Chapter 9
Advances in the Treatment of Neuropathic Pain

Li Xu*, Yuguan Zhang*, and Yuguang Huang

Abstract Neuropathic pain is pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system. Treatments for neuropathic pain include pharmacological, nonpharmacological, and interventional therapies. Currently recommended first-line pharmacological treatments include antidepressants and anticonvulsants (gabapentin and pregabalin). However, in some cases, pharmacological therapy alone fails to give adequate control of the chronic pain. New techniques have been invented and have been proved effective on neuropathic pain, such as behavioral, cognitive, integrative, and physical therapies. In this review, we focused on the advances in the treatment of central neuropathic pain, diabetic peripheral neuropathy, postherpetic neuralgia, and cancer pain.

Keywords Neuropathic pain • Antidepressant • Anticonvulsant • Radio frequency • Neural stimulation

9.1 Introduction

Clinical evaluation of neuropathic pain (NP) requires a thorough history and physical examination to identify characteristic signs and symptoms. In many cases, other laboratory investigations and clinical neurophysiological testing may help identify the underlying etiology and guide treatment selection. Mechanisms for NP include aberrant ectopic activity in nociceptive nerves, peripheral and central sensitization, impaired inhibitory modulation, and pathological activation of microglia. Available treatments essentially provide only symptomatic relief and may include nonpharmacological, pharmacological, and interventional therapies.

*Author contributed equally with all other contributors

L. Xu • Y. Zhang • Y. Huang (✉)
Department of Anesthesiology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China
e-mail: garybeijing@163.com

C. Ma, Y. Huang (eds.), *Translational Research in Pain and Itch*, Advances in Experimental Medicine and Biology 904, DOI 10.1007/978-94-017-7537-3_9

Most extensive evidence is available for pharmacological treatment, and currently recommended first-line treatments include antidepressants (tricyclic agents and serotonin-norepinephrine reuptake inhibitors) and anticonvulsants (gabapentin and pregabalin). Individualized multidisciplinary patient care is facilitated by careful consideration of pain-related disability as well as patient education, repeat follow-up and strategic referral to appropriate medical/surgical subspecialties, and physical and psychological therapies. Despite the availability of many effective drugs and guidelines for the treatment of NP, evidence from the United States and Europe suggests that they are not widely used, and many cases remain under- or untreated (Gilron et al. 2015). This chapter focuses on the advances in the treatment of NP.

Neuropathic pain mechanisms relevant to diagnosis and treatment include ectopic activity, peripheral sensitization, central sensitization, impaired inhibitory modulation, and activation of microglia (Hehn et al. 2012). Although the signs and symptoms characteristic of neuropathic pain varies a lot, the sensory quality descriptors "tingling" (or "pins and needles" or "prickling"), "burning" (or "hot"), and "shooting" (or "electrical shocks") are included in nearly all these various tools, and these three descriptors are perhaps the most characteristic of neuropathic pain. Much of this characteristic has emerged from the development and publication of several screening tools. Such as the Michigan Neuropathy Screening Instrument (MNSI), Neuropathic Pain Scale (NPS), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Questionnaire (NPQ), "Douleur Neuropathique en 4 questions," Pain Quality Assessment Scale, and the Short-Form McGill Pain Questionnaire-2.

Through the signs, symptoms, and tests, neuropathic pain can be diagnosed. However, epidemiological surveys have indicated that many patients with NP do not receive appropriate treatment for their pain. A number of pharmacological agents have been found to be effective in NP on the basis of randomized controlled trials including, in particular, tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitor antidepressants, pregabalin, gabapentin, opioids, lidocaine patches, and capsaicin high-concentration patches. Evidence-based recommendations for the pharmacotherapy of NP have recently been updated. The treatment protocol is described in Fig. 9.1. Improving the current way of conducting clinical trials in NP could contribute to reduce therapeutic failures and may have an impact on future therapeutic algorithms (Attal and Bouhassira 2015; Helfert et al. 2015).

The treatment strategies for neuropathic pain involve a variety of methods such as physical therapy, psychotherapy, teamwork medical, traditional Chinese medicine, transcutaneous electrical nerve stimulation, and interventional therapy.

