Multidisciplinary consensus on the diagnosis and treatment of peripheral and localized neuropathic pain in Mexico

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Abstract

Neuropathic pain is an entity that causes great disability to patients and its diagnosis and treatment is a challenge for doctors. A significant percentage of patients with neuropathic pain have restricted it to one dermatome or a specific region of the body, thus, naming it localized neuropathic pain. There are no clinical guidelines that propose recommendations for the diagnosis and treatment of regional neuropathic pain in our population. This paper describes the recommendations of a Multidisciplinary Consensus conducted with specialists from different areas involved in the diagnosis and treatment to which these patients are exposed.

KEY WORDS: Neuropathic pain. Localized neuropathic pain. Consensus. Recommendations. Diagnostic. Treatment.

Resumen

El dolor neuropático es una entidad que provoca una gran discapacidad al paciente y su diagnóstico y tratamiento es un reto para los médicos. Un porcentaje importante de pacientes afectados con dolor neuropático, lo presentan circunscrito a un dermatoma o a una región concreta del cuerpo, denominándose en ese caso dolor neuropático localizado. No existen guías clínicas mexicanas que postulen recomendaciones para el diagnóstico y tratamiento del dolor neuropático regional en nuestra población. En este artículo se exponen las recomendaciones de un Consenso Multidisciplinario realizado con especialistas de distintas áreas implicadas en el diagnóstico y tratamiento de estos pacientes.

PALABRAS CLAVE: Dolor neuropático. Dolor neuropático localizado. Consenso. Recomendaciones. Diagnóstico. Tratamiento.

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Introduction

Neuropathic pain (NP) is a syndrome with specific characteristics; it is the result of damage or disease that affects the somatosensory system. It can be classified according to its location or distribution:¹

Neuropathic pain classification	
Location	Distribution
Central	Localized
Peripheral	Diffuse

Regarding all the types of pain that a patient can present, NP is the one that produces more disability since it tends to become chronic, to cause severe functional limitations, and is frequently refractory to treatment. Hence, timely diagnosis and treatment should be performed.

Localized neuropathic pain (LNP) is taken to mean a NP model that occurs in consistent and circumscribed areas no larger than a piece of letter-size paper (21.6 x 27.9 cm²).² It presents as maximum pain associated with abnormal skin sensitivity and/or spontaneous symptoms, which are characteristic of neuropathic pain, e.g., burning pain.

NP is estimated as affecting 2% of the population in Latin America.³ The most frequent clinical cases reported during medical consultations are low back pain with a neuropathic component representing 34.2% of NP cases, diabetic neuropathy in 30.4% of cases, postherpetic neuralgia in 8.7% and postsurgical neuropathic pain in 6.1%.

LNP etiology is: (Fig. 1).

LNP treatment includes topical and/or systemic drugs and other non-pharmacological measures. The regional or circumscribed characteristics of LNP allows for the use of topical or local drugs, which constitutes a different approach from other NP models. However, there is a need to create new effective and safe therapeutic options. Recently, Mexico has authorized the marketing of one of these new drugs, the 5% lidocaine patch, for LNP topical treatment.

Given the special characteristics of LNP, as well as the complexity involved in its correct diagnosis and treatment, a bibliographic database search was conducted in order to identify and locate therapeutic guidelines for this pathology.

The literature on this subject is scarce and most of these guidelines appear on reviews written in English and focused on LNP management with different health

situations that are clearly different from those in Mexico. Though there are publications written in Spanish, most of them have been made in contexts that are not similar to the Mexican health environment.

Thus, a multidisciplinary group of national specialists was convened in order to develop and adapt recommendations as reference guidelines for the definition, diagnosis and management of LNP, so that group consensus can be finally reached.

In this way, the main objective of this Multidisciplinary Consensus of Diagnosis and Treatment of Peripheral and Localized Neuropathic Pain was to generate a document for doctors who, in their daily practice, treat patients with this pathology, which helps them to optimise the clinical results since there are currently no guidelines for the diagnosis and specific treatment of LNP.

Literature search was performed initially on PubMed, MEDLINE, Cochrane databases with the terms “Neuropathic Pain”, “Localized Neuropathic Pain”, “Clinical Guidelines”, “Diagnosis and treatment”, “Algorithms”, limited to the last 5 years. The publications identified were submitted to the panel of experts for review before the meeting was held.

Subsequently, following the Delphi methodology,⁴ an electronic questionnaire was sent prepared specifically for this consensus, which should be answered within a maximum period of 48 hours. The answers to this questionnaire were quantified and weighted, this being the first voting session.

