

## INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY

### Review Article

# Neuropathic Pain: An Overview

Ankur Rohilla<sup>1\*</sup>, Pinki<sup>1</sup>, Seema Rohilla<sup>2</sup>, Amarjeet Dahiya<sup>1</sup> and Ashok Kushnoor<sup>1</sup>

<sup>1</sup>Department of Pharmaceutical Sciences, Shri Gopi Chand Group of Institutions, Baghpat, Uttar Pradesh, India.

<sup>2</sup>Department of Pharmaceutical Sciences, Hindu College of Pharmacy, Sonapat, Haryana, India.

### ABSTRACT

The capacity to experience pain has a protective role for counseling the tissue damage that bring forth coordinated reflexes and behavioral responses in order to keep such damage to least amounts. Neuropathic pain (NP) has been considered as a condition caused by various central and peripheral nerve disorders. NP results from various causes affecting brain, spinal cord and peripheral nerves like cervical or lumbar radiculopathy, diabetic neuropathy, cancer-related NP, HIV-related neuropathy and spinal cord injury. Recommended therapies of NP involve antidepressants, certain antiepileptics, topical lidocaine and opioid analgesics. The present review aims at explaining various causes and treatments for the prevention and treatment of NP.

**Keywords:** Neuropathic pain, Nerve, Treatment.

### INTRODUCTION

Neuropathic pain (NP) refers to pain that occurs due to various central and peripheral nerve disorders resulted from injury to a single or several nerves in the body.<sup>1-2</sup> Various diseases, injuries and interventions have been noted to cause NP by producing lesions in somatosensory pathways in central or peripheral nervous system. Nerves that remain intact following tissue injury remain hyperactive, signaling pain in the dearth of painful stimuli.<sup>3</sup> The epidemiology studies of NP pain have not been sufficiently premeditated because of the multiplicity of the associated conditions. However, numerous causes for the occurrence of NP have been widely reported that include chemotherapeutic drugs, radiation therapy, tumor pushing on a nerve, surgery for cancer, trauma, herpes zoster infections, chronic conditions like diabetes, nutritional deficiencies, toxins, trigeminal neuralgia and complex regional pain syndrome type II.<sup>4-7</sup> Moreover, various symptoms of NP have been recorded in various studies that include burning, cramping, jolting, numbness, pressure, squeezing, stabbing and tingling. Plenty of evidences have suggested that NP impairs patients' mood, quality of life, activities of daily living and performance at work. Hence, the treatment strategies of NP have been aimed at eliminating the cause of pain, providing relief from pain, maintaining usual activity level and improving the quality of life.<sup>8-9</sup> In addition, treatments with one or more medicines have also been reported that include anti-seizure

drugs, antidepressants, anticancer drugs, opioids, steroids, topical and local anesthetics.<sup>10-11</sup> The review article highlights about various causes and treatment strategies of NP.

### TYPES OF NP

NP is referred to as the pain caused by primary lesion or dysfunction in the nervous system. The types of NP can be primarily studied under three main headings, i.e., Postherpetic Neuralgia (PHN),<sup>12</sup> Painful HIV-Distal Sensory Polyneuropathy (HIV-DSP)<sup>13</sup> and Painful Diabetic Neuropathy (PDN).<sup>14</sup> PHN is a chronic pain disorder resulting from varicella zoster virus reactivation, commonly known as shingles.<sup>15</sup> The definitions of PHN ranges from persistent pain for one month to long six years after shingle rash crusting. Moreover, PHN has been noted to occur frequently in elderly and immunosuppressed populations.<sup>16-17</sup> In addition, the incidence of PHN has been vitally seen to occur in patients with enhanced immune suppression like in cancer and human immuno virus (HIV). Further, HIV-DSP has been considered as the most common neurological complication of HIV infection. HIV-DSP has been noted to primarily caused by direct activation of sensory neurons by HIV, fight of immune system against HIV and antiretroviral drugs.<sup>18</sup> The HIV-DSP has been characterized by significant chronic pain in the hands and feet leading to loss of sensation in the arms and legs. The symptoms range from mild tingling to severe pain in response to normal daily stimuli.<sup>18-19</sup> The third type of PN is

PDN which can be regarded as the chronic pain resulting from damage to sensory nerves due to multiple factors like high glucose-mediated metabolic insult and inadequate oxygenation related to diabetic microvascular damage.<sup>20-21</sup> The symptoms of PDN include paraesthesias, stabbing, shooting and burning pains that are commonly present in the feet often worsening at night.<sup>22-23</sup> Other types of NP have also been reported to be associated with traumatic nerve injury, stroke, multiple sclerosis, syringomyelia, epilepsy, spinal cord injury and cancer.

