up to 600 mg PO TID. Max daily dose = 3600 mg.	Reduce dose for renal impairment
	Pregabalin	Start at 150 mg PO BID or TID. Max daily dose = 600 mg.	
Serotonin and norepinephrine reuptake inhibitors	Duloxetine	Start at 30 mg PO daily. Max daily dose = 60 mg.	Renal or liver disease
	Venlafaxine	Start at 37.5 mg PO daily. Max daily dose = 225 mg.	
Tricyclic antidepressants	Nortriptyline	Start at 10–25 mg PO QHS. Max daily dose = 150 mg.	Autonomic neuropathy, urinary retention, glaucoma
	Amitriptyline	Start at 10–25 mg PO QHS. Max daily dose = 150 mg.	Taking SNRI, SSRI, MAOI, and/or tramadol
Topicals (focal neuropathic pain)	5% lidocaine	Available in cream or patch. Apply to site of pain 12 hours on, 12 hours off. Max of three patches at one time.	
	8% capsaicin	Apply for 60 minutes under supervision of a physician.	Avoid in diabetic peripheral neuropathy
Combination therapy	Gabapentinoid + TCA	Only use if single agent provides inadequate relief and no adverse effects.	Avoid in elderly
	Gabapentinoid + SNRI	Titrate as indicated for single agent. Aim for lower doses of both.	
Weak μ-opioid agonists and serotonin and norepinephrine reuptake inhibitors	Tramadol	Start at 50 mg IR PO BID-QID prn. Max daily dose = 400 mg.	Seizure disorder Taking SNRI, SSRI, TCA, and/or MAOI Reduce dose for renal impairment

BID = twice daily; IR = immediate-release; MAOI = monoamine oxidase inhibitor; PO = orally; prn = pro re nata (as needed); QHS = quaque hora somni (at night before bed); QID = four times a day; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = serotonin-specific reuptake inhibitor; TCA = tricyclic antidepressant; TID = three times daily.

noradrenaline reuptake [3,9]. They have been shown to be effective in peripheral diabetic neuropathy, painful peripheral neuropathy [8,13], and more recently in central neuropathic pain secondary to multiple sclerosis [50]. However, venlafaxine is not effective in post-herpetic neuralgia [13]. Beyond neuropathic pain, SNRIs have been shown to be effective in osteoarthritis, chronic low back pain, fibromyalgia, and depression [3]. Systematic review of 14 RCTs, nine looking at duloxetine and five at venlafaxine, demonstrated a combined NNT of 6.4 (5.2–8.4) and an NNH of 11.8 (9.5–15.2) [2]. The period of trial should be limited to four to six weeks [13]. Inability to tolerate the medication or failure to achieve satisfactory pain relief should prompt dose adjustment, progression to other firstline medications, or progression to combination therapy.

Gabapentinoids. Gabapentanoids include gabapentin and pregabalin. They are a group of anticonvulsant medications that act by blocking presynaptic alpha-2-delta calcium channels in the dorsal horn, inhibiting neurotransmitter release [9,13,51]. They are considered firstline agents in the treatment of neuropathic pain by multiple international societies [2,8,52]. Gabapentin and pregabalin both have been shown to be effective in post-herpetic neuralgia [53–55] and diabetic peripheral neuropathy [52,56,57]. Pregabalin also has been shown to be superior to placebo in the treatment of spinal cord injury [58,59].

A Cochrane review of gabapentin for chronic neuropathic pain in adults confirmed that gabapentin is associated with greater rates of pain relief compared with placebo in post-herpetic neuralgia and diabetic peripheral neuropathy, but it concluded that evidence for other neuropathic pain conditions was weak [60]. Finnerup and colleagues' systematic review of pharmacologic management of chronic neuropathic pain [2] calculated that the combined NNT[1] of 14 RCTs of gabapentin was 6.3 (5.0–8.3). Similarly, the combined NNT from six RCTs of gabapentin extended-release/encarbil was 8.3 (6.2–13). The NNH[2] for gabapentin for all etiologies combined was 25.6 (15.3–78.6) [2].

