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Neuropathic pain and treatment
Many questions still hang in the air

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abstract

Objective: to review the particular characteristics of neuropathic pain and propose criteria for adequate management based on current evidence. **Material and methods:** a critical appraisal was made based on the data from meta-analyses, clinical trials, and observational studies available on Medline and the data bases of the FDA and EMA, updated upto January 1st, 2011. **Results and conclusions:** neuropathic pain is characterized by a diverse etiology and the presence of multiple and complex symptoms. Pharmacological management has very limited efficacy. In our Health System, the first line management option is tricyclic antidepressants, and the alternatives include gabapentin and duloxetine. Treatment should be initiated at low doses and increments should be gradual until the effective dose is reached. Combined pharmacological treatment with non-pharmacological measures such as reduction of stress, sleep hygiene and physiotherapy is recommended. **Key words:** neuropathic pain, postherpetic neuralgia, diabetic neuropathy, tricyclic antidepressants, gabapentin, duloxetine.

Introduction

Pain represents one of the most frequent motives for consultation. There are numerous proposals for a definition of pain, which in turn reflects the enormous difficulty to find a suitable and precise one. Perhaps the most accepted definition now is that proposed by the International Association for the Study of Pain (IASP), which in 1979 defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[1].

Pain therefore is both a sensation and an emotion, which leads us to consider pain as a subjective experience of great complexity in which physical and psychological factors come into play.

There are different classifications of pain with respect to duration, location, type, intensity, etc. In this review, we will focus on chronic pain and more specifically on neuropathic pain.

Chronic pain can be classified in three categories: nociceptive pain (due to tissue damage or disease), neuropathic pain (secondary to damage or disease affecting the somatosensory system) and mixed pain: where both nociceptive and neurosensorial pain co-exist.

Definition

Neuropathic pain is defined as that caused by damage or dysfunction of the nervous system. It is a neurological disorder that appears as a consequence of alterations in either or both the central or peripheral nervous systems, leading to "central neuropathic pain" and "peripheral neuropathic pain" respectively[2].

It is characterized by the presence of paradoxical sensations with pain as the dominant positive symptom, combined with a reduction in sensitivity, secondary to nerve damage, or concomitant hypersensitivity and hyposensitivity. The alterations in sensation are characteristic of this type of pain and are crucial findings in the differential diagnosis of pain affecting the patient.

An approach to the diagnosis of neuropathic pain should include the following: diagnosis of the cause of pain, identification of the type of pain, evaluation of the importance of its components, and determination of appropriate management (see table 1)

Etiology

The causes of neuropathic pain are considerably diverse. In the majority of classifications, we find two major groups according to the origin of pain (central or peripheral). Table 2 describes the pathologies that can produce this type of pain, irrespective of the origin.

Physiopathology

Nociceptors are a class of neurons in the peripheral nervous system responsible for the detection

Table 1. Differences between nociceptive pain and neuropathic pain[3].

TYPE	NOCICEPTIVE	NEUROPATHIC
Definition	Pain caused by the activation of peripheral pain receptors.	Pain caused by damage or dysfuntion of the nervous system.
Mechanism	Natural physiological nerve conduction (nociceptor)	Ectopic generation of impulses (axon membrane)
Site of symptoms	Local and referred pain	Territory of the affected nerve pathway.
Quality of symptoms	Common pain sensations	New, unknown and aberrant sensations
Management	Effective, conventional analgesia	Partial efficacy, anticonvulsants, antidepressants.

Table 2. Common causes of neuropathic pain.

