Efficacy of Diversified Therapeutics Agents in the Management of Peripheral Neuropathy

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ABSTRACT:
Peripheral neuropathy is caused either by diseases or trauma to the nerve or the side effects of systemic illness or due to the neurotoxicity and due to some drugs as a side effect. Owing to peripheral neuropathy, patients suffer from neuropathic pain. In this review author strive to gathered succinct literature on diversified therapeutic agents used for the treatment of neuropathic pain, with and without clinically proven efficacy for the nerve repair. Some herbal remedies also claimed to have the nerve repair properties with a little significant data. Many synthetic agents like methylcobalamin, thiamine many anti-convulsant, neuromuscular blocking agents, are being used for treating pain. The remedies like Vitamin D, B vitamins, vitamin B6, Vitamin B12, St. John’s Wort, fish oil, Cannabinoids, Opioids, etc. Controlling the underlying disease process and treating troublesome symptoms are the basic goals of the treatment. This review explains how to revive the neuropathy symptoms, diagnostic approaches, and the conventional as well as alternative approaches for the treatment.

KEYWORDS: Peripheral neuropathy, Nerve trauma, Neurotoxicity, Neuropathic pain.

INTRODUCTION:
Peripheral neuropathy are defined as the degeneration or damage to peripheral nerves, which may be caused either by diseases or trauma to the nerve or the side effects of systemic illness or due to the neurotoxicity. Neuropathy may be associated with varying combinations of weakness, autonomic changes, and sensory changes. Loss of muscle bulk or fasciculation’s, a particular fine twitching of muscle, may be seen. Sensory symptoms encompass loss of sensation and "positive" phenomena including pain. Symptoms depend on the type of nerves affected (motor, sensory, or autonomic) and where the nerves are located in the body. Lone or multi types of nerves may affect muscle and causes of common symptoms like muscles weakness, cramps, and spasms which are associated with neuropathic pain with loss of balance and coordination of body organs. Damage to the sensory nerve can produce tingling, numbness, and a burning pain. As studied by Lynn R et.al. in a multicenter study on various patients with post-herpetic neuralgia, HIV-associated distal sensory polyneuropathy, or painful diabetic neuropathy which were treated with (8% capsaicin) via post therpetic neuralgia following pre treatment with any tropical anesthetic showed relief from pain as well as safe and well tolerated.

These Pain associated with this nerve is described in various ways by patient such as burning, freezing, or electric-like, extreme sensitivity when touched.

1. Neuropathic pain
Neuropathic pain results from damage or disease affecting the nervous system. It may be associated with abnormal sensations called dysesthesia, and pain produced by normally non-painful stimuli (allodynia). Neuropathic pain may have continuous and/or episodic (paroxysmal) components. The latter are likened to an electric shock who is due to the hyper sensation of nerves. Common qualities include burning and coldness, "pins and needles" sensations, itching and numbness. It is a chronic pain which is the results of the nerve injury first and many times due to diabetes, cancer, infection, autoimmune disease. Such Neuropathic pain is generally insolent to general analgesics. There is a rapidly growing body of evidence indicating that spinal microglia play crucial roles in the pathogenesis of neuropathic pain.

1.1 Peripheral neuropathy
Peripheral neuropathy can be the result of genetics, chronic disease, environmental toxins, alcoholism, nutritional deficiencies, or side effects of certain medications. Among chronic diseases, diabetes mellitus is the most common cause of peripheral neuropathy. Other endocrinological
abnormalities that can result in neuropathy include hypothyroidism. The neuropathy associated with hypothyroidism commonly manifests as carpal tunnel syndrome. Other manifestations resemble diabetic neuropathy, with tingling paresthesias in a stocking-glove distribution. Peripheral neuropathy of acromegaly (excess growth hormone) includes carpal tunnel syndrome and sensorimotor polyneuropathy (Fig. 1). Human immunodeficiency virus (HIV) also results in peripheral neuropathy, usually involving distal, nonpainful paresthesias, decreased ankle reflexes, and abnormal pain and temperature perception. Amyloidosis is another chronic disease resulting in peripheral neuropathy.

2. Classification
Peripheral neuropathy may be classified according to the number of nerves affected or the type of nerve cell affected (motor, sensory, autonomic), or the process affecting the nerves (e.g., inflammation in neuritis).

2.1 Mononeuropathy:
It is a one kind of neuropathy that only affects a single nerve of peripheral nervous system. This type of nerves damage could distinguish them from polyneuropathies, and find out the cause of localized trauma or infection.

The major cause of such neuropathy is due to physical compression of the any nerve, and distinguished as compression neuropathy; Carpal tunnel syndrome and axillary nerve palsies are examples of mononeuropathy. The "pins-and-needles" sensation of one's "foot falling asleep" (paresthesia) is caused by a compression mononeuropathy at a temporary one which can be resolved merely by moving around and adjusting to a more appropriate position. A further cause might be direct injury to a nerve, interruption of its blood supply (ischemia), or inflammation which cause mononeuropathy.