#### TERMS ASSOCIATED WITH NP

There are various terms that have been frequently used in regard to the understanding of NP like allodynia, paraesthesia, hyperesthesia, hyperalgesia, hyperpathia and hypoesthesia.<sup>24-28</sup> A situation where a normal stimulus elicits an abnormal painful response is referred to as allodynia, for example, touch, light pressure and cold have been felt as pain.<sup>29</sup> Paresthesia is defined as an abnormal sensation whether spontaneous or provoked, whereas, hyperesthesia is an increased sensitivity to stimulation, which requires specific mention of stimulus and location.<sup>30-31</sup> It may be due to reduced threshold to any stimulus and an enhanced response to stimuli that are normally recognized. In general, the hyperesthesia to painful stimulus is regarded as hyperalgesia, whereas, hyperesthesia to touch is referred to as allodynia.<sup>32-33</sup> Moreover, an increased response to a stimulus which is normally painful is called as hyperalgesia.<sup>27</sup> It may also be defined as an increased response to normal threshold or at a normal threshold. Further, hyperpathia is another term that is frequently used in reference to NP which can be defined as a painful syndrome characterized by increased reaction to a stimulus, especially a repetitive stimulus as well as increased threshold. Another related term associated with NP is hypoesthesia which is known to be condition of decreased sensitivity to stimulation, accept the special senses, in which stimulation and location must be specified. Furthermore, two more terms have been noted to be associated with NP that includes hypoalgesia and dyesthesia.<sup>26</sup> However, hypoalgesia can be identified as the diminished pain in response to a normally painful stimulus, whereas, dyesthesia is an unpleasant abnormal sensation, whether spontaneous and evoked.<sup>34</sup>

#### CLINICAL PRESENTATION OF NP

It has been widely accepted that the blockade of nerve conduction in neuropathic conditions lead to nerve dysfunction resulting in numbness, weakness and loss of deep tendon reflexes in the affected nerve area.<sup>35</sup> NP can be classified on the basis of the etiology of the insult to the nervous system or to the anatomical distribution of the pain.

Moreover, the neuropathic conditions cause uncharacteristic symptoms of spontaneous and stimulus-evoked pain.<sup>36</sup> However, spontaneous pain may be described as a sensation of burning, shooting or shock-like, whereas, stimulus-evoked pain includes allodynia and hyperalgesia.<sup>37-38</sup> The allodynia can be caused by the lightest stimulation like skin contact with clothing and cold. Such sensory abnormalities extend beyond nerve distributions ultimately causing inappropriate diagnosis of a functional or psychosomatic disorder. The diagnosis of neuropathic pain is based primarily on history and findings on physical examination, sudomotor and other changes and neurological deficits.<sup>39</sup> Without recognition of the mechanisms of NP, the optimum treatment strategy for the clinically presented patient cannot be selected. Hence, the assessment of patient presented with suspected NP should focus on ruling out treatable conditions like, spinal cord compression, confirming the diagnosis of NP and identifying clinical features like insomnia and autonomic neuropathy that might help for the individualized treatment.<sup>40-41</sup>