9.2 Pharmacological Treatment

The first line drugs include tricyclic antidepressants (TCAs), selective serotonin norepinephrine reuptake inhibitors (SSNRI), anticonvulsants, and topical lidocaine. TCAs are efficacious for several types of neuropathic pain including DPN, nerve

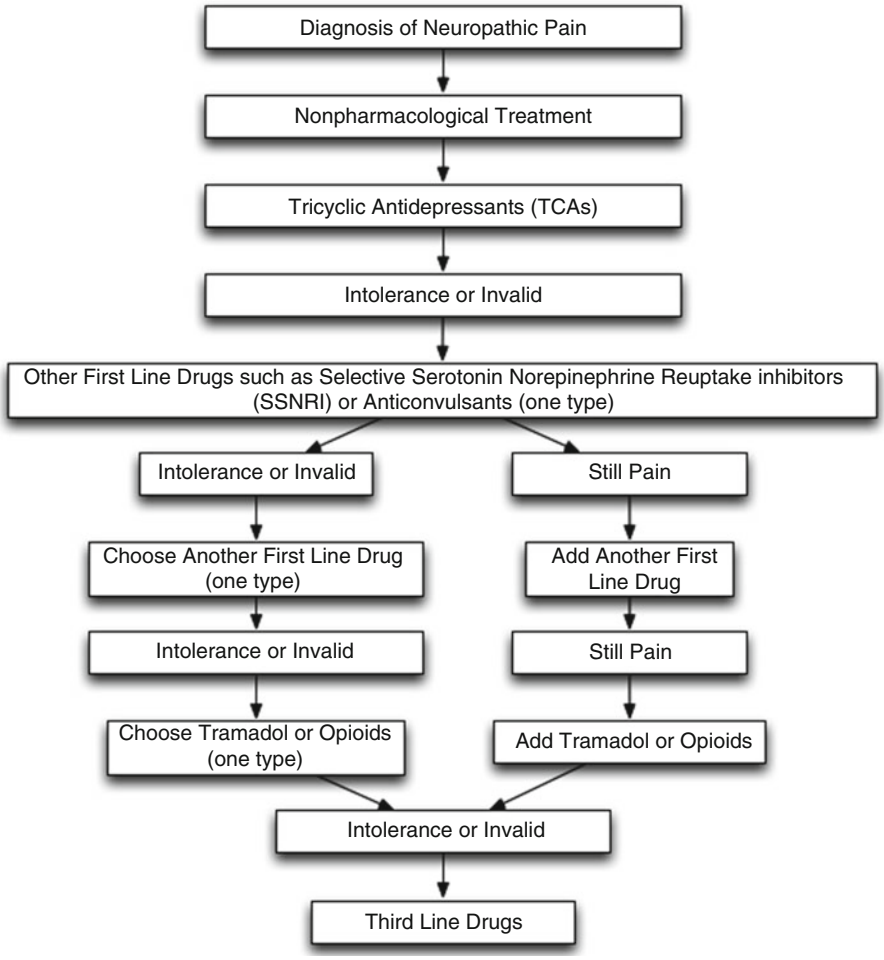

Fig. 9.1 Treatment protocol

injury pain, PHN, and central post-stroke pain (Xu et al. 2012). The analgesia effects of TCAs are attributed to inhibiting reuptake of serotonin and noradrenaline from presynaptic terminals. And they show analgesia efficacy as well as antidepressant effect, the pain-relieving effect is independent of their mood-elevating properties SSNRIs such as duloxetine and venlafaxine have shown consistent efficacy in DPN. Anticonvulsants, such as gabapentin and pregabalin, are quite used as the first choice of neuropathic pain. The efficacy of gabapentin for PHN and DNP has been repeatedly demonstrated. The use of gabapentin in a variety of neuropathic pain conditions was recently reviewed. Overall, the efficacy of gabapentin (50 % pain relief compared to baseline) in PHN, DNP, complex regional pain syndrome type I (CRPS-1), nerve injury pain, small fiber sensory neuropathy, phantom pain, and

