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

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ABSTRACT

One of the most frequent problems in medical care is the management of patients 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 agents 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 patients 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 agents 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.

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. 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 activity 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 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.[11]

The damage of peripheral nerve fibers can express the adrenergic receptors (adrenoceptors) and possesses increasing sensitivity to sympathetic stimulation. This 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.[15,16] 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, mechanically, 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 lumbo-sacral plexus, and cranial nerves (except the first and second ones) as well as other sensory, motor, or mixed nerves.[17]

**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 ineradicability 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

**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 paroxysmal 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]
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). Although TCAs were mentioned as the first line of management, a considerable percentage of patients do not respond to this line of treatment. No significant differences were seen in TCAs group compared to the placebo group in chronic lumbar root pain, HIV neuropathy, neuropathic cancer pain, and spinal cord injury.

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. In this regard, the secondary amine TCAs such as nortriptyline and desipramine seem to be better tolerated than third amine TCAs (amitriptyline and imipramine). Especially in elderly people who have neuropathic pain, the administration of amitriptyline should be avoided. 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. It is also reported that TCAs should be used cautiously when the risk for suicide or accidental death regarding overdose is predicted.

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.

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. Compared to the placebo, gabapentin provides significant pain relief as well as significant improvement in quality of life and mood measures in recent investigations. 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. Studies have shown that pregabalin provides significant pain relief and improved quality of sleep in both PHN and painful diabetic neuropathy. Pregabalin also exert significant analgesic effects on the chronic central neuropathic pain related to spinal cord injury. 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. Beside these anticonvulsant medicines, lamotrigine is also considered as a choice for trigeminal neuralgia and painful diabetic neuropathy. 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. 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.

Second line of analgesics for the management of neuropathic pain consists of serotonin norepinephrine reuptake inhibitors, topical lidocaine, and similar local anesthetic agent. 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. The effectiveness of Venlafaxine in polyneuropathy was observed at doses of 150–225 mg/day in 2-4 weeks. 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. As a second-line analgesic medicine, lidocaine may be applied topically to manage the neuropathic pain. Mechanically, this medicine is a sodium channel blocker with rare systemic side effects. In fact, the low systemic absorption results in mild local reactions (e.g. erythematous reactions and localized rash). 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. 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.

Third line of analgesic medications consists of those drugs that may be used instead of the first-line medicines in certain circumstances. 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. 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. 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. The effectiveness of this group is not less than anticonvulsants and TCAs. But regarding the safety in long-term therapy, such as...
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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]\n
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]\n
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]\n
The required dose of opioid generally varies from a patient to another. Accordingly, individualized opioid titration, sustained release formulations, and adjustment in dose with regard to neuropathic pain trials should be considered for long-term therapy.\[29]\n
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]\n
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]\n
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]\n
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.\[16,52]\n
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]\n
So, this medicine should be administered 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]\n
NSAIDs are commonly applied to reduce pain and manage the inflammatory conditions in complex regional pain syndrome.\[58]\n
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]\n
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]\n
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]\n
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]\n
Results of trials on the evaluation of capsaicin cream (0.075%) versus placebo for DPN and PHN were inconsistent.\[57]\n
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]\n
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]\n
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]\n
Additionally, it may cause a localized desensitization of nociceptive afferents in long-term application.\[66]\n
Other undesirable effects of capsaicin are burning, erythma, and stinging of the application site whereas systemic adverse effects are rare.\[63]\n
Although these unwanted effects are mild and transient in some conditions, they may be a cause of withdrawal.\[67]\n
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]\n
whereas in a relevant study, applying higher concentrations of these medicines (4% and 2% of amitriptyline and ketamine, respectively) resulted in significant analgesia.\[69]\n
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]\n
### 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.

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