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Peripheral Neuropathy: Diagnosis, Management and Pharmacotherapy

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ABSTRACT

Neuropathy a disease of nerve is the common cause of pain in modern world. Chronic neuropathic pain is the most disturbing symptom of lesions in the peripheral nervous system that can be of many forms. Peripheral neuropathy is often distressing may produce disabilities or even found to be fatal. There are several things that cause neuropathies, understanding of the different types of neuropathies as well as their causes, symptoms, treatment options and prognoses is important for management of the painful disease. Symptoms of different painful neuropathies can be similar that sometimes diagnosing the exact type becomes a long and challenging process. This review explores various aspects of neuropathy and explains how health care practitioners should approach the assessment and diagnosis for management and pharmacotherapy of neuropathic pain.

Key Words: Peripheral Neuropathy, Painful Nerve Disease, Neuropathic Pain.

INTRODUCTION

The term neuropathy is short for peripheral neuropathy, meaning nerve damage in the peripheral nervous system and so affects nerves outside of the brain and spinal cord - it does not include nerve damage in the central nervous system. The peripheral nervous system is divided into the somatic and the autonomic nervous systems (ANS). Somatic motor nerve fibers control skeletal muscle function, while the sensory fibers mediate cutaneous and some deep sensations. The autonomic sensory and motor nerve fibers control most aspects of cardiovascular, gastrointestinal, bladder, and sexual functions.

Neuropathy Known as Polyneuropathy in which it typically affects more than one nerve, simply as nerve pain a complication found in a number of different underlying conditions. Doctors call idiopathic neuropathy when the underlying cause has not been diagnosed,. Neuropathic pain syndromes exhibit both positive and negative sensory symptoms and signs. Nonsensory neurological symptoms and signs depend on the underplaying cause and may independently contribute to pain and disability. According to International Association for the Study of Pain, neuropathic pain is the pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system [1, 2].

DIAGNOSIS:

The diagnosis of neuropathic pain is based on a medical history, review of systems, physical and neurological examination, and appropriate laboratory studies including blood and serologic tests, magnetic resonance imaging and electrophysiological studies, nerve biopsy or skin biopsy is required for some cases. Symptoms of different painful neuropathies can be similar therefore sometimes diagnosing the exact type becomes a long and challenging process. The evaluation of pain and other symptoms is required for the diagnosis and on the basis of that therapy is decided. Neuropathic pain is due to the disease or injury to the peripheral nervous system; clinically neuropathic pain includes positive as well as negative sensory symptoms and signs however motor signs and symptoms are often present [3].

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Assessment of pain:

A difference between stimulus-evoked pain and spontaneous (stimulus-independent) pain should be recognized which may have different underlying mechanisms. Spontaneous pain can be either constant or intermittent even paroxysmal and most patients describe having both type of pain like constant "burning" pain plus intermittent pain that is "shooting" or "electric shock–like". Spontaneous paresthesias and dysesthesias in addition exist as abnormal sensations, including crawling, numbness, itching, and tingling. It is important to assess the intensity, quality, and duration of spontaneous pain and abnormal sensations while investigating patient's history [4].

Common neurological examination tools, including a cotton wisp, a foam brush, a tuning fork, and cold and warm water filled tubes, can be used to mimic everyday environmental stimuli like the gentle touch and pressure of clothing, wind, riding in a bus, and hot and cold temperatures evokes pain. Pain intensity can be rated with any of several reliable and validated verbal, numerical, or visual analog scales. Patients rate their pain using some type of progressive scale depending on perception of "no pain" to "worst possible pain" [5]. Unusual abnormal sensations associated with neuropathic pain can be assessed with measures of pain quality using Neuropathic Pain Scale and Neuropathic Pain Questionnaire [6]. Various measures of physical and emotional function can also be used to evaluate a patient's response to treatment because chronic pain has a significant negative effect on quality of life. Assessment of psychological additional disorders like depression or anxiety, sleep disturbance, work-related issues, treatment expectations, rehabilitative needs, and the availability of social support from family and friends should be important [7, 8].

Altered sensation, pain, weakness, or autonomic symptoms were seen for patients with peripheral neuropathy. The clinical features vary widely and may resemble myelopathy, radiculopathy, muscle disease, or even hyperventilation. The symptoms usually begin in the toes before the fingers and spread proximally. The classic picture of advanced polyneuropathy with distal wasting and weakness, absent tendon reflexes, and glove and stocking sensory loss should be easy to recognize. The clinical features allow acute symmetrical peripheral neuropathy, chronic symmetrical peripheral neuropathy, and multiple mononeuropathy to be distinguished, each with a different differential diagnosis.