mixed neuropathic pain was reported to be superior to placebo (Risk ratio: RR 1.7, 95 % CI: 1.46–1.99; NNT: 6.8, 95 % CI: 5.4–9.2) at the expense of relatively frequent, but most often tolerable, adverse effects (Moore et al. 2011). Fatigue is one of these adverse effects. There are an increasing number of clinical studies on pregabalin that provides supportive evidence for the treatment of DNP, PHN, and other neuropathic pain conditions. The suggestion that the overall cost of care may be reduced in gabapentin-refractory neuropathic pain by switching to pregabalin has been made. A retrospective analysis of data from nine controlled trials of pregabalin for painful diabetic peripheral neuropathy and postherpetic neuralgia suggests that the advantages of pregabalin are the twice-daily administration schedule, a narrower dosage range (between 150 and 600 mg/day), fewer potential adverse effects, and a more rapid therapeutic effect (Sharma et al. 2010). The combination of pregabalin with oxycodone did not clearly show benefit compared with pregabalin alone in a randomized controlled trial (RCT) for PHN or DNP (Jongen et al. 2014; Wettermark et al. 2014). The most widely studied relevant clinical presentations of localized neuropathic pain (LNP) are postherpetic neuralgia, diabetic neuropathy, and neuropathic postoperative pain. They successfully respond to treatment with 5 % lidocaine-medicated plaster with equal if not better pain control but with fewer side effects versus conventional systemic treatments (Casale and Mattia 2014; Likar et al. 2012; Zis et al. 2014). The choice of first line drugs on neuropathic pain is concluded in Table 9.1.

Table 9.1 The first line drugs on neuropathic pain

Type of drug	Level	Side effect	Relative contraindication	Main indication
Tricyclic antidepressants (TCAs)	+	Drowsiness, dry mouth, blurred vision, weight gain, urinary retention	Heart disease, glaucoma, suicide risk, epilepsy, combined with tramadol	DPN, PHN, central post-stroke pain
Selective serotonin norepinephrine reuptake inhibitors (SSNRI)	+	Nausea	Liver function damage, renal inadequacy, alcohol abuse, combined with tramadol	DPN
Anticonvulsants	++	Drowsiness, dizziness, peripheral edema	Renal inadequacy	PHN, DNP, complex regional pain syndrome type I (CRPS-1), small fiber sensory neuropathy, phantom pain, mixed neuropathic pain
Topical Lidocaine	++	Skin rash	None	PHN, allodynia

DPN diabetic peripheral neuropathy, *PHN* postherpetic neuralgia

Table 9.2 The second line drugs on neuropathic pain (TCAs, tricyclic antidepressants; SSNRIs, selective serotonin norepinephrine reuptake inhibitors)

Type of drug	Level	Side effect	Relative contraindication	Other benefits
Opioids	+	Nausea, vomiting, constipation, drowsiness and dizziness	Drug abuse, suicide risk	Fast
Tramadol	+	Nausea, vomiting, constipation, drowsiness and dizziness, epilepsy	Drug abuse, suicide risk, epilepsy, combined with TCA, SSNRI	Fast

The second line drugs include opioids, tramadol. Due to the side effects of opioids, it limits the usage on the treatment of neuropathic pain. However, opioids are being prescribed in stronger potencies and larger doses for musculoskeletal injuries (Mai et al. 2015). A comparative review of available extended release tramadol formulations shows that these medications are not equivalent in their pharmacokinetic profile and this may have implications for selecting the optimal therapy for patients with pain syndromes where tramadol is an appropriate analgesic agent (Kizilbash and Ngo-Minh 2014). The choice of second line drugs on neuropathic pain is concluded in Table 9.2.

The third line drugs include antiepileptic drugs such as citalopram, paroxetine, mexiletine, and others. New evidence which genotyped 34 participants from a placebo-controlled trial of escitalopram in peripheral neuropathic pain for polymorphisms in five genes: the serotonin receptor 2A (HTR2A) gene, the serotonin receptor 2C (HTR2C) gene, the ABCB1 gene encoding for the P-glycoprotein, the CYP2C19 gene, and the serotonin transporter gene (SLC6A4), shows that the serotonin receptor 2C is involved in pain relief in patients with neuropathic pain during treatment with escitalopram, which is the pharmacologically active S-enantiomer of citalopram (Brasch-Andersen et al. 2011).

9.3 Nonpharmacological Treatment

A number of new techniques have been invented and have been proved effective on chronic pain. Nonpharmacologic approaches can be classified as behavioral, cognitive, integrative, and physical therapies. Core principles in developing a treatment plan are explaining the nature of the chronic pain condition, setting appropriate goals, and developing a comprehensive treatment approach and plan for adherence. Clinicians should become familiar with these interventions so that they can offer patients flexibility in the pain management approach. Effective noninvasive treatment modalities for chronic pain include behavioral therapy for short-term pain relief; cognitive behavioral therapy for reducing long-term pain and disability; hypnosis as adjunctive therapy; guided imagery, diaphragmatic breathing, and muscle

relaxation, especially for cancer-related pain; mindfulness-based stress reduction for patients with chronic low back pain; acupuncture for multiple pain conditions; combination manipulation, manual therapy, endurance exercise, stretching, and strengthening for chronic neck pain; animal-assisted therapy; and S-adenosyl-L-methionine for joint pain (Chang et al. 2015).