2.2 Mononeuritis multiplex:
It is sequential involvement of individual noncontiguous nerve trunks, either partially or completely, evolving over days to years or typically presenting with acute or sub-acute loss of sensory and motor function of individual nerves. Here the pattern of involvement is asymmetric; however, as the disease progress droughts and becomes symmetrical, which make it difficult to differentiate from polyneuropathy. Thus, the pattern of early symptoms consideration is more important.

Mononeuritis multiplex may also be one cause of pain, and could be distinguished as deep, aching pain at night, feel frequently in the lower back, hip, or leg. In diabetes patients, mononeuritis multiplex is typically encountered as acute, unilateral and severe thigh pain followed by anterior muscle weakness and loss of knee reflex. Electrodiagnostic studies showed multifocal sensory motor axonal neuropathy.

It is associated with, several medical conditions:
- Diabetes mellitus
- Vasculitides: polyarteritis nodosa, Wegener's granulomatosis, and Churg–Strauss syndrome
- Immune-mediated diseases like rheumatoid arthritis, lupus erythematosus (SLE), and sarcoidosis
- Infections: leprosy, lyme disease, HIV
- Amyloidosis
- Cryoglobulinemia
- Chemical agents, including trichloroethylene and dapsone
- Rarely, the sting of certain jellyfish, such as the sea nettle

2.3 Polyneuropathy:
Polyneuropathy is a quite different pattern of nerve damage from mononeuropathy, and considered more serious and have an effect on wide area of the body. Generally "peripheral neuropathy" is used loosely to refer to polyneuropathy, but in cases of polyneuropathy, many nerve cells in various parts of the body are affected, without regard to the nerve through which they pass; not all nerve cells are affected in any particular case. In distal axonopathy, one common pattern is seen that is the hang of cell bodies of neurons intact, but the axons are affected in proportion to their length. Diabetic neuropathy is considered most common cause of this pattern. In case of demyelinating polyneuropathies, the myelin sheath around axons is damaged, which affects the ability of the axons to conduct electrical impulses. The third and least common pattern affects the cell bodies of neurones directly. This usually picks out either the motor neurones (known as motor neurone disease) or the sensory neurones (known as sensory neuronopathy or dorsal root ganglionopathy).

In case of any neuropathy, the chief symptoms include weakness or clumsiness of movement (due to motor nerves); unusual or unpleasant sensations such as tingling or burning occur and reduces the ability to feel texture, temperature and impaired balance when standing or walking (sensory). In many polyneuropathies, these symptoms occur first and amplify in to lower limb with more severely. It also affects Autonomic symptoms of body, such as dizziness on standing up, difficulty controlling urination (difficulty beginning to urination) and erectile dysfunction.
Diabetes and impaired glucose tolerance are the most common causes, but causes relate to the particular type of polyneuropathy, are many includes; vitamin deficiencies, blood disorders, inflammatory diseases such as lyme disease and rare toxins.

Most types of polyneuropathy progress fairly slowly, over months up to years, but rapidly progressive polyneuropathy may also occurs occasionally. It is important to recognize that glucose levels in the blood can spike to nerve-damaging levels after eating even though fasting blood sugar levels and average blood glucose levels can still remain below normal levels. Studies have shown that many of the cases of peripheral small fiber neuropathy with typical symptoms of tingling, pain and loss of sensation in the feet and hands are due to glucose intolerance before a diagnosis of diabetes or pre-diabetes. Such damage is often reversible, particularly in the early stages, with diet, exercise and weight loss.

The treatment of polyneuropathies is aimed firstly at eliminating or controlling the cause, secondly at maintaining muscle strength and physical function, and thirdly at controlling symptoms such as neuropathic pain.

2.4 Autonomic neuropathy:
Autonomic neuropathy is a form of polyneuropathy which affects the non-voluntary, non-sensory nervous system (i.e., the autonomic nervous system) affecting mostly the internal organs such as the bladder muscles, the cardiovascular system, the digestive tract, and the genital organs. These nerves are not under a person’s conscious control and function automatically. Autonomic nerve fibers form large collections in the thorax, abdomen and pelvis outside spinal cord, however they have connections with the spinal cord and ultimately the brain. Most commonly autonomic neuropathy is seen in persons with long-standing diabetes mellitus type I and II. In most but not all cases, autonomic neuropathy occurs alongside other forms of neuropathy, such as sensory neuropathy.

This kind of neuropathy is also cause of malfunction of the autonomic nervous system, but not the only one; some conditions affecting the brain or spinal cord can also cause autonomic dysfunction, such as multiple system atrophy, and therefore cause similar symptoms to autonomic neuropathy.

Autonomic neuropathy signs and symptoms are as follows:

- Urinary bladder relate symptomatic conditions: bladder incontinence or urine retention.
- Gastro- symptomatic conditions: dysphagia, abdominal pain, nausea, vomiting, malabsorption, fecal incontinence, gastroparesis, diarrhoea, constipation.
- Cardiovascular symptomatic conditions: disturbances of heart rate (tachycardia, bradycardia), orthostatic hypotension, inadequate increase of heart rate on exertion.
- Other symptomatic areas: hypoglycemia unawareness, genital impotence, sweat disturbances.

