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Painful Peripheral Neuropathies

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Summary: Kraychete DC, Sakata RK – Painful Peripheral Neuropathies.

Background and objectives: Painful neuropathies are common and often difficult to treat. The objective of this report was to review the subject to facilitate diagnosis and pain relief.

Contents: The classification, causes, type of fibers involved, manifestations, diagnosis, adjuvant tests, questionnaires used in the diagnosis, and treatment are described.

Conclusions: The subject is very broad and involves several causes and treatments that often should be combined to obtain adequate pain control.

Keywords: Polyneuropathies; Pain Measurement; Signs and Symptoms.

INTRODUCTION

The estimated prevalence of peripheral neuropathies in the general population is approximately 2%, and in adults over 55 years of age it can reach 8% [1]. For adequate treatment of pain the knowledge about the etiology and mechanisms involved is important. Because neuropathies have several causes assessment and diagnosis become difficult. Thus, even with appropriate evaluation, between 25% and 40% of neuropathies will remain without a defined cause [2,3].

In this article we will focus on the differential diagnosis of peripheral neuropathies emphasizing the most prevalent disorders associated with neuropathic pain. We also will discuss the treatment of neuropathic pain.

CLASSIFICATION

Peripheral neuropathies can be divided into three large groups:

- Mononeuropathies involving only one nerve trunk;
- Multiple mononeuropathies with successive involvement of several nerve trunks;
- Distal polyneuropathies with diffuse, symmetrical involvement of all four limbs.

Polyradiculoneuropathies can be distinguished from distal neuropathies by the presence of proximal and distal sensorial or motor changes. They can be hereditary, metabolic, toxic, and idiopathic. Neuropathies can be acute (up to one month), subacute (months), and chronic (years) [4].

CAUSES

Sensorial neuropathy involving small fibers can affect patients with diabetes mellitus, leprosy, HIV infection, sarcoidosis, amyloidosis, Tangier disease, and Fabry disease.

Diseases that commonly cause sensorial and autonomic changes include: diabetes mellitus, amyloidosis, paraneoplastic syndrome, Sjögren syndrome, prophyria, HIV infection, and demyelinating inflammation.

Large fiber polyneuropathies are seen in monoclonal IgM-associated demyelinating disorders with anti-glycoprotein activity, inflammatory chronic polyradiculoneuropathies (Guillain-Barré syndrome), and gangliopathies (secondary to paraneoplastic syndrome, Gougerot-Sjögren syndrome, or drug intoxication) [4].

Weight loss suggests metabolic (diabetes mellitus), immunologic (vasculitis), or neoplastic (lymphoma) disorders. Alcoholism is associated with neuropathy secondary to nutritional deficiencies. Depending on an individual's work, neuropathies can be associated with lead, arsenic, thalium, organophosphates, trichloroethylene, hexacarbons, and acrylamide intoxication. Other agents listed below also should be investigated in the history regarding drug use, since they are also neurotoxic (Box 1).

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Box 1 – Classes of Drugs and Agents Related to Peripheral Neuropathy [4,16,17]

Antibiotics: Isoniazid, metronidazole, etambutol, nitrofurantoin, colistin, dapsone
Antimitotics: Vincristine, cisplastin, taxol, vinblastine, doxorubicin
Antivirals: DDI, DDC, alpha-interferon
Others: Amiodarone, thalidomide, colchicine, gold salts, penicillamine, chloroquine, cyclosporine, phenytoin, disulfiram, lithium, cimetidine

TYPE OF FIBER INVOLVED

It is important to determine the type of nerve fiber involved. Peripheral neuropathies can be sensorial, motor, or autonomic. In case of neuropathy it is necessary to identify whether it is due to disease of the axon, myelin, or neuron.

The most common motor manifestations include muscle spasms, clonus, fasciculations, amyotrophies, and loss of dexterity and muscle strength. Negative sensorial manifestations include hypoalgesia and hypoesthesia; and positive manifestations include paresthesia, dysesthesia, hyperpathia, and allodynia in addition to sensations of stinging, tingling, or tinnitus. Neuropathies with large fiber dysfunction (motor or sensorial) with loss of proprioception, vibration, or light touch related to demyelination cause muscle weakness with or without ataxia and positive sensorial manifestations, such as tingling. Positive or negative sensorial manifestations usually indicate involvement of small type Aδ and C fibers. However, positive sensorial manifestations can suggest acquired neuropathy, since hereditary neuropathies have a tendency to present more physical changes than symptoms. In most cases identification of sensorial fiber involvement excludes upper motor neuron, neuromuscular junction, and muscle disorders. Inflammatory demyelinating neuropathies may cause muscle weakness, concealing sensorial manifestations.

