Review Article

A glimpse into the pathophysiology, mechanisms, and management of neuropathic pain

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Received December 28, 2014. Accepted January 28, 2015

Abstract

One of the most frequent problems in medical care is the management of patient presenting with chronic pain. Neuropathic pain is related to the injury or disorders affecting peripheral and central nervous systems and is resistant to over-the-counter analgesics and conventional treatment methods. The estimated prevalence for patients presenting classical symptoms of neuropathic pain is eventually reported to be 6%–8%. Several mechanisms have been considered and proposed for this disorder. The involvement of small and large sensory fibers as well as motor fibers is a reason for the presence of neuropathic pain. In addition to the lifestyle modification, a number of different therapeutic approaches and treatment protocols have been applied to control the neuropathic pain. However, management is still unsatisfactory. Comorbidities such as depression, anxiety, and sleep disorders are associated with this disorder and should be previously considered and eliminated. Analgesics, tricyclic antidepressants, anticonvulsant, serotonin– norepinephrine reuptake inhibitors, and local anesthetic agent as well as opioid analgesics and herbal medicaments such as capsaicin are known treatment lines for the management of neuropathic pain. Regarding the unsuccessfulness of single therapy, poly-pharmacy or combination therapy of two or more agents with synergistic mechanisms and different modes of action seems necessary.

KEY WORDS: Neuropathy; Neuropathic Pain; Chronic Pain

Introduction

One of the most frequent problems in medical care is the management of patient presenting with chronic pain.[1] The pain that is complained by a patient can be categorized into three main groups. First is the nociceptive pain, which is related to a tissue disease or damage. This type of pain is due to the appropriate physiological activation of nociceptors, receptors that are responsible for the painful afferent impulse. Nociceptive pain conditions are usually observed following inflammation, ischemia or trauma, and typically respond to nonsteroidal anti-inflammatory agents, such as COX-II inhibitors and opioids.[2] The second type of pain is neuropathic pain resulting from peripheral or central nervous system disease or damage. And the last type is a combination of first and second types of the pain and is often spoken as mixed pain.[3]

Despite the nociceptive pain conditions, neuropathic pain is defined as a challenging pain that is particularly resistant to over-the-counter analgesics and conventional treatment methods.[4–5] In fact, this type of pain is often chronic and severe, and additionally occurs in a body part that appears normal in other conditions. However, neuropathic pain represents a delayed and persistent response to damage that may be expressed as painful sensation.[6]

Access this article online	
Website: http://www.njppp.com	Quick Response Code:
DOI: 10.5455/njppp.2015.5.2812201418	

Epidemiology, Pathophysiology, and Possible Mechanisms

Although findings on the epidemiology of neuropathic pain are not much accurate, investigators have estimated that up to 3% of

general population is having this disorder.[7] But the estimated prevalence for the patients presenting classical symptoms is eventually reported to be 6%–8% in the population.[8]

The pathophysiology of neuropathic pain is not yet well understood. However, several mechanisms have been considered and proposed for this condition. It should be noted that most ideas related to the mechanism and pathophysiology of neuropathic pain come from the experimental work on animal models.[9] Changes in central processing may be induced by pathologic active or sensitized nociceptors. The alteration can lead to spinal cord hyperexcitability, which causes input from mechanoreceptive A-β fibers (light touching). In this case, patients usually complain of spontaneous pain and heat hyperalgesia. Other than these issues, static mechanical allodynia and dynamic mechanical allodynia may also be presented. The result can be perceived as pain.[10] However, the allodynic skin may selectively impair the function of nociceptors. Accordingly, the sensation of temperature and pain may deeply be impaired whereas light moving stimuli can produce severe pain (dynamic allodynia).[11] Unremitting inflammatory reactions of the nerve mass can induce ectopic activity in primary afferent nociceptors, and it is reported as a potential reason for spontaneous pain and allodynia.[1]

