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## Evidence-Based Treatment of Postherpetic Neuralgia

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### 1. Introduction

Postherpetic neuralgia (PHN) is the most common and feared complication of herpes zoster (HZ); it is mainly reported among the elderly and is described as painful and refractory. It is a complication rather than a continuation of acute HZ, and is defined as persistent pain in HZ-involved areas that continues for > 3 months after disappearance of the vesicles (Rowbotham & Fields, 1989). It is considered one of the most important neuropathic pains for the reasons set out in table 1.

1. There is an elevated incidence of PHN among the elderly. PHN occurs in 10.20% of all HZ patients but in >50% of elderly HZ patients.
2. Neurosensory lesions frequently have a pain component (Rowbotham & Petersen 2001) - Sensitive: dysesthesia, paresthesia, allodynia... - Motor: paresis, paralysis...
3. There is a high associated comorbidity in previously healthy individuals: loss of nocturnal sleep, loss of appetite, marked functional limitation, and major emotional component, which all impair the long-term quality of life of patients (Jensen et al, 2007)
4. The pain is highly intense and often disproportionate to the initial injury.
5. It is characterized by a high chronicity, although only around 50% of patients developing PHN are moderately symptomatic at 1 year after onset.
6. Diverse pathophysiological mechanisms are involved in the different spontaneous and evoked symptoms in PHN, resulting in: - A very heterogeneous symptomatology that varies between one patient and another. - Symptoms that change over time - Highly complex and difficult treatment, with the need to test and combine different therapies to obtain a satisfactory outcome. - Only partial pain relief
7. These patients consume large amounts of healthcare resources, making PHN an important institutional and public health problem (Gauthier et al, 2009).
8. PHN and diabetic neuropathy (DPN) are the models preferentially selected and required by the FDA and EMA in controlled trials for any drug or technique seeking approval against peripheral neuropathic pain.

Table 1. Clinical relevance of postherpetic neuralgia (Watson & Evans, 1986; Rowbotham & Fields, 1989; Helgason et al, 2000; Dubinsky et al, 2004; Scholz & Woolf 2007).

Mixed inflammatory and neuropathic pain is experienced in acute HZ, whereas neuropathic pain is highly predominant in PHN and the symptoms persist over time (Rowbotham et al, 2001). The clinical symptoms presented by these patients are very heterogeneous, and some are spontaneous while others are evoked. Spontaneous symptoms frequently include a constant deep and burning pain and an intermittent intense and lancinating pain throughout the painful area, leaving it hypersensitive and painful for some minutes. Other disagreeable symptoms are pruritus and painless, but nevertheless disabling, sensations of coldness or numbness (Anne et al, 2005; Treede et al, 2008).

<p>SPONTANEOUS PAIN (due to spontaneous firing of axons or dorsal horn neurons):</p> <ul style="list-style-type: none"> <li>- Burning, constant pain</li> <li>- Cramping and dysesthesia</li> <li>- Lancinating and paroxysmal pain</li> </ul>
<p>EVOKED PAIN (due to damage in peripheral and central sensory neurons):</p> <ul style="list-style-type: none"> <li>- Hyperalgesia (mechanical and thermal)</li> <li>- Allodynia (mechanical and thermal)</li> </ul>
<p>OTHER CLASSIC SYMPTOMS:</p> <ul style="list-style-type: none"> <li>- Positive: hyperhidrosis, pruritus, tic</li> <li>- Negative: hypoesthesia, paresis, paralysis</li> </ul>

Table 2. Classic PHN symptomatology

The characteristics of PHN often lead to two well-known situations:

- a. Desperation of the affected patients and their relatives.
- b. Frustration of the professionals treating it.

As a result, patients complaining of PHN are often referred by primary care centers and emergency departments to the Pain Unit or Neurology and Dermatology specialists in an attempt to seek a definitive solution that cannot, unfortunately, be completely achieved.

Treatments are either partially or totally ineffective for many people with PHN. The development of PHN may be prevented by the antiviral agents used to treat the rash. Once PHN is established, various well-known selection drugs and techniques may alleviate the pain (Dubinsky et al, 2004). The recent appearance of specific evidence-based analgesic guidelines and algorithms for neuropathic pain, including PHN, offers an excellent opportunity to improve pain management in these patients.

## 2. Background and objectives

Despite the social and public health importance of PHN, there is a wide variability in its routine clinical management by different healthcare professionals. The objective of this chapter was to review and update the different treatments available for PHN in light of the analgesic drugs and techniques that have appeared in this field (especially pharmacological therapy), from the time of its detection and diagnosis in primary care to its treatment in the Pain Unit if not controlled. We also describe current approaches to PHN in the most recent clinical guidelines, according to the available evidence, and offer a practical view of analgesia for the different professionals involved in PHN. No attempt is made to review the available evidence, given the existence of excellent guidelines published in different specialist journals.

### 3. Analgesic strategy

As with other neuropathic pains, the approach to PHN is complex but always in the pursuit of clear and, when possible, viable objectives (see Table 3), usually shared by the specialist and primary healthcare professional (Dubinsky et al, 2004; Galvez, 2009; Dworking et al, 2010). The majority of PHN patients are initially and sometimes exclusively attended at the level of primary care, which is the entry gate into the health system in many countries and therefore plays a key role in the prevention of PHN. In the case of children, it is the pediatrician who has the possibility to educate parents to vaccinate their children against chickenpox and thereby reduce its incidence, explaining that when this infection reactivates, e.g., in an immunodepressed state, it can produce re-infection by HZ virus, which is the virus that produces chickenpox in children, emphasizing that the severest complication of this re-infection is HZ and subsequently PHN. Since 2008, HZ vaccines have been recommended that can be administered to over-70-year-olds, the age group most susceptible to complications (Anne & Mounsey, 2005; Redondo et al, 2007).