2.5 Diabetic Peripheral Neuropathy:
The mechanisms of peripheral neuropathy depend on etiology of disorder, diabetes, being the most common etiological factor, is also the most studied in terms of pathogenesis. While conventional theory holds that prolonged hyper-glycemia results in the complications associated with diabetes, including neuropathy. In a recent study Peripheral neuropathy affects 30 percent of hospitalized and 20 percent of non-hospitalized individuals with diabetes. It is observed that PN can manifest even in individuals with abnormal glucose tolerance, a pre-diabetic condition. Recently, Fas-mediated apoptosis has been proposed as a causative factor responsible for neuronal degeneration in diabetic polyneuropathy (DPN), but there are very few studies to show association of serum soluble Fas ligand (sFasL) level with severity of neuropathy.

2.6 Oxidative Stress induced:
Diabetes results in increased products of oxidation. In hyperglycemia, glucose combines with protein, yielding glycosylated proteins, which can become damaged by free radicals and combine with fats, yielding AGEs that damage sensitive tissues. In addition, glycosylation of antioxidant enzymes can render the defense system less efficient.

2.7 Alcohol-related Neuropathy:
Vascular factors have also been implicated in the pathogenesis of diabetic PN. Nerve blood flow is diminished in experimental diabetic neuropathy, and numerous studies indicate it may be mediated by alterations in nitric oxide metabolism. One such study examined nerve blood flow and nitric oxide synthase (NOS) activity in the microvasculature serving peripheral nerves in diabetic rats. Hyperglycemia resulted in a significant diminution of nerve blood flow compared to controls. N-nitro-L-arginine, an inhibitor of NOS, also resulted in decreased nerve blood flow. L-arginine reversed the effects of NOS inhibition and restored blood flow to the nerves. An animal study also found disruptions in neuronal nitric oxide synthase (nNOS) in experimental diabetes. Decreased nNOS expression was associated with increased neuropathic pain.

2.8 AIDS-associated Neuropathy:
Peripheral neuropathy affects as many as one-third of individuals with acquired immunodeficiency syndrome (AIDS), most commonly manifested as distal, symmetrical polyneuropathy. A study of 251 HIV-positive individuals found the incidence of neuropathy was significantly
Numerous cancer chemotherapy drugs are associated with neuropathy:

2.10 Cancer Chemotherapeutic Agents induced alkaloids may exert neurotoxic effects by inhibiting tumor cells, may be a cause of neurotoxicity. Vinca may be the cause of PN in this population. Taxoids such as paclitaxel and docetaxel result in peripheral neuropathy, decreased S-adenosylmethionine production, and impaired repair mechanisms caused by decreased S-adenosylmethionine.

2.9 Antiretroviral Agents drugs induced neuropathy:
Antiretroviral drugs used to treat individuals with HIV are implicated in PN. One study of HIV-positive adults found exposure to diganosine (ddI) or stavudine (d4T) significantly increased the risk of developing Peripheral Neuropathy; zalcitabine (ddC) can also cause neuropathies. It is believed the neuropathies occur in part because of drug-induced mitochondrial defects. In a rabbit model, ddC resulted in demyelination via Schwann cell mitochondrial toxicity. High lactic acid levels are associated with the use of antiretroviral drugs and may be used to differentiate drug-induced versus AIDS-related neuropathy in people with HIV.

2.10 Cancer Chemotherapeutic Agents induced neuropathy:
Numerous cancer chemotherapy drugs are associated with neurotoxicity and PN. High cumulative doses of cisplatin result in incidence of PN as high as 70-100 percent, with more conventional lower doses resulting in a PN rate of 12 percent. Impaired DNA repair mechanisms are believed to be the cause of PN in this population. Taxoids such as paclitaxel and docetaxel result in peripheral neuropathy, particularly at high doses. The mechanism is unknown but large arrays of disordered microtubules, a major effect on tumor cells, may be a cause of neurotoxicity. Vinca alkaloids may exert neurotoxic effects by inhibiting microtubular assembly.

3. Symptoms
The symptoms of peripheral neuropathy vary depending on which nerves are affected. Anti-cancer drugs that cause nerve damage are most likely to affect sensory nerves, but some can also affect the motor nerves and the autonomic nerves. Peripheral neuropathy often affects the hands, feet and lower legs. This is because the longer a nerve is, the more vulnerable it is to injury. Nerves going to the hands, feet and lower legs are some of the longest in the body. Symptoms of peripheral neuropathy are usually mild to begin with and gradually get worse.