The damage of peripheral nerve fibers can express the adrenergic receptors (adrenoceptors) and possesses increasing sensitivity to sympathetic stimulation. This issue may raise the possibility of a sympathetically mediated component to neuropathic pain conditions.[12] Subsequently, central sensitization in the second- and third-order neurons may take effect from increased peripheral nerve activity.[13]

Taken as a whole, neuropathic pain is related to the injury or disorders affecting peripheral and central nervous systems,[14] and it is a symptom of heterologous conditions possessing different etiology and location. Some of these conditions, such as injuries in the spinal cord and amputations, are acute and others are in the category of systemic diseases such as diabetes, uremia, trigeminal, and post-herpetic neuralgia.[4,15] Other than these conditions, neuropathic pain may be experienced in disorders such as HIV, lumbar and sacral radiculopathy, immune deficiencies, multiple sclerosis, ischemic disorders, cancers and malignant diseases as well as complex regional pain syndrome type II.[7] Although these disorders are all associated with nerve injuries or neurological complications, mechanistically, there are many differences relating to their etiological conditions.[16]

Regarding the affected area, the origination of pain may be in the central or peripheral nervous system. Outside the brain and spinal cord, peripheral nerves that have been injured encompass but they are not limited to dorsal nerve root and ganglia, ventral nerve roots, brachial or lumbosacral plexus, and cranial nerves (except the first and second ones) as well as other sensory, motor, or mixed nerves.[17]

Diagnosis and Clinical Manifestation

The diagnosis of neuropathic pain is basically related to the patient's history and physical examination. In the physical examination process, the involvement of small and large sensory fibers as well as motor fibers should be evaluated.[17–19] The small sensory fiber involvement in neuropathic pain is usually accompanied by burning and paining feet in patients as the fiber mediates pain and temperature sensation.[20] However, vibration, proprioception, and alteration in reflexes may be seen in large sensory fiber.[21] In addition to the issues related to the small and large sensory fibers, the involvement of motor fibers is often associated with weakness.[17]

Patients' description about the feeling of neuropathic pain is different. Compared to the nociceptive pain, verbal description for the characterization of neuropathic pain is poor.[22] Usually, the symptoms are categorized into spontaneous and evoked sensory symptoms. The spontaneous sensory symptoms are classified into continuous or paroxistic pain whereas the evoked symptom is experienced frequently and may be felt as burning, tingling, and pricking as well as stabbing.[23] It should be noted that in spontaneous pain condition, the existence of intense tightness may be superimposed by shooting or lancinating pain.[24] Patients who may complain of strange pain on sensory examination can be labeled as cases of neuropathic pain if the diagnosis on this issue would be confirmed.[22] Whereas the neuropathy affects small sensory fiber in usual conditions, patient's feelings on the relevant pain are often presented as burning pain, numbness, and paresthesia in the feet.[25]

Treatment Lines

Although a number of different therapeutic approaches have been applied to control the neuropathic pain, but management is still unsatisfactory. The first line of the management deals with the lifestyle modification. It is believed that high alcohol intake may deteriorate the disorder. Coping skills, management of stress, and relaxation as well as biofeedback approaches are examples of lifestyles modification that can be considered beneficial.[26] As a large group of patients with diabetes have neuropathic pain, maintaining a balanced diet as well as glycemic control is highly recommended.[27]

Other than lifestyle modification, many clinical trials and pharmacological investigations have been carried out to control and manage the complications related to neuropathy. But management of patients having chronic neuropathic pain can often be challenging. Owing to the severity and inexorability of neuropathic pain, it is very important to recognize and eliminate the comorbidities associated with this disorder.[24] Coexisting depression, anxiety, and sleep disorders as well as other adverse impacts of neuropathic pain should be evaluated. Therefore, reduction in stress conditions, sleep improvement approaches, physical therapy, and other beneficial interventions are to be considered.[28] Additionally, neuropathic pain may be often accompanied with other types of pain such as low back pain and other musculoskeletal abnormalities.[29]

Analgesics are a large group of medications that are highly used for the management of chronic neuropathic pain. In this category, antidepressants and anticonvulsants are

recommended and administered by physicians.[24,29] These two types of medicines are classified as the first line of neuropathic pain medication.