It is common to find in the neurologic exam, symmetrical hypo- or areflexia in polyneuropathies or asymmetrical in mononeuropathies. However, in the motor form of Guillain-Barré syndrome or in the spinal form of Charcot-Marie Tooth syndrome, tendon reflexes may be normal.

MANIFESTATIONS

Main manifestations of small fiber neuropathy include burning sensation in feet and changes in thermal and pain sensitivity. Epicritic sensitivity and proprioception are normal, as well as tendon reflexes [4].

In sensorial neuropathy associated with neurovegetative system involvement the following changes can be observed [5,6]:

- Pupillary neuropathy, with loss of pupillary adaptation to light;
- Cardiovascular, with tachycardia, exercise intolerance, orthostatic hypotension, and silent myocardial ischemia;
- Sudomotor, with anhidrosis, heat intolerance, and dry skin;
- Gastrointestinal, with esophageal dysmotility, gastroparesis, diarrhea, constipation, and fecal incontinence;
- Genitourinary, with erectile dysfunction, retrograde ejaculation, and neurogenic bladder.

In neuropathies with involvement of large fibers, generalized areflexia, ataxia with instability upon walking and orthostatic position, and tremors in the extremities can be seen [4].

The development of other manifestations, such as restless leg syndrome in dialysis-related neuropathy can be seen; tremor of the extremities is common in hereditary neuropathies such as Charcot-Marie-Tooth and monoclonal antibody-associated demyelinating neuropathies [7].

LOCATION

The location can determine whether the distribution of the neuropathy depends on the length of the nerve and whether it is symmetrical or asymmetrical.

Nerve length-dependent neuropathies initially manifest in the feet and they are symmetrical. Nerve length-independent neuropathies can be focal or multi-focal and in general they are associated with infectious or immunologic diseases. They include polyradiculopathies, plexopathies, poly-ganglionopathies, and multiple mononeuritis.

In polyneuropathies usually the onset of signs and symptoms is slow according to what is seen in axonal involvement, and motor changes evolve from distal to proximal portions of the affected limb. However, in polyradiculoneuropathies motor changes are proximal. Mononeuropathies are characterized by asymmetrical motor or sensorial changes compromising one or several nerve trunks. If the dorsal root ganglion is damaged, with compromised large myelinated fibers, neuropathy is usually asymmetrical characterized by proprioceptive ataxia, tremors of the extremities, and areflexia [4,8].

Involvement of cranial nerves is rare in peripheral neuropathies, but it can be seen in sarcoidosis, Lyme disease or Gougerot-Sjögren syndrome [7].

TYPE OF ONSET

Acute and subacute neuropathies are related to infectious or immune-mediated diseases. A slow and insidious onset is more common in hereditary, metabolic, toxic, and idiopathic neuropathies [4].

PATHOPHYSIOLOGY

The pathophysiology of neuropathic pain is complex and involves the following topics [9,10]:

- Sensitization of nociceptors;
- Spontaneous activation of afferent fibers and silent nociceptors;
- Ascending regulation of sodium channels (Nav 1.3, Nav 1.7, Nav 1.8);
- Sensitization of primary afferent fibers and catecholamines;
- Ectopic discharges of the dorsal root ganglion;
- Activation of the immune system and glial cells with release of proinflammatory cytokines, chemokines, and other neuroexcitatory compounds.

In diabetic neuropathy, changes due to excess glucose out of the cells are observed [5,6], which causes:

- Increased glucose flow to the polyol pathway or hexosamine pathway;
- Excessive or inappropriate activation of the C-protein phosphokinase;
- Accumulation of glycosilated end products;
- Imbalance of the reduced state in the mitochondrial pathway;
- Increased formation of superoxide radicals.