1. To relieve the pain by drugs/techniques with reduced adverse effects that are acceptable to the patient.
2. To recover nocturnal sleep.
3. To reduce symptoms related to hypersensitivity and allodynia by at least 3 points on the 11-point Likert scale.
4. To improve the ability of the patient to deal with the pain.
5. To stabilize the patient's emotional state.

Table 3. Analgesic objectives in PHN

The analgesic strategy is based on the application of the drugs with the strongest scientific evidence on their effectiveness in PHN, but with reduced and tolerable adverse effects. Table 4 contains a summary of this global strategy.

1. Immediate initiation of treatment (PHN worsens with passage of time)
2. Communication of correct information and realistic expectations to the patient
3. Analgesia using drugs with the best evidence on their usefulness in PHN
4. Evidence-based pharmacological therapy as the main approach
5. Active rehabilitation program
6. Educational resources for patients with neuropathic pain
7. Some invasive techniques in certain cases

Table 4. Key points of PHN treatment strategy (Turk & Stieg, 1987; Dubinsky et al, 2004; Argoff et al, 2004; Baron et al, 2010)

Antidepressants ( tricyclic antidepressants, ...) Antiepileptics (gabapentinoids, carbamazepine...) Tramadol and opioids (morphine, oxycodone, methadone...) Other drugs acting on modifications generated in the synapses of injured neurons (N-methyl-D-aspartate receptor antagonists, etc.) Topical agents (5% lidocaine patch, capsaicin cream or patch...) Other drugs (baclofen, mexiletine, clonidine...) Some techniques: nerve blocks, transcutaneous electrical nerve stimulation, spinal cord stimulation, intrathecal infusion ...
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Table 5. Main drugs used in PHN

However, despite the ever-expanding therapeutic arsenal of drugs and techniques against PHN (table 5), there is little scientific evidence on the majority of analgesic treatments and they are rarely compared in head-to-head trials (Dubinsky et al, 2004). In fact, analgesic responses are frequently highly disparate, even among patients in similar situations of PHN and treated with identical analgesic regimens, explaining the need to individualize PHN therapy (Papagallo & Haldey, 2003)

Classically, the symptoms and signs of pain in PHN have been treated globally, regardless of the specific clinical symptoms. However, a new approach has been developed over the past decade, which proposes the selective analgesic treatment of the different spontaneous or evoked symptoms that arise (Jensen & Baron 2003; Hanson, 2003). A recent article described six clinical subtypes of neuropathic pain according to the predominant symptoms, each with a different profile and obtained from a sample of 2100 patients with diabetic neuropathy (DPN) or PHN (Arning & Baron, 2009; Baron et al, 2009; Wasner & Baron, 2009; Baron et al, 2010). Treatment may vary as a function of the clinical subtype of neuropathic pain and the symptoms detected. However, considerable research remains to be done before protocols can be established for the treatment of distinct subtypes and symptoms in daily clinical practice.

#### 4. Analgesic pharmacology

Analgesic pharmacotherapy is considered the basis of PHN treatment, and there has been a major strategic change with the proposal of a series of specific drugs for this type of pain. It is recognized by the scientific community that the classic Analgesic Ladder of the WHO, based on the use of analgesics as a function of pain intensity, does not adequately address PHN pain or other types of peripheral neuropathic pain which do not respond satisfactorily to therapy with classic analgesics (non-steroidal anti-inflammatory drugs [NSAIDs] and opioids). There is a need to evaluate other drugs considered as basic analgesic pillars in PHN, including antiepileptics, certain antidepressants, and one or other opioid that has evidenced analgesic effectiveness in this type of neuropathic pain (McCleane, 2004; Dubinsky, 2004; Backonja et al, 2006; Jensen et al, 2009; Martinez-Salio et al, 2009). It has been proposed that the analgesic management ladder (figure 1) for peripheral neuropathic pain (e.g., PHN) would include the reference analgesic drugs cited above, unlike those established in the classic WHO ladder (Galvez et al, 2006; Galvez et al, 2007).