Evidences deriving from clinical trials revealed that tricyclic antidepressants (TCAs) were useful in the management of neuropathic pain. These results were promising, especially in the treatment of patients with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN).[30–32] Although TCAs were mentioned as the first line of management, a considerable percentage of patients do not response to this line of treatment. No significant differences were seen in TCAs group compared to the placebo group in chronic lumbar root pain,[33] HIV neuropathy,[34] neuropathic cancer pain,[35] and spinal cord injury.[36]

Although TCAs are considered as first-line analgesics for management of neuropathic pain, the undesirable effects related to this group should be considered. Commonly, sedation, orthostatic hypotension, and anticholinergic effects such as constipation, dry mouth, and urinary retention may occur following oral intake of the TCAs.[37] In this regard, the secondary amine TCAs such as nortriptyline and desipramine seem to be better tolerated than third amine TCAs (amitriptyline and imipramine).[38] Especially in elderly people who have neuropathic pain, the administration of amitriptyline should be avoided.[39] TCAs may also cause cognitive impairment and gait disturbances in elderly. So, intensive care should be taken while administering TCAs in elderly with neuropathic pain. Other than these considerations, the application of TCAs in cardiac complications could be hazardous. Sinus tachycardia and increased ventricular ectopy are reported following the application of nortriptyline.[40] It is also reported that TCAs should be used cautiously when the risk for suicide or accidental death regarding overdose is predicted.[29]

In all, the lowest effective dose of TCAs should be applied in patients with neuropathic pain. Besides, the starting dose is to be adjusted at the lowest amount and subsequently, and gradually titrated until pain is adequately controlled.[29]

As mentioned previously, the group of anticonvulsant medicines such as gabapentin and pregabalin (an analogue of gabapentin) are used as first-line analgesics. They link to the presynaptic voltage-gated calcium channels in dorsal horn. The result of this binding is the reduction in the release of excitatory neurotransmitters such as glutamate and substance P.[41] Compared to the placebo, gabapentin provides significant pain relief as well as significant improvement in quality of life and mood measures in recent investigations.[42] However, the application of pregabalin may have more advantages compared to gabapentin because this medicine has linear pharmacokinetics and shows higher affinity for the presynaptic calcium channels.[29] Studies have shown that pregabalin provides significant pain relief and improved quality of sleep in both PHN and painful diabetic neuropathy.[43] Pregabalin also exert significant analgesic effects on the chronic central neuropathic pain related to spinal cord injury.[44] Furthermore, the analgesic effect of pregabalin seems to be faster than gabapentin as initial dosage of 150 mg/day has been found to be effective in some investigations.[45]

Beside these anticonvulsant medicines, lamotrigine is also considered as a choice for trigeminal neuralgia and painful diabetic neuropathy.[46,47] Although lamotrigine may be well tolerated by the patient, slow and careful titration should be considered during the administration. Other than these medicines, carbamazepine, topiramate, and valproic acid may be applied for neuropathic pain syndromes.[30] As an anticonvulsant medicine, carbamazepine is also considered as a medicine of choice for idiopathic trigeminal neuralgia but not for the management of neuropathic pain.[7]

Second line of analgesics for the management of neuropathic pain consists of serotonin norepinephrine reuptake inhibitors, topical lidocaine, and similar local anesthetic agent.[24] From the selective serotonin reuptake inhibitor (SSRI) group, duloxetine and venlafaxine have been clinically evaluated at certain doses. Compared to the placebo, they have shown analgesic effects and satisfactory results in DPN.[48–50] The effectiveness of Venlafaxine in polyneuropathy was observed at doses of 150–225 mg/day in 2-4 weeks.[29] As these medications may have various undesirable effects, care should be taken while application and discontinuation. Hence, one of the most important points to be considered for the application of these medications is the risk of discontinuation syndrome. Therefore, the patients should be tapered before leaving the intervention.[29] As a second-line analgesic medicine, lidocaine may be applied topically to manage the neuropathic pain.[24] Mechanistically, this medicine is a sodium channel blocker with rare systemic side effects.[51] In fact, the low systemic absorption results in mild local reactions (e.g., erythematic reactions and localized rash).[51] As lidocaine has this advantage, it can be a good candidate for elderly people.