Additional studies are required as there is no single diagnostic test for neuropathic pain or pain in general can confirm or exclude underlying causes and suggest disease specific treatments like for diabetes mellitus in patients with painful neuropathy or spinal disorders in patients with radiculopathy. Nerve conduction velocity tests and electromyography provide information about large myelinated peripheral nerve function that will not test smaller myelinated or unmyelinated nerve fibers

carrying pain and temperature information. Quantitative thermal sensory testing depends on the patient's psychophysical ability to differentiate between fine changes in thermal stimuli; it requires specialized equipment and training so not widely used.

There is no single diagnostic test for neuropathic pain or pain in general. Ancillary studies can confirm or exclude underlying causes and suggest disease specific treatments, such as for diabetes mellitus in patients with painful neuropathy or spinal disorders in patients with radiculopathy. To assess peripheral nerve function, nerve conduction velocity tests and electromyography provide information about large myelinated peripheral nerve function but do not test smaller myelinated or unmyelinated nerve fibers carrying pain and temperature information. Quantitative thermal sensory testing relies on the patient's psychophysical ability to discriminate between fine changes in thermal stimuli; it is not widely used because it requires specialized equipment and training. Anatomical integrity of thermonociceptive sensory-processing regions can be made by magnetic resonance imaging (MRI).

Table No. 1: Types of peripheral neuropathic pain

Acute and chronic inflammatory demyelinating	Nutritional deficiency–related neuropathies
Polyradiculoneuropathy	Painful diabetic neuropathy
Alcoholic polyneuropathy	Phantom limb pain
Chemotherapy - induced polyneuropathy	Postherpetic neuralgia
Complex regional pain syndrome	Postradiation plexopathy
Entrapment neuropathies	Radiculopathy (cervical, thoracic, or lumbosacral)
HIV sensory neuropathy	Toxic exposure–related neuropathies
Iatrogenic neuralgias	Tic douloureux (trigeminal neuralgia)
Idiopathic sensory neuropathy	Posttraumatic neuralgias
Nerve compression or infiltration by tumor	

Table No. 2: Peripheral Neuropathy

Acute Symmetrical Peripheral Neuropathy	Chronic Symmetrical Peripheral Neuropathy
Polyneuropathy	Multiple Mononeuropathy

Acute symmetrical peripheral neuropathy:

Acute symmetrical peripheral neuropathy is rare but important because the commonest cause is Guillain-Barré syndrome, which can be fatal. Common early symptoms are distal paraesthesiae and proximal or distal weakness occurring one to two weeks after a respiratory or gastrointestinal infection. Traditionally, the reflexes are absent, but their retention during the first hours of the illness has led many patients to be dismissed as "hysterical." Once a patient loses the ability to walk and develops facial and bulbar weakness the diagnosis becomes obvious. The rapid progression of sensory or motor deficit requires emergency investigation. Patients usually have to be admitted to hospital because of the danger of respiratory failure. Early treatment should stop the pathological process before axonal dysfunction becomes irreversible.

Guillain-Barré syndrome is usually due to acute inflammatory demyelinating polyradiculoneuropathy caused by an autoimmune response directed against the Schwann cells or myelin. Some cases are due to acute axonal neuropathy, in which glycolipid in the axolemma is targeted. In both forms, treatment with intravenous immunoglobulin hastens recovery and reduces the long term disability and is more convenient than plasma exchange. A recent trial suggests that combination treatment with steroids is more effective than intravenous immunoglobulin alone, but the full results are awaited.

Table No. 3: Causes of acute sever generalized peripheral neuropathy

Reason	Nerves affected
Guillain-Barré syndrome	Predominantly Motor & Mixed
Vasculitis	Mixed
Diabetes mellitus	Predominantly Sensory & Mixed
Porphyria	Predominantly Motor
Diphtheria	Mixed
Paraneoplastic neuropathy	Predominantly Sensory &Mixed
Acute idiopathic sensory Neuronopathy	Predominantly Sensory
Critical illness	Predominantly Motor & Mixed
Drugs Eg. nitrofurantoin, vincristine, cisplatin, and reverse transcriptase inhibitors.	Predominantly Sensory & Mixed

Multiple mononeuropathy:

Acute multiple mononeuropathy is also a neurological emergency because the commonest cause is vasculitis. Prompt treatment with steroids may prevent further irreversible nerve damage. If multiple mononeuropathy develops in a patient with an established connective tissue disorder (such as rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, or Churg-Strauss syndrome) it is reasonable to conclude that vasculitis is the cause. Steroids are the main treatment, with cyclophosphamide being added depending on the severity and general medical condition.