Neural blockade therapy is a classic method on pain management, the role of it for chronic pain syndromes is still to be discovered. There are some evidences that neural blockade is a valid method on chronic pain. A case of an 18-year-old girl who underwent an uneventful laparoscopic cholecystectomy complained of chronic pain at the site of the surgery postoperatively. Multiple interventions had failed to relieve the pain. However, a successful transversus abdominis plane (TAP) block confirmed the peripheral (somatic) source of the abdominal pain and provided temporary analgesia, after which an indwelling catheter was inserted, which provided prolonged pain relief (Guirguis et al. 2013). Neural blockade of the scalp may be used as an adjunct to general anesthesia or serve as the principal anesthetic for both intracranial and extracranial procedures. Effective scalp blockade typically requires anesthetizing multiple peripheral nerves, blockade of one or more of these is often used to diagnose and treat conditions such as chronic headache (Papangelou et al. 2013). There is a growing body of evidence suggesting that regional anesthesia, even if it requires supplement with sedation or general anesthesia, may be superior to opioids for improved pain control along with increased patient satisfaction and decreased perioperative morbidity and mortality comparing to general anesthesia in patients with significant medical disease(s). Despite successful implementation of neural blockade, and to avoid opioid withdrawal, at least half the chronic pain patient's daily pre-admission opioid dose should be continued daily throughout the perioperative period (Souzdalnitski et al. 2010).

Radio frequency (RF) treatment is a minimally invasive technique with multiple therapeutic applications. The basic researches supposed that RF could regulate some channel expression in the DRG (Liu et al. 2015). Pulsed radiofrequency (PRF) has been proved to reduce neuropathic pain after nerve injury, even though the underlying mechanism remains unclear. The components of PRF are described in Fig. 9.2 (Chua et al. 2011). A case report describes the use of ultrasound-guided PRF to reduce neuropathic pain in a double-level upper extremity nerve injury. And it showed that PRF is a useful tool when pharmacological therapy is inadequate for pain control in posttraumatic neuropathic pain (Magistroni et al. 2014).

Implantation of drug delivery (IDD) system replaced the administered routes such as oral, intravenous, subcutaneous, transdermal, and transmucosal. The system consists of an implantable pump that stores and delivers medication through a catheter to the IT space. Programmability is achieved by positioning an external devise over the implanted pump to change the mode of drug delivery. The innovations in programmable IT drug delivery systems are expanding more rapidly than ever before (wilkes 2014). Unfortunately, the clinical pain field suffers from a lack of randomized controlled trials (RCTs).

Neural stimulation has been widely used in Europe for many years. It involves spinal cord stimulation (SCS), transcutaneous electrical nerve stimulation (TENS),

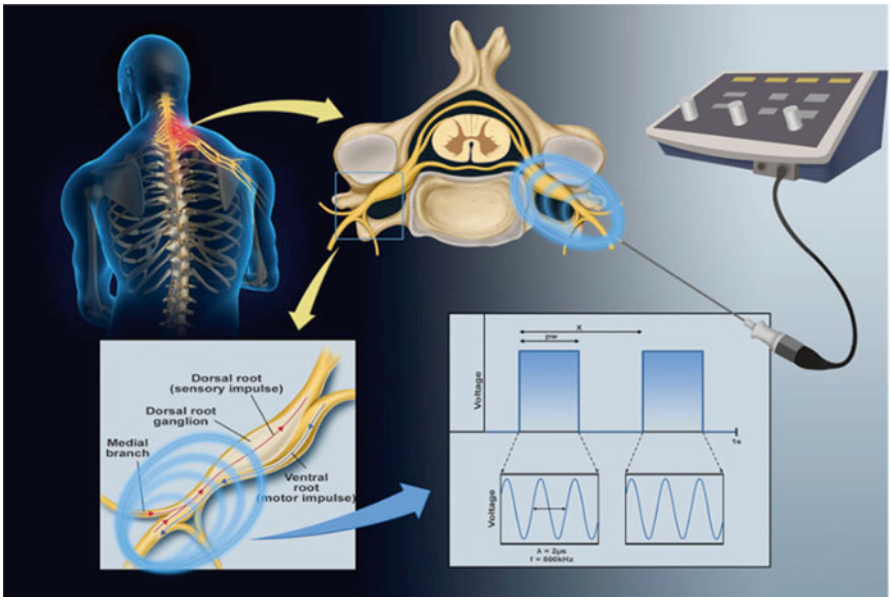

Fig. 9.2 The components of PRF(*23*) λ wavelength of intrinsic RF current; f frequency of intrinsic RF current at usually 500 kHz; pw pulse width; *x* duration of each pulse cycle and therefore pulse frequency = 1/*x* (Adapted from Chua et al. 2011)