- In terms of sensory function, there are commonly loss of function (negative) symptoms, which include numbness, tremor, and gait abnormality.
- Gain of function (positive) symptoms include tingling, pain, itching, crawling, and pins and needles. Pain can become intense enough to require use of opioid (narcotic) drugs (i.e., morphine, oxycodone).
- Motor symptoms include loss of function (negative) symptoms of weakness, tiredness, heaviness, and gait abnormalities; and gain of function (positive) symptoms of cramps, tremor, and muscle twitch (fasciculations).
- There is also pain in the muscles (myalgia), cramps, etc., and there may also be autonomic dysfunction.
- During physical examination, specifically a neurological examination, those with generalized peripheral neuropathies most commonly have distal sensory or motor and sensory loss, though those with a pathology (problem) of the nerves may be perfectly normal; may show proximal weakness, as in some inflammatory neuropathies like Guillain–Barré syndrome; or may show focal sensory disturbance or weakness, such as in mononeuropathies. Ankle jerk reflex is classically absent in peripheral neuropathy.
- A change in sensation: Generally have a feeling of heaviness, burning or pins and needles in the affected area. Alternatively, you may notice unusual sensations, such as a feeling of warmth or burning when touching something cold.
- Increased sensitivity: In such conditions patients may find that even the lightest touch or pressure in the affected area feels uncomfortable or painful.
- Pain: This could be mild or more severe. The pain may be felt as sharp and stabbing or as a burning sensation, or it may feel like minor electric shocks. There are treatments to help relieve pain.
- Numbness: There may be a loss of sensitivity or feeling in the affected area. Commonly the feet and fingertips are the first places to be affected.
- Muscle weakness: Muscle may lose strength if it isn’t being stimulated by a nerve. Depending on which muscles are affected, this may make it difficult to walk, climb stairs or do other tasks.
- Difficulty buttoning clothes or picking up small objects: If the nerve endings in the fingers are affected, patients may not be able to do ‘fiddly’ tasks, such as fastening small buttons or tying shoelaces.
- Difficulty with balance, walking and coordination: In neuropathic conduction Patient may find that he or she stumble or trip when walking; uneven surfaces may be particularly difficult. Patient may feel clumsy at times, or may feel isn’t doing what patient want it to do.
- Constipation and feeling bloated: This can happen when the nerves that control the rate at which food passes through the bowel (autonomic nerves) are affected.
Peripheral neuropathy can be the result of genetics, chronic and from healthy cells that can still produce myelin. Have the ability to differentiate into myelin-making cells, after damage. Demyelization can occur from stem cells that are damaged first and maximally. Thus the symptoms and deficiencies, or side effects of certain medications. Ultimately we can say that damage to myelin sheath may occur in our health care system.

The nervous system can regenerate itself up-to an extent being used increasingly in discussions of changes that may occur in our health care system. Demyelization can occur from stem cells that are damaged first and maximally. Thus the symptoms and deficiencies, or side effects of certain medications. Ultimately we can say that damage to myelin sheath may occur in our health care system.

Table 1. Causes of Peripheral Neuropathy:

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Cause</th>
<th>Comments</th>
<th>Laboratory tests</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acquired immunodeficiency</td>
<td>Mainly sensory</td>
<td>Human immunodeficiency virus test</td>
<td>12,13,14</td>
</tr>
<tr>
<td></td>
<td>Syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Immune mediated PN (Radiation</td>
<td>Usually sensory</td>
<td>HIV test</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>induced)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Carcinoma</td>
<td>Mainly demyelination of nerve,</td>
<td>Paraneoplastic panel (anti-Hu, anti-Yo,</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>(Radiation induced)</td>
<td>especially in viral Hepatitis</td>
<td>anti-Ri, anti-Tr, anti-Ma, and anti-CV2</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Chronic liver disease</td>
<td>Chronic; axonal may predominate</td>
<td>Hepatic transaminase, bilirubin, albumin,</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Diabetes mellitus</td>
<td></td>
<td>Fasting blood glucose level, glucose</td>
<td>7,8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>tolerance test, A1C level</td>
<td></td>
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<tr>
<td>6.</td>
<td>End-stage renal disease</td>
<td></td>
<td>Serum creatinine and blood urea nitrogen</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Levels</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Leprosy</td>
<td>Usually sensory</td>
<td>Phenolic glycolipid-1 antibody, skin biopsy</td>
<td>19</td>
</tr>
<tr>
<td>8.</td>
<td>Amyloidosis</td>
<td>Usually sensory</td>
<td>Porphyrin titer</td>
<td>20</td>
</tr>
<tr>
<td>9.</td>
<td>Porphyria</td>
<td>Acute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Vitamin B6 deficiency</td>
<td>Sensory more than motor</td>
<td>Vitamin B6 level</td>
<td>21</td>
</tr>
<tr>
<td>11.</td>
<td>Vitamin B12 deficiency</td>
<td>Peripheral neuropathy is intermixed with upper motor neuron signs</td>
<td>CBC; vitamin B12 and homocysteine levels;</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methylmalonic acid test</td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Charcot-Marie-tooth hereditary</td>
<td>Chronic motor and sensory</td>
<td>Characterized by Distal muscles weakness</td>
<td>22-B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polyneuropathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Mechanism of agents used in nerve repair:
The nervous system can regenerate itself up-to an extent after damage. Demyelization can occur from stem cells that have the ability to differentiate into myelin-making cells, and from healthy cells that can still produce myelin. Peripheral neuropathy can be the result of genetics, chronic disease, environmental toxins, alcoholism, nutritional deficiencies, or side effects of certain medications. Ultimately we can say that damage to myelin sheath may repaired. In a poly-neuropathy, the peripheral nerves are affected symmetrically, and usually the longest nerve fibers are damaged first and maximally. Thus the symptoms and signs involve both feet first, and as the disorder progresses, the hands are also both involved.