Sometimes peripheral neuropathy is the presenting or sole feature of vasculitis. In this case, vasculitis can be diagnosed only by nerve biopsy. In addition, recent biopsy studies indicate that diabetic amyotrophy is due to microvasculitis in the lumbosacral plexus. It presents acutely with pain, weakness, and then wasting in one or both quadriceps muscles [9-11].

Vasculitis:

1. Primary systemic vasculitis
   - Polyarteritis nodosa
   - Churg-Strauss syndrome (vasculitis with blood eosinophilia and asthma)
2. Systemic vasculitis associated with connective tissue diseases
   - Rheumatoid arthritis
   - Sjögren's syndrome
3. Vasculitis confined to peripheral nerves

Other causes:

1. Sarcoidosis
2. Lymphoma
3. Carcinoma
4. Amyloid

Multiple compression palsies:

1. Associated with metabolic or toxic neuropathy
2. Hereditary neuropathy with liability to pressure palsies

Chronic symmetrical peripheral neuropathy:

Most peripheral neuropathies are chronic and usually develop over several months. Diagnosis of the underlying cause may require three stages of investigation. Any history of a general medical disorder could be relevant. Patients should always be asked about alcohol consumption, toxin exposure (insecticides, solvents), and drugs. They should also have a full examination, including breasts and genitalia, to exclude underlying carcinoma.

The commonest causes of neuropathy can be identified from the history, examination, and simple investigations called the complete neurological exam and workup. A thorough physical and neurological examination is useful to determine the non neuropathic cause to the patient's pain, most commonly musculoskeletal, inflammatory, myofascial, and psychological processes [3].

Stage 1 investigation: Physical Examination:

Patients are instructed to carefully describe their symptoms and rate the severity of their abnormal sensations. Patients are some time confused by the complexity of their sensory pain experiences; they often have trouble in identifying and describing the unusual nature of their symptoms, also the fear that they will not be believed.

When specific stimuli in the standard neurological sensory examination are applied first to the unaffected area and then to the area affected by pain, patients should be instructed to first respond in simple terms that is, whether the stimulus applied to the painful area causes the same sensation as in the unaffected area or whether it is less or more intense before describing their perception of the quality of the stimulus. For example, pin prick may be more painful (hyperalgesia) but less sharp because of the underlying sensory deficit.

The term allodyniais is used for pain in response to a normally nonnoxious stimulus. Lightly rubbing or brushing the skin with a cotton swab or brush dynamic mechanical allodynia can be elicited where as static mechanical allodynia can be provoked by blunt pressure with a finger, and thermal allodynia can be assessed with a warm or cool tuning fork. An increased sensation of pain in response to a normally painful stimulus is termed hyperalgesia, which can be assessed using painful thermal (cold or heat) or punctate (eg, pin prick) stimuli. Painful summation and hyperpathia to repeated stimuli, especially when the initial sensation is reduced, is important evidence of abnormal sensory processing. Non sensory neurological and musculoskeletal symptoms can also contribute strongly to overall disability. Motor system symptoms and signs include weakness, fatigability, hypotonia, tremor, dystonia, spasticity, ataxia, apraxia, and motor neglect. Other musculoskeletal symptoms and signs include decreased range of motion, stiffness of joints, spontaneous muscle spasms, localized muscle tenderness, and myofascial trigger points.

Sometimes the neuropathy is predominantly sensory and subacute with ataxia that is worse in the dark because of loss of large fiber function and postural sensation. This pattern is produced by some drugs (such as cisplatin), an underlying neoplasm, Sjögren's syndrome, or idiopathic sensory neuronopathy. If other members of the family have similar symptoms, pes cavus, or claw toes, the patient may have hereditary motor and sensory neuropathy or Charcot Marie-Tooth disease, which is usually autosomal dominant. Difficulty with walking in childhood also suggests a hereditary neuropathy. If patients have a clear cause for their neuropathy and a typical clinical picture, treatment for instance, of diabetes mellitus or alcohol misuse can be started without further investigation [12].

