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Changing the paradigm in postherpetic neuralgia treatment: lidocaine 700 mg medicated plaster

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Abstract. – OBJECTIVE: Chronic pain is currently considered a disease state with biopsychosocial consequences and a negative impact on patients' quality of life (QoL). Pain from postherpetic neuralgia (PHN) can persist for months or years and is a prototypical example of chronic pain. We analyzed PHN as a model of chronic pain, including its effects on QoL and clinical aspects. We explored treatment options, focusing on the topical treatment with lidocaine 700 mg medicated plaster (LMP) and how this impacts PHN management.

MATERIALS AND METHODS: This article is a narrative review of published studies. Preclinical and clinical studies were retrieved from literature through a search performed in PubMed/MEDLINE.

RESULTS: To choose the appropriate treatment for chronic pains, such as PHN, not only efficacy but also tolerability, manageability, practicality, and compliance are important factors, especially in the long term. It is also important to set treatment expectations with the patients as total suppression of pain may be unrealistic, and a balance needs to be found between pain control and the minimization of adverse events. In this respect, LMP may be the best currently available treatment: it is easy to use, has low systemic absorption and thus a low risk for pharmacological interactions. Therefore, treatments can be personalized, and concomitant medications can be added, if needed. Recent data from a real-world study support this view by showing that LMP has superior effectiveness in reducing pain and improving the QoL compared to other commonly used systemic treatments and confirming its good tolerability profile that is mainly characterized by localized skin reactions.

CONCLUSIONS: LMP is one of the best currently available treatment options for PHN patients balancing good efficacy with an excellent tolerability profile and can therefore be considered for use as a first-line treatment for PHN.

Key Words:
Herpes zoster, Postherpetic neuralgia, Lidocaine 700 mg medicated plaster, Pain management, Chronic pain, Localized neuropathic pain, Quality of Life, Versatis®.

Introduction

Pain from postherpetic neuralgia (PHN) is a chronic pain that can persist for months or years after the resolution of the herpes zoster (HZ) rash[1]. This duration is in accordance with the 2019 International Association for the Study of Pain (IASP) definition of chronic pain, which defines chronic pain as a persistent or recurrent pain lasting more than 3 months or beyond normal tissue healing, and which has been integrated into the 11th revision of the International Classification of Diseases (ICD-11)[2,3]. In 2020, the chronic pain definition was further refined by the IASP as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage[4]". PHN, which falls into the category of localized neuropathic pain (LNP), is the most common complication of HZ and can persist for years after the resolution of the HZ rash[5]. The cause of PHN-associated

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chronic pain – often described as shooting, stabbing, or hot-burning – was traditionally thought to be an alteration of the central nervous system (CNS) signal processing following an injury of the peripheral nerves resulting in allodynia and hyperalgesia[5,6].

Chronic pain has been recently reconsidered as a disease state[4], with a negative impact on patients' quality of life (QoL), consequent psychological and social problems, and related conditions of discomfort, anxiety and impaired functional status, which can complicate treatment[7,8].

In this review, we analyze the new evidence in PHN physiopathology, PHN as a model of chronic pain with biopsychosocial consequences and its impact on the patients' QoL, its clinical aspects and treatment options, with a focus on the 700 mg lidocaine medicated plaster (LMP) and how it changed the management of PHN.

Materials and Methods

This article is a narrative review of published studies. Preclinical and clinical studies were retrieved from literature through a search performed in PubMed/MEDLINE. Keywords used for the search included but were not limited to, "herpes zoster", "postherpetic neuralgia", "lidocaine 700 mg medicated plaster", "pain management", "chronic pain", "localized neuropathic pain", "quality of Life" and "Versatis".

Physiopathology of LNP and PHN

The resurgence of a longstanding varicella zoster virus (VZV) infection in a single dorsal root ganglion causes HZ ("shingles"). In the corresponding dermatome, this gives rise to a severely painful skin rash with the presence of vesicles. If the dermatomal pain persists long (i.e., more than 3 months) after the rash has cleared, it results in the chronic pain condition, known as PHN[5,9]. A complete overview of the known and possible mechanisms underlying PHN pain is beyond the scope of this review. Nevertheless, knowledge of these mechanisms is of utmost importance to select the best treatment option for the patient and to strengthen the rationale for using the selected medication in PHN, as later illustrated in other sections of this manuscript. Although the viral etiology of HZ/PHN appears to be solid, the presumed causes of pain in HZ and PHN are perhaps less clear[9].

In contrast to other parts of the nervous system, cell bodies of neurons in sensory, sympathetic, and parasympathetic ganglia are tightly enveloped by satellite glial cells (SGCs), which have functions similar to those of astrocytes in the CNS. In herpes-infected patients, the virus may reside in these SGCs rather than in the neurons, although the role of the SGCs in herpetic infection and pain is still controversial. SGCs can be triggered by different types of nerve injury and inflammations. In various rodent pain models, where the herpes simplex virus type 1 (HSV-1) is used instead of the VZV (as VZV cannot infect murine cells), changes in SGCs augment neuronal activity and contribute to the development of chronic pain. An *in vitro* study with freshly dissociated neurons and SGCs infected with one HSV-1 showed intercellular Ca^{2+} waves, resulting in neuronal hyperexcitability that may lead to increased neuronal firing and, thus, pain[10]. The potential role of SGCs warrants further exploration to clarify the further pathophysiology of PHN.