Compression–entrapment	Median entrapment of the carpal tunnel Other nerve entrapment syndromes Chronic radiculopathy Spine stenosis
Trauma	Accident injuries Surgery Complex regional pain syndrome Amputation (phantom pain of an extremity) Injury to the spinal cord
Infection	Herpes zoster Infectious mononucleosis Acquired Immune deficiency syndrome (AIDS) Tabes dorsalis Diphteria Leprosy
Metabolic disorders	Diabetes mellitus Uremia Amyloidosis Hypothyroidism Porphyria
Ischemia / Vascular disease	Stroke Systemic erythematous lupus Polyarteritis nodosa
Oncological	Compresive Infiltration Metastasis Paraneoplastic Iatrogenic
Toxins	Chemotherapy agents (vincristine, cisplatin) Other drugs: nitrofurantoin, isoniazid, phenytoin, hidralazine, thalidomide Metals: arsenic, lead, gold, mercury Organic substances
Nutritional deficits	Alcohol related neuropathy Niacin Tiamine Pyridoxine
Genetics	Fabry disease Hereditary sensory neuropathy
Autoimmune	Multiple sclerosis Sarcoidosis
Others	Guillain-Barre syndrome Syringomielia Painful sensory partial seizures Recurrent or progressive polyneuropathy

Table 3. Mechanisms of neuropathic pain.

Direct stimulation of sensory pain nerves	The primary sensory nerves that transmit pain signals (type C nociceptor fibres) can be activated by compression or stretching.
Automatic discharge of damaged nerves	Damaged nerves can produce spontaneous discharges at the injured zones or at ectopic foci along the damaged nerve. This leads to continuous and burning pain that can be accompanied by lancinating, electrical or cutting-like paroxysms .
Deafferentation	The interruption of the transmission of sensations from peripheral tissue to connections in the spinal cord upto the cerebral trunk and brain. This could lead to irritability and discharges from the nerves and along the pathways above the zone of nerve damage (phantom limb).
Sympathetic mediated pain.	Any pain stimulus can induce autonomic activity with respect to the same level of the sensory dermatome of the spinal cord, leading to regional changes in temperature and circulation. Damaged and undamaged axons start to express alpha adrenergic receptors and produce discharges in response to epinephrine and norepinephrine circulating in the blood stream or released from the adrenal medulla or sympathetic post-ganglion terminations. The sympathetic axons develop connections with the dorsal root ganglion, and catecholamines released can stimulate the primary afferent fibres, producing constant pain produced by the sympathetic nervous system.
Activation of A sensory fibres	A low intensity stimulus that fires Aβ sensory fibres can lead to the release of substance P in the dorsal horn of the spine producing a nociceptive stimulus.
Lack of central inhibitory mechanisms	The posterior fibres of the spinal cord produce an inhibitory effect on the pain afferents of the lateral pathway.

and transmission of pain stimuli. Depending on the diameter, myelination and speed of transmission of the skins sensory fibres, these fibres are divided into three groups: types Aβ, Aδ and C. The nociceptors can also be classified in seven classes based on their neurochemical properties.

Studies have shown that neuropathic pain can be caused by different mechanisms simultaneously which not only originate pain but also prolong it, and involve peripheral and central nervous systems. The mechanisms of neuropathic pain are multiple and polytopic and can act all along the pathway of the nociceptive pain stimulus. Their effects can occur simultaneously at different sites of the pathway. Table 3 shows a summary of the different mechanisms involved in neuropathic pain.

Characteristics of pain

Table 4 shows the relation between positive and negative phenomena related to central and peripheral pain.

Symptoms and signs

Patients with neuropathic pain present multiple and complex symptomatology. A single patient can present more than one symptom which in occasions can be due to the same mechanism. Usually the location of the symptoms is limited to the area innervated by the affected nerve and these symptoms are difficult to describe. When describing the symptoms most patients often employ analogies.

Table 4. Positive and negative sensory phenomena related to pain.

	NEGATIVE PHENOMENA	POSITIVE PHENOMENA
Motor	Paresia, paralysis	Neuromyotonia, fasciculations, dystonia
Sensory	Hypoesthesia, hypoalgesia, anesthesia, analgesia, deafness, anosmia, amaurosis, etc.	Paresthesia, dysesthesia, pain, tinnitus, photopsias, etc.
Autonomous	Vasodilation, hypohidrosis/anhidrosis, deficit of piloerection.	Vasoconstriction, hyperhidrosis, piloerection.

Taking into account the emotional component, paresthesia is defined as an anomalous sensation which is *not unpleasant* while disesthesia is an anomalous and unpleasant sensation.