These associated factors cause inflammatory reactions, changes in angiogenesis, thickening of capillary basement membrane, proliferation of vascular endothelium and vascular smooth muscle, changes in capillary permeability, reduction in the neurovascular flow and metabolism, and activation of transition factors (NF-κB, TGFβ), in addition to neural dysfunction, responsible for phenotypic changes, and mitochondrial and cellular death that facilitates nerve excitation and pain [6,11-15].

DIAGNOSIS

History and physical exam are fundamental for the diagnosis. The differential diagnosis of neuropathies is important and avoids unnecessary investigations. Personal antecedents, prior and current treatments, and social history are also important.

Based on the physical exam some diagnostic hypothesis can be suggested. Investigating the presence of joint deformities and spinal column deviations, besides lumbosacral root hypertrophy, is important. Plantar ulcers are characteristic of nutritional, alcoholic or diabetic deficiencies; the presence of purpura or necrosis of the fingers suggests vasculitis; and depigmentation, sarcoidosis or leprosy. Alopecia can be seen in hypothyroidism, systemic lupus erythematosus, and thalium intoxication [4,5,8,16-18]. Box 2 describes some neuropathies.

Diagnosis of neuropathic pain

Neuropathic pain is secondary to injury or disease affecting the somatosensorial system.

Diagnosis is based on history, physical examination, specific questionnaires, laboratory tests using quantitative systems and measurement of objective responses, besides the sensitive-quantitative test.

Some authors have suggested the classification in Box 3 to characterize neuropathic pain [13].

In a study of 214 patients using the aforementioned classification only 24 patients that would normally be classified with

Box 2 – Examples of Neuropathies

Peripheral polyneuropathy: Burning pain, sting, shock-like pain in feet and fingertips, worse when walking, discomfort to light touch, reduced sensitivity in feet, absence of Achilles tendon reflex.

Trigeminal neuralgia: severe, acute, shock-like pain lasting seconds in upper lip and nose, worse when chewing or brushing teeth, without neurologic changes.

Carpal tunnel syndrome: acute, tingling pain, with reduction in sensitivity in the 1st, 2nd, and 3rd fingers and palms, worse at night, weakness in thumb abduction, Phalen's sign positive.

Mononeuropathy of the lateral femoral cutaneous nerve or paresthetic meralgia: burning sensation and stinging on lateral aspect of the thigh, circumscribed area of hypersensitivity to light touch with cotton and pinprick.

Post-herpetic neuralgia: burning pain in the thoracic region after the development of vesicles, without improvement after healing, hyperchromic skin discoloration, allodynia.

Box 3 – Classification Regarding the Possibility of Neuropathic Pain

Neuropathic pain

Pain localized in neuroanatomical area meeting two of the following criteria:

- Reduction in sensitivity in all or part of the painful area
- Current or prior disease that justifies nerve damage and which has a relationship with the pain
- Nerve damage confirmed by neurophysiologic studies, neuroimaging studies, or surgery

Possible neuropathic pain

Pain localized in a neuroanatomical area meeting two of the following criteria:

- Reduction in sensitivity in all or some part of the painful area
- Etiology unknown
- Current or prior disease that could cause inflammatory or neuropathic pain with a relationship with the pain
- Presence of irradiated or paroxysms of pain

Neuropathic pain is unlikely

Pain meeting two of the following criteria:

- Pain is not located in a neuroanatomical area
- Current or prior disease that can cause inflammatory pain
- No sensorial loss

neuropathic pain were excluded, of which 22 were diagnosed with possible neuropathic pain and two with improbable neuropathic pain [13]. This can be justified by the type of sample (large and heterogeneous) or by the fact that the diagnosis was considered after the physical examination during patient inclusion. The words in the affective group according to McGill's questionnaire were also used less often by patients with a diagnosis of neuropathic pain or possible neuropathic pain. The symptom more commonly mentioned was continuous superficial pain or pain secondary to touch, brushing, or cold [11].

Bedside exam

The site, quality, and intensity of pain should be evaluated, with identification of positive and negative signs and symptoms. Neuropathic pain can be spontaneous or provoked. Spontaneous pain is usually burning, intermittent or paroxistic, and includes dysesthesias. Induced pain (hyperalgesia or allodynia) can be seen after thermal, chemical, or mechanical stimulus. Evaluation of the motor, sensorial, and autonomous system is necessary. Tactile, thermal (hot and cold), and vibratory sensitivity should be investigated with simple instruments.