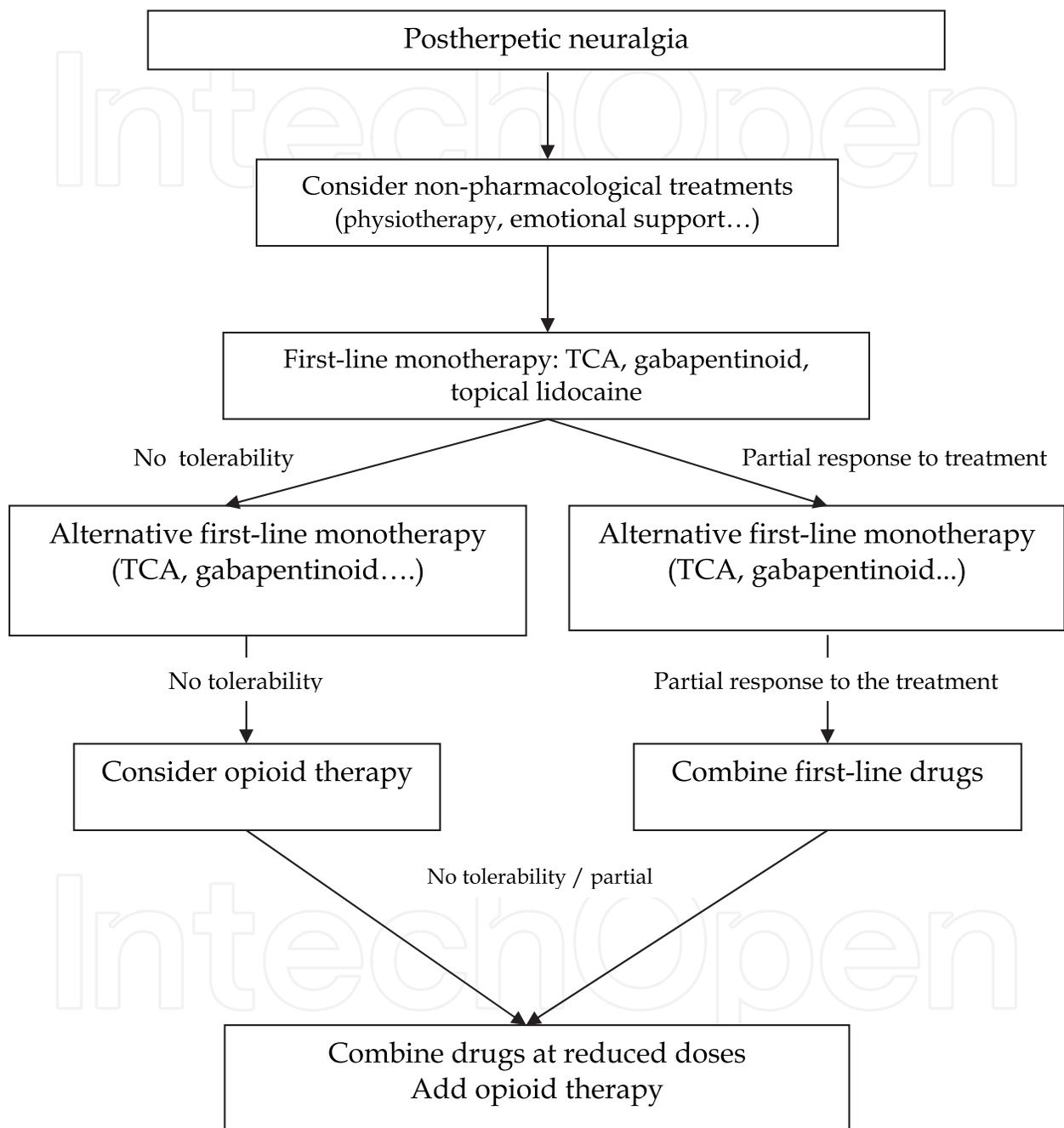


Fig. 1. Proposed Algorithm for PHN

The first step of the new ladder for neuropathic pain calls for certain antiepileptic drugs (AEDs), such as gabapentinoids (gabapentin or pregabalin), and some antidepressants, such as tricyclic antidepressants (TCAs) or serotonin and norepinephrine reuptake inhibitors (SNRIs), e.g., venlafaxine and duloxetine. Some topical treatments, such as lidocaine or capsaicin patches, can be considered. Opioids like oxycodone or tramadol have demonstrated effectiveness in neuropathic pain but are on the second or third step of the ladder due to their adverse effects. If the pain is not alleviated, the second step is the combination of first-step drugs with tramadol. On the third step, the first-step drugs are maintained and combined with potent opiates (morphine, oxycodone, methadone, fentanyl transdermal, or buprenorphine transdermal) (Gilron et al, 2005). Nerve blocks or transcutaneous electrical nerve stimulation (TENS) can be useful at any point. If these drugs and techniques fail, patients must be referred to more specialized departments, e.g., the Pain Unit or Neurosurgery, for more invasive techniques such as Dorsal Root Entry Zone (DREZ), Spinal Cord Stimulation (SCS), or spinal infusions.

1 <sup>st</sup> STEP	2 <sup>nd</sup> STEP	3 <sup>rd</sup> STEP
TCAs, SNRIs GABAPENTINOID TOPICAL AGENTS Lidocaine or capsaicin patches	COMBINATION OF 1 <sup>st</sup> STEP DRUGS + TRAMADOL	COMBINATION OF 1 <sup>st</sup> STEP DRUGS + POTENT OPIOID

Fig. 2. Neuropathic Pain Analgesic Ladder

## 5. Antidepressants

For more than 30 years, antidepressants have played an important role in the treatment of chronic pain. The most widely known and used drugs have been TCAs (amitriptyline, imipramine, chlorimipramine, and desipramine) (Mc Quay et al, 1996). TCAs have a proven analgesic effect in neuropathic pain that is independent of their effect on the state of mind, with reports that the analgesic effect appears before the antidepressant effect and that a lower dose is required for analgesia than for the treatment of depression (Mc Quay et al, 1996; Saarto & Wifien 2005). TCAs have different action mechanisms with primarily analgesic effects. The main mechanism is the modulation of neurotransmitters by inhibiting the reuptake of serotonin (5HT) and noradrenaline (NA) at presynaptic level, increasing their bioavailability. NA and 5HT are involved in modulating pathways mediated by endorphins at both central nervous system (CNS) and spinal cord level. There is also evidence that they antagonize N-methyl-D-aspartate (NMDA) receptors and block muscarinic, cholinergic, histamine H1, and alpha-adrenergic receptors, which may participate in the modulation of the nociceptive response. TCAs also act on sodium channels in neuronal tissue, thereby stabilizing peripheral nerves and modulating the hyperexcitability of neurons at CNS level.

As already noted, PHN is a major cause of chronic pain among the elderly, in whom TCAs have also been traditionally used. Meta-analysis of TCA trials for this indication found that they are able to significantly relieve pain in PHN (Watson et al, 1982; Mc Quay et al, 1996; Saarto & Wifien 2005; Sindrup et al, 2005). Amitriptyline has proven effective as an analgesic

and is the most widely used drug with the best outcomes. In a recent controlled trial, nortriptyline showed practically the same efficacy as opioids in PHN (Raja et al, 2002).