Among the spontaneous symptoms, which can either be continuous or paroxystic we find:
· **burning pain:** burning sensation
· **lancinating pain:** sensation of sharp pain of great intensity, limited by space to a concrete point, and difficult to explain or define.
· **deep pain:** sensation of oppression usually described as a sensation of great compression deep inside.

The provoked symptoms may include:
· **alodynia:** pain provoked by a stimulus that usually does not provoke pain.
· **hyperalgesia:** exaggerated response to a stimulus, which is normally painful.

Diagnosis

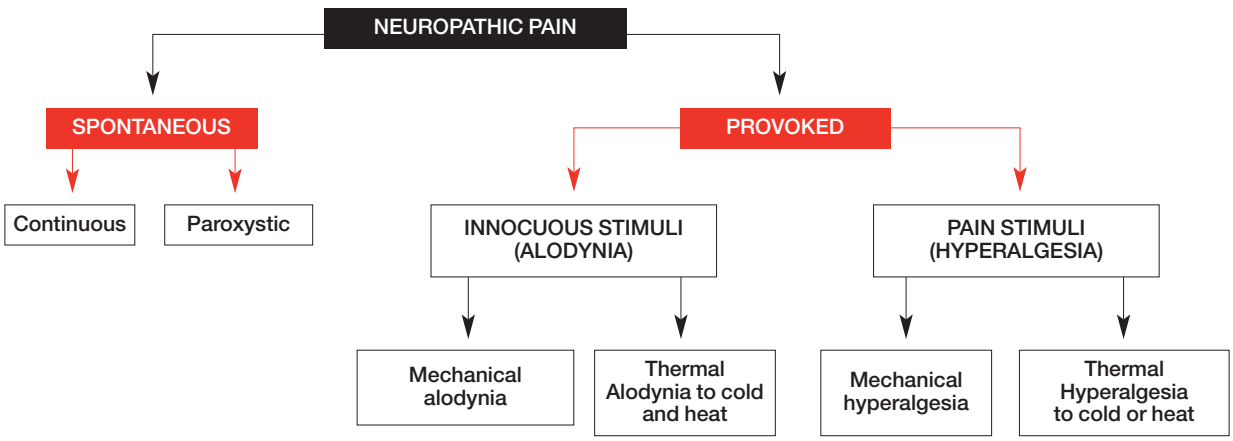
The diagnosis of neuropathic pain is a challenge in clinical practice, because pain is essentially subjective and standard tests can only offer indirect signs of pain.

In the medical literature available there are no sufficient data that give way to any specific recommendation when diagnosing neuropathic pain. Diagnosis is essentially clinical and is based on the clinical history and physical examination of the patient. Laboratory tests, imaging, electrophysiological studies may help, but in no case are they determining evidence. With these tests, not more than 10-20% of patients with a clinical diagnosis are identified as having neuropathic pain.

Verbal, numerical and visual-analogue scales are employed to evaluate the intensity of pain. The most frequently employed tool is the visual-analogue scale (VAS), in which the patient evaluates pain by marking a sign on a horizontal line where "0" represents absence of pain and "10" represents the worst possible pain one can imagine.

There are some standard questionnaires (*Neuropathic pain questionnaire, Pain detect, ID-pain, DN4*) based on the description of the symptoms made by the patient. These questionnaires

Graph 1. Signs and symptoms of neuropathic pain.



consist of a series of scales which are easy to perform by patients and whose objective is to determine whether pain is dominated by neuropathic mechanisms. In daily clinical practice these questionnaires are less frequently applied than the VAS.

The physical examination of patients should include an evaluation of the sensory, motor and somatosensory nervous systems. The sensory examination from skin dermatomes can identify deficits in nerve-skin function. To carry out this examination simple manoeuvres can be employed such as: apply a piece of cotton or wool over the skin, a needle can be used to prick the skin, a diapason over bony edge or joint and a thermal stimulus (metal object at 10-20ºC).