The Chinese medicines astragalus, salvia, and yam have anti-apoptotic actions on Schwann cells cultured under hyperglycemic conditions. These medicines increased levels of Bcl-2 expression, while inhibiting expression of caspase-3. Chinese medicine has the advantage of providing multiple therapeutic effects on multiple targets, compared with Western medicine, which uses conventional chemical agents and focuses on a single target. Evidence-based medicine and comparative effectiveness research (CER) are being used increasingly in discussions of changes that may occur in our health care system.

Herbs such as Skullcap (Scutellaria lateriflora), Cramp bark (Viburnum opulus) and Oat seed (Avena sativa) can be used to treat muscle weakness, nerve damage, and numbness. St. John’s Wort (Hypericum perforatum) can either be massaged topically or taken internally for its antiviral and nervous system tonic properties.

5. Diagnostic testing
The evaluation of a patient with peripheral neuropathy starts with simple blood tests, including a complete blood count, comprehensive metabolic profile, and measurement of erythrocyte sedimentation rate and fasting blood glucose, vitamin B12, and thyroid stimulating hormone levels. Additional tests, if clinically indicated, may include a paraneoplastic panel to evaluate for occult malignancy; antmyelin-associated glycoprotein antibodies to evaluate for sensorimotor neuropathies; antiganglioside antibodies; demyelinating neuropathy; CSF protein levels may be elevated in patients with these conditions.

5.1 Electrodiagnostic Studies:
Electrodiagnostic studies are recommended if the diagnosis remains unclear after initial diagnostic testing and a careful history and physical examination. There are two primary types of Electrodiagnostic studies:

1. Nerve conduction studies and electromyography (EMG).
2. Nerve conduction studies assess the shape, amplitude, latency, and conduction velocity of an electrical signal conducted over the tested nerve.
Axonal loss leads to lower amplitudes, and demyelination causes prolonged latency and slow conduction velocity. EMG can detect active axonal damage, as evidenced by the presence of spontaneous muscle fiber activity at rest resulting from the absence of neuromuscular junctional activity. The motor unit action potential on voluntary muscle contraction also is assessed.

Electrodiagnostic studies can help determine whether the neuropathy is the result of damage to the axons (axonal neuropathy) or the myelin (demyelinating neuropathy), or both (mixed). Normal nerve conduction studies and needle EMG significantly decrease the likelihood of peripheral neuropathy, whereas abnormal nerve conduction findings confirm the diagnosis. A potential limitation of Electrodiagnostic studies is that they are able to test only the large, myelinated nerve fibers. This limits their sensitivity in detecting neuropathies of the small nerve fibers (i.e., those with pain, temperature, and autonomic functions).

5.2 Nerve Biopsy

Nerve biopsy are to be considered when the diagnosis remains uncertain after laboratory and electrodiagnostic testing, or when confirmation of the diagnosis is needed before initiating aggressive treatment (e.g., in cases of vasculitis when steroids or chemotherapy is used). Sural and superficial peroneal nerves are preferred for biopsy. When all investigations fail to identify a cause and electrodiagnostic studies show axonal-type symmetric peripheral neuropathy, idiopathic peripheral neuropathy is the presumptive diagnosis.[6] Kim SB et al has designed the PEMFs (Pulsed Electromagnetic Fields) system which can stimulate only an acupoint. There have been no researches which reported therapeutic effect when stimulating at an identical acupoint by Transcutaneous Electrical Acupoint Stimulation (TEAS) and PEMFs. Hence, there study investigated the therapeutic effect on the muscle fatigue after the strenuous knee extension/flexion exercise by two stimulations. Such kind of Nerve Biopsy studies demonstrated that PEMFs were better than TEAS as a non-invasive method to replace the manual acupuncture.

6. Treatment

Treatment of peripheral neuropathy has two goals: controlling the underlying disease process and treating troublesome symptoms. The former is usually achieved by eliminating offending agents, such as toxins or medications; correcting a nutritional deficiency; or treating the underlying disease (e.g., corticosteroid therapy for immune-mediated neuropathy). These steps are important to halt the progression of neuropathy, and they may improve symptoms. Acute inflammatory neuropathies require more urgent and aggressive management with intravenous immunoglobulin or plasmapheresis. It is important to help patients control troublesome symptoms of peripheral neuropathy, such as severe numbness and pain, as well as to alleviate disability resulting from weakness. Several pharmacologic options exist to treat neuropathic pain, including some antiseizure medications (e.g., gabapentin [Neurontin], topiramate [Topamax], carbamazepine [Tegretol], pregabalin [Lyrica]) and antidepressants (e.g., amitriptyline). Topical patches and sprays containing lidocaine (Lidoderm) or capsaicin (Zostrix) also may relieve pain in some patients. Other supportive measures, such as foot care, weight reduction, and shoe selection, may also be helpful. Narcotics may have a role in the treatment of chronic neuropathic pain in selected patients. Candidates initially should be evaluated for their risk of substance abuse and addiction, and several nonnarcotic regimens should be tried first. A second opinion regarding the patient’s diagnosis and management also should be considered before initiating long-term opioid therapy.