The adverse effects of TCAs are largely related to their anticholinergic action: dryness of the mouth, constipation, urinary retention, and tachycardia. The blocking of alpha-1 adrenergic receptors can produce orthostatic hypotension, and the blocking of histamine receptors is associated with sedation and weight gain. All of these adverse effects can be minimized by slow titrations. The adverse effect that causes greatest concern is the alteration of cardiac conduction (through inhibition of noradrenalin reuptake). The response is dose-dependent, and it is recommended to start treatment at low doses (10 mg in over 65-year-olds and 25 mg in others) before bedtime and to titrate the dose very slowly according to the clinical response, without exceeding 75 mg/day. TCAs have a lower NNT (number needed to treat) value in comparison to other analgesic drugs in neuropathic pain and are attributed with the best evidence in clinical guidelines. Amitriptyline has an NNT of 2.2 for PHN, but its adverse effects, lack of recommendation in the elderly, and the small sample size of studies have relegated it behind antiepileptics for certain PHN cases (Saarto & Wifien 2005; Dworking et al, 2007). Nortriptyline, maprotiline, and desipramine have also proven effective, but less so than amitriptyline.

The SNRIs duloxetine and venlafaxine are efficacious in painful polyneuropathy but have not been studied in PHN. Selective serotonin reuptake inhibitors (SSRIs) have shown little effectiveness in neuropathic pain and practically none in PHN (McQuay et al, 1996; Saarto & Wifien 2005).

### 5.1 Conclusions

TCAs have shown lower NNT values in comparison to other drugs against PHN. Amitriptyline has demonstrated the strongest evidence on effectiveness. Other non-tricyclic antidepressants have shown no evidence of efficacy in PHN.

## 6. Anticonvulsant drugs (AEDs)

AEDs or anticonvulsants have been used in pain management since the 1960s and represent a very important therapeutic option in chronic neuropathic pain, especially when this is lancinating or burning. Since the initial use of carbamazepine, a new generation of antiepileptic drugs have been incorporated into clinical practice (>40 controlled trials) with characteristics that distinguish them from the classical drugs, including greater tolerability, fewer pharmacological interactions, and novel action mechanisms (Robotham et al, 1998; Rice et al 2001; Dworking et al, 2003; Sabatowsky et al, 2004; Van Seventer et al, 2006). A Cochrane meta-analysis (Wifien et al, 2005) yielded significant evidence to support the efficacy of AEDs in the treatment of PHN, especially calcium channel  $\alpha_2\text{-}\delta$  ligands (gabapentin and pregabalin) (Wifien et al, 2005; Gilron et al, 2011). The results evidenced their effectiveness, highlighting the use of pregabalin and later gabapentin in PHN treatment. There have only been small observational studies on carbamazepine in PHN, with no controlled trials.

AEDs took their place as analgesics in neuropathic pain, which is accompanied by hyperexcitability and lancinating pains suggestive of a somatosensory lesion. Although the action mechanism differs among AEDs and is not fully understood, it is known that they can alter pathophysiological mechanisms implicated in the genesis and/or maintenance of neuropathic pain, primarily by stabilizing the neuronal membrane and reducing the number of repetitive discharges in nerves lesioned by different mechanisms (Tremont-Lukats et al, 2000).

Structurally, gabapentin is analogous to gamma-aminobutyric acid (GABA) but does not interact with its receptors. Its action mechanism has not been fully elucidated but appears to be related to specific alpha-2-delta subunits of calcium channels. Pregabalin, which appeared after gabapentin, is a GABA analog but does not bind to the receptor or develop GABAergic activity, and its action mechanism, although not completely understood, is also based on its capacity to bind to the alpha-2-delta protein subunit of voltage-dependent calcium channels. In PHN, effective doses range between 1200 and 2400 mg/day for gabapentin but between only 220 and 600 mg/day for pregabalin. Their adverse effects are observed in more than 30% of patients and are related to the CNS, notably somnolence, vertigo and the loss of concentration, which are closely linked to the speed of dose titration and sensitivity of the patient. As a result, around 15-30% of patients cannot tolerate these drugs and abandon treatment (Dworking et al, 2007; Jensen et al, 2009).

### 6.1 Conclusions

There is good-quality evidence that gabapentinoids are the most effective antiepileptic drugs in PHN. Pregabalin is somewhat more effective than gabapentin. A slow titration is necessary to reduce adverse effects.

## 7. Opioids

Since the editorial by Dubner in *Pain* at the beginning of the 1990s (Dubner, 1991), evidence has begun to emerge on the use of opioids to treat neuropathic pain. The first systematic Cochrane review appeared in 1999 (Dellemin et al, 1999), followed by a meta-analysis in 2006 that included 23 clinical trials and clearly evidenced the efficacy of opioids in neuropathic pain (Eisenberg et al, 2006).

Opioid analgesics are agonists of presynaptic and postsynaptic opioid receptors. Their efficacy has been reported in several randomized controlled trials in different peripheral neuropathic pain disorders. Their effectiveness is probably lower for certain symptoms, such as thermal hyperalgesia and allodynia, due to the involvement of fibers with no opioid receptors. The same may be true for static mechanical allodynia and hyperalgesia (Dickenson AH et al, 2005; Trescot AM et al, 2008; Besson M et al, 2008).

In more recent reviews, morphine, oxycodone, and methadone have demonstrated a similar effectiveness to that of TCAs in PHN, but opioids are relegated to the second analgesic line due to their possible adverse effects (Watson et al, 1998; Przewlocki et al, 2005). The most recent studies have been on oxycodone in PHN and DPN, showing an acceptable effectiveness. Combined gabapentin and morphine was very useful in neuropathic cancer pain (Keskinbora et al, 2007).

Tramadol exerts a weak opiate effect on mu receptors in comparison to opioids and a weak monoaminergic effect in comparison to TCAs and AEDs. However, the adverse effect profile of tramadol is more acceptable than that of TCAs and AEDs, and tolerance and dependence complications are uncommon. Tramadol has demonstrated effectiveness but in studies offering low-quality evidence (Boureau et al, 2003). Its administration starts with an oral dose of 12.5-25 mg every 6 or 8 hours, with rescue doses of the same amount remaining available until the pain is controlled and then passing to sustained formulations up to a maximum recommended dose of 400 mg/day (Hollingshead et al, 2006; Eisenberg et al, 2006).