Responses should be classified as *normal, reduced or increased.* Evoked stimuli (positive phenomena) are classified as *alodynia* or *hyperalgesia* according to the dynamic or static characteristics of the stimuli. Moreover, motor function should be assessed though strength, tone and reflexes, and the autonomous nervous system by exploring for temperature, sweating and trophic disorders. In some specific cases, complementary tests can be employed such as nerve conduction studies, or imaging studies which can help confirm a clinical diagnosis. It should be noted that negative results of the tests do not exclude the possibility of neuropathic pain.

Types of neuropathic pain

The concept of neuropathic pain includes a large amount of pathologies with different management approaches. In this review we will focus mainly on peripheral pain, and more precisely on the classes of pain most frequently observed in our context (table 5). For this reason, mononeuropathies caused by compression, entrapment or traumatism or those with more defined treatments (ferulas, orthesis, surgery, etc.) will not be considered[4].

Diabetic neuropathy

Diabetic neuropathy is one of the most common complications of long term diabetes mellitus, and may affect more than 50% of the diabetes population[5]. There are two different pathologies affecting diabetes patients, the sensorimotor polyneuropathy and autonomic diabetic neuropathy.

Sensorimotor polyneuropathy

This is the most frequent variety of diabetic neuropathy. This sensorimotor polyneuropathy is symmetrical and presents an insidious and progressive evolution. The initial symptoms are numbness, tingling, prickling sensation or burning in the feet. Nocturnal exacerbation of pain is typical and is alleviated by walking. When pain progresses it follows a stocking and glove distribution, and with time is accompanied by distal weakness of absence of reflexes. In addition there may be loss of distal sensitivity to pricking, temperature, contact or vibration stimuli. Inadequate glycemic control is the greatest risk factor. This complication is also associated with the development of diabetic retinopathy and nephropathy.

Autonomic diabetic neuropathy

This neuropathy appears about ten years after the onset of diabetes and progresses slowly. Diverse organs and systems can be affected:

Cardiovascular

This is probably the main cause of the higher incidence of sudden death and silent myocardial ischemia. The most frequent symptoms are rest tachycardia and orthostatic hypotension.

Table 5. Description of frequent classes of neuropathic pain.

CLASS OF PAIN	SYMPTOMS	PREVALENCE
Diabetic neuropathy (most frequent: peripheral polyneuropathy)	numbness, tingling, pain in the feet and the ankles, known as “the glove and stocking” distribution	50% of diabetes patients
Post-herpetic neuralgia	Burning sensation, itchiness, cramps. Located in affected dermatome	7-27% of the population with active herpes zoster. Increases with age
Trigeminal neuralgia	Sudden, intense, paroxystic, generally affects one side of the face	5-8 cases per 100,000 patients-year. Increases with age

Reproductive and urinary systems

Bladder dysfunction can occur producing dysuria and urgent micturition. Erectile dysfunction can occur and is probably the most frequent symptom at the onset.

Digestive

The most frequent symptoms include slow gastric emptying with distension (gastroparesis), abdominal pain and diarrhoea, especially nocturnal.

Sweat gland function

A reduction in sweat production in lower extremities can occur with compensating hyperhidrosis in the trunk.

Post-herpetic neuralgia

This represents the most frequent complication of herpes zoster. It is believed to be caused by inflammation and viral injury to afferent primary fibres of sensory nerves and the spinal cord. According to the duration it can be classified in: acute (<30 days after the rash), subacute (<120 days) and persistent (>120 days).

The probability of developing post-herpetic neuralgia increases with age. The incidence in patients under 20 years is 1 case per 1000 patients per year. The incidence increases by 5 to 10 times in patients over 80 years and it is more frequent in patients with cancer or HIV infection.

The clinical manifestations of pain in patients with post-herpetic neuralgia are considerably variable. Perhaps the burning sensation is the most frequently cited. Normally symptoms present as an intense, continuous, and sharp pain, but in other occasions, symptoms may present as alodynia[6].

Trigeminal neuralgia

This disorder affects a sensory portion of the nerve. Pain is usually unilateral and in more than 95% of the cases it affects the second and third branches of the trigeminal nerve. The onset of pain lasts briefly and is intense with a sudden end. It usually lasts a few seconds upto a maximum of one or two minutes and can recur several times during the day, with intervals of no pain.