Antidepressants

The functioning of antidepressants is different in neuropathic pain from that observed in depression. Activation of descending nor epinephrinergic and serotoninergic pathways to the spinal cord limit pain signals ascending to the brain. Antidepressants will relieve neuropathic pain in non-depressed persons.

In animal models of neuropathic pain it has been found that compounds which only block serotonin reuptake do not improve neuropathic pain. Similarly, compounds that only block norepinephrine reuptake also do not improve neuropathic pain. Dual serotonin-nor epinephrine reuptake inhibitors such as duloxetine, venlafaxine, and milnacipran, as well as tricyclic antidepressants such as amitriptyline, nortriptyline, and desipramine improve neuropathic pain and are considered first-line medications for this condition.

Anticonvulsants

Pregabalin (Lyrica) and gabapentin (Neurontin) work by blocking specific calcium channels on neurons and are preferred first-line medications for diabetic neuropathy. The anticonvulsants carbamazepine (Tegretol) and oxcarbazepine (Trileptal) are especially effective in trigeminal neuralgia. The actions of these two drugs are mediated principally through sodium channels.

Lamotrigine may have a special role in treating two conditions for which there are few alternatives, namely post stroke pain and HIV/AIDS-related neuropathy in patients already receiving antiretroviral therapy.

6.4. Opioids

Opioids, also known as narcotics, are increasingly recognized as important treatment options for chronic pain. They are not considered first line treatments in neuropathic pain but remain the most consistently effective class of drugs for this condition. Opioids must be used only in appropriate individuals and under close medical supervision.

Several opioids, particularly methadone, and ketobemidone possess NMDA antagonism in addition to their µ-opioid agonist properties. Methadone does so because it is a racemic mixture; only the l-isomer is a potent µ-opioid
agonist. The d-isomer does not have opioid agonist action and acts as an NMDA antagonist; d-methadone is analgesic in experimental models of chronic pain. Clinical studies are in progress to test the efficacy of d-methadone in neuropathic pain syndromes29.

There is little evidence to indicate that one strong opioid is more effective than another. Expert opinion leans toward the use of methadone for neuropathic pain, in part because of its NMDA antagonism. It is reasonable to base the choice of opioid on other factors30.

Cannabinoids

Marijuana's active ingredients are called cannabinoids. Use of Medical Marijuana for pain relief has been approved in some locations around the world, including many states in the United States. A recent study showed smoked marijuana is beneficial in treating symptoms of HIV-associated peripheral neuropathy. Nabilone is an artificial cannabinoid which is significantly more potent than delta-9-tetrahydrocannabinol (THC). Cannabinoids have relieved neuropathic pain in different animal models. But their therapeutic activities could be affected by their psychoactive properties. NMR analysis reveals a direct interaction between CBD and S296 in the third transmembrane domain of purified α3 GlyR30. Nabilone produces less relief of chronic neuropathic pain and had slightly more side effects than dihydrocodeine. The predominant adverse effects are CNS depression and cardiovascular effects which are mild and well tolerated but, psychoactive side effects limit their use. A complicating issue may be a narrow therapeutic window; lower doses decrease pain but higher doses have the opposite effect. Sativex, a fixed dose combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol, is sold as an oromucosal spray. The product is approved in both Sweden and Canada as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis, and for cancer related pain. Long-term studies are needed to assess the probability of weight gain, unwanted psychological influences and other adverse effects31-32.

Botulinum toxin

Botulinum toxin type A (BTX-A) is best known by its trade name, Botox. Local intradermal injection of BTX-A is helpful in chronic focal painful neuropathies. The analgesic effects are not dependent on changes in muscle tone. Benefits persist for at least 14 weeks from the time of administration. The utility of BTX-A in other painful conditions remains to be established. botulinum toxin is effective in the treatment of neuropathic pain syndromes such as postherpetic neuralgia or painful scars. On the basis of the analysis of the reports published in the literature, it would seem that factioned peripheral subcutaneous and perineural injections of botulinum toxin type A may be useful for the treatment of various chronic pain conditions with neuropathic component33.

Aspartate antagonist

The N-methyl-D-aspartate (NMDA) receptor seems to play a major role in neuropathic pain and in the development of opioid tolerance. Dextromethorphan is an NMDA antagonist at high doses. Experiments in both animals and humans have established that NMDA antagonists such as ketamine and dextromethorphan can alleviate neuropathic pain and reverse opioid tolerance. Unfortunately, only a few NMDA antagonists are clinically available and their use is limited by a very short half life (dextromethorphan), weak activity (memantine) or unacceptable side effects (ketamine). in rats with neuropathic pain model of chronic constriction of one sciatic nerve (CCI rats), we administered methadone before or after opioid receptor blockade with naloxone and checked its effects on the spinal Wide Dynamic Range (WDR) neuron dynamics in three experimental conditions: on the spontaneous and noxious evoked neuronal activities in control rats (sham operated and naïve); on iontophoretic NMDA induced neuronal hyperactivity in intact rats; on pain-related spontaneous and noxious evoked hyperactivities in CCI rats. The results, as from the spike-frequency analysis, show that:

(i) In control rats, methadone inhibits the noxious evoked neuronal activity and naloxone prevents or reverses about 94% of methadone inhibitory effect.
(ii) In intact rats, pretreated with naloxone, methadone reduces the NMDA induced neuronal hyperactivity.
(iii) In CCI rats, methadone inhibits the neuronal spontaneous and noxious evoked hyperactivities, and naloxone prevents or reverses about 60% of methadone inhibitory effect.