### 7.1 Conclusions

These drugs have an effect on neuropathic pain but are not considered first-line drugs due to issues around dependence, cognitive impairment, tolerance, and possible hormonal problems.

## 8. Topical drugs

The ease and effectiveness of topical applications have led to the increasing introduction of topical drugs with local analgesic effects. However, despite the thinness of skin, only drugs with certain characteristics are able to pass through it, limiting the use of this administration route. Topical drugs can be in cream, ointment, lotion, spray, or patch form. Topical analgesics provide pain relief with minimal risk of systemic toxicity or drug-drug interactions, because they are formulated to produce a local effect while avoiding high plasma concentrations and adverse systemic events. Among patients with PHN, especially those with peripheral symptoms, various topical agents have proven effective and represent a viable treatment option. Topical treatment also offers a therapeutic approach to patients in whom systemic treatment is contraindicated.

## 9. Lidocaine

The analgesic effectiveness of topical local anesthetics has long been known, based on the direct binding of the local anesthesia with anomalous sodium channels of skin nerve endings (which participate in the maintenance of both spontaneous and evoked neuropathic pain), blocking them and thereby stabilizing the neuronal membrane and the production of ectopic discharges (Robotham, 1995). The first drug to be used was EMLA cream, a mixture of lidocaine and prilocaine, which had already shown some effectiveness in some PHN patients (Wheeler JG 1991; Stow, 1989). Subsequently, after a report on the usefulness of 5% lidocaine-medicated plaster (LMP) in PHN (Robotham, 1996; Galer et al, 1999) as a new topical treatment and its FDA approval for PHN pain in 1999, multiple studies evaluated this therapy. In 2007, the Cochrane Library produced a review (Khalick, 2007) of three articles on lidocaine treatment of PHN, although two of these were on lidocaine gel and only one used 5% LMP. The authors of the review concluded that there was inadequate evidence to recommend 5% LMP as a first-line analgesic against PHN.

A new exhaustive review of articles on 5% LMP (up to May 2010) was recently published, comparing its effects in PHN with those of other therapies or placebo (Wolff, 2011). Out of 2417 references, it included 32 articles reporting on 20 studies on 5% LMP. Patches (10 x 14 cm) containing 700 mg lidocaine each were daily placed for a maximum of 12 hours and then removed, generally using 3 or sometimes 4 patches simultaneously to cover the painful area. The 5% LMP patch showed effectiveness *versus* placebo, especially for allodynia, one of the most important and disagreeable symptoms in PHN. Pain relief was achieved, and there were no cases of anesthesia or loss of cutaneous sensitivity. Comparison between 5% LMP and pregabalin showed them to have the same efficacy for pain relief, while 5% LMP had a greater positive effect on almost all quality of life dimensions (in the SF-36 survey), with much lower adverse effects, and received a higher overall rating by patients. In the meta-analysis, only gabapentin and 5% LMP produced a reduction in baseline pain (on VAS scale) in comparison to placebo, and this reduction was larger with 5% LMP. Pain relief was greater with gabapentin or 5% LMP than with capsaicin or pregabalin. Topical lidocaine in

patients with various localized peripheral neuropathic pain syndromes had a good NNT, leading to the recommendation of lidocaine plaster for PHN patients (Woolf 2011).

All articles reported the good tolerability and low (< 3%) systemic absorption of lidocaine (Davies, 2004), with the consequent scarcity of adverse systemic reactions. Patients receiving pregabalin reported dizziness, somnolence, and tiredness whereas the only effect in those treated with 5% LMP was local irritation and mild erythema (in 6-28% of cases). The dropout from treatment was also more frequent among pregabalin-treated patients. The review by Woolf noted various major limitations in studies, primarily the small sample sizes in most reports and the short treatment duration, which was usually 4 weeks. A further limitation was the scarcity of studies directly comparing 5% LMP with other drugs, so that comparisons had to be indirect (Liedgens et al, 2008). There was only one head-to-head study, comparing 5% LMP and pregabalin (Baron 2009; Rehm 2010). Comparative economic analysis of six-month courses of 5% LMP, gabapentin, and pregabalin found 5% LMP to be the most cost-effective treatment (Dakin et al, 2007); moreover, these authors concluded that the good tolerability and efficacy of 5% LMP places it as first-line topical analgesic treatment in PHN. In this sense, another economic study has ended favourable toward 5% LMP (Ritchie et al, 2010).

### 9.1 Conclusions

Lidocaine has demonstrated high analgesic effectiveness in PNH, especially in the form of 5% patches, and is indicated as first-line drug for the treatment of localized pain.

## 10. Capsaicin

Capsaicin is an alkaloid substance of natural origin and is the main chemical compound (70%) in capsaicinoids, which include more than 90 varieties of chili. Capsaicin is a selective agonist of transient receptor potential vanilloid type 1 (TRPV1), preferentially bound to small-diameter amyelinated nociceptive nerve fibers such as C fibers, capable of synthesizing and releasing primarily substance P and other excitatory neurotransmitters (Green 1988; Bjerring 1989). The topical application of capsaicin initially activates C-fiber nociceptors by depolarization of the neuronal membrane and alteration of calcium and sodium ions, producing an initial erythematous sensation and skin reddening. However, if this contact with capsaicin is maintained, it leads to a transient and reversible desensitization and degradation of TRPV1-expressing cutaneous nerve endings, without altering other sensations (Nolano 1999; Szolcsany 2004).