Finnerup et al. also assessed the efficacy of pregabalin. The combined NNT of 25 RCTs was 7.7 (6.5–9.4), and the NNH was 13.9 (11.6–17.4). Unlike gabapentin, they also reported a dose response, with a greater response being seen in those taking 600 mg daily than in those taking

1 NNT = 50% reduction in pain intensity (or 30% plus patient rating of good pain relief).

2 NNH was defined as the number needed to treat for one subject to drop out of a study due to adverse effects [2].

300 mg [2]. Pregabalin has also been shown to decrease health care and non–health care costs compared with gabapentin in the treatment of peripheral neuropathic pain [61–63]. Gabapentanoids should be trialed for a four- to six-week period with two weeks at the maximum tolerated dose [10,13]. Poorly tolerated side effects or inadequate pain relief should prompt dosage adjustment, cessation of the medication, progression to other firstline agents, or a trial of combination therapy. The most common adverse effects include somnolence, fatigue, dizziness, and lower extremity edema [60].

Topical—Lidocaine, Capsaicin, and Transdermal Substances

The side effect profile of TCAs, SNRIs, and gabapentanoids requires extremely cautious dosing in many patients, especially the elderly, with some patients having side effects with the lowest available doses. As an alternative, topical medications are supported by multiple guidelines, but where they fit into the algorithm varies from firstline to not at all [2,3,8,13,14]. The topical preparations referred to in guidelines are limited to lidocaine patches and capsaicin. However, there is some evidence on other topical antineuropathics that may provide a practical solution in some patients who are intolerant, or in whom it is unsafe to use oral medications.

Lidocaine. Topical lidocaine works by decreasing ectopic firing of peripheral nerves [64]. It is recommended as firstline [14] or second-line [9] for the treatment of focal neuropathic pain such as post-herpetic neuralgia. However, it has been shown to be ineffective in postsurgical neuropathic pain and diabetic peripheral neuropathy with allodynia or hyperalgesia [65,66]. It is difficult to apply topical lidocaine to the distal extremity neuropathies. A 5% lidocaine patch has been shown to be effective in five RCTs in post-herpetic neuralgia with brush allodynia [8] and to be noninferior to pregabalin with better tolerability [67]. A modest decrease in pain is commonly seen, but it is safe and well tolerated by the elderly [68]. A standard trial period should be three weeks [13].

Capsaicin. Capsaicin has its action through binding to the TRPV1 receptor located on the Aδ and C-nerve fibers. This results in release of substance P and depolarization of the nerve. Long-term exposure causes overstimulation, depletion of substance P, desensitization of the nerve, and reversible nerve degeneration [69]. High-concentration capsaicin (8%) is recommended as third-line [70], fourth-line, and as an alternative in focal neuropathic pain for those who "wish to avoid, or who cannot tolerate, oral treatments" [1]. Capsaicin is painful on initial application, and its efficacy depends on regular consistent use, thus making compliance with a capsaicin-based regimen challenging for many [71].

A recent Cochrane review of 8% capsaicin in PHN showed 30–50% pain relief at 12 weeks, and the NNT was 10–12 for PHN and 11 for HIV-related peripheral neuropathy. Ten percent of patients with diabetic peripheral neuropathy reported feeling "much improved," and for HIV peripheral neuropathy, the NNT to report being "much improved" was 8.8 (5.3–2.6) [72]. Finnerup and colleagues' meta-analysis for the treatment of PHN and HIV peripheral neuropathy demonstrated a combined NNT of 10 (7.4–19) [2].

Transdermal Substances

Only lidocaine and capsaicin are referred to in the various international guidelines on management of neuropathic pain. However, some limited evidence is available on topical preparations of ketamine, amitriptyline, diclofenac, and clonidine. A transdermal approach may provide an alternative approach for some patients. It is also worth noting that some medications are ineffective topically.

Ketamine at 10% has been shown to be effective in CRPS [73], whereas lower doses were not more beneficial than placebo in PHN and DPN [74,75]. Diclofenac may decrease burning in PHN and CRPS but has no effect on other features of neuropathic pain [76]. Clonidine has a limited effect, decreasing pain up to 30% in diabetic peripheral neuropathy [77], with an NNT of 8.33 (4.3–5.0) [78]. Alternatively, amitriptyline in concentrations of 1–5% has been shown to be ineffective in the treatment of PHN, DPN, postsurgical neuropathic pain, and painful peripheral neuropathy [69].