Various physiopathology dynamics have explained the complexity of PHN pain. The most recent explanation, the ectopic pacemaker hypothesis, has been proposed by Devor[9]. This hypothesis comprises two elements: (1) spontaneous HZ/PHN pain is proposed to be caused by spontaneous firing arising at ectopic pacemaker sites in the peripheral nervous system (PNS). These sites are associated with the dying-back of axon's extremities and pathology in sensory pyrenophora, in the dorsal root ganglion infected by the VZV; and (2) tactile allodynia would be the result of the augmentation by central sensitization of the sensory effect arising from normal cutaneous Aβ touch afferents. The spontaneous ectopic discharge would, in turn, maintain this central sensitization. Presumably, central sensitization also amplifies spontaneous firing in peripheral nociceptors, and Aβ afferents are also "amplified" (i.e., rendered painful and more intense). This factor augments spontaneous pain[9].

PHN, a Model of Chronic Pain with Biopsychosocial Consequences and Its Impact on Patients' QoL

PHN pain intensity has been very high compared to other chronic pain conditions, such as rheumatoid arthritis, atypical facial pain, and osteoarthritis[11]. This high-intensity pain and the presence of a clear correlation between increasing severity of pain and greater interference on mood, daily activities, and working status[12,13] deeply affect the patients' QoL across all four

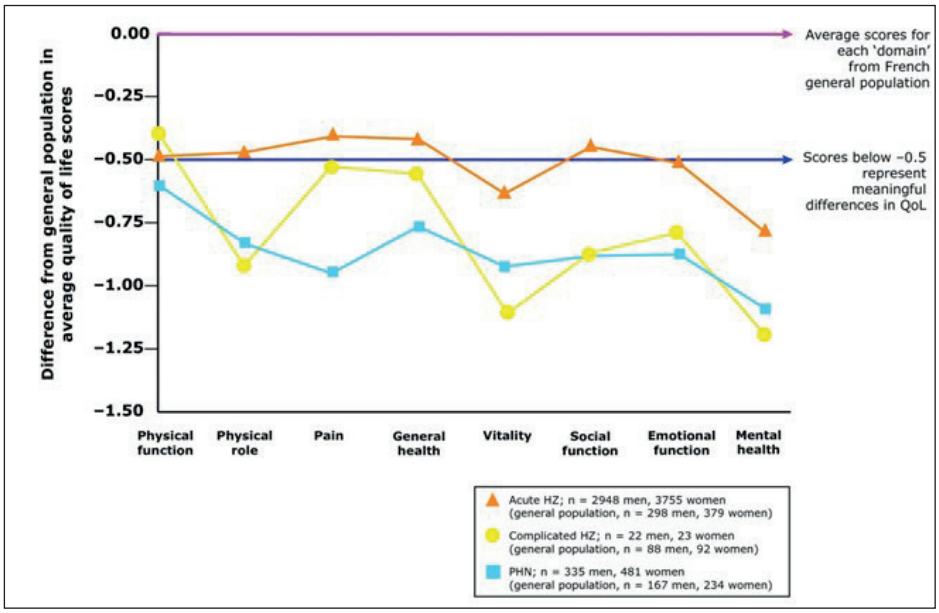

Figure 1. Quality-of-life scores in a French general population cohort *vs.* patients with herpes zoster or post-herpetic neuralgia. H.Z.: Herpes zoster; PHN: Post-herpetic neuralgia; QoL: Quality-of-life. Source: Johnson et al[8] 2010. Reproduced from BioMed Central Ltd. under the terms of the Creative Commons Attribution License.

Table I. Domains of the patients' QoL affected by PHN and H.Z.

Physical
- Fatigue
- Anorexia
- Weight loss
- Reduced mobility
- Physical inactivity
- Insomnia

Social
- Withdrawal
- Isolation
- Attendance at fewer social gatherings
- Loss of independence
- Change in social role

Psychological
- Depression
- Anxiety
- Emotional distress
- Difficulty concentrating
- Fear

Functional
- Dressing, bathing, eating, mobility
- Travelling, cooking, housework, shopping

Source: Johnson et al[8]. Reproduced from BioMed Central Ltd. under the terms of the Creative Commons Attribution License.