peripheral nerve stimulation (PNS), and motor cortex stimulation (MCS). Spinal cord stimulation consists of implantation of peri-epidural electrode in the posterior columns of the spinal cord at the spinal level of the dermatomes on which we want to produce the analgesic effect. The mechanism of function of SCS is that the stimulation is applied directly to the posterior horns of the spinal cord does not allow us to conclude on the specific neurophysiological mechanisms of this analgesia. The stimulation may recruit afferents from the periphery, afferents from the spinal cord to the higher centers, local neuron circuits, and even fibers of the anterior horns of the spinal cord. Some studies seem to suggest that the efficacy of SCS in reducing neuropathic pain is probably related to a direct effect on central sensitization measured by temporal summation (TS) (Marchand 2015; Zhang et al. 2014). Transcutaneous electrical nerve stimulation (TENS) relieves pain by inhibiting pain-related potentials on the spinal and supraspinal level, known as "gate control." It is alternating current or modulated DC, comprising rectangular impulses. The analgesic effects of TENS are seen in both the ipsilateral and contralateral spinal segmental regions (Samuel and Maiya 2015). Peripheral nerve stimulation (PNS) is a neuromodulation technique in which electrical current is applied to the peripheral nerves to ameliorate chronic pain through preferential activation of myelinated fibers, inducing long-term depression of synaptic efficacy (Johnson et al. 2015). When damage to the peripheral nerves causes severe pain that does not respond to targets in the spinal cord, such as postherpetic neuralgia, occipital or C2 neuritis,

intercostal nerve pain from trauma or disease, and ilioinguinal nerve entrapment. When SCS alone fails to give adequate control of the pain, peripheral nerve stimulation alone, or in combination with SCS, will often salvage a good outcome (Deer 2011). Motor cortex stimulation (MCS) was first used for the treatment of central post stroke pain and now has been proved more effective in the treatment of chronic neuropathic pain of central post stroke pain and peripheral neuropathic pain types than in the treatment of SCI pain in the long-term follow-up (Im et al. 2015). There is a concern that infectious complications related to IDD system and SCS at a comprehensive cancer pain center. Researchers reported that 142 devices were implanted in 131 patients during the examined period. Eighty-three of the devices were IDD systems and 59 were SCS systems. Four infectious complications were noted with an overall infectious risk of 2.8 %. The infection rate was 2.4 % for IDD systems versus 3.4 % for SCS systems ($P = 1$) (Engle et al. 2013).

9.4 The Treatment of Common Neuropathic Pain

9.4.1 Central Pain

Central pain, also is named as central neuropathic pain, is the pain raised from the brain and the spinal disease such as central post stroke pain (CPSP), multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease (PD), and central nervous infection. For pharmacological treatment, amitriptyline, an adrenergic antidepressant, is currently the first-line drug for CPSP. GABAergic drugs with potential calcium channel-blocking effects, such as gabapentin or pregabalin, have recently emerged as a potentially useful therapy. Pregabalin may improve pain-related anxiety and sleep disturbances. Given the safety, efficacy, well tolerability, and lack of interaction with other drugs, a recent study suggests gabapentin to be more considered as a first line therapy or as add-on therapy for reducing the pain severity in patients with thalamic syndrome (Hesami et al. 2015). It is important to note that large randomized, controlled trials on gabapentin and pregabalin have shown an improved safety profile over the older antiepileptic agents. Indeed, studies have shown gabapentin's superiority over placebo for chronic SCI pain, and other randomized controlled trial have verified the efficacy of oral pregabalin for patients with SCI with central neuropathic pain, at least for 3-month increments (Lee et al. 2013). Lamotrigine, an antiepileptic, was also found to be effective in a controlled trial and can be used as an alternative or additive therapy (Kim 2014).