Second-Line Treatment

Combination Therapy

No one drug is effective for all patients, and, as seen above, pain relief is usually partial and side effects limit tolerability [13]. Not surprisingly, 45% of those with neuropathic pain utilize two or more medications for their pain [79]. Ninety percent of patients with DPPN require multiple medications for their pain [80]. Combination therapy is acknowledged as a significant part of the management of neuropathic pain by most guidelines; however, there is limited evidence on effective strategies [1,2,9,13,14]. In some cases, combination therapy may increase efficacy and, due to smaller doses of individual drugs, enable dose reductions and reduce side effects [1,14].

A Cochrane review of combination therapy for neuropathic pain demonstrated that gabapentin and opioids provide better pain relief than gabapentin or opioids alone, but this was associated with increased levels of adverse events. The calculated NNT was 9.5 (5.0–86), and the NNH was 10 (6.5–25). This indicates that approximately 10% of patients will gain benefit from the combination [81].

In a large multinational trial, the combination of duloxetine 60 mg and pregabalin 300 mg was no better than monotherapy for pain in diabetic peripheral neuropathy, but all secondary measures favored combination

therapy [82]. However, in diabetic peripheral neuropathy, nortriptyline plus pregabalin was shown to be more effective at decreasing pain than monotherapy [83]. Similarly, the combination of the TCA imipramine and pregabalin saw improved pain scores, with an average two-point (31%) decrease on the Numeric Pain Rating Scale (NPRS) scale, significantly greater than pregabalin or imipramine alone; however, side effects were higher [84]. Combination therapy should be trialed for the trial duration of the second medication and ceased if ineffective or if there are significant side effects.

Tramadol and Tapentadol

Tramadol is considered second-line treatment in most guidelines [3,8,9,13] but firstline in acute neuropathic pain, cancer-related neuropathic pain, and intermittent exacerbations of neuropathic pain. Tramadol has multiple mechanisms of action but primarily acts as a weak μ-opioid agonist and inhibitor of serotonin and norepinephrine reuptake. Tramadol and has been shown to be effective in the treatment of DPPN [85], PHN [86], and cancer-related neuropathic pain [87]. Finnerup analyzed seven RCTs to demonstrate a combined NNT of 4.7 (3.6–6.7) and an NNH of 12.6 (8.4–25.3) [2].

Tapentadol is a newer weak μ-receptor agonist and norepinephrine reuptake inhibitor. It is considered third- or fourth-line treatment by some guidelines due to its increased potency over tramadol [9], but the evidence was inconclusive in others [2]. Its mechanism of action is slightly different to that of tramadol, with stronger noradrenaline reuptake inhibition and nearly no effect on serotonin reuptake. Some efficacy has been shown in the treatment of DPPN [88].

Third-Line Treatment

Serotonin-Specific Reuptake Inhibitors/Anticonvulsants/NMDA Antagonists

For the patient who does not tolerate or fails to gain adequate pain relief from first- or second-line therapy, a referral to a specialist pain clinic is recommended [13]. The specialist setting may consider use of serotonin-specific reuptake inhibitors (SSRIs); anticonvulsants such as lamotrigine, carbamazepine, topiramate, and sodium valproate; and NMDA antagonists [13]. However, with regard to level of evidence, the most recent update of the International Congress on Neuropathic Pain (NeuSPIG) guidelines has rated all these as inconclusive [2]. At this time, it is recommended that these medications not be started in the primary care setting [1].

Interventional Therapies

Epidural Injection. The recommendations around the use of epidural injections in neuropathic pain are mixed. The American Pain Society (APS) reported that there was fair evidence and provided a weak recommendation for the use of epidural steroid injection in persistent radiculopathy due to herniated lumbar disc [17]. The American Society for Interventional Pain Physicians (ASIPP) concluded that there was good evidence for caudal, interlaminar, and transforaminal epidural injections, with or without steroids, for treatment of disc herniation or radiculitis [18]. Neuropathic Pain SIG (NeuPSIG) recommendations from 2013 reported that the evidence for treatment of herpes zoster was moderate, but low for radiculopathy. They gave a "weak" recommendation for the use of epidural injections in the treatment of herpes zoster and radiculopathy. For failed back surgery syndrome (FBSS) with radiculopathy, they suggested that epidural injection should be considered in patients who have incompletely responded or failed to respond to other therapies and in whom more invasive techniques are being considered. They stated that it is likely that the effects will be short lived and that repeat injections may be needed; the frequency, timing, and required number were not prescribed [16].