Because only one answer could be given to each question, an initial consensus was not reached in any of them. During the meeting with all the panelists, all the answers were discussed and analyzed in working groups, in order to draft a recommendation. Then, these recommendations were exposed to and justified for all the panel of experts. This opened a venue for discussion in case of discordant views.

The next step consisted of voting on the proposed consensus proposals. Consensus was considered when 80% of the participants reached an agreement. If voting on the matter under consideration was <80%, new opinions and comments were incorporated to the matter, and a new voting session ensued.

The document presented herein was the object of consensus in the first voting session on all the questions, except for the LNP diagnosis and treatment algorithm, in which consensus was reached in the second voting session. Consensus level was 100% in all the questions discussed, except for the need of skin biopsy for PNL diagnosis, and the parameters to

Figure 1. Etiology of localized neuropathic pain (LNP).

be considered in the control visit (89% and 88% consensus level respectively).

Neuropathic pain definition

There are several definitions for NP. The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG-IASP) defines it as “pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system”.

This panel of experts recommends this definition, recognizing that it is the most accepted internationally.^{5,6}

Recommendation: Neuropathic pain is pain that arises from a lesion or diseases affecting the somatosensory system at the central or peripheral level (100% consensus).

NP classification

Through literature review, we found that neuropathic pain is classified according to its anatomical location or etiology.

The working group responsible for proposing a recommendation in this regard stated that the most recently consulted publications suggest its classification according to etiology.^{6,8} One of these publications was issued by the Mexican Association for the Study and Treatment of Pain (AMETD).

The panel concluded that the classification by etiology as well as by anatomical location are acceptable. It considered that the group recommendations should not be limited to a single option; hence, consensus was reached to recommend that criteria for NP classification should include etiology and location.

Recommendation: NP must be classified according to its etiology and location (100% consensus).

Localized Neuropathic Pain -LNP-

In different publications, LNP is defined as a special type of peripheral neuropathic pain in consistent and circumscribed area(s) of maximum pain, associated with abnormal skin sensitivity and/or spontaneous symptoms that are typical of neuropathic pain.¹ Its origin can be traced back to a lesion or disease of the the somatosensory system affecting a small body area (equal or smaller) to a letter paper size (DinA4) and which, due to its limitation, is initially treated with specific topical painkillers.⁹

Regarding the demarcation of the anatomical area, the original publication (Ralf Baron 2008) includes the use of an A4 paper sheet as an essential part of its diagnostic tool. It was later disclosed that the size of the affected area could be equal to or smaller than a letter paper size. Given this small variation (letter paper size: 21.6 cm x 27.9 cm; A4 paper size: 21 x 29.7 cm) the Mexican consensus panel suggests the letter paper size be set out as reference, as it is widely used in this country.

Recommendation: LNP is a pain characterized by being consistent and circumscribed to an area of letter paper size. (100% consensus).

Epidemiology

NP epidemiology in Mexico was the subject of intense debate among the members of the panel of experts.

The working group concluded that LNP is the most common form of NP, affecting 60% of patients with NP.⁹ Conversely, 7-8% of adults in a population study, who present chronic pain, experience pain with characteristics that correspond to NP. Sixty percent (60%) of this population meet the criteria for LNP.¹¹ Diabetic neuropathy and postherpetic neuralgia are the two most frequent and prevalent causes of PNL.¹²⁻¹⁸

During the discussion with the entire group, it became clear that there are no statistical data on NP prevalence and incidence in Mexico. In general, the data used for the Mexican population are based on extrapolated data published in other countries with similar population features. However, the characteristics of the Mexican population differ from the Anglo-Saxon population, mainly due to miscegenation and a different genetic expression. Therefore, the group of experts deems it necessary to make an inference of the existing data from other countries in order to present a recommendation for an estimated percentage of patients who are likely to present LNP symptoms in Mexico.

Recommendation: "There are no statistics in Mexico, but considering international statistics it can be inferred that 7-8% of the Mexican population suffer from chronic pain of the neuropathic type corresponding to LNP in 60% of cases. (100% consensus).

Pathophysiology

NP is the result of changes that occur in the generation and normal transmission of impulses of pain. These alterations have been detected in the peripheral nerve endings, in the dorsal root ganglion (DRG), in the posterior grey column of the spinal cord and in the somatosensory cortex, sites in which remaining normal neurons undergo alteration of their electrical properties. The increase in the expression of neural growth factors, cytokines and their receptors produces spontaneous and/or facilitated activity of these neurons.^{19,20}

The relationship between disease, mechanism and symptoms can be unpredictable. The pain caused by various diseases can be due to common mechanisms. Conversely, it should be borne in mind that a mechanism could be responsible for many symptoms and the same symptom observed in two different patients could be caused by different mechanisms. Moreover, the pattern of mechanisms and symptoms in a single patient may change over time.