These findings allow to conclude that methadone inhibition of the noxious evoked activity in normal rats is achieved predominantly through the agonism of the μ-opioid receptors, while the inhibition of the pain-related hyperactivity in rats with signs of neuropathic pain (CCI rats), involves also the NMDA receptors antagonism. Clinical reports have described a long-lasting relief in neuropathic pain patients treated with NMDA receptor antagonists34-35.

Alpha-Lipoic Acid

Several smaller studies confirm the potential benefit of ALA for diabetic peripheral neuropathy. Fifteen randomized controlled trials met the inclusion criteria. The treatment group involved the administration of ALA 300-600 mg i.v. per day. Compared with the control group, nerve conduction velocities increased significantly in the treatment group. The weighted mean differences in nerve conduction velocities were 4.63 (95% confidence interval 3.58-5.67) for median MNCV, 3.17 (1.75-4.59) for median SNCV, 4.25 (2.78-5.72) for peroneal MNCV, and 3.65 (1.50-5.80) for peroneal SNCV in favor of the treatment group. The odds ratio in terms of efficacy was 4.03 (2.73-5.94) for ALA. Furthermore, no serious adverse events were observed during the treatment period. Both oral and intravenous administration of alpha-lipoic acid (ALA) has
been investigated as add-on treatment for diabetic peripheral neuropathy.\(^{36-37}\)

**Acetyl-L-Carnitine (ALC)**

Infection with HIV has been associated with a secondary deficiency of the amino acid L-carnitine. This deficiency may be due to mala absorption and other gastrointestinal disturbances, renal loss, shifts in metabolism, and use of antiretroviral drugs. Antiretroviral drugs are a major cause of peripheral neuropathy in HIV-positive individuals, potentially due to a drug-induced deficiency of L-carnitine or ALC. Twenty-one subjects completed the study. ALC was generally well tolerated. Improvements in neuropathic pain, paresthesias, and symptoms of numbness were observed. Similarly, improvement was noted on the Gracely Pain Intensity Score.\(^{38}\) Nerve regeneration was documented in one trial. The supplement was well tolerated. A proprietary form of ALC was used in both studies.\(^{39}\) Patients who had neuropathic pain reported reductions in pain using a visual analog scale.

**Vitamin E**

Oxidative stress appears to play a significant role in peripheral neuropathy, particularly in the case of PN due to diabetes. Latest study data of double-blind study using placebo-controlled trial, in type-II diabetics with PN were given either 900 mg vitamin E for six months. Electrophysiological parameters of nerve function, examined at baseline and at the end of the study, found significant improvement in two of 12 parameters – median motor NCV and tibial motor nerve distal latency – in the vitamin E group compared to placebo. In an animal study of streptozotocin-diabetic rats, depletion of vitamin E resulted in a depletion of reduced glutathione in nerves of diabetic and normal rats and an induction or aggravation of abnormalities in nerve conduction, particularly in sensory nerves. Cisplatin might induce a vitamin E deficiency that may be a cause of the neurotoxicity associated with this chemotherapy drug. Plasma vitamin E levels were found to be low in five patients who had developed severe neuropathy following cisplatin treatment. Two and four cycles of cisplatin also were found to noteworthy decrease plasma vitamin E levels in another group of five patients in whom vitamin E levels were measured at baseline and after cisplatin treatment.\(^{40}\)

**Peptide**

Paclitaxel produces a sensory neuropathy which are commonly characterized by mechanical and cold hypersensitivity, which are abated by antioxidants. The vanilloid 4 (TRPV4) channel as transient receptor potential has been reported to contribute to paclitaxel-evoked allodynia in animals. It is evident that TRP ankyrin 1 (TRPA1) channel mediates oxaliplatin-evoked cold and mechanical allodynia, and the drug direct target the ankyrin (TRPA1) via generation of oxidative stress. In this review, authors explained whether TRPA1 activation contributes to paclitaxel-induced mechanical and cold hypersensitivity or this activation might be mediated by oxidative stress generation. Paclitaxel-evoked mechanical allodynia was reduced partially by the TRPA1 antagonist, HC-030031, and the TRPV4 antagonist, HC-067047, which was completely declined by the combination of the two antagonists. Exposure to paclitaxel on the slices of mouse esophagus released the sensory neuropeptide, calcitonin gene-related peptide (CGRP). This effect was abolished by capsaicin desensitization and in calcium-free medium (indicating neurosecretion from sensory nerve terminals), partially reduced by either HC-030031 or HC-067047, and completely abated in the presence of glutathione (GSH). Finally, the reduced CGRP release was observed in esophageal slices of TRPA1-deficient mice, and was inhibited by GSH. Paclitaxel via oxygen radical formation targets TRPA1 and TRPV4, and both channels are key factor for the delayed development of mechanical allodynia. Cold allodynia is, however, entirely dependent on TRPA1.\(^{40-41}\) In very common that Diabetic rats are prone to sensory neuropathy as evidenced by mechanical and thermal hyperalgesia, which showed a higher incidence and severity of cataract as revealed by slit lamp examination. In early stage insulin treatment also protected the rats from the development of neuropathy and cataract, but late insulin administration failed to do so. The results demonstrate the benefits of early glycemic control in preventing neuropathy and cataract development in diabetic rats.\(^{42}\)