Thus, in the analysis of neuropathic pain, the following investigations should be routinely performed:

- Static mechanical allodynia by mild manual pressure on the skin;
- Punctiform allodynia by pinprick with Von Frey filaments;
- Dynamic mechanical allodynia by brushing the skin;
- Deep somatic mechanical allodynia by mild manual pressure;
- Thermal cold allodynia by contact with objects at 20°C;
- Mechanical heat allodynia by contact with objects at 40°C;
- Mechanical pinprick hyperalgia;
- Cold hyperalgia by contact with acetone;
- Heat hyperalgia by contact with objects at 46°C.

Pain secondary to touch, cold, or brushing is more common in patients with neuropathic pain.

INVESTIGATION

Laboratories tests

Neurophysiologic responses to nociceptive stimuli, such as nerve conduction and somatosensorial evoked potential studies, can identify, locate, and quantify the injury along central or peripheral sensorial pathways, although they do not evaluate nociceptive function [19].

Radiation and LASER, which releases radiating heat pulses for the selective stimulation of Aδ and C fibers, are used preferentially. Through investigation a consensus that the delayed response to evoked potentials by LASER (Aδ-LEPs) is nociceptive in nature was reached [20,21].

Ultra-delayed response by activating C fibers is technically more difficult to record and is little used in clinical studies. The involvement of small fibers is characteristic of painful neuropathies. Skin biopsy reveals minimal invasion, being useful to quantify the density of intradermal fibers and it is very good to define the prognosis [22].

QUANTITATIVE SENSORY TESTING

Quantitative sensory testing (QST) assesses the perception in response to a controlled-intensity external stimulus. The pain threshold is detected after the increasing and decreasing painful stimuli applied on the skin [23].

Mechanical sensitivity to tactile stimulus is measured with filaments that produce:

- Graduated pressure (Von Frey filaments);
- Pinprick sensation (needles);
- Vibration sensation (electronic vibrometer).

Thermal sensitivity is measure through the thermoelectric effect with devices.

Quantitative sensory testing is useful in the early diagnosis of diabetic neuropathy, when nerve conduction studies cannot demonstrate the presence of small fiber neuropathy [5]. In these patients, the QST can reveal thermal (hot or cold) sensorial dysfunction in the foot, with increased threshold activity of C fibers. However, this finding is not predictive for the presence or intensity of pain. QST is not specific for neuropathic pain – occasionally changes can be observed in rheumatoid arthritis and arthomyalgia – but it can quantify allodynia and thermal or mechanical hyperalgia.

Questionnaires

Several questionnaires for neuropathic pain have been validated, including the NPQ, IDPain, and PainDetect [14]. The presence of dysesthesias, autonomic dysfunction, associated with pain paroxysms and altered sensitivity, is associated with neuropathic pain. PainDetect has been validated for patients with lumbar pain and it has an 80% sensitivity and specificity [24].

History data, such as physical examination, are used both in LANSS and DN4 with elevated sensitivity and specificity [25,26].

In StPEP a combination of six questions with ten physical tests are used. This questionnaire can differentiate between several phenotypic pain manifestations, reflecting individual pathophysiologic mechanisms of neuropathic pain, with possibility of specific treatment. The sensitivity and specificity of the StPEP are approximately 90% for lumbar pain [27].

In neuropathic pain symptom inventory (NPSI), there is an association between positive manifestations and neuropathic pain in specific diseases [28]. For example:

- Trigeminal neuralgia with electrical shocks;
- Post-herpetic neuralgia with burning pain, allodynia by brushing, and absence of deep pain, dysesthesia, or paresthesia;
- Brachial plexus avulsion or amputation of a limb with pain paroxysms like electrical shock and stabbings.

Electrophysiology study

Electroneuromyography (ENMG) allows the definition of the injury site (troncular, radicular, plexular, or the body of sensorial or motor neurons), determination of the injury mechanism (axonal or demyelinating), orientation of the etiologic diagnosis, and the establishment of the prognosis [4]. In the presence of motor conduction delay or blockade in areas of anatomical narrowing with spaces with hypersensitivity to pressure on the physical examination, one should suspect of hereditary neuropathy. Conduction velocity blockades also suggest demyelinating neuropathy common in acute and chronic polyradiculoneuropathy and motor neuropathies. However, these changes are out of the point of nerve compression, they are persistent and proximal in motor neuropathies and transitory in polyradiculoneuropathies. On the other hand, the severity of neuropathy is characterized by reduction in the amplitude of motor and sensorial potential and motor and sensorial conduction velocity, and by active denervation on electromyography (fibrillations and positive slow waves) [4,8].