With regards to technique of epidural injection, the transforaminal approach is more likely to provide a positive outcome when compared with interlaminar techniques for radiculopathy, although results are mixed [16]. Regarding particulate vs nonparticulate steroids, a recent systematic review has found no evidence of a significant difference in efficacy. On the basis of potential catastrophic complications with particulate steroids, nonparticulate steroids are recommended [89].

Pulsed Radiofrequency. Pulsed radiofrequency is a nondestructive radiofrequency technique that passes an electrical field across the nerve, likely resulting in changes in synaptic transmission, in a neuromodulatory-type effect [90]. The APS and ASIPP provide no recommendations for the use of pulsed radiofrequency in radicular or neuropathic lower back pain [17,18]. NeuPSIG recommendations rated the effectiveness of pulsed radiofrequency (PRF) for treatment for PHN and lumbar and cervical radicular pain as "inconclusive" [16]. More recently, Chang reported a review of PRF and supported its use in the treatment of post-herpetic neuralgia and occipital neuralgia. However, Chang also concluded that it was ineffective in treating trigeminal neuralgia and that evidence was lacking for its use in other peripheral neuropathies [91]. A meta-analysis by Shi et al. [92] supported the use of PRF in PHN with significant effects out to three months, with a weighted mean difference (MD) in pain score of –1.26 (95% confidence interval [CI] = –1.69 to –0.84). No statistically significant results were seen for radicular pain (MD = –0.28, 95% CI = –0.62 to –0.06). A more recent meta-analysis of PRF for the treatment of cervical DRG supported its use, with positive benefits out to six months; however, gains in VAS were small, with a standardized mean difference (SMD) of −1.84, (95% CI = −2.33 to −1.34) [93]. From a practical perspective, epidural injection is likely to provide short-term benefit, and PRF possibly moderate relief out to six months. Their use in neuropathic pain can be

considered when trying to control an exacerbation of pain or before moving to more invasive therapies. Due to limitations on the duration of effect, more than a single procedure may be required.

Adhesiolysis. Adhesiolysis for FBSS and radicular pain is performed based on the premise that epidural adhesions are partly responsible for generation of pain. Injection of hyaluronidase, normal or hypertonic saline, and steroids is performed via a catheter in the epidural space to breakdown adhesions [16]. In the setting of failed conservative management, the ASIPP recommends the use of adhesiolysis in post–lumbar surgery syndrome and central spinal stenosis [18]. Counter to this position, NeuPSIG stated that while adhesiolysis may be beneficial in FBSS, its efficacy for neuropathic pain with FBSS is unclear, and thus provided an "inconclusive" recommendation [16].

Sympathetic Blockade. Sympathetic block with local anesthetic can be used for treatment of CRPS. High-quality evidence to confirm or refute efficacy or safety is lacking, as most studies are of short duration, providing no indication of long-term benefits [94]. NeuPSIG provided an "inconclusive" recommendation; however, given the paucity of effective treatment options for CRPS, they suggested that in patients refractory to other treatments, it was reasonable treatment option, particularly in the early phase of the disease [16].

Radiofrequency Denervation. Radiofrequency (RF) denervation is a destructive technique where the nerve is ablated using heat. Lesioning of the DRG has been suggested as a viable option for treating radiculopathy. This technique has been tested against sham in both the cervical and lumbosacral regions. Cervical RF of the DRG demonstrated a significant difference to sham in pain at eight weeks (treatment group VAS = 3.3, sham group VAS = 6.0) [95]. Similar results were not seen in the lumbar region. Based on the short-term data for cervical radiculopathy and evidence that the technique is no better than sham in the lumbar region, NeuPSIG provided recommendations of "inconclusive" and "against" RF denervation of the DRG [16]. The APS has rated the evidence for radiofrequency denervation in radiculopathy as poor and stated that they were unable to estimate benefit [17]. Based on the limited evidence, we do not recommend RF denervation of the DRG for treatment of radiculopathy.