Nonpharmcological treatment on central pain has been studied in recent years. A study recruited 14 consecutive patients with thalamic pain, atypical facial pain, post-brachial plexus avulsion injury pain, phantom pain, and pain in syringomyelia were treated with motor cortex stimulation. It suggests that MCS significantly reduces the intensity of neurogenic pain. The best long-term results in the present study were achieved in patients with thalamic syndrome (Sokal 2015). Cury et al. observed the effects of deep brain stimulation on pain and other nonmotor symptoms

in Parkinson disease and found that subthalamic nucleus deep brain stimulation (STN-DBS) decreased pain after surgery, but had different effects in different types of PD-related pain. Motor and nonmotor symptom improvements after STN-DBS did not correlate with pain relief (Cury et al. 2014).

Practitioners should carefully consider factors including concomitant disease states, renal function, and side effect of the drugs when prescribing the oral agents for spinal cord injury patients. Patients with post-spinal cord injury may suffer depression for numerous reasons, having a tricyclic antidepressant or serotonin / norepinephrine reuptake inhibitor as first-line or part of combination therapy would be recommended. When choosing combination therapies, using agents with different mechanisms of action. For example, using gabapentin with tricyclic antidepressants or serotonin/norepinephrine reuptake inhibitors would provide multiple targets at the nerves, while using combinations such as gabapentin with pregabalin will only augment side effects (DeFrates and Cook 2011). A number of studies have begun to use non-invasive neuromodulatory techniques therapeutically to relieve neuropathic pain and phantom phenomena in patients with SCI. The utility of these protocols in combination with pharmacological approaches should also be explored (Nardone 2014).

9.4.2 Peripheral Pain

Diabetic peripheral neuropathy (DPN) is the most common peripheral neuropathy and has been studied for many years. The management of diabetic neuropathic pain consists basically in excluding other causes of painful peripheral neuropathy, improving glycemic control as a prophylactic therapy, and using medications to alleviate pain. First line drugs for pain relief include anticonvulsants, such as pregabalin and gabapentin, and antidepressants, especially those that act to inhibit the reuptake of serotonin and noradrenaline. There is difference with respect to the maximum approved dose of pregabalin for the treatment of DPN in the United States (300 mg/day) and European Union (600 mg/day), though clinical data demonstrate that pregabalin doses >300 mg/day may be beneficial in some patients. Pregabalin has shown efficacy (and is approved) as a monotherapy for DPN. There are data demonstrating the efficacy of pregabalin in some patients with DPN who have not responded to other pharmacological treatments, including those unresponsive to treatment with gabapentin (Juhn et al. 2015). In addition, there is experimental and clinical evidence that opioids can be helpful in pain control, mainly if associated with first line drugs. A study which examines the proportion of DPN patients receiving pharmacologic DPN treatments and specifically identifies the rates and factors associated with opioid use and first-line opioid use proves that 53.47 % had DPN-related opioid use and 33.33 % received opioid as first-line treatment (Patil et al. 2015). Other agents, including for topical application, such as capsaicin cream and lidocaine patches, have also been proposed to be useful as adjuvants in the control of diabetic neuropathic pain, but the clinical evidence is insufficient to support their use (Schreiber et al. 2015).

Table 9.3 The therapy protocol on PHN

Patient	Age	Treatment		
		Antivirus	Anti-inflammatory	Analgesia
Normal immune function	<50	+ (within 70 h)	+	Sympathetic blockade
	>50	–	+	Epidural, body/sympathetic nerve block and infiltration
Insufficient immune function	<50	+ (within 70 h)	–	Oral analgesics
	>50	+ (within 70 h)	+	Nerve block and adjuvant use of oral analgesics

– no need
+ useful
++ necessary

Another common peripheral neuropathy is postherpetic neuralgia (PHN). The treatment of PHN contains two stages, the acute stage and the postherpetic neuralgia stage. The therapy protocol on PHN is described in Table 9.3.

9.4.3 Cancer Pain

Pain and neuropathic symptoms impact quality of life in patients with cancer. A study shows that over 40 % of the patients with moderate to severe pain also have neuropathic symptoms, causing increased interference with daily activities (Oosterling et al. 2015). The most efficacious adjuvant analgesics used as first-line treatment for NP includes tricyclic antidepressants, calcium channel α2-d ligand anticonvulsants, and serotonin-norepinephrine reuptake inhibiters. Adjuvant analgesics are often combined with opioids when NP is refractory or severe (Smith et al. 2014). A number of studies suggest that traditional herbal medicine (THM) combined with conventional therapy is efficacious as an adjunctive therapy for patients with cancer pain (Lee et al. 2015). Interventional pain management techniques are an indispensable arsenal in pain physician's armamentarium for severe, intractable pain and can be broadly classified into neuroablative and neuromodulation techniques. An array of neurolytic techniques (chemical, thermal, or surgical) can be employed for ablation of individual nerve fibers, plexuses, or intrathecalneurolysis in patients with resistant pain and short life expectancy. Neuraxial administration of drugs and spinal cord stimulation to modulate or alter the pain perception constitutes the most frequently employed neuromodulation techniques. Laying standardized guidelines based on existing and emerging evidence will act as a foundation step towards strengthening, credentialing, and dissemination of the specialty of interventional cancer pain management (Bhatnagar and Gupta 2015).