Small fiber neuropathies are difficult to diagnose by ENMG, and other methods are needed. Electroneuromyography can be normal [4]. In acute axonal polyneuropathy changes in sensorial and motor potentials associated with normal motor pathways and neurogenic changes associated to denervation (fibrillations and slow positive waves) are seen. One should consider the axonal forms of Guillain-Barré syndrome, *Campylobacter jejuni* infection, acute intermittent prophyria, lithium, arsenic and thalium intoxication, alcoholic and diabetic neuropathies, uremic polyneuropathies, and necrotizing vasculitis [4,8].

In demyelinating polyneuropathies, diffuse delay of nerve conduction, elongation of F-waves, conduction blockades, dispersion of the motor amplitude potential, and length-independent multifocal changes are seen. Guillain-Barré syndrome or diphtheria should be considered [29].

In motor selective neuropathies changes in motor neurons are observed. It is common in acute polyradiculoneuropathies and multifocal neuropathies associated with conduction blockade affecting mainly the upper limbs in the spinal forms of distal amyotrophic and toxic especially by lead [30].

In neuropathies changes in motor (cellular body of motor neuron) or sensorial potentials are observed in ENMG. In multiple mononeuropathies axonal changes can be observed in several nerve trunks. It is common in diabetes mellitus, lymphomas, paraneoplastic syndromes, polyarteritis nodosa type of rheumatologic disorders, in Churg-Strauss disease, and Wegener's disease [4,30].

Autonomic Nervous System Examination

Autonomic nervous system examination consists of the assessment of cardiac function by checking systolic blood pressure after changing position (a reduction greater than 30 mmHg) and diastolic blood pressure after exercise (increase lower than 16 mmHg), or measurement of PR interval on ECG (variation in heart rate at rest, with deep breathing, change in position, and Valsalva maneuver) [6].

Sudomotor function can be analyzed with surface electrodes placed on palms and soles. After sound or electrical stimulation the amplitude of cutaneous sudomotor response is measured. If this response is absent or reduced by 50% these fibers of the autonomic nervous system are compromised. This is not a quantitative test [31].

Laboratory tests will depend on the suspected diagnostic [4,5,8,16,18,30]. The following tests should be performed when the diagnostic hypothesis is:

- **Inflammatory disease:** complete blood count, ESR (erythrocyte sedimentation rate), and C-reactive protein;
- **Metabolic syndrome:** fasting and postprandial glucose level, glycosilated hemoglobin, BUN, creatinine, T3, T4, TSH, cholesterol, and triglycerides;
- **Toxic or infectious causes:** AST, ALT, GGTP, 24-hour urine, and samples of nails and hair for analysis;
- **Nutritional deficiency:** vitamins;
- **Lyme disease:** hepatitis serology, HIV, HTLV;
- **Light chain monoclonal gammopathy:** protein immunoelectrophoresis, cryoglobulin;
- **Mediastinal masses or interstitial syndrome:** Chest X-ray;
- **Intermittent acute prophyria:** δ-aminolevulinic acid and porphobilinogen;
- **Lupus, Gougerot-Sjögren syndrome, or Wegener's disease:** antinuclear antibodies;
- **Celiac disease:** specific antibodies;
- **Paraneoplastic syndrome:** anti-Hu, anti-Ri, anti-amphiphysin, and anti-VPS antibodies;
- **Motor neuropathies with conduction blockade:** anti-GM1 IgM antibodies;
- **Guillain-Barré:** antibodies;
- **Miller-Fisher syndrome:** antibodies.

In the CSF, there is an increase in proteins in patients with polyradiculoneuropathies, paraneoplastic neuropathies, or diabetes mellitus. Lymphocytosis is commonly seen in lymphomas, HIV infection, or Lyme disease. The presence of abnormal cells and anti-neuronal antibodies suggest a neoplastic origin of the neuropathy [4,17].