Fourth-Line Treatment

Neurostimulation

As noted in the European Federation of Neurological Societies (EFNS) guidelines on neurostimulation, "In real life, a sufficient level of pain relief is probably one that allows the patient to have an acceptable quality of life" [7]. For those patients with neuropathic pain who are unable to achieve an acceptable quality of life, neurostimulation is a treatment option. The National Institute of Health and Care Excellence (NICE) and EFNS have both recommended neuromodulation for treatment of neuropathic pain [11,96,97]. The NeuPSIG recommendations on interventional management of neuropathic pain [16] gave a weak recommendation for use of spinal cord stimulation in failed back surgery syndrome with radiculopathy and CRPS. These recommendations were based on limited evidence and did not include recent RCTs of newer neurostimulation modalities. The most recent meta-analysis, performed by Lamer and colleagues, compared neurostimulation with medical therapies. Lamer et al. concluded that spinal cord stimulation produced better pain reduction than medical therapy in patients with chronic spine and leg pain [98]. This analysis found that compared with medical therapy, conventional spinal cord stimulation (low frequency, paresthesia based) significantly increased the odds of achieving 50% pain relief (odds ratio [OR] = 13.1, 95% CI = 4.46 to 34.17) and significantly decreased pain on a visual analog scale. Furthermore, newer neuromodulation technologies including high-frequency and burst spinal cord stimulation and dorsal root ganglion stimulation were shown to have an even greater odds of decreasing pain than conventional spinal cord stimulation (OR = 2.37, 95% CI = 1.58 to 3.54).

Currently, NeuPSIG recommendations on interventional management of neuropathic pain are "inconclusive" for the use of spinal cord stimulation in PHN, DPN, spinal cord injury, and poststroke pain [16]. Counter to this position, NICE updated their guidelines for spinal cord stimulation most recently in 2014 [97], and their Neuropathic Pain Overview recommendations in 2018 [96]. They recommended spinal cord stimulation as a treatment option for all chronic pain conditions of neuropathic origin, with ≥50/100 on a 100-mm VAS, and that have persisted for at least six months despite appropriate medical management. Importantly, they recommended that the patient have a successful trial of stimulation (>50% pain relief) before permanent implant and that care be provided in a multidisciplinary environment.

A systematic review of spinal cord stimulation for failed back surgery syndrome noted that the biological consequences of SCS were less than those of long-term opioid use and concluded that spinal cord stimulation should be placed before long-term opioids in the treatment algorithm [12]. Recently, Krebs et al. [99] reported the results of a randomized trial of patients with chronic back, hip, or knee pain, showing no benefit of opioid medications over nonopioid medications for pain-related function or pain intensity over 12 months of follow-up.

With consideration of the limited efficacy of opioids in neuropathic pain, the authors have recommended a trial of neurostimulation before commencing low-dose opioids, placing it as fourth-line treatment after appropriate conservative, pharmacological, and interventional management has failed to achieve an acceptable quality

of life for the patient. This also fits with the current CDC guidelines on commencing opioids and the 2017 Canadian guidelines on the use of opioids in chronic pain [9,100]. The authors have experience in both interventional and medical management of pain and have developed a predisposition toward interventional and implantable techniques based on the morbidity and mortality associated with the use of oral opioids.

Fifth-Line Treatment

Low-Dose Opioid

Opioids have been recommended as second- [9], third- [2,3,8] or fourth-line therapy [14] for neuropathic pain. However, the authors suggest that opioids should be firmly considered fourth-line, after a trial of neurostimulation has been attempted, as per the NICE guidelines [1], and Safety, Appropriateness, Fiscal Neutrality, and Effectiveness (SAFE) analysis of neurostimulation in FBSS [12]. Concerns about a lack of long-term efficacy data and significant side effects relegate opioids to second- to fourth-line therapy [2,3,9,14] in most guidelines.

Multiple opioids (e.g., oxycodone, morphine, methadone, and levorphanol) have demonstrated efficacy in RCTs ranging from eight days to eight weeks, in patients with a variety of neuropathic pain conditions [101–107]. On the other hand, morphine did not differ from placebo in an RCT for chronic nerve root pain [108]. The magnitude of pain reduction associated with relatively short-term opioid analgesics is at least as great as that obtained with other treatments for neuropathic pain.