Some types of peripheral neuropathic pain such as PHN are reported to be controlled with topical application of lidocaine.[30] Although the abundance of lidocaine in the form of gel and cream is more than patch form, it may be more practical to have these forms clinically evaluated. Accordingly, lidocaine gel (5%) has shown significant pain alleviation for up to 8 h in post-herpetic neuralgia.[52]

Third line of analgesic medications consists of those drugs that may be used instead of the first-line medicines in certain circumstances.[53] Many randomized clinical trials have been performed to assess the effectiveness of tramadol and other opioid analgesics in this group, and the results were found to be apparently affirmative. As a weak opioid μ-receptor agonist but providing rapid pain relief, tramadol has been shown to exert satisfactory effects in several neuropathic pain conditions. Investigators have also reported the serotonin and norepinephrine reuptake inhibition by tramadol.[30] Other than those common undesirable effects attributed to opioid analgesics, tramadol may additionally reduce the seizure threshold and hereupon interact with certain medications such as SSRIs.[53] Result of this interaction may cause serotonin syndrome, a potentially fatal response.

Like tramadol, other opioid analgesics were also found to be effective in the neuropathic pain management.[30,54] The effectiveness of this group is not less than anticonvulsants and TCAs. But regarding the safety in long-term therapy, such as

risks of hypogonadism, immunological imbalance as well as abuse conditions, these medicines are not recommended as the first line of management and should be considered for patients who do not respond to the first-line medications.[53]

It should be noted that patients using tramadol and other opioid analgesics may experience undesirable effects such as nausea, constipation, and sedation. Therefore, having the initial dose in lowest amount and titrating gradually would reduce these complications.[29] As chronic neuropathic pain needs long-term intervention, physical dependence may occur during opioid application. Therefore, intensive care and tapering process should be considered whenever the drug is to be discontinued.[53] The required dose of opioid generally varies from a patient to another. Accordingly, individualized opioid titration, sustained release formulation, and adjustment in dose with regard to neuropathic pain trials should be considered for long-term therapy.[29] Neuropathic pain can also be controlled by other analgesics such as methadone and other cannabinoids. Proven evidences on the efficacy of this group exist in animal studies.[53]

Other drugs such as mexiletine, clonidine, dextromethorphan, memantine, and capsaicin as well as nonsteroidal anti-inflammatory drug (NSAID) group are also applied for the management of neuropathic pain.[29] Mexiletine, which is defined as an orally administered lidocaine analogue, is a class 1B local anesthetic antiarrhythmic agent. This medicine blocks sodium channels and suppresses the ectopic neural pacemaker sites.[55] Mexiletine has been evaluated for possible neuropathic pain potentiality. Although the drug has shown effectiveness in some trials but the results were not much satisfactory.[30,56] To achieve the better results, higher dosages of mexiletine should be administered. Patients may experience more side effects. These undesirable effects are often chest pain, dizziness, gastrointestinal disturbances, palpitations, and tremor.[55] So, this medicine should be administrated only in the event of failure of other measures and interventions.