#### TREATMENTS FOR NP

Ample research has concluded that treatment specifically adapted may help in managing the pain associated with NP. Depending on the specific needs, it has been suggested the treatment strategies of NP include increasing the physical activity, using stress management techniques to help with mood and functioning, using medications to help with pain and mood, managing stress, improving blood pressure and lowering blood sugar levels.<sup>42</sup> The main aim of treating NP is centered on improvements in the daily life by physical activities like swimming, water aerobics, walking and biking. Moreover, cognitive-behavioral and stress management strategies have been shown to help people better manage and cope up with NP.<sup>43</sup> The cognitive-behavioral approach emphasizes about thoughts, ideas and beliefs that affect behavior and emotions. Additionally, in cognitive-behavioral therapy, change of thinking styles in order to decrease sufferings is learnt.<sup>44-45</sup> Further, medications are prescribed to decrease pain and discomfort associated with NP. It has been shown that nonsteroidal anti-inflammatory drugs (NSAIDs) decrease mild to moderate pain and inflammation for a short period of time.<sup>46-47</sup> In addition, medications such as tricyclic antidepressants (TCAs) like amitriptyline, nortriptyline and desipramine have been noted to help in reducing the pain and help with sleep and mood.<sup>48-50</sup> In addition, based on various methodologically flawed trials, it has been suggested that various anticonvulsants can be used as second line therapy for the treatment of NP.<sup>51-52</sup> Moreover, Capsaicin and Lidocaine cream have

been found to soothe the skin sensitivity and relieve from pain.<sup>53</sup>

### CONCLUSION

NP is generally considered as the pain caused by dysfunction in the central or peripheral nervous system. Various causes of NP have been found like radiation therapy, surgery and trauma, diabetic neuropathy and cancer. The treatments available for NP are generally palliative and include conservative nonpharmacological therapies as well as drugs. The individualizing management requires deliberation of functional impacts like mood disorders and depression. However, various treatments have been well reported for NP like topical lidocaine, tricyclic antidepressants and opioids but it can be suggested that the field of NP research and treatment is in the preliminary stages of development with several unidentified. Hence, several advances are expected in the basic and clinical sciences of NP in the upcoming years in order to afford prevention and better treatments.

### REFERENCES

1. Baron R. Neuropathic pain: a clinical perspective. *Hand. Exp. Pharmacol.* 2009; 194: 3-30.
2. Austin PJ, Wu A and Moalem-Taylor G. Chronic constriction of the sciatic nerve and pain hypersensitivity testing in rats. *J. Vis. Exp.* 2012; in press.
3. Cepeda MS, Berlin JA, Gao CY, Wiegand F and Wada DR. Placebo response changes depending on the neuropathic pain syndrome: results of a systematic review and meta-analysis. *Pain Med.* 2012 13:575-595.
4. Singleton JR. Evaluation and treatment of painful peripheral polyneuropathy. *Semin. Neurol.* 2005; 25:185-195.
5. Garg RK, Malhotra HS, Verma R. Trigeminal neuralgia. *J. Ind. Med. Assoc.* 2011;109:631-636.
6. Hui F, Boyle E, Vayda E and Glazier RH. A randomized controlled trial of a multifaceted integrated complementary-alternative therapy for chronic herpes zoster-related pain. *Altern. Med. Rev.* 2012;17:57-68.
7. Hussain AM and Khan MA. Pain management after traumatic spinal cord injury. *J. Coll. Physicians Surg. Pak.* 2012;22:246-247.
8. Nicholson B. Responsible prescribing of opioids for the management of chronic pain. *Drugs.* 2003; 63: 17-32.
9. Connolly I, Zaleon C and Montagnini M. Management of Severe Neuropathic Cancer Pain: An Illustrative Case and Review. *Am. J. Hosp. Palliat. Care.* 2012; in press.
10. Przewłocki R and Przewłocka B. Opioids in chronic pain. *Eur. J. Pharmacol.* 2001; 429: 79-91.
11. Mannino R, Coyne P, Swainey C, Hansen LA and Lyckholm L. Methadone for cancer-related neuropathic pain: a review of the literature. *J. Opioid Manag.* 2006; 2: 269-276.
12. Benzon HT, Chekka K, Darnule A, Chung B, Wille O and Malik K. Evidence-based case report: the prevention and management of postherpetic neuralgia with emphasis on interventional procedures. *Reg. Anesth. Pain Med.* 2009; 34: 514-521.
13. Zhou L, Kitch DW, Evans SR, Hauer P, Raman S and Ebenezer GJ. Correlates of epidermal nerve fiber densities in HIV-associated distal sensory polyneuropathy. *Neurology.* 2007;68:2113-2119.
14. Webster LR, Peppin JF, Murphy FT, Lu B, Tobias JK and Vanhove GF. Efficacy, safety, and tolerability of NGX-4010, capsaicin 8% patch, in an open-label study of patients with peripheral neuropathic pain. *Diabetes Res. Clin. Pract.* 2011; 93: 187-197.
15. Mahn F and Baron R. Postherpetic neuralgia. *Klin. Monbl. Augenheilkd.* 2010;227:379-383.
16. Johnson RW. Herpes zoster and postherpetic neuralgia. *Expert Rev. Vaccines.* 2010; 9: 21-26.
17. Nalamachu S. Comment: Systematic Review and Meta-Analysis of Efficacy, Safety, and Tolerability Data from Randomized Controlled Trials of Drugs Used to Treat Postherpetic Neuralgia (May). *Ann. Pharmacother.* 2012; in press.
18. Herrmann DN, McDermott MP, Henderson D, Chen L and Akowuah K, Schifitto G. Epidermal nerve fiber density, axonal swellings and QST as predictors of HIV distal sensory neuropathy. *Muscle Nerve.* 2004; 29: 420-427.
19. England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ and Cohen JA. Evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). *Muscle Nerve.* 2009; 39:106-115.
20. Ziegler D. Painful diabetic neuropathy: advantage of novel drugs over old drugs? *Diabetes Care.* 2009; 32: S414-S419.
21. Gibbons CH and Freeman R. Treatment-induced diabetic neuropathy: a