It is possible to detect lung carcinoma, lymphoma, or other systemic diseases in positron emission tomography. Molecular biology tests should be requested with precise clinical and electrophysiological criteria. It is possible to perform biopsies of fat or muscle in neuropathies that develop during amyloidosis [4,32,33].

Salivary gland biopsy is useful in the diagnosis of Gougerot-Sjögren syndrome, sarcoidosis, amyloidosis, and vasculitis. Bone marrow biopsy is important in the diagnosis of lymphoma, monoclonal gammopathies, and POEMS syndrome [4,17].

Indications for neuromuscular biopsies are rare especially after the advances seen in molecular biology [4,34,35]. They are indicated in vasculitis, amyloidosis, sarcoidosis, tumor infiltrations, leprosy, atypical forms of inflammatory polyradiculoneuritis, and in specific hereditary neuropathies [4].

In diabetic neuropathy, skin biopsy is useful to determine abnormalities of fibers with little myelin. There is a reduction in the density of C fibers. Patients with few signs of peripheral neuropathy, but with complaints of recent onset of pain may have C fiber abnormalities. Abnormalities may not be observed in those with advanced neuropathy. Patients with pain show degeneration and regeneration of thin myelinated fibers and in those without pain there is a reduction in the density of C fibers [4,6,8,16-18].

TREATMENT

Pain treatment should be multimodal including pharmacologic and non-pharmacologic techniques. However, therapeutic recommendations should be based on clinical evidence and supported by controlled clinical studies [15,36-49]

The objectives are:

- Accurate diagnosis of neuropathic pain, with use of instruments;
- Identification and treatment of other associated diseases that might contribute for the clinical manifestations of neuropathic pain;
- Recognition of other morbidities that frequently complicate the clinical evolution of neuropathic pain, such as depression, anxiety, and sleep disorders;
- Improving physician-patient relationship, explaining the disease, expectations of the outcome, and side effects;
- Orientation on non-pharmacologic techniques, including stress reduction, sleep improvement, and physiotherapy;
- Understanding the differences in pharmacodynamic effects of the different agents;
- Evaluating the cultural influence (exercise, diet), alcohol and smoking, and associated diseases (obesity, metabolic disease, kidney and liver failure) on the results of treatment.

Administration of drugs should always start with oral preparations, being careful not to associate drugs with the same mechanism of action. The choice of drug should be based on its characteristics, pharmacokinetic, and pharmacodynamics, considering the clinical experience, risks of side effects, physical dependency, abuse, or risk related to excessive doses. Furthermore, it is important to evaluate contraindications in specific diseases or the possibility that the agent chosen is also effective in the treatment of depression, anxiety, or insomnia. Drug combinations can promote additive and synergistic effects. One should not forget the side effects, risks of drug interactions, and cost [36].

Treatment of neuropathic pain requires the use of drugs that reduce neuronal hyperexcitability through the following actions [37]:

- Blockade of sodium and calcium channels;
- Increase in GABAergic transmission;
- Inhibition of the release of glutamate;
- Inhibition of the formation of nitric oxide;
- Increase in serotonergic action.

The clinical efficacy of different therapeutic options can be compared by calculating the number needed to treat (NNT), the number of patients receiving a specific drug to obtain a 50% reduction in pain severity in one patient. The lower the NNT the better is the drug efficacy. On the other hand, the number needed to harm (NNH) indicates how many patients are necessary to obtain major or minor side effects in one patient. In this context, adequate medications to treat neuropathic pain should have an NNT between two and six [50].

Drugs are considered:

- **First line drugs** are those whose efficacy in neuropathic pain has been established in randomized clinical studies (class A recommendation) and whose results are consistent with the clinical experience of the authors;
- **Second line drugs** are those whose efficacy in neuropathic pain has been established in several randomized studies (class A recommendation), but there are reservations on the use of the drug compared to first line drugs based in the authors experience;
- **Third line drugs** are those that only one randomized clinical study showed efficacy or the results of two or more randomized clinical studies are inconsistent (class B recommendation), but the authors accept that, in special circumstances, the drug could be a reasonable treatment option.

These consensus guidelines have not been proposed to be used in pediatric patients and those with trigeminal neuralgia. Many patients treated with a single effective drug do not have satisfactory pain relief and patients may benefit from the use of effective drug combinations [51].