In a Cochrane Database review of morphine vs placebo for chronic neuropathic pain in adults, Cooper et al. found only a moderate (30%) improvement in neuropathic pain, which was experienced by 63% of patients, and the NNT to achieve this moderate reduction in pain was 3.7 (2.6–6.5) [109]. Cooper concluded that there is insufficient high-quality evidence to support or refute the suggestion that morphine is efficacious in any neuropathic pain condition.

Another Cochrane Database review identified and analyzed five randomized, double-blind studies of oxycodone vs placebo for two weeks' duration and longer for chronic neuropathic pain in adults, reporting on 687 participants (637) with painful diabetic neuropathy and 50 with post-herpetic neuralgia [110]. Gaskell et al. found that none of the five studies reported pain relief of 50% or greater. Three studies including 537 participants with diabetic neuropathy showed a moderate pain relief of 30% in only 44% of the patients. The associated number needed to treat for an additional beneficial outcome was 5.7. More participants experienced adverse events with oxycodone alone (86%) than with placebo (63%); the number needed to treat for an additional harmful outcome (NNH) was 4.3. As a result, Gaskell et al. concluded that there was very low-quality evidence to support the long-term treatment of patients with painful diabetic neuropathy and PHN with oxycodone. Furthermore, in conducting their literature search, Gaskell et al. found no studies of oxycodone for any other neuropathic pain conditions.

In 2010, Finnerup et al. reviewed 174 placebo-controlled RCTs (105 from an earlier review in 2005 and 69 additional as of 2010) of firstline drugs, including opioids, for chronic neuropathic pain [111,112]. They calculated an NNT to achieve ≥30% pain reduction and an NNH (number treated for one patient to drop out of the study due to adverse effects) for specific drug classes and pain etiologies. In the case of opioids, the NNT ranged from 2.1 (1.5–3.3) for mixed neuropathic pain to 5.1 (2.7–36.0) for peripheral nerve injury. The combined NNH for opioids for all etiologies was 17.1 (9.9–66). The authors concluded that the lack of proven long-term effectiveness and the high risk for adverse effects called for alternative treatment options to target chronic neuropathic pain. More recently, Finnerup et al. from 13 trials of strong opioids calculated a combined NNT of 4.3 (3–4.5.8), with an NNH of 11.7 (8.4–19.3) [2].

CDC and Canadian guidelines on use of opioids in non-cancer chronic pain recommend optimization of nonpharmacological and non-opioid-based therapies [113,114]. Commencement should be with immediate-release forms of the drug with the aim of utilizing the lowest possible dose. The patient is converted to slow release once a stable, effective dose has been achieved. Caution should be taken when exceeding 50 mg per day of morphine (or morphine equivalent dose [MED]), and >90 MED should be avoided or have careful justification. A trial of therapy should occur for one to four weeks, after which the benefits relative to the risks should once again be reviewed. This should occur every three months [113].

Sixth-Line Treatment

Targeted Drug Delivery

Targeted drug delivery is used to deliver medications directly to their site of action at the dorsal horn of the spinal cord, bypassing the first pass effect and the blood–brain barrier. This significantly increases the potency of the medication, allowing much smaller doses to be used [115]. Currently, morphine and ziconotide are the only Food and Drug Administration–approved pain medications for TDD. Recommendations for the use of targeted drug delivery vary between organizations. NeuPSIG rates its strength of recommendation as "inconclusive" [16]. The APS guidelines state that for nonradicular pain there is insufficient evidence to evaluate benefits of intrathecal therapy with opioids or other medications. However, no reference is made to radicular or neuropathic pain for the use of TDD [17]. ASSIP concluded in the positive and stated, "Intrathecal infusion pumps are indicated in the treatment of recalcitrant non-cancer pain with post-surgery syndrome" [18]. The Polyanalgesic Consensus

Conference (PACC) recommends the use of TDD for those with refractory pain [15]. TDD is included in this algorithm as a management option for patients who are considered to suffer refractory pain:

> Pain is defined as refractory, regardless of etiology, when 1) multiple evidence-based biomedical therapies used in a clinically appropriate and acceptable fashion have failed to reach treatment goals that may include adequate pain reduction and/or improvement in daily functioning or have resulted in intolerable adverse effects, and when 2) psychiatric disorders and psychosocial factors that could influence pain outcomes have been assessed and appropriately addressed. [116]