Diagnosis is based on the clinical history and physical examination

Pain is described as sharp, lancinating or electrical and can appear spontaneously or by stimulation of sensitive areas known as trigger zones, located generally at the lip, cheek or nose.

Pharmacological management

The difficulty in management of these patients derives from the heterogeneity of the mechanisms of neuropathic pain and the frequent co-existence of psychological and emotional factors. It is not uncommon to find patients presenting anxiety and depression. It is important to explain treatment options and the possible side effects in order to gain the trust of the patient. In addition, it is convenient to avoid unrealistic expectations with regard to the efficacy and tolerance of treatments, as in many cases there is only a moderate reduction of pain. In clinical practice, the complexity of management requires a multidisciplinary approach.

Trigeminal Neuralgia

There are few studies on the efficacy of the different management options. Moreover these studies are short term. The elective option is carbamazepine[7] with a NNT=1.9 for the reduction of pain and NNT=2.6 for chronic pain. Efficacy diminishes as years go by and dose increments or substitution of treatment or additional treatments may be required[8].

Carbamazepine presents a complex pharmacokinetic profile and can produce serious adverse effects (alterations affecting the hematopoietic system and the central nervous system), especially in the elderly (NNH=3.7). As secondary treatment oxcarbacepine can be employed, although part of the studies carried out on this agent have not been published. Lamotrigine or surgical intervention can be employed in patients with no response to initial treatment. There is no evidence available

Treatment should commence at low doses and increments made gradually

from well designed clinical trials proving the efficacy of other drugs other than antiepileptic agents in the management of trigeminal neuralgia[9].

Diabetic neuropathy and postherpetic neuralgia

The different recommendations on the management of peripheral neuropathic pain coincide in describing tricyclic antidepressants (mainly amitriptyline), antiepileptic agents (gabapentine and pregabaline) and the selective norepinephrine reuptake inhibitors (mainly duloxetine) as first line treatment options[10,11,12]. Among the second and third line management options, topical lidocaine or capsaicine (in particular cases), major opioids and tramadol can be employed[12].

A brief review of the evidence available on the treatments available will follow. When considering the efficacy of a drug, it is important to take into account that the majority of the trials are short term studies (less than three months), with a small sample size, a reduction of 30% of pain is accepted as significant and a considerable percentage of patients do not show improvement[13]. For this reason the values of NNT should be considered within this context. In daily clinical practice, in a substantial amount of cases pharmacological treatments do not resolve the management of pain, nor do they provide significant improvement.

First line treatments

Tricyclic antidepressants

These agents have proven effective in the reduction of neuropathic pain, both in diabetes patients and in those with post-herpetic neuralgia[14], with a NNT compared to placebo of about 3 (see table 6). The majority of the trials evaluated the efficacy of amitryptline. In 20% of the participants who received antidepressants, treatment was discontinued because of intolerable adverse effects. Adverse effects associated with tricyclic antidepressants include somnolence, dry mouth, blurred vision, constipation, and urinary retention. Among the severe adverse effects, the most important are arrhythms and heart block. The number necessary to harm (NNH) up to withdrawal from the trial due to adverse effects was 28 (CI95%, 18-69) with regard to amitriptyline.

It is important to manage the medication well. It is appropriate to start with low doses preferably before going to bed to reduce the incidence of the adverse effects. The use of the minimum effective dose is also recommended. The efficacy of the treatments should also be evaluated, at least after 2 weeks under the standard dose.

Gabapentin and pregabaline

A review found two studies comparing gabapentin and placebo in patients with post-herpetic neuralgia and seven studies comparing the same treatment in patients with diabetic neuropathy[15]. The NNT values to provide effective pain relief oscillated between 3 and 4 (table 6). There was a greater percentage of withdrawals in the group under gabapentin.