Thus, although LNP causes have multiple factors, the recommendation of the panel of experts is that the most relevant ones should be considered.

The main causes of LNP are those produced by systemic or metabolic diseases (mainly diabetic neuropathy), those of infectious origin (mainly postherpetic neuralgia) and those of traumatic and surgical origin. In this sense, the existing literature is sufficiently abundant and categorical, so there are no grounds for debate in such regard.^{8,10,21}

Recommendation: The main causes of LNP are those produced by systemic or metabolic diseases (mainly diabetic neuropathy), those of infectious origin (mainly postherpetic neuralgia) and those of traumatic and surgical origin (100% consensus).

Clinical diagnosis

The IASP algorithm, adopted globally by physicians involved in the diagnosis and treatment of neuropathic pain, distinguishes between possible, probable and definite NP. In this sense, NP is deemed possible when there is a clinical history that suggests relevant nerve lesion or disease, and from a neuroanatomical view, the distribution of pain is concordant. In addition, if the neurological exam shows some positive or negative sensory sign in the area of the possible affected nerve, NP is deemed probable. Neurophysiological confirmation will only be required in some patients through diagnostic imaging for NP be deemed definite.

The panel of experts, after reviewing the existing literature, indicated that all diagnostic tools mentioned therein should be used. For the diagnosis of LNP, it was emphasized that a concordant distribution of pain should be verified from a neuroanatomical viewpoint, in addition to the pain being located in a circumscribed and consistent area. Moreover, the pain should be in a dermatome or in a specific cutaneous nerve to be deemed as such. It was also pointed out that there should be a clinical history suggestive of a lesion or nervous disease as the cause of pain and that a specific part of the physical examination should pay special attention to the neurological examination, by emphasizing the presence of positive and/or negative sensory signs and symptoms.^{10,21}

Recommendation: For the clinical diagnosis of PNL, a clinical history suggestive of a nerve lesion or previous nervous disease is necessary to verify that the distribution of pain is concordant from a neuroanatomical viewpoint as well as the conduction of a neurological examination emphasizing the presence of

Figure 2. Most usual form of diagnosis and treatment of patient with LNP: there was a unanimous, 100% consensus.

positive and/or negative sensory signs and symptoms (100% consensus).

Pain assessment scales

During this consensus, different pain assessment scales were grouped into specific scales for NP, scales that distinguish NP from Nociceptive Pain.

Regarding all the possible pain scales that can be used, general scales such as NP4, Pain Detect or LANSS do not allow for, by themselves, specific LNP diagnosis. However, a specific LNP scale has been published and validated, which is the Diagnostic Tool scale.^{22,23}

Recommendation: Use the Diagnostic Tool scale when specific LNP assessment is required (100% consensus).

Skin biopsy

In the first vote, 54.5% of the panel of experts indicated that skin biopsy is not necessary in a patient with a possible diagnosis of LNP, 27.3% indicated that this does not provide any additional information whilst 9.1% said it should be performed and 9.1% said it must be carried out but seldom.

The group of experts indicated that recommending a skin biopsy is not necessary for the vast majority of patients with possible LNP. Only in a few very select and infrequent cases, especially those in which usual neurophysiological examinations are inconclusive, skin biopsy could be useful.^{24,25}

However, during the discussion, some members of the panel of experts indicated that it was important for the detection of antibodies targeting cytoplasmic proteins, while others indicated that it is a test not performed frequently but should be included in the recommendations for diagnostic tests. In this case, the consensus was not reached unanimously, as 89% of the panel of experts agreed that it is not necessary to recommend a skin biopsy and 11% did not agree.

Recommendation: It is not necessary to recommend skin biopsy to the vast majority of patients with possible LNP (89% consensus).

Additional topic

Patient journey with LNP in order to obtain an adequate diagnosis and treatment (patient Journey)

The process through which patients come to a LNP diagnosis, and then have proper treatment, according to the panel of experts, can be seen in Figure 3 and has been based on the experience of the panel members, as well as in the existing literature (Fig. 2).^{26,27}

Guidelines and recommendations

For the diagnosis of LNP, the group of experts recommends the use of the NeuPSIG-IASP guidelines as they are based on a consensus of

international experts and supported by the IASP. In addition, it is one of the most widely used diagnostic and treatment guidelines internationally. There are other guidelines that may also be useful for LNP diagnosis, such as the guidelines of the European Federation of Neurological Societies (EFNS) or the Latin American Federation of Associations for the Study of Pain (FEDELAT).