These patients have moved through the preceding algorithm, all psychosocial factors have been addressed, and they have failed medication-based therapies, neurostimulation, and low-dose opioids. Due to the increasing risk of harm from opioids above 50 MED, it is recommended that TDD be considered for the above patients requiring >50 MED of opioids, and it is strongly recommended for those requiring >90 MED. In certain circumstances, it may be appropriate to proceed directly to TDD following failed neurostimulation. The PACC recommendations place TDD after neurostimulation in its noncancer and cancer pain algorithm when the pain is well localized, has a clear diagnosis, is largely neuropathic or mixed, and neurostimulation fails or cannot adequately cover the areas of pain [15]. Before initiating TDD, patients must undergo an intrathecal medication trial. Although multiple dosing strategies exist, there are no data to support superiority. A successful trial is defined as achieving >50% pain relief without significant adverse effects.

For effective therapy, patient selection is crucial. Patients with localized pain are likely to respond best to TDD (e.g., axial back pain, focal abdominal pain, or dermatomal pain), whereas those with diffuse (e.g., entire extremity), global, and whole-body pain are less likely to respond well. This is due to the limited spread of drugs in the cerebrospinal fluid. There are some patients who may benefit from a trial of TDD before neurostimulation, but in general the higher safety profile of neurostimulation places it ahead of TDD in a neuropathic pain algorithm. For select patients, due to ziconotide's safety profile, intrathecal ziconotide may be considered before initiating oral opioids. However, in most cases, TDD should be considered after low-dose oral opioid therapy has failed to provide adequate pain relief.

Conclusions

Neuropathic pain is highly debilitating, difficult to diagnose, and only partially responsive to nearly all treatment. A multidisciplinary, structured stepwise approach is needed to decrease pain and attain an acceptable quality of life for patients. We propose a treatment algorithm to guide the primary physician through a step-by-step, time-limited treatment process. The initial step is comprehensive assessment utilizing targeted history and examination, with screening tools such as the PainDETECT, DN4, and LANSS being used to prompt the clinician to the possibility of chronic pain. Tools such as the POMS, HADS, and Depression, Anxiety, Stress Scales (DASS) can be used to identify the presence of psychosocial consequences of neuropathic pain, and thus prompt appropriate referral to allied health. Firstline treatment includes multidisciplinary care in conjunction with TCAs, gabapentanoids, SNRIs, topical lignocaine, and capsaicin. These should be trialed over an average of four to six weeks; if acceptable pain relief is not achieved, they should be ceased, and progression to the next medication or next line of treatment should occur. Second-line treatment included tramadol and combination therapy. Tramadol is currently recommended for exacerbation of symptoms only, with caution in the elderly. Combination therapy is common in the treatment of neuropathic pain; its use should be on a trial basis for the duration of the second medication, and the patient should be followed for increased side effects and lack of efficacy. For patients who fail to respond to first- and second-line therapies, referral to a specialist pain center is recommended. In this setting, a trial of SSRIs, anticonvulsants, or NMDA receptor antagonists may be considered. Third-line treatment includes interventional therapies such as epidural injection, pulsed radiofrequency, sympathetic blockade, and adhesiolysis. They should be considered if first- and second-line therapies have failed to achieve adequate pain relief or before proceeding to neurostimulation. That said, it is important to note that all interventional therapies are limited to specific indications. Neurostimulation is proposed as a fourth-line treatment before commencement of low-dose opioids. The patient should have a diagnosis of neuropathic pain of greater than six months' duration, have a pain score of ≥5/10, and have failed to respond adequately to other therapies. Before proceeding to implant, neurostimulation should be trialed over a one- to four-week period, with a positive trial being >50% pain relief and the patient being happy with the result. Low-dose oral opioids are recommended as fifth-line due to the limited duration of efficacy and the significant risk of side effects. Commencement should be with immediate-release medication and should be titrated to the lowest possible dose. The patient should then be converted to slow-release opioids. Caution should be taken when exceeding 50 MED of morphine, and 90 MED should be exceeded only with significant justification. Patients failing to gain adequate pain relief with the above algorithm are considered to have "refractory pain." For patients requiring >50 MED of opioids, it is recommended that a trial of TDD be considered. Due to the significant risks associated with >90 MED, it is strongly recommended that TDD be considered for these patients.

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