The cream started to be applied at low capsaicin concentrations (0.025% and 0.075%) several times a day, obtaining pain relief, although moderate and short-lived, as well as producing local discomfort, occasionally refractory, which sometimes led to the suspension of the treatment (Berstein et al, 1989; Peikert et al, 1991; Watson et al, 1993). A high-concentration (8%) capsaicin dermal patch (179 mg capsaicin; 280 cm<sup>2</sup>) was recently introduced, which is applied for 60 minutes in the peripheral pain area after its treatment with topical local anesthesia to avoid the initial burning pain. The relief obtained persists for around 12 weeks. One week after exposure to the 8% capsaicin patch there was also an 80% reduction in the density of the majority of epidermal nerve fibers (ENFs) in treated areas compared to untreated areas of healthy volunteers. It has been demonstrated that reinnervation practically returns to normality at 224 weeks after patch application (Kennedy 2010). These data support its topical utilization for different symptoms related to peripheral neuropathic pain.

In 2009, a Cochrane review was conducted of randomized, double blind placebo-controlled studies of at least six weeks duration in which topical capsaicin was used to treat neuropathic pain (Derry et al, 2009). Six studies (389 participants in total) compared the regular application of low-dose (0.075%) capsaicin cream with placebo cream, reporting a very good NNT for any pain relief. Two initial studies (709 participants in total) compared a single application of 8% capsaicin patch with placebo patch, finding a good NNT for < 30% pain relief over 12 weeks. The authors concluded that capsaicin may provide a degree of pain relief to some patients with painful neuropathic conditions, either through the repeated application of a low-dose (0.075%) cream or the single application of a high-dose (8%) patch. Earlier studies with repeated applications of low-dose capsaicin have not convincingly demonstrated good efficacy, while the single application of an 8% capsaicin patch has emerged as a new strategy.

Jones et al in 2011 reviewed the evidence on the 8% capsaicin patch in PHN pain, finding that its topical application decreased pain linked to TRPV1 receptors and transiently reduced the number of nociceptive nerve endings at the application site. Their review was based on two pivotal studies in which the 8% patch was compared with 0.04% capsaicin. The primary endpoint of both trials was the reduction in numerical pain rating scale (NPRS) score. The 8% capsaicin patch reduced the pain from baseline to weeks 2-8 (by 29.6% and 32%), a significantly greater reduction ( $P \leq 0.01$ ) than found in 0.04% capsaicin-treated controls to weeks 2-8 (19.9% and 24.4%). At the end of week 12, the reduction in pain was more pronounced ( $P \leq 0.03$ ) in the 8% capsaicin group (by 29.9% and 32.3%) than in the controls (by 20.4% and 25%). Around 40% of all treated patients were responders, considered an acceptable proportion in controlled trials of other analgesics in neuropathic pain. Applications of 8% patch can be repeated a maximum of once every 3 months, as needed. In conclusion, the author concluded that one 8% capsaicin patch every 3 months offers acceptable efficacy in comparison to other PHN treatments requiring daily doses.

With regard to safety, the systemic absorption is low, and drug interactions are not expected, with virtually no systemic repercussions. All remains of capsaicin metabolites have practically disappeared at 6 hours after removing the capsaicin patch (Babbar et al, 2010; Irving et al, 2010). The only adverse effect is a mild increase in blood pressure in some patients during application of the 8% patch. There have also been reports of eye and airway irritation due to aerosolization of capsaicin during patch removal or inhalation of the dried cream (Rains et al, 1995). The most common adverse drug reactions with capsaicin are at the application site, with burning reported by 60% of patients using 0.075% capsaicin cream (Dubinsky 2004) and mild or moderate erythema (63%) and burning pain (42%) described by 63% and 42% of patients, respectively, at the 8% capsaicin patch site. It is often necessary to administer analgesics or local cold during the first 24-72 hours after patch application.

Withdrawals due to adverse events were nearly all due to skin reactions. In two single-dose studies, 37 patients (15%) withdrew out of 242 patients receiving 0.075% capsaicin cream, whereas only three patients (0.7%) had to cease treatment out of 430 patients receiving 8% capsaicin patches. Withdrawals were more frequent with repeated low-dose capsaicin applications than with a single high-dose patch application (Derry et al, 2009).

A 48-week study was conducted to test the long-term efficacy and tolerability of the 8% capsaicin patch (Backjonja et al, 2010), finding virtually no changes in analgesic efficacy over the passage of time and no increase in treatment dropout or topical adverse effects.

Another recent study indirectly compared the cost-effectiveness of 8% capsaicin patch with that of other PHN treatments (Angstrom et al, 2011), evaluating the analgesic improvement, adverse effects, and cost per quality-adjusted life-year (QALY) of the treatments. It reported that the 8% capsaicin patch and topical lidocaine patch were significantly more effective in comparison to oral agents used to treat PHN. The cost-effectiveness and cost per QALY of the 8% capsaicin patch were similar to those of the lidocaine patch and superior to those of the oral products.

### 10.1 Conclusions

The 8% capsaicin patch is effective to reduce PHN pain, and its usefulness is supported by stronger evidence in comparison to other topical agents. Studies have demonstrated some benefit from the use of 0.075% capsaicin cream in PHN.

## 11. Other topical drugs

Other trials of topical drugs in PHN have not yielded noteworthy results. A crossover trial of single doses of indomethacin, aspirin, and diclofenac in solutions with diethyl-ether against placebo (Beneditti, 1996) found that solutions prepared with aspirin and indomethacin were effective in PHN, but not those with diclofenac. However, the data were inadequate for conclusions to be reached.

A double-blind multiple-dose cross-over study comparing 3% benzydamine cream with placebo in PHN treatment (Mc Quay et al, 1990) found no significant differences, which the authors attributed to the short treatment periods studied.

## 12. Other modalities for PHN

Interventional treatment is indicated when the pharmacological treatment is not effective or cannot be tolerated by the patient. It can also be considered in patients who need continued high-dose treatment to control the pain and may prefer an invasive or surgical approach.