FIRST LINE DRUGS

Antidepressants that inhibit the reuptake of noradrenaline and serotonin

Tricyclic antidepressants are effective in several different types of neuropathic pain. They have the lower NNT and are indicated, as well as selective serotonin-noradrenaline reuptake inhibitors (SNRI), as first line drugs with class A recommendation (based on several controlled, randomized, double-blind studies) [36,39,40,42-45].

The efficacy of tricyclic antidepressants in the treatment of neuropathic pain has been well documented in several clinical trials [52-57]. Amitriptyline particularly is effective in diabetic neuropathic pain and post-herpetic neuralgia, and it can be beneficial in other neuropathic pain syndromes, but one should be careful when using it in patients at risk of adverse events [58].

In polyneuropathies the NNT of tricyclic antidepressants is approximately two [59]. In post-herpetic neuralgia the NNT is 2.5 [38,39]. The independent NNT of the syndrome is 2-3 for tricyclic antidepressants [60].

The effective dose of amitriptyline is considered to be 25-75 mg.day^{-1} [60]. The dose of nortriptyline is usually 25-150 mg.day^{-1} [60]. Secondary amines (nortriptyline or desipramine) have less adverse effects. Adverse effects include dry mouth, orthostatic hypotension, somnolence, tachycardia, constipation, and urinary retention.

Duloxetine and venlafaxine are selective serotonin-noradrenaline reuptake inhibitors (SNRI). They are associated with less anti-cholinergic effects and lower cardiovascular risk.

Duloxetine is effective in diabetic peripheral neuropathy. It can be used at a dose of 30 to 120 mg.day^{-1}, and nausea is a common side effect [36]. It causes drowsiness, dizziness, fatigue, insomnia, headache, sexual dysfunction, and hypertension [61].

Venlafaxine is effective in painful diabetic peripheral neuropathy and painful polyneuropathies of different origins, but not in post-herpetic neuralgia. The NNT for 150-225 mg of venlafaxine in peripheral polyneuropathy is 4.5-5.0 [60]. Venlafaxine can cause cardiac conduction abnormalities, increase blood pressure, and orthostatic hypotension.

Calcium channel alpha-2-delta ligands (gabapentin and pregabalin)

Gabapentin and pregabalin have been used for pain relief in post-herpetic neuralgia and diabetic neuropathy, being considered first line drugs for the treatment of neuropathic pain. Their action is in the alpha-2-delta subunit of voltage-dependent calcium channels inhibiting the release of neurotransmitters. In studies with gabapentin in doses up to 2,400 mg.day the NNT is approximately four [62].

The efficacy and tolerability of pregabalin seem to be similar to those of gabapentin. One can use a dose of 150 mg.day^{-1}, which can be titrated up to 300 mg.day^{-1} after one to two weeks. For patients who can tolerate 300 mg.day^{-1} but who do not experience enough pain relief, the dose can be titrated up to 600 mg.day^{-1}. The time required to titrate to a higher total dose is smaller than for gabapentin [51]. The NNT of pregabalin for diabetic neuropathy and post-herpetic neuralgia, with doses ranging from 150 to 600 mg, is approximately four. Drowsiness, dizziness, and sedation may be present [36,37].

LOCAL ANESTHETICS

Intravenous lidocaine infusion is indicated for relief of neuropathic pain of different causes with adequate effects [63-65]. It can be used in association with systemic drugs.

The NNT of lidocaine patches in the treatment of post-herpetic neuralgia is 4.4 [60,65]. The patch is also useful in other painful neuropathic syndromes [65]. Topical lidocaine is more appropriate to treat localized pain [66].

SECOND LINE DRUGS

In specific circumstances they can be considered first line. Tramadol and opioids are effective in patients with different types of neuropathic pain. As for long-term safety regarding first line drugs, they are recommended for patients who do not obtain pain relief with them. However, these drugs are recommended as first line treatment in patient with acute neuropathic pain, cancer-induced neuropathic pain, and episodic exacerbations of severe neuropathic pain, as well as when there is a need for immediate pain relief during titration of one of the first line medications.