- reversible painful autonomic neuropathy. *Ann. Neurol.* 2010; 67:534-541.
22. Taylor-Stokes G, Pike J, Sadosky A, Chandran A and Toelle T. Association of patient-rated severity with other outcomes in patients with painful diabetic peripheral neuropathy. *Diabetes Metab. Syndr. Obes.* 2011;4:401-408.
  23. Bellows BK, Dahal A, Jiao T and Biskupiak J. A Cost-Utility Analysis of Pregabalin Versus Duloxetine for the Treatment of Painful Diabetic Neuropathy. *J. Pain Palliat. Care Pharmacother.* 2012; in press.
  24. Caspani O, Zurborg S, Labuz D, Heppenstall PA. The contribution of TRPM8 and TRPA1 channels to cold allodynia and neuropathic pain. *PLoS. One.* 2009; 4:7383.
  25. Lennertz RC, Tsunozaki M, Bautista DM and Stucky CL. Physiological basis of tingling paresthesia evoked by hydroxy-alpha-sanshool. *J. Neurosci.* 2010;30: 4353-4361.
  26. Martin-Pichora AL, Mankovsky-Arnold TD and Katz J.J. Implicit versus explicit associative learning and experimentally induced placebo hypoalgesia. *Pain Res.* 2011;4:67-77.
  27. Petersen GL, Finnerup NB, Nørskov KN, Grosen K, Pilegaard HK, Benedetti F, Price DD, Jensen TS and Vase L. Placebo manipulations reduce hyperalgesia in neuropathic pain. *Pain.* 2012; in press.
  28. Qi DB and Li WM. Effects of electro acupuncture on expression of c-fos protein and N-methyl-D-aspartate receptor 1 in the rostral ventromedial medulla of rats with chronic visceral hyperalgesia. *Zhong. Xi. Yi. Jie. He. Xue. Bao.* 2012; 10: 416-423.
  29. Burstein R, Jakubowski M, Garcia-Nicas E, Kainz V, Bajwa Z and Hargreaves R. Thalamic sensitization transforms localized pain into widespread allodynia. *Borsook D. Ann. Neurol.* 2010; 68: 81-91.
  30. Gaffen AS and Haas DA.J. Retrospective review of voluntary reports of nonsurgical paresthesia in dentistry. *Can. Dent. Assoc.* 2009; 75: 579.
  31. Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L and Kidd BL. Normalisation of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. *Arthritis. Rheum.* 2012; in press.
  32. Ciribassi J. Understanding behavior: feline hyperesthesia syndrome. *Compend. Contin. Educ. Vet.* 2009; 31: 116-132.
  33. Waldinger MD, Venema PL, van Gils AP and Schweitzer DH. New insights into restless genital syndrome: static mechanical hyperesthesia and neuropathy of the nervus dorsalis clitoridis. *J. Sex Med.* 2009; 6:2778-2787.
  34. Slater H, Thériault E, Ronningen BO, Clark R and Nosaka K. Exercise-induced mechanical hypoalgesia in musculotendinous tissues of the lateral elbow. *Man Ther.* 2010; 15: 66-73.
  35. Zimmermann M. Pathobiology of neuropathic pain. *Eur. J. Pharmacol.* 2001; 429: 23-37.
  36. Fornasari D. Pain mechanisms in patients with chronic pain. *Clin. Drug. Investig.* 2012;32:45-52.
  37. Bouhassira D, Attal N and Fermanian J. Development and validation of the neuropathic pain symptom inventory. *Pain.* 2004; 108: 248-257.
  38. Bouhassira D, Attal N and Alchaar H. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain.* 2005;114:29-36.
  39. Backonja MM and Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurol. Clin.* 1998; 16:775-790.
  40. Dworkin RH, Panarites CJ, Armstrong EP, Malone DC and Pham SV. Is treatment of postherpetic neuralgia in the community consistent with evidence-based recommendations?. *Pain.* 2012; 153: 869-875.
  41. Sarzi-Puttini P, Vellucci R, Zuccaro SM, Cherubino P, Labianca R, Fornasari D. The appropriate treatment of chronic pain. *Clin. Drug Investig.* 2012; 32: 21-33.
  42. Berger A, Sadosky A, Dukes E, Edelsberg J and Oster G. Clinical characteristics and patterns of healthcare utilization in patients with painful neuropathic disorders in UK general practice: a retrospective cohort study. *BMC. Neurol.* 2012; 12: 8.
  43. Rojo ML, Rodríguez-Gaztelumendi A, Pazos A and Díaz A. Differential adaptive changes on serotonin and noradrenaline transporters in a rat model of peripheral neuropathic pain. *Neurosci. Lett.* 2012; 515:181-186.
  44. Evans S, Fishman B and Spielman L. Randomized trial of cognitive behavior therapy versus supportive psychotherapy