9.5 Conclusion

The mechanism of neuropathic pain is complicated. We haven't found a single way to effectively relief the neuropathic pain up to present. Gabapentin and pregabalin are the first line drugs which are widely used in PHN, DNP, and SCI patients. Besides pharmacological therapy, physical therapy, psychotherapy, teamwork medical, traditional Chinese medicine, electrical nerve stimulation and interventional therapy are effective in many cases.

References

Attal N, Bouhassira D. Pharmacotherapy of neuropathic pain: which drugs, which treatment algorithms? Pain. 2015;156 Suppl 1:S104–14.

Bhatnagar S, Gupta M. Evidence-based clinical practice guidelines for interventional pain management in cancer pain. Indian J Palliat Care. 2015;21:137–47.

Brasch-Andersen C, Moller MU, Christiansen L, et al. A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor 2C (HTR2C). Eur J Clin Pharmacol. 2011;l67:1131–7.

Casale R, Mattia C. Building a diagnostic algorithm on localized neuropathic pain (LNP) and targeted topical treatment: focus on 5% lidocaine-medicated plaster. Ther Clin Risk Manag. 2014;10:259–68.

Chang KL, Fillingim R, Hurley RW, Schmidt S. Chronic pain management: nonpharmacological therapies for chronic pain. FP Essent. 2015;432:21–6.

Chua NH, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications-a review. Acta Neurochir (Wien). 2011;153:763–71.

Cury RG, Galhardoni R, Fonoff ET, et al. Effects of deep brain stimulation on pain and other nonmotor symptoms in Parkinson disease. Neurology. 2014;83:1403–9.

Deer TR. Spinal cord and peripheral nerve stimulation should be used earlier in the treatment algorithm for neuropathic pain. Pain Manag. 2011;1:7–10.

DeFrates S, Cook AM. Pharmacologic treatment of neuropathic pain following spinal cord injury. Orthopedics. 2011;34:203.

Engle MP, Vinh BP, Harun N, Koyyalagunta D. Infectious complications related to intrathecal drug delivery system and spinal cord stimulator system implantations at a comprehensive cancer pain center. Pain Physician. 2013;16:251–7.

Gilron I, Baron R, Jensen T. Neuropathic pain: principles of diagnosis and treatment. Mayo Clin Proc. 2015;90:532–45.

Guirguis MN, Abd-Elsayed AA, Girgis GL, Soliman M. Ultrasound-guided transversus abdominis plane catheter for chronic abdominal pain. Pain Pract. 2013;13:235–8.

Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012;73:638–52.

Helfert SM, Reimer M, Hoper J, Baron R. Individualized pharmacological treatment of neuropathic pain. Clin Pharmacol Ther. 2015;97:135–42.

Hesami O, Gharagozli K, Beladimoghadam N, Assarzadegan F, et al. The efficacy of gabapentin in patients with central post-stroke pain. Iran J Pharm Res. 2015;14:95–101.

Im SH, Ha SW, Kim DR, Son BC. Long-term results of motor cortex stimulation in the treatment of chronic, intractable neuropathic pain. Stereotact Funct Neurosurg. 2015;93:212–8.