Another review showed that pregabaline was superior to placebo with regard to the improvement of neuropathic pain[16]. With the 600 mg daily dose, the values of NNT to obtain at least 50% pain relief over the initial value (significant benefit) oscillated between 3 and 4 (table 6). The main adverse effects observed were somnolence (15-25%), and dizziness (27-46%). Between 18 and 28% of the patients interrupted treatment because of the adverse effects. The authors concluded that a minority of the patients under pregabaline obtained significant benefits. The majority of the patients did not obtain any benefit whatsoever, or experienced only slight improvements or abandoned treatment due to the adverse effects.

There are no trials comparing gabapentin to pregabaline. In one review on pregabaline and gabapentin[17] it was concluded that the benefit-risk balance of pregabaline was similar to gabapentin, although the former is much more expensive.

Serotonin-norepinephrine seletive reuptake inhibitors or SNRIs (venlafaxine and duloxetine).

Duloxetine has only been compared to placebo in diabetes patients with painful peripheral neuropathy. The 60 mg daily dose was more effective than placebo in the short term (12 weeks), with a NNT of about 6 for 50% pain relief[18]. The adverse episodes were frequent and were dose depen-

dent. The number necessary to harm (NNH) until interruption of treatment was 17 (95%CI, 12-50). There are no long term trials or comparative studies with other agents.

There are three studies evaluating the efficacy of venlafaxine. One of them was carried out in women after mastectomy. Another cross-over trial of only four weeks duration compared venlaxafine with imipramine or placebo. Venlafaxine showed worse results than imipramine and was not superior to placebo. The third trial was carried out in patients with polyneuropathy. A systematic review evaluated the global effect observed in the three trials[14]. The NNT observed was 3 (95%CI, 2-5) for improvement in pain management. The NNH to discontinue treatment due to adverse effects was 16 (CI 95% 8-436). It is not clear whether it is coherent to extrapolate the data from the first study to the rest of the population with neuropathic pain, especially when the results of this trial are not replicated in the other two later studies.

What is the best first line treatment?

There are no trials that compare these treatments. Therefore, only indirect comparisons can be made, which greatly undermine the quality of the evidence[10]. In the global review (tricyclic antidepressants, SNRIs, gabapentin and pregabaline) carried out by the Canadian Agency for Drugs and Technologies in Health[10], tricyclic antidepressants obtained the best results with regard to efficacy (NNT =3-6) while the SNRIs were the least effective. After considering costs in Canada, the agency concluded that the first line treatment option was tricyclic antidepressants.

The NICE guidelines concluded that the elective management options should be tricyclic antidepressants, pregabaline and duloxetine[11]. In the report issued, the cost of the drugs for the NHS was considered. One motive for controversy was that the agency considered amitriptyline only at high doses. Another criticism was the inclusion of pregabaline and not gabapentin. As a result of this criticism a review of this guideline is expected[19].

The elective management option is tricyclic antidepressants

Taking into account the absence of comparative trials, the evidence with regard to efficacy and safety when compared to placebo, the costs for the Navarre Health Services and the existence of low dose presentations of tricyclic antidepressants in Spain, make these the elective option for treatment. In the case of no response to treatment or the existence of contraindications, then gabapentin may be employed, after which duloxetine may also be considered as the next option. Table 7 shows the adequate doses of the principal agents indicated in the management of neuropathic pain.

Second line treatment

Tramadol

Trials involving tramadol are short term and with a few patients. In a meta-analysis of three of the trials comparing tramadol with placebo (269 patients)[20], the number necessary to obtain at least 50% pain relief was 4 (95%CI, 3-8). All the trials

Table 6. Number of patients needed to treat to reduce one case of neuropathic pain when compared to placebo. Data from short term clinical trials.

INDICATION	ACTIVE SUBSTANCE	NNT (CI95%)
Diabetic or post-herpetic neuralgia	**Tricyclic Antidepressants**	**3.6 (3.0-4.5)**
	Amitriptyline	3.1 (2.5-4.2)
	Desipramine	2.6 (1.9-4.5)
	Imipramine	2.2 (1.7-3.22)
Diabetes neuralgia	Gabapentin	2.9 (2.2-4.3)
	Pregabaline	3.9 (3.1-5.1)
	Duloxetin	6.0 (5-10)
Post-herpetic neuralgia	Gabapentin	3.9 (3-5.7)
	Pregabaline	5.6 (3.5-14)

measured pain relief during similar periods (4-7 weeks) and the highest benefit was obtained in the first four weeks. There are no data on the mid to long term efficacy and safety.