NSAIDs, which are mentioned as anti-inflammatory agents, can also be considered for the management of neuropathic pain. Although results for this intervention are contradictory,[57] NSAIDs are commonly applied to reduce pain and manage the inflammatory conditions in complex regional pain syndrome.[58]

Dextromethorphan and memantine block *N*-methyl-D-aspartic acid receptor. A few previous studies have reported that the medicine exerts analgesic effect on neuropathic pain. But results of some later investigations are not satisfactory.[30]

Clonidine is an α-2-agonist sympathetic blocker and generally is an antihypertensive agent. Clonidine has shown to be effective in the management of neuropathic pain especially painful DPN. The drug was applied in the form of topical gel via dermal route and found to be effective in neuropathic pain.[59,60]

Other than the conventional therapeutic lines, several clinical trials have been conducted to evaluate the potency of capsaicin in the management of neuropathic pain.[61] Capsaicin, a pungent component of hot chili peppers, is widely investigated and applied via topical route in the form of cream (0.075%). The medicine has also been evaluated in the form of topical patch (8%) and has shown some promise.[62] Results of trials on the evaluation of capsaicin cream (0.075%) versus placebo for DPN and PHN were inconsistent.[57] However, clinical experience suggests that this intervention may occasionally be effective in individual conditions. Therefore, topically applied capsaicin may have beneficial effects to be considered as an additive or single therapy in limited groups of patients who are unresponsive to or may not tolerate other treatments.[63]

In topical application, capsaicin first reduces threshold for chemical, mechanical, and thermal nociception via direct activation of vanilloid receptor-1 on free nerve endings related to the C fibers.[64] It should be noted that capsaicin is also considered as a neurotoxin. This medicament destroys a large subset of population of primary afferent C fibers as well as thin-myelinated Aδ fibers.[65] Additionally, it may cause a localized desensitization of nociceptive afferents in long-term application.[66] Other undesirable effects of capsaicin are burning, erythma, and stinging of the application site whereas systemic adverse effects are rare.[63] Although these unwanted effects are mild and transient in some conditions, they may be a cause of withdrawal.[67]

Other open-label trials on neuropathic pain have also been conducted via topical administration. A combined topical cream of 2% amitriptyline and 1% ketamine was assessed via a double-blind placebo-controlled trial. Outcomes showed no significant differences between all intervention groups and placebo[68] whereas in a relevant study, applying higher concentrations of these medicines (4% and 2% of amitriptyline and ketamine, respectively) resulted in significant analgesia.[69] Accordingly, absorption of drug by skin, which is highly concentration-related, has a significant impact on the topical management of neuropathic pain. In another investigation, doxepin 5% cream was topically effective in reducing pain as compared to the placebo in a twice-daily application for 4 weeks.[70]

Conclusion

Management of neuropathic pain may be of challenge for physicians, and treatment with sole therapy may not be much beneficial and may rarely provide desirable outcome. However, administration of a single medication is often restricted due to dose-related side effects. Hence, poly-pharmacy or combination therapy with application of two or more agents with synergistic mechanisms of action and also different action modes at suboptimal doses seems necessary.

References

1. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9(8):807–19.
2. Smith HS, Sang CN. The evolving nature of neuropathic pain: individualizing treatment. Eur J Pain. 2002;6:13–18.