- for HIV-related peripheral neuropathic pain. *Psychosomatics*. 2003;44:44-50.
45. Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. *Pain*. 2004; 108: 192-198.
  46. Pergolizzi J, Alon E, Baron R, Bonezzi C, Dobrogowski J and Gálvez R. Tapentadol in the management of chronic low back pain: a novel approach to a complex condition?. *J. Pain. Res.* 2011;4:203-210
  47. Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M and Oliveira VC. Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis. *BMJ*. 2012; 344e:497.
  48. Saarto T and Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane. Database. Syst. Rev.* 2007; 4: CD005454.
  49. Saarto T and Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. *J. Neurol. Neurosurg. Psychiatry*. 2010; 81: 1372-1373.
  50. Matsuzawa-Yanagida K, Narita M, Nakajima M, Kuzumaki N, Niikura K and Nozaki H. Usefulness of antidepressants for improving the neuropathic pain-like state and pain-induced anxiety through actions at different brain sites. *Neuropsychopharmacol.* 2008; 33: 1952-1965.
  51. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A and Moore A. Anticonvulsant drugs for acute and chronic pain. *Cochrane. Database. Syst. Rev.* 2005; 3: CD001133.
  52. Wiffen PJ, Collins S, McQuay HJ, Carroll D, Jadad A and Moore RA. Anticonvulsant drugs for acute and chronic pain. *Cochrane. Database. Syst. Rev.* 2010; 1: CD001133.
  53. Kajjume T, Sera Y, Nakanuno R, Ogura T, Karakawa S and Kobayakawa M. Continuous Intravenous Infusion of Ketamine and Lidocaine as Adjuvant Analgesics in a 5-Year-Old Patient with Neuropathic Cancer Pain. *J. Palliat. Med.* 2012; in press.