**Thiamine and Benfotiamine**

Vitamin B1 (thiamine) deficiency occurs due to various causes and is known to be a factor in peripheral neuropathy. Even as Gastrectomy is also associated with thiamine deficiency which is the result of Peripheral Neuropathy. In various study alcoholic or diabetic neuropathy prone patients were included. In the comparison of vitamin B with placebo, two small trials showed no significant short-term benefit in pain intensity while one of the trials showed a small significant benefit in vibration detection from oral benfotiamine, a derivative of thiamine. In the larger of two trials comparing different doses of vitamin B complex, there was some evidence that higher doses resulted in a significant short-term reduction in pain and improvement in paraesthesiae, in a composite outcome combining pain, temperature and vibration, and in a composite outcome combining pain, numbness and paraesthesiae. There was some evidence that vitamin B is less efficacious than alpha-lipoic acid, cilostazol or cytidine triphosphate in the short-term improvement of clinical and nerve conduction study outcomes but the trials were small. There were few minor adverse effects reported.\(^{43}\) Neuropathy was assessed by five parameters: the pain sensation (evaluated by a modified analogue visual scale), the vibration sensation (measured with a tuning fork using the Riedel-Seyfert method) and the current perception threshold. An overall beneficial therapeutic effect on the neuropathy status was observed in many studies. It is concluded that benfotiamine is most effective in large doses, although even in smaller daily dosages, either in combination or in monotherapy, it is effective.
Methylcobalamin
Vitamin B12 deficiency has been associated with significant neurological pathology, including peripheral neuropathy. Serum metabolites like homocysteine and methylmalonic acid could also help clinically to identify patients at risk for a deficiency-associated neurological syndrome. One of the mechanisms showed that vitamin B12 deficiency neuropathy is also due to hypomethylation in the central nervous system. Inhibition of the B12-dependent enzyme methionine synthase results in a fall in the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine; the resultant deficiency in SAM impairs methylation reactions in the myelin sheath. The methylation of homocysteine to methionine requires both methylcobalamin (an active form of vitamin B12) and the active form of folic acid (5-methyltetrahydrofolate). An animal model of B12 deficiency neuropathy, however, does not support the hypomethylation theory. It was observed that fixed dose combination of sustained-release methylcobalamin and pregabalin significantly reduced neuropathic pain, with significant improvement in both the positive and negative symptoms associated with neuropathy, in Indian patients and was well tolerated.

Dietary supplements:
There are two dietary supplements that have clinical evidence showing them to be effective treatments of diabetic neuropathy; alpha lipic acid and benfortiamine. Apart from these two supplements, fish oil, a source of essential fatty acids, can also be used to treat peripheral neuropathy. Up to 75 percent of the myelin is composed of fat. It is noted that Fish oil contained Decahexanoic acid (DHA) which lines the nervous system and is used for rapid message relay. It is suggested to avoid deep fried foods, animal and Tran’s fats, hydrogenated oils and saturated fats—these are the heavy fats that compete with thinner oils for placement in the myelin sheath and effectively slow down message relay. In such neuropathic conditions patient should take a diet high in fruit, vegetables, and fresh fish, and should keep away from high intake of caffeine, sugar, rich meat, and artificial sweetener like aspartame. Because such agents contained in NutraSweet and Equal, has been linked to degenerative nervous system conditions, while vitamins, supplements, and diet can help to lessen some of the symptoms associated with peripheral neuropathy. There are best ways to treat chronic conditions in a clinic environment where a practitioner takes into account the whole body and designs a program specific to an individual’s needs.

CONCLUSION:
Peripheral neuropathy is now a days are very common either by diseases or the side effects of systemic illness or due to the neurotoxicity and some cases may be due to postural or accidental trauma to the nerve. There are various natural or synthetic agents used for the treatment of neuropathic pain but very less clinical evidences in support of the nerve repair. Some herbal remedies claims to have the nerve repair properties but no significant data is found. Many synthetic drugs like methylcobalamin, thiamine many anti-convulsant, neuromuscular blocking agents, are being used for treating pain. Controlling the underlying disease process and treating troublesome symptoms are the basic goals of the treatment. The review summarized the causes, symptoms associated with neuropathy, diagnostic approaches, and the conventional as well as alternative approaches for the treatment.

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