Tramadol was compared in one trial with morphine and in another with clomipramine, but no conclusions could be obtained with regard to relative efficacy. Despite the brief duration of the trials adverse effects observed were frequent, with a number necessary to harm of 8 (95%CI, 6-17).

Opioids

A recent meta-analysis showed that the mid term clinical trials (nine of which with a an average duration of 28 days and a median of 57 patients), a reduction of 13 points on a scale between 0 and 100 was observed[21]. The clinical significance is not clear, given a reduction of 20 to 30% of the baseline pain. The adverse effects registered with opioids were frequent and there were more withdrawals from the opioid group than placebo group (11% vs 4%).

The results of the very short term trials (24 hours) are contradictory. For this reason, they should not be used during short periods as a predictive tool to decide on starting treatment for a mid term period.

Long term clinical trials are necessary to evaluate the reduction of pain, the improvement in quality of life and safety (including the potential for addiction). In patients under opioid treatment efficacy and safety should be monitored more rigorously than those treated with other drugs.

Topical therapy: lidocaine or capsaicin

The use of lidocaine patches as first line treatment is not recommended as there are only few studies carried out with placebo and with discordant results with regard to efficacy[22]. Some reviews consider that lidocaine can be employed as rescue treatment in patients with localized neuropathic pain and who do not tolerate or respond to oral treatment[11].

Capsaicin, whether employed at repeated intervals in the low dose presentation (0,075%) or in the single high dose patch (8%) produces considerable skin irritation. Up to one third of the patients abandon treatment[23]. The estimations of the efficacy are not coherent and present various methodological problems[24]. It can be considered as the third option in post-herpetic neuralgia[12]. The treatment with capsaicin patches at high doses administered once daily has shown short term efficacy, but there is no long term data. This is especially important because epidermal dennervation has been discovered in skin biopsies after capsaicin application which is associated with a loss in functionality and pain sensation[12].

Publication bias

This bias, which very often appears in scientific literature, has also affected the management options of neuropathic pain. As a result of a court case involving the pharmaceutical manufacturer of Neurontin (gabapentin), due to promotion of the drug for unapproved indications, a series of unpublished studies have been released showing that gabapentin was not as effective as previously believed[17]. On adding this data to the previous evidence available, the efficacy was reduced to about 15% of the previous value. The new NNT obtained was 6-8 and the percentage of patients with adverse effects increased, with a NNH of 8.

Another example is the DPN-040 trial regarding pregabaline which appeared in the EMA´s report[25]. In this study pregabaline 600 mg was compared to placebo. The study also incorporated a third branch, with amitriptyline 75 mg. This study was not published though the results showed that ami-

Table 7. Doses of the main drugs indicated in the management of neuropathic pain.

ACTIVE AGENT	INITIAL DOSE	MAXIMUM DOSE
Amitriptyline	10 mg (preferably at dinner)*	75 mg (150 mg in some patients)
Nortriptiline**	25 mg	75-100 mg (25 mg / 6-8h)
Gabapentin	300 mg, followed by 300-600 mg / 8h	3.600 mg / day***.
Pregabaline	150 mg (75 mg / 12h)	600 mg (300 / 12h)
Duloxetine	60 mg	120 mg

*In some patients the initial dose may be 25 mg.
** Not indicated in neuropathic pain.
*** Maximum dose recommended to be reached after at least three weeks.

triptyline was statistically better than placebo in the reduction of pain, which was not the case with pregabaline. The percentage of patients abandoning treatment was 28% and 26% in the groups under pregabaline and amitriptyline respectively.

COMBINED TREATMENT: FIRST LINE, SECOND LINE OR WHO KNOWS WHAT OPTION?