First stage investigations: Some of the investigations through lab tests are advised to find out the cause of the neuropathy. This includes tests to check for vitamin deficiencies, immune responses, blood sugar levels or the presence of any toxins or infections.

Stage 1:

- ✓ *Urine:* Glucose, protein
- ✓ *Haematology:* Full blood count, erythrocyte sedimentation rate, vitamin B-12, folate
- ✓ *Biochemistry:* Fasting blood glucose concentration, renal function, liver function, thyroid stimulating hormone

Second stage investigations: If the cause of the neuropathy is not clear from the stage 1 investigations or is atypical, the patient should be referred to a neurologist. The most important stage 2 investigation is neurophysiological testing. About 80% of symmetrical peripheral neuropathies are axonal and are due to gradual dying back of the axons. In the remaining 20% (demyelinating neuropathies) most of the damage is to the myelin, although axonal degeneration often occurs as the disease advances. The other second stage investigations are simple outpatient tests for the commonest causes of peripheral neuropathy.

Electromyography (EMG) electronically studies that measures and records muscle activity. This tells about the location of any muscle, nerve or neuromuscular junction damage as well as its cause. A nerve conduction study to find out damage in the peripheral nervous system by measuring the efficiency and speed of electrical signals of the nerves indicates any abnormality of the nerves. An EMG and nerve conduction studies usually are simultaneously performed to get accurate diagnosis. Magnetic resonance imaging (MRI) may be performed to exclude any other causes of the neuropathy, like trauma or impingement. A spinal tap lumbar puncture may be done for the presence of protein or something else in the cerebrospinal fluid that can indicate the cause of the neuropathy.

Stage 2:

- ✓ *Neurophysiological tests:* Assessment of distal and proximal nerve stimulation
- ✓ *Biochemistry:* Serum protein electrophoresis, serum angiotensin converting enzyme
- ✓ *Immunology:* Antinuclear factor, antiextractable nuclear antigen antibodies (anti-Ro, anti-La), antineutrophil cytoplasmic antigen antibodies
- ✓ *Other:* Chest radiography

Third stage investigation: When the diagnosis cannot be made in any other way biopsy should be done in a specialist centre, there specimens are usually taken from the sural nerve after giving local anaesthetic. Nerve biopsy or muscle biopsy option should be used only on patients with distressing neuropathy to provide useful treatment in which small piece of nerve or muscle may be taken in order to look for the cause of the damage [13]. These tests are only done if some very specific conditions are suspected or to completely rule out a specific condition. The choice of third stage investigation will depend on whether neurophysiological testing has shown the neuropathy to be demyelinating or axonal

Demyelinating neuropathy:

The causes of demyelinating neuropathy are limited. If the slowing of nerve conduction affects all nerves roughly equally the diagnosis is likely to be the demyelinating form of Charcot-Marie-Tooth disease (type 1). Seventy per cent of such patients have a duplication of the gene for a 22 kDa peripheral nerve myelin protein on chromosome 17. The duplication causes over expression of the protein. Genetic counseling and prenatal diagnosis may be suggested.

About 10% of patients with a demyelinating neuropathy have a serum paraprotein. Although occasionally associated with a solitary plasmacytoma, the paraprotein is usually benign. The commonest syndrome is a slowly progressive predominantly sensory neuropathy with an IgMêparaprotein. The paraprotein is an autoantibody directed against the carbohydrate antibody is directly responsible for the neuropathy.

Chronic inflammatory demyelinating polyradiculoneuropathy is the commonest form of acquired demyelinating neuropathyin which Protein concentrations in the cerebrospinal fluid found to be increased and affects about 2 per 100000 of the population. The patients show a proximal as well as distal pattern of weakness, predominantly motor and the condition may be relapsing and remitting. It is thought to be an autoimmune disease because of the inflammation in the nerves and response to immunotherapy. There is no diagnostic immunological test, but antibodies to the 28 kDa P0 myelin glycoprotein were identified in about a quarter of cases in a recent series and have been shown to induce experimental demyelination [14, 15].