Johnson S, Ayling H, Sharma M, Goebel A. External noninvasive peripheral nerve stimulation treatment of neuropathic pain: a prospective audit. Neuromodulation. 2015;18:384–91.
Jongen JL, Hans G, Benzon HT, Huygen F, Hartrick CT. Neuropathic pain and pharmacological treatment. Pain Pract. 2014;14:283–95.
Juhn MS, Parsons B, Varvara R, Sadosky A. Pregabalin for painful diabetic peripheral neuropathy: strategies for dosing, monotherapy vs. combination therapy, treatment-refractory patients, and adverse events. Curr Med Res Opin. 2015;31:1017–26.
Kim JS. Pharmacological management of central post-stroke pain: a practical guide. CNS Drugs. 2014;28:787–97.
Kizilbash A, Ngo-Minh CT. Review of extended-release formulations of Tramadol for the management of chronic non-cancer pain: focus on marketed formulations. J Pain Res. 2014;7:149–61.
Lee S, Zhao X, Hatch M, Chun S, Chang E. Central neuropathic pain in spinal cord injury. Crit Rev Phys Rehabil Med. 2013;25:159–72.
Lee JW, Lee WB, Kim W, Min BI, et al. Traditional herbal medicine for cancer pain: a systematic review and meta-analysis. Complement Ther Med. 2015;23:265–74.
Likar R, Kager I, Obmann M, Pipam W, Sittl R. Treatment of localized neuropathic pain after disk herniation with 5% lidocaine medicated plaster. Int J Gen Med. 2012;5:689–92.
Liu Y, Feng Y, Zhang T. Pulsed radiofrequency treatment enhances dorsal root ganglion expression of hyperpolarization-activated cyclic nucleotide-gated channels in a rat model of neuropathic pain. J Mol Neurosci. 2015;57:97–105.
Magistroni E, Ciclamini D, Panero B, Verna V. Ultrasound-guided pulse-dose radiofrequency: treatment of neuropathic pain after brachial plexus lesion and arm revascularization. Case Rep Med. 2014;2014:429618.
Mai J, Franklin G, Tauben D. Guideline for prescribing opioids to treat pain in injured workers. Phys Med Rehabil Clin N Am. 2015;26:453–65.
Marchand S. Spinal cord stimulation analgesia: substantiating the mechanisms for neuropathic pain treatment. Pain. 2015;156:364–5.
Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2011;4:CD007938.
Nardone R. Invasive and non-invasive brain stimulation for treatment of neuropathic pain in patients with spinal cord injury: a review. J Spinal Cord Med. 2014;37:19–31.
Oosterling A, Te Boveldt N, Verhagen C, van der Graaf WT, et al. Neuropathic pain components in patients with cancer: prevalence, treatment, and interference with daily activities. Pain Pract Cancer. 2015. doi:10.1111/papr.12291.
Papangelou A, Radzik BR, Smith T, Gottschalk A. A review of scalp blockade for cranial surgery. J Clin Anesth. 2013;25:150–9.
Patil PR, Wolfe J, Said Q, Thomas J, Martin BC. Opioid use in the management of diabetic peripheral neuropathy (DPN) in a large commercially insured population. Clin J Pain. 2015;31:414–24.
Samuel SR, Maiya GA. Application of low frequency and medium frequency currents in the management of acute and chronic pain-a narrative review. Indian J Palliat Care. 2015;21:116–20.
Schreiber AK, Nones CF, Reis RC, Chichorro JG, et al. Diabetic neuropathic pain: physiopathology and treatment. World J Diabetes. 2015;6:432–44.
Sharma U, Griesing T, Emir B, Young JP. Time to onset of neuropathic pain reduction: a retrospective analysis of data from nine controlled trials of pregabalin for painful diabetic peripheral neuropathy and postherpetic neuralgia. Am J Ther. 2010;17:577–85.
Smith EM, Bridges GM, Kanawa G, Knoetl R, et al. Cancer treatment-related neuropathic pain syndromes--epidemiology and treatment: an update. Curr Pain Headache Rep. 2014;18:459.
Sokal P. Motor cortex stimulation in patients with chronic central pain. Adv Clin Exp Med. 2015;24:289–96.
Souzdalnitski D, Halaszynski TM, Faclier G. Regional anesthesia and co-existing chronic pain. Curr Opin Anaesthesiol. 2010;23:662–70.

Wettermark B, Brandt L, Kieler H, Boden R. Pregabalin is increasingly prescribed for neuropathic pain, generalised anxiety disorder and epilepsy but many patients discontinue treatment. Int J Clin Pract. 2014;68:104–10.

Wilkes D. Programmable intrathecal pumps for the management of chronic pain: recommendations for improved efficiency. J Pain Res. 2014;7:571–7.

Xu B, Descalzi G, Ye HR, Zhuo M, Wang YW. Translational investigation and treatment of neuropathic pain. Mol Pain. 2012;8:15.

Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. Brain Res. 2014;1569:19–31.

Zis P, Apsokardos A, Isaia C, Sykioti P, Vadalouca A. Posttraumatic and postsurgical neuropathic pain responsive to treatment with capsaicin 8% topical patch. Pain Physician. 2014;17:E213–8.