There is no trial of sufficient methodological rigour that establishes whether a patient will benefit more from an initial combined therapy approach or whether a new drug should be added to or substitute the first option after this has failed.

There are no data that confirm a better response of patients to combined therapy, but there is evidence of increased adverse effects. Thus, given the lack of evidence, combined therapy cannot be recommended as the initial management approach.

Future well designed trials, with adequate sample sizes, sufficient follow up periods and appropriate primary endpoints will help us know the role of the different combined therapies.

Prevention of post-herpetic neuralgia

There is no preventive treatment that has proven effective in reducing the prevalence of post-herpetic neuralgia, although some treatments seem to reduce the duration or severity of symptoms[26,27].

Antiviral agents (acyclovir, valacyclovir, famcyclovir and brivudine). It has been demonstrated that, if employed in the first 72 hours, there is a reduction in the duration of the skin rash and acute pain. However there are only modest reductions in the duration of post-herpetic neuralgia. The sooner the medication is started the greater the efficacy.

Corticosteroids, administered for 21 days do not reduce the prevalence or severity of post-herpetic neuralgia.

There is a small trial[28] (72 patients, over 60 years) in which the author affirm that after a protocol analysis, treatment with amitriptyline 25 mg for 90 days was greater than placebo in reducing post-herpetic neuralgia after 6 months, NNT=5. Given the data from the trial, the statistical significance is not clear (p=0.051). Neither was there an ITT analysis. There is no other trial since 1997 to confirm these data.

It is important to combine pharmacological treatment with other therapeutic measures

The risk of presenting post-herpetic neuralgia increases with age and the severity of the symptoms at the onset of herpes. A rule of 50-50-50 has been proposed, which means that antiviral treatment should be given within 50 hours of the onset of symptoms in patients over 50 years of age, and when there are at least 50 or more vesicular lesions[26]. Patients that fulfil these criteria will benefit from treatment. In addition those patients **with ophthalmic affectation should also receive antiviral treatment**. Other authors consider that antiviral agents should be given to patients over 50 years of age within 72 hours of the onset of the skin eruption[29].

Non-pharmacological management

There are few trials of substantial quality that have studied the efficacy of the different non-phamacological management options. Given the relative efficacy of medications, non-pharmacological options are always recommended as part of the management approach to patients with neuropathic pain[8].

In general, the reduction of stress, sleep hygiene and physiotherapy can all contribute towards pain relief.

Trigeminal neuralgia

Patients refractory to pharmacological management are candidates for surgical intervention (microvascular decompression or ablation). The majority of studies are observational. One systematic review, based on indirect comparisons, found that microvascular decompression could produce a more prolonged analgesic effect[30].

Diabetic neuropathy

Transcutaneous electrical nerve stimulation (TENS) may also prove effective in some patients with diabetic neuropathy[31]. The efficacy of lipoic acid has been studied in a small trial which did not evaluate pain relief[32]. This trial has not been reproduced, nor any other similar trial been carried out, thus there is no evidence of its efficacy. Nor is there proven evidence of the efficacy of surgical procedures involving multiple peripheral nerve decompression[33].

Post-herpetic neuralgia

There are no studies on the efficacy of TENS or acupuncture in the treatment of post-herpetic neuropathy. In a small study, short term improvement after criotherapy (massage with ice) was described[34]. Surgical interventions (thalamic electrostimulation, dorsal root electrocoagulation) have an important risk of causing neurological deficits.

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Conclusions

Neuropathic pain is very complex and currently its management represents one of the major challenges in patients with chronic pain.

The mechanisms of neuropathic pain are multiple and polytopic, where more than one may exist in the same patient.

Diagnosis is essentially clinical, based on the history and physical examination of the patient.

Before starting treatment it is convenient to explain to the patient the management options and possible adverse effects of the drugs.

Avoid unrealistic expectations with regard to efficacy and tolerance.

Tricyclic antidepressants represent the first line treatment option. Alternatives include gabapentin and duloxetine. Treatment should start with low doses followed by gradual increases until the minimum effective dose is reached.

Combining pharmacological treatment with non-pharmacological measures is highly recommended.

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