In a randomized, controlled, single-blind study, four weekly injections of 60 mg of preservative-free methylprednisolone were administered intrathecally or into the epidural space in PHN patients. There was a substantial benefit for the intrathecal group at 1 and 24 weeks after completion of the treatment, with a good NNT, but no improvement was observed in the epidural group. In a double-blind, randomized, controlled clinical trial, 277 patients with PHN were randomized for the intrathecal administration of 60 mg of preservative-free methylprednisolone in 3 ml of 3% lidocaine, or 3 mL of 3% lidocaine alone, or no lumbar puncture. In the methylprednisolone group, 90% of the patients reported good to excellent pain relief at the end of the treatment, which continued during 2 years of follow-up. No adverse events were reported during the 2-year follow-up period (Kikuchi et al, 1999; Kotani et al, 2000).

The aim of neuromodulation treatments of pain is to use minimally invasive and reversible techniques that can be modified as a function of changes in patient symptoms. Implantable systems with opioids or ziconotide are used in patients with refractory pain (Cruccu et al, 2007; Deer et al, 2007), but there is scant evidence on their use in PHN patients.

Electricity has been used to relieve pain for thousands of years. TENS, defined by the American Physical Therapy Association as the application of electrical stimulation to the skin for pain control, is non-invasive, inexpensive, safe, and easy to use. TENS has multiple

indications and has demonstrated some efficacy in PHN (Nonahan & Kumbang 2008; Cruccu et al, 2007). However, the scientific evidence on its use in PHN is limited and does not allow definitive recommendations to be made (McQuay H, et al, 1998). For its part, the usefulness of spinal cord stimulation has not been supported by a randomized controlled trial (Benzon et al, 2009)

### 13. Clinical guidelines for PHN treatment

Over the past decade, numerous European and American guidelines on neuropathic pain have emerged. Most of them are specific to peripheral neuropathic pain (e.g., PHN) but their preparation has been difficult because almost all of the studies only offer comparisons with placebo and were conducted in small samples of patients for short time periods, despite the chronicity of the disease (Feder et al, 99). There is also a shortage of data on long-term outcomes and on the usefulness of combining different drugs. Methodological limitations include the retrospective calculation of data from studies with different experimental designs and results. Taking this into account, most of the proposals for the treatment of neuropathic pain are based on cost-effectiveness estimations using indirect indicators such as the NNT (number needed to treat to obtain 50% pain relief in one patient) and NNH (number of patients needed for harm, i.e., for withdrawal of one patient from the study due to adverse effects), positively rating treatments with a low NNT and high NNH. Table 6 provides a global summary of the analgesic evidence.

- a. Finnerup established an algorithm for peripheral neuropathic pain (including PHN) in 2005 (Finnerup et al, 2005) and published a revised version in 2007 (Finnerup et al, 2007), based on the available evidence and with many limitations. However, it served as a guide for analgesic treatment in neuropathic pain. They reviewed 105 randomized clinical trials against placebo that were considered to offer high-quality evidence, gathered by a search of Medline, EMBASE and the Cochrane Database, taking the NNT and NNH as reference. Studies of oncologic neuropathic pain and those with a sample of < 10 patients were excluded.
- b. Recommendations:
  - Based on the results of these studies, the authors recommend that localized pain in PHN be treated by the topical administration of the 5% lidocaine patch. When the pain is more widespread, they recommend initiating monotherapy with TCAs or gabapentinoids (oral gabapentin oral or pregabalin) as first-line analgesics.
  - Second-line drugs are the new SNRIs, such as venlafaxine and especially duloxetine, although the studies have been in peripheral neuropathic pain.
  - Opioids, including tramadol, can be considered as third-line options because they have an effect on neuropathic pain, but they are associated with dependency, tolerance, cognitive impairment, and even long-term hormonal disorders.
- c. In 2006 (Attal et al, 2006), a group of experts in neuropathic pain from the EFNS published guidelines on the pharmacological management of neuropathic pain according to the quality of evidence in studies available in Medline or the Cochrane Database. They only analyzed controlled trials (from 1966 to 2006) considered class I or II trials according to the EFNS classification, using the NNT value as reference. They mainly took account of the drugs' analgesic efficacy to reduce the signs and symptoms of neuropathic pain and of their adverse effects, but they also considered the repercussions on the quality of life and state of mind of the patient.

- d. Recommendations in PHN:
- First-line analgesics: TCAs, pregabalin, and gabapentin, with grade A evidence.
  - Second-line: SNRIs (e.g., duloxetine and venlafaxine), although their effectiveness and lesser adverse effects in comparison to TCAs mean that the new SNRI antidepressants are often prioritized.
  - Lower-quality evidence is available for opioids (tramadol and oxycodone) and lamotrigine.
  - When the pain relief is inadequate, they proposed using combinations of first-line drugs that do not interact and have complementary action mechanisms, despite the scant scientific evidence on this approach, and as a last resort, combinations with opioids.
- e. In 2007 (Moulin et al, 2007), the Canadian Pain Society published evidence-based guidelines on the clinical management of neuropathic pain, directed at Canadian healthcare professionals. The main treatment lines and a concise management algorithm were included. They only considered well-designed controlled clinical trials against a placebo or effective substance with a minimum of 10 patients, gathered from Medline and the Cochrane Database. Recommendations were based on four criteria: analgesic efficacy with at least grade 1B evidence, tolerability, ease of management, and cost-effectiveness.
- f. Recommendations for PHN:
- First-line analgesics: TCAs (amitriptyline and imipramine) or antiepileptics (gabapentin and pregabalin). If the drug fails or cannot be tolerated, it is recommended to try another from the same group.
  - Second-line: SNRIs (e.g., venlafaxine and duloxetine) due to the weaker evidence and their higher cost. Lidocaine patches.
  - Third-line: opioids such as tramadol and oxycodone for moderate or intense pain.
  - Fourth-line: cannabinoids, methadone, SSRIs and other AEDs.
  - Non-pharmacological procedures, such as physiotherapy, moderate exercise and psychological support are recommended alongside the different drugs.
- g. A group of neuropathic pain experts from the IASP (Dworking et al, 2007) provided an evidence-based update on recommendations for neuropathic pain management. They reviewed articles (from 1966 to 2007) in Medline and the Cochrane Database on controlled clinical trials (grade 1b evidence or higher) as well as relevant book chapters and other publications. They highlighted the lack of head-to-head studies of the drugs, making it difficult to clearly establish their relative efficacy or safety. The main criteria applied for establishing recommendations were: degree of efficacy of the drug in neuropathic pain, its safety and tolerability, drug-drug interactions, ease of management, impact on patient quality of life, improvement in comorbidities associated with neuropathic pain (sleep, anxiety, etc.), costs associated with the therapy, the potential risk of abuse and addiction, and the risk of overdose.