Tramadol

Tramadol is effective in several painful neuropathic syndromes. It is a weak *mu* receptor agonist and it inhibits the reuptake of serotonin and noradrenaline in spinal synapses. Abuse seems to be lower than with opioids. Treatment with tramadol is usually initiated with 50 mg once or twice a day, which is gradually increased as needed up to 400 mg.day^{-1} [51].

Opioids

Opioids promote pain relief in different types of neuropathic pain with similar efficacy to that of tricyclic antidepressants and gabapentin. However, due to concerns regarding long-term safety including the risks of hypogonadism, immunologic changes, and misuse or abuse opioids are not recommended for routine use as first line drugs. They can be used during titration of first line drugs. One should not forget the general rules for the administration of opioids for chronic non-oncologic pain.

For post-herpetic neuralgia the NNT of morphine is 2.5 [40]. In the treatment of post-herpetic neuralgia and diabetic neuropathy the NNT of oxycodone is 2.6 [40]. Methadone can be

safely used for prolonged time, since its risk of inducing dependency and tolerance is lower and its action is at the level of NMDA (N-methyl-D-aspartate) receptors.

The probability to misuse or abuse opioids is greater in patients with personal and family history of substance abuse. One should take into account this risk before initiating treatment with opioids [51]. Opioids can cause hypotension or hypertension, palpitations, sinus bradycardia, and orthostatic hypotension. Methadone can cause an increase in the QT interval [61].

THIRD LINE DRUGS

Drugs that demonstrated consistent efficacy for the treatment of neuropathic pain, alone or not, in several randomized clinical studies. These drugs are indicated for patients who do not tolerate or who do not have pain relief with first and second line drugs. Third line drugs include [51]:

- Antidepressants: bupropiona, citalopram, and paroxetine;
- Anticonvulsant: carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid;
- Capsaicin;
- Dextrometorphan;
- Memantine;
- Mexiletine.

ANTIDEPRESSANTS

The NNT of serotonin reuptake inhibitors for neuropathic pain is approximately seven [38,60].

ANTICONVULSANTS

Carbamazepine is indicated especially in cases of generalized head and neck pain. It is a first line drug in the treatment of trigeminal neuralgia. In a study with patients with diabetic neuropathy the NNT was approximately two with doses of 200 to 600 mg [38].

Oxcarbamazepine can be an alternative in case of intolerance to carbamazepine, since it has similar analgesic activity with fewer side effects. In controlled studies some authors observed analgesia with lamotrigine in the treatment of post-herpetic neuralgia, and with oxcarbamazepine in several types of neuropathic pain. The NNT in trigeminal neuralgia in doses of up to 400 $mg.day^{-1}$ was approximately two, while in diabetic neuropathy, four [38].

Regarding topiramate, the results in neuropathic pain are controversial. There are several studies in diabetic neuropathy with NNT of about seven [38].

Other anticonvulsants such as valproic acid and hydantoin are not commonly used. Some authors have used hydantoin in diabetic neuropathy observing a NNT of two [67]. Studies with valproic acid are controversial, but there are reports on its efficacy in diabetic neuropathy and post-herpetic neuralgia with dose of up to 1,200 mg. Tolerability is the greatest problem in using anticonvulsants. These drugs cause drowsiness, dizziness, ataxia, gastrointestinal disorders, fatigue, anorexia, nausea, vomiting, skin changes, and cognitive, liver, cardiac, kidney, and hematologic dysfunction [41].

OTHERS

Other drugs that can be effective in relieving neuropathic pain include NMDA receptor blockers (ketamine), α_2-adrenergic agonists (clonidine, dexmedetomidine), anticholinergics (prostigmine), cannabinoids, and enkephalinase inhibitors [68]. However, none of these drugs is recommended for isolated use and besides having adverse effects they are not validated by controlled clinical assays. Capsaicin is indicated in diabetic neuropathy and post-herpetic neuralgia with a NNT of 6.7 [40].

New drugs should be tested one at a time. In prolonged use, the lowest effective dose should be used [61].

PERSPECTIVES

The discovery of new agents such as selective blockers of specific sites in NMDA receptors and sodium and calcium channel blockers is expected. In the biomolecular field other drugs could be developed: cytokine blockers, blockers of trophic factors and their receptors, signal translator blockers, and immunotherapy. This challenge will contribute for the improvement and physical and social rehabilitation of countless people who suffer from chronic pain.