Causes of chronic demyelinating neuropathy

- Charcot-Marie-Tooth disease type 1
- Other forms of Charcot-Marie-Tooth disease
- Hereditary liability to pressure palsies
- Other genetic causes - for example, Refsum's disease, metachromatic leucodystrophy
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Multifocal motor neuropathy
- Paraproteinaemic demyelinating neuropathy:
  - ✓ Associated with monoclonal gammopathy of undetermined significance

✓ Associated with solitary myeloma

Chronic inflammatory demyelinating polyradiculoneuropathy is diagnosed from neurophysiological testing that shows multifocal abnormalities with partial conduction block. This causes the compound muscle action potential following proximal stimulation to be smaller than that following distal stimulation. Distal and proximal stimulation is given to a nerve of abductor pollicis brevis muscle. The upper trace of each pair shows the record for distal stimulation.

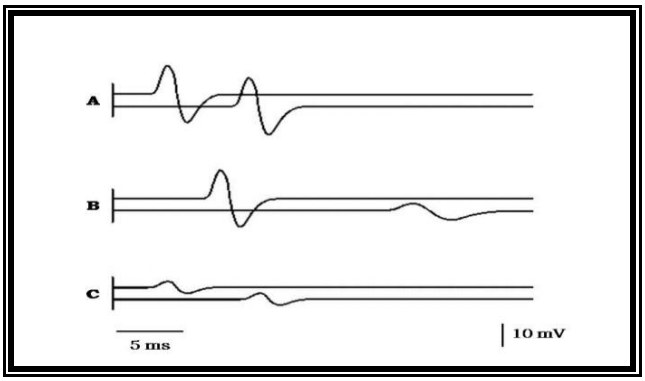

Fig. 1: Muscle Action Potentials

A. Normal nerve:	**Distal motor latency is short and nerve conduction velocity rapid (>50m/sec)**
B. Demyelinating Neuropathy:	The distal motor latency is prolonged and nerve conduction velocity slowed to less than 80% of normal.
C. Axonal Neuropathy:	The action potential is reduced, but the distal motor latency and nerve conduction velocity are unaffected.

Chronic axonal neuropathy:

Sensory or sensory and motor axonal polyneuropathy has many causes and can be suggested by the history or examination. The third stage investigations may indicate less common general medical disorders also it is useful to identify cases of diabetes mellitus that were not detected by the fasting blood glucose test [16].

Chronic idiopathic axonal neuropathy in 25% of elderly patients cases may not clearly identified after exhaustive investigation. This type of neuropathy is often indolent, predominantly sensory, and length dependent. Disease will slowly progress without causing serious disabilities [17].

Prominent symptoms of axonal neuropathy are loss of pain and temperature sensation and spontaneous neuropathic pain, described as burning or pricking occur due to degeneration of thinly myelinated and unmyelinated nerve fibres. Sometimes small fibre neuropathy occurs without affecting the thicker myelinated nerve fibres in such cases nerve conduction test results remain normal. The diagnosis depends on clinical symptoms and signs which can be justified with skin biopsy or enumeration of unmyelinated nerve fibres in electron micrographs of a nerve biopsy specimen. The diagnosis in some conditions is suggested by other neurological and systemic features for chronic axonal neuropathy in patients with many multisystem hereditary disorders. The axonal form of Charcot-Marie-Tooth disease (type 2) hereditary neuropathy is considered as difficult to diagnose, the symptoms of disease usually begin in childhood and are associated with pes cavus and claw toes but may not come to attention until middle or old age [18-20].

Stage 3 investigation:

- ✓ Urine: Bence-Jones protein
- ✓ Biochemistry: Oral glucose tolerance test
- ✓ Cerebrospinal fluid: Cells, protein, immunoglobulin oligoclonal bands
- ✓ Immunology: Anti-HIV antibodies, antineuronal antibodies (Hu, Yo), antigliadin antibodies, serum angiotensin converting enzyme, antiganglioside antibodies, antimyelin associated glycoprotein antibodies.
- ✓ Tests for Sjögren's syndrome: Salivary flow rate, Schirmer's test, Rose Bengal test, labial gland biopsy.
- ✓ Search for carcinoma, lymphoma, or solitary myeloma: Skeletal survey, pelvic ultrasonography, abdominal and chest computed tomography, mammography, or positron emission tomography.
- ✓ Molecular genetic tests: Peripheral nerve myelin protein 22 gene duplication (the commonest cause of Charcot-Marie-Tooth disease type 1) or deletion (hereditary neuropathy with liability to pressure palsies), connexin 32 mutation (X linked Charcot-Marie-Tooth disease), PO gene mutation (another cause of Charcot-Marie-Tooth disease type 1), etc