Recommendations:

- First-line: TCAs, SNRIs (duloxetine and venlafaxine), calcium channel alpha2delta ligands (pregabalin and gabapentin), and topical lidocaine.
- Second-line: opioids (morphine, oxycodone, methadone) and tramadol, based on trials with grade A evidence, the clinical experience of the experts, and guidelines on the management of opioids in non-oncologic pain, although it can be considered as first-line treatment in certain circumstances (more intense pain or during titration of other drugs).

- Third-line: capsaicin, mexiletine, or NMDA receptor antagonists, based on controlled trials with grade B evidence alongside the clinical experience of the experts, although these drugs can be used as first-line treatment in certain specific situations.
  - For non-responding patients, they recommended trying combinations among first-line drugs with different action methods or even with a third-line drug, although there is scant evidence on these strategies.
- h. In 2009 (Attal et al,2009), the group of experts in neuropathic pain of the EFNS again published an update, using Medline and the Cochrane Database and classifying trials according to the etiology. All class I and II randomized controlled trials were considered.

#### Recommendations

- First-line: TCAs (amitriptyline or imipramine 25-150mg/day), pregabalin (150-600 mg/day), and gabapentin (1200-3600 mg/day), supported by the strongest evidence. As topical analgesics, 5% lidocaine patch (maximum of 3 patches at a time, with special indication in the elderly) and 8% capsaicin patch.
- Second- or third-line: 0.075% capsaicin cream and valproate, with weaker supporting evidence. Opioids such as morphine, oxycodone, or methadone and tramadol (200-400 mg/day), with good evidence in PHN but in 2<sup>nd</sup> or 3<sup>rd</sup> line due to their adverse effects.
- When first-line treatments fail, combinations are recommended, despite the little evidence available. The association of morphine with gabapentin has shown some effectiveness in PHN.

DRUG	NNT
1. TCAs (tricyclic antidepressants)	2.8 (2.2-3.8) Amitriptyline (better evidence)
2. SNRIs	ND
3. Gabapentin	3.8 (3.1-5.1),
4. Pregabalin	3.7 (3.2-4.4),
5. Opioids	2.6 (1.9-4.1) Oxycodone (better evidence)
6. Tramadol	4.8 (2.6-27)
7. NMDA antagonists	NE
8. 5% Lidocaine patch	UK
9. 8% Capsaicin patch	UK
10. Capsaicin cream	3.2 (2.2-5.9)

ND: No data available; NE: No efficacy in PHN; UK: Unknown

Table 6. NNT of pharmacological therapies in PHN (Dubinsky et al, 2004; Argoff et al, 2004; Finnerup et al, 2007; Attal et al, 2010; Baron et al, 2010)

#### 14. Conclusions (Hemperstal 2005; Baron, 2010; Dubinsky et al, 2004; O'Connor et al, 2009)

1. A multidisciplinary approach is needed, using pharmacological and non-pharmacological treatments.
2. The optimum individual pharmacological regimen in PHN should balance analgesia with harm in terms of side-effects, comorbidities, and drug interactions.
3. Drugs providing the greatest pain relief with fewest side-effects should be identified.
4. Drugs with strongest evidence as first-line analgesics should be used. TCAs (amitriptyline, imipramine), calcium channel  $\alpha 2\text{-}\delta$  ligands (gabapentin, pregabalin), topical 5% lidocaine patch, and topical 8% capsaicin patch have shown consistent efficacy in randomized controlled clinical trials and meta-analyses in PHN (Table 6). Figure 1.
5. Some opioid analgesics and tramadol may be indicated if there is no response to other drugs. Despite the evidence on their efficacy, they are relegated to the second-line due to the possible adverse effects. They can only be considered as first-line treatment in certain circumstances (severe pain or poor tolerability of first-line drugs).
6. Topical agents may be first-line in PHN patients who are elderly or with the presence of multiple diseases, despite weak evidence.
7. There is no evidence-based treatment of PHN with NSAIDs.
8. In clinical practice, a combination of two or more drugs is often needed to achieve satisfactory pain relief, although there have been few trials to support this clinical observation. Regular assessment is mandatory.

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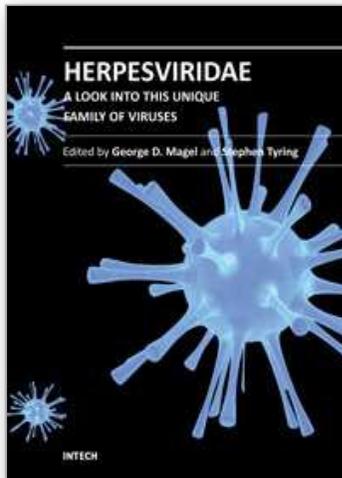
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## **Herpesviridae - A Look Into This Unique Family of Viruses**

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In order to fully understand the nature of viruses, it is important to look at them from both, their basic science and clinical, standpoints. Our goal with this book was to dissect Herpesviridae into its biological properties and clinical significance in order to provide a logical, as well as practical, approach to understanding and treating the various conditions caused by this unique family of viruses. In addition to their up-to-date and extensive text, each chapter is laced with a variety of diagrams, tables, charts, and images, aimed at helping us achieve our goal. We hope that this book will serve as a reference tool for clinicians of various specialties worldwide.

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