3. Tanelian DL, Cousins MJ. Combined neurogenic and nociceptive pain in a patient with Pancoast tumor managed by epidural hydromorphone and oral carbamazepine. Pain. 1989;36(1):85–8.
4. Jensen TS, Gottrup H, Sindrup SH, Bach FW. The clinical picture of neuropathic pain. Eur J Pharmacol. 2001;429(1–3):1–11.
5. Max MB, Schafer SC, Culnane M, Dubner R, Gracely RH. Association of pain relief with drug side effects in postherpetic neuralgia: a single-dose study of clonidine, codeine, ibuprofen, and placebo. Clin Pharmacol Ther. 1988;43(4):363–71.
6. Galluzzi KE. Management of neuropathic pain. J Am Osteopath Assoc. 2005;105(4):12–19.
7. Gilron I, Watson CPN, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. Can Med Assoc J. 2006; 175(3):265–75.
8. Smith BH, Torrance N. Epidemiology of neuropathic pain and its impact on quality of life. Curr Pain Headache Rep. 2012;16(3):191–8.
9. Baron R. Mechanisms of disease: neuropathic pain—a clinical perspective. Nat Clin Pract Neuro. 2006;2(2):95–106.
10. Baron R. Neuropathic pain: a clinical perspective. In: Canning BJ, Spina D (eds.), Sensory Nerves. Berlin Heidelberg: Springer, 2009. pp. 3–30.
11. Baron R. Peripheral neuropathic pain: from mechanisms to symptoms. Clin J Pain. 2000;16(2):12–20.
12. Bennett GJ. The role of the sympathetic nervous system in painful peripheral neuropathy. Pain. 1991;45(3):221–3.
13. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet. 1999;353(9168):1959–64.
14. Chong MS, Bajwa ZH. Diagnosis and treatment of neuropathic pain. J Pain Symptom Manage. 2003;25(5):4–11.
15. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain. 1999;83(3):389–400.
16. Truini A, Cruccu G. Pathophysiological mechanisms of neuropathic pain. Neurol Sci. 2006;27(2):179–82.
17. Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson J, et al. *Harrison's Principles of Internal Medicine*, 17 edn. , New York: McGraw-Hill, 2008.
18. Holland NR, Crawford TO, Hauer P, Cornblath DR, Griffin JW, McArthur JC. Small-fiber sensory neuropathies: clinical course and neuropathology of idiopathic cases. Ann Neurol. 1998;44(1):47–59.
19. Sorensen L, Molyneaux L, Yue DK. The relationship among pain, sensory loss, and small nerve fibers in diabetes. Diabetes Care. 2006;29(4):883–7.
20. Lacomis D. Small-fiber neuropathy. Muscle Nerve. 2002;26(2):173–88.
21. Apfel SC, Kessler JA, Adornato BT, Litchy WJ, Sanders C, Rask CA, et al. Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. Neurology. 1998;51(3):695–702.
22. Schestatsky P, Nascimento OJ. What do general neurologists need to know about neuropathic pain? Arq Neuropsiquiatr. 2009;67(3):741–9.
23. Bennett MI. Theories, history and current taxonomy. Neuropathic Pain. London: Oxford University Press, 2006.
24. Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag. 2007;12(1):13–21.
25. Ho TW, Backonja M, Ma J, Leibensperger H, Froman S, Polydefkis M. Efficient assessment of neuropathic pain drugs in patients with small fiber sensory neuropathies. Pain. 2009;141(1):19–24.
26. Wolfe GI, Barohn R. Painful peripheral neuropathy. Curr Treat Options Neurol. 2002;4:177–88.
27. Huizinga MM, Peltier A. Painful diabetic neuropathy: a management-centered review. Clin Diabetes. 2007;25(1):6–15.
28. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol. 2003;60(11):1524–34.
29. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237–51.
30. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain. 2005;118(3):289–305.
31. Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med. 2005;2(7):164.
32. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain. 2002;18(6):350–4.
33. Khoromi S, Cui L, Nackers L, Max MB. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. Pain. 2007;130(1–2):66–75.
34. Kieburtz K, Simpson D, Yiannoutsos C, Max MB, Hall CD, Ellis RJ, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. AIDS Clinical Trial Group 242 Protocol Team. Neurology. 1998;51(6):1682–8.
35. Mercadante S, Arcuri E, Tirelli W, Villari P, Casuccio A. Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study. Tumori. 2002;88(3):239–42.
36. Cardenas DD, Warms CA, Turner JA, Marshall H, Brooke MM, Loeser JD. Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. Pain. 2002;96 (3):365–73.
37. Westenberg HG. Pharmacology of antidepressants: selectivity or multiplicity? J Clin Psychiatry. 1999;60(17):4–8.
38. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992;326(19):1250–6.
39. Williams GO. Management of depression in the elderly. Prim Care. 1989;16(2):451–74.
40. Roose SP, Laghrissi-Thode F, Kennedy JS, Nelson JC, Bigger JT, Jr., Pollock BG, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA. 1998;279 (4):287–91.
41. Taylor CP. The biology and pharmacology of calcium channel alpha2-delta proteins Pfizer Satellite Symposium to the 2003 Society for Neuroscience Meeting. Sheraton New Orleans Hotel, New Orleans, LA November 10, 2003. CNS Drug Rev. 2004; 10(2):183–8.
42. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. JAMA. 1998;280(21):1831–6.
43. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain. 2005;115(3):254–63.
44. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology. 2006;67(10): 1792–800.
45. Stacey BR, Barrett JA, Whalen E, Phillips KF, Rowbotham MC. Pregabalin for postherpetic neuralgia: placebo-controlled trial of