TREATMENT:

Pain is an important symptom of neuropathy and patients usually complain of discomforts like burning or tingling that go along with having numbness, any underlying medical cause like diabetes mellitus or vitamin B-12 deficiency should be treated first. Medications that are specialized for managing nerve pain are often used the NSAIDs nonsteroidal anti-inflammatory drugs can relieve mild symptoms; most useful drugs are anticonvulsants, especially pregabalin, gabapentin, carbamazepine and tricyclic antidepressants, especially amitriptyline. Severe cases may require stronger narcotic medications like the opioid analgesics. Chronic inflammatory demyelinating polyradiculo neuropathy is important to recognize and diagnose because it is treatable. The cheapest treatment corticosteroids are usually used initially, but the condition can also be treated with intravenous immunoglobulin (high levels of proteins that work as antibodies), plasma exchange (removing antibodies and other proteins from the blood), and some immunosuppressant drugs. The uncommon variant, multifocal motor neuropathy, responds to intravenous immunoglobulin and possibly immunosuppressant drugs but not to corticosteroids or plasma exchange. Unfortunately, no specific treatment is available for chronic idiopathic axonal polyneuropathy. Neuropathic pain is usually treated by pain medications having limited effect and/or dose-related side effects when given alone therefore combinations of more than one drug are often used with the goal of achieving better pain relief or less side effects [21].

Table No. 4: Medications for Neuropathic Pain

Medication	Dosage
Pregabalin	100-300 mg every night or 100-300 mg 3 times daily
Gabapentin	100-300 mg every night or 100-300 mg 3 times daily
Tricyclic antidepressants Eg: nortriptyline or desipramine	10-25 mg every night
NSAIDs Eg Ibuprofen combination with Pregabalin and/or Gabapentin	200-400 mg every 4 to 6 hours as needed
Serotonin-noradrenaline reuptake inhibitors Eg: duloxetine and venlafaxine	60–120 mg, once a day, 150–225 mg, once a day extended release
Tramadol hydrochloride	50 mg once or twice daily
Opioid Analgesics Eg: morphine sulfate	5-15 mg every 4 hours as needed
5% Lidocaine Patchs	Maximum of 3 patches daily for a maximum of 12 hr
8% Capsaicin Patches	One to four patches to the painful area for 30-60 min every 3 months
Botulinum Toxin A (subcutaneously)	50–200 units to the painful area every 3 months

MANAGEMENT:

Painful neuropathy is difficult to treat because patients may experience pain, which can be severe and out of proportion to any sensory or motor deficit therefore various therapies and procedures can be utilized to help ease the signs and symptoms of peripheral neuropathy. Preventive and palliative treatments include foot care, weight reduction, and sensible shoes, boots, or ankle foot orthoses. Physical therapy for muscle weakness can helps to improve movements, patients with severe leg weakness may need sticks, crutches, or a walking frame or a wheelchair, and wrist splints can help weak wrist extension and complex splints for weak fingers and hands are usually provided by the physiotherapists. Disabled patients may be advised special utensils and home adaptations, they require help from a multidisciplinary team by the including an occupational therapist. Some drugs like Sildenafil may be used to correct erectile impotence. Transcutaneous electrical nerve stimulation (TENS) applied for 30 minutes daily for about a month by placing adhesive electrodes on the skin which delivers a gentle electric current at varying frequencies provides relief from neuropathic pain [21].

CONCLUSION

Neuropathies can be sensory, motor or autonomic depending on symptoms presents in the type of nerve and the location. Sensory nerves tell us how things feel where as motor nerves stimulate muscle contraction and initiate movement and autonomic nerves control functions that our body unconsciously regulates, such as breathing and heart rate. Epidemiological surveys around the globe suggest that many patients with neuropathic pain do not receive appropriate treatment; the reasons might be low diagnostic accuracy insufficient knowledge about the nerve disease, effective drugs and their appropriate use in clinical practice. Management of the nerve disease and pharmacotherapy of neuropathic pain are therefore essential. Current drugs as monotherapy are associated with limited efficacy and dose related side effects where as combining two or more different drugs may improve analgesic efficacy and reduce overall side effects.

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