Recommendation: Use the NeuPSIG-IASP guidelines for the diagnosis of LNP. (100% consensus).^{2,28-30}

Pharmacological and non-pharmacological management for LNP

First-line systemic treatment for LNP

One of the existing problems regarding LNP is its pharmacological management and non-pharmacological measures. International guidelines for the management of LNP indicate that different types of systemic drugs can be used with different mechanisms of action, all of which are deemed useful.

First-line pharmacological drugs include gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants (amitriptyline, imipramine and nortriptyline), selective Inhibitors of Serotonin and Noradrenaline Re-uptake (duloxetine, venlafaxine).^{29,30} In the case of first-line therapy in trigeminal neuralgia, and its only current indication recommends carbamazepine and oxcarbazepine²⁷⁻³³ and in the case of localized neuropathic pain, 5% lidocaine patches²⁸ and 8% capsaicin patches are recommended as first or second-line therapy.²⁹

In all the guidelines that have been consulted, tramadol is the only option included in the group of opioids. Similarly, ketamine is not considered as a drug of first choice.

Recommendation: Use tricyclic antidepressants (amitriptyline, imipramine and nortriptyline), dual-action antidepressants (duloxetine, venlafaxine), antiepileptic gabapentinoids (gabapentin, pregabalin) and tramadol among opioids, as first-line systemic treatment for LNP (100% consensus).^{10,31}

Ideal treatment for LNP

According to the reviewed studies, the first-line therapy for LNP is 5% lidocaine patches or 8% capsaicin patches. Both treatments have shown efficacy, with a low level of side effects and without significant drug interactions.

Whilst both treatments are comfortable, lidocaine 5% may be easier to use, since the patient can be treated on an outpatient basis.

Recommendation: Use as topical painkillers as first-line non-systemic treatment such as 5% lidocaine patches or 8% capsaicin patches. Opioids should be used as a second-line therapy for rapid or delayed action. (100% consensus).⁵

Patient control/follow-up

Recent publications indicate that the maximum response to the treatment is expected to be between the 2nd and the 4th week. If there is no improvement in pain after the fourth week of starting treatment, one should think about a lack of response and clarify the reason for this.¹⁰ Recommendation: Follow up of patients every two to four weeks (100% consensus).

Parameters that should be considered in the control visit

As for patient control, assessment should not be limited to a single parameter, as they are usually interrelated. Thus, experience and evidence show that the appearance of adverse effects represents a limiting factor of the treatment being related to the type of drug or its dosage. Conversely, patient satisfaction will be determined by the treatment effectiveness, absence of adverse effects and the reduction of pain.

Recommendation: During the control visit the pain intensity must be monitored, the dosage, drug dosage, adverse effects and patient satisfaction should be assessed (88% consensus).

Algorithm

The IASP algorithm is presented for the treatment of LNP,³² as a possible algorithm to be followed in the present recommendations. No agreement was reached during the first voting session. 100% consensus was only reached in the second voting session (Fig. 3).

Summary of recommendations

1. Neuropathic pain is pain that arises from a lesion or diseases affecting the somatosensory system at the central or peripheral level.
2. NP must be classified according to its etiology and location.

Figure 3. Algorithm of diagnosis and treatment of localized neuropathic pain. Based on reference.³²

- LNP is pain that is characterized by being circumscribed and consistent.
- There are no statistics in Mexico, but considering international statistics, it can be inferred that 7-8% of the Mexican population suffer from chronic pain of the neuropathic type corresponding to LNP in 60% of cases.
- The main causes of LNP are those produced by systemic or metabolic diseases (mainly diabetic neuropathy), those of infectious origin (mainly postherpetic neuralgia) and those of traumatic and surgical origin.
- For the clinical diagnosis of PNL, a clinical history suggestive of a nerve lesion or previous nervous disease is necessary to verify that the distribution of pain is concordant from a neuro-anatomical viewpoint as well as the conduction of a neurological examination emphasizing the presence of positive and negative sensory signs and symptoms.
- It is recommended to use the Diagnostic Tool scale when specific LNP assessment is required.
- It is not necessary to recommend skin biopsy to the vast majority of patients with possible LNP.

9. It is recommended to use the NeuPSIG-IASP guidelines for the diagnosis of LNP.
10. As the first line of systemic treatment of LNP, tricyclic antidepressants are recommended (amitriptyline, imipramine and nortriptyline) and dual ones (duloxetine, venlafaxine), gabapentinoid antiepileptics (gabapentin, pregabalin) and opioid analgesics, tramadol.
11. As a first line of topical treatment, the use of lidocaine 5% or capsaicin 8% patches is recommended 8%.
12. Patients under treatment should be followed up every 2-4 weeks.
13. It is recommended that pain intensity, drug dosage, adverse effects and patient satisfaction should be assessed during the control visit.
14. It is recommended to use the treatment algorithm of Allegri et al. (Figure 3).³²

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