fixed and flexible dosing regimens on allodynia and time to onset of pain relief. J Pain. 2008;9(11):1006–17.
46. Lunardi G, Leandri M, Albano C, Cultrera S, Fracassi M, Rubino V, et al. Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. Neurology. 1997;48(6):1714–17.
47. Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study. Neurology. 2001;57(3):505–09.
48. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005;116(1–2):109–18.
49. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Med. 2005;6(5):346–56.
50. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. Neurology. 2003;60(8):1284–9.
51. Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. Ann Pharmacother. 2002;36(2):236–40.
52. Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. Ann Neurol. 1995;37(2):246–53.
53. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc. 2010;85(3):3–14.
54. Wu CL, Agarwal S, Tella PK, Klick B, Clark MR, Haythornthwaite JA, et al. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. Anesthesiology. 2008;109(2):289–96.
55. Jackson KC, 2nd. Pharmacotherapy for neuropathic pain. Pain Pract. 2006;6(1):27–33.
56. Tremont-Lukats IW, Challapalli V, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and meta-analysis. Anesth Analg. 2005;101(6):1738–49.
57. Stacey BR. Management of peripheral neuropathic pain. Am J Phys Med Rehabil. 2005;84(3):4–16.
58. Namaka M, Leong C, Grossberndt A, Klowak M, Turcotte D, Esfahani F, et al. A treatment algorithm for neuropathic pain: an update. Consult Pharm. 2009;24(12):885–902.
59. Campbell CM, Kipnes MS, Stouch BC, Brady KL, Kelly M, Schmidt WK, et al. Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. Pain. 2012;153(9): 1815–23.
60. Byas-Smith MG, Max MB, Muir J, Kingman A. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage "enriched enrollment" design. Pain. 1995;60(3): 267–74.
61. Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults Cochrane Database Syst Rev 2009(4) CD007393.
62. Wagner T, Roth-Daniek A, Sell A, England J, Kern K-U. Capsaicin 8% patch for peripheral neuropathic pain: review of treatment best practice from "real-world" clinical experience. Pain Manag. 2012; 2(3):239–50.
63. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ. 2004;328(7446):991.
64. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389(6653):816–24.
65. Jancso G, Kiraly E, Jancso-Gabor A. Pharmacologically induced selective degeneration of chemosensitive primary sensory neurones. Nature. 1977;270(5639):741–3.
66. Minami T, Bakoshi S, Nakano H, Mine O, Muratani T, Mori H, et al. The effects of capsaicin cream on prostaglandin-induced allodynia. Anesth Analg. 2001;93(2):419–23.
67. Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2012;9:CD010111.
68. Lynch ME, Clark AJ, Sawynok J. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Anesthesiology. 2005;103:140–6.
69. Lockhart E. Topical analgesics: topical combination of amitriptyline and ketamine for post herpetic neuralgia. J Pain. 2004;5:82.
70. McCleane GJ. Topical doxepin hydrochloride reduces neuropathic pain: a randomized, double-blind, placebo controlled study. Pain Clin. 2000;12:47–50.

How to cite this article: Zarshenas MM, Petramfar P, Samani SM, Moein M. A glimpse into the pathophysiology, mechanisms, and management of neuropathic pain. Natl J Physiol Pharm Pharmacol 2015;5:160-165

Source of Support: Nil, **Conflict of Interest:** None declared.