health domains – physical, psychological, functional and social (Table I)[8]. Indeed, in patients with HZ or PHN, QoL scores are lower in all domains when compared with a general population, including healthy people and those with different chronic conditions, such as arthritis, chronic lung disease, congestive heart failure, and others. In particular, scores for the physical functioning, pain and general health showed substantially larger decreases in the PHN group than in the other patients, including those with acute or complicated HZ (Figure 1)[14]. Thus, the longer the pain and the higher its intensity, the higher the burden on the QoL. Patients who had PHN for longer than 6 months have greater disability and psychological distress than those who had it for less than 6 months[15]. A survey[16] conducted in > 1,000 patients with HZ or PHN aged ≥ 50 years showed significantly higher mean pain scores, both on average and at its worst, in those with PHN compared with those with HZ. In the same study, significantly more respondents with PHN than with HZ reported consequences regarding anxiety and/or depression (11% *vs.* 5%), overall health status (54% *vs.* 24%), and social and family life (54% *vs.* 42%). The higher burden of PHN compared with HZ seems to be present in the physical

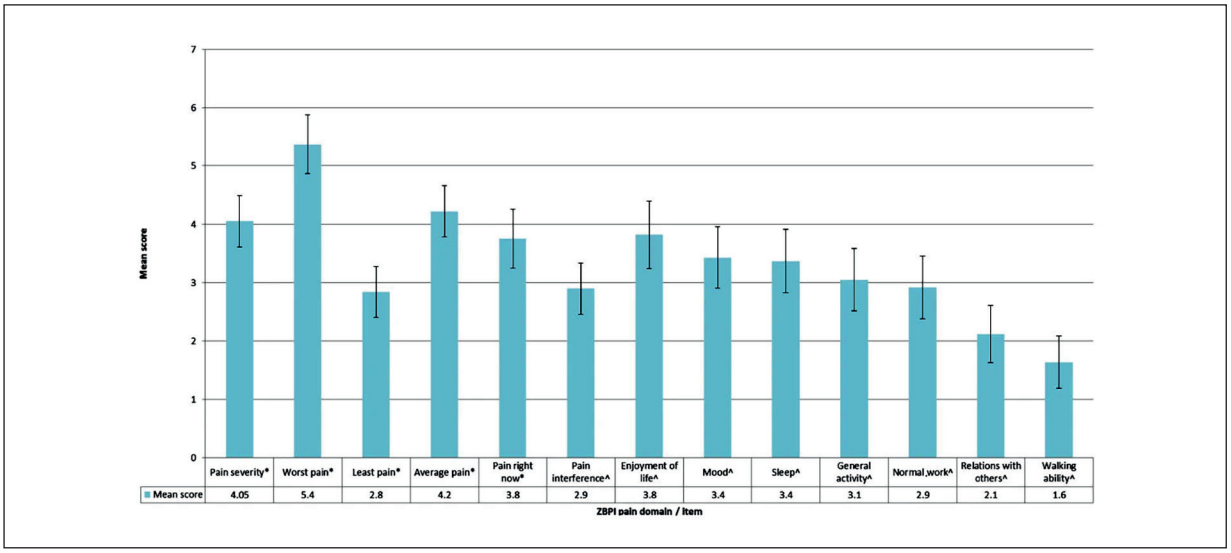

Figure 2. Zoster Brief Pain Inventory domain and component scores among post-herpetic neuralgia zoster quality of life study patients. Scores of items marked with * range from 0 (no pain) to 10 (pain as bad as you can imagine). Scores of items marked with ^ range from 0 (does not interfere) to 10 (completely interferes). ZBPI*:* Zoster Brief Pain Inventory. Source: Serpell et al[17] 2014. Reproduced from BioMed Central Ltd under the terms of the Creative Commons Attribution License.

functioning domain[17] and the psychosocial one. Psychosocial scores improve in patients who fully recover from the acute symptoms of HZ, but they remain low in patients who develop PHN[18]. HZ/PHN patients' perception of QoL is mostly affected by restrictions in daily activities due to chronic pain. These include limitations in concentrating on mental tasks, being touched by a person, even wearing clothes, going shopping, and getting out of the house – with the latter two having the highest impact – but also in moderate physical efforts and climbing a flight of stairs[16]. In the observational zoster QoL study, which included 152 UK patients with PHN, more than half of the patients reported pain at levels typically considered indicative of significant health-related QoL (HR-QoL) burden[17]. Study participants showed statistically and clinically relevant deficits on all facets of HR-QoL, assessed with various questionnaires, compared to age-matched UK norms. Physical, mental, and affective components were affected, with 'pain' being the most relevant problem reported by 90.1% of the participants. The impact of such pain was greatest in terms of 'enjoyment of life', 'mood' and 'sleep' (Figure 2)[17]. The impact of PHN on QoL is also confirmed by other smaller but more recent studies[19,20]. PHN patients have difficulties in completing complex activities (e.g., shopping, traveling, performing household chores) and undertaking the most basic ones, such as dressing, bathing, eating, or concentrating on a task. They experience anorexia, weight loss, reduced mobility, fatigue, and insomnia due to PHN-caused loss of physical function[21]. The reduced independence and reduced participation in social gatherings may result in withdrawal, loss of social contact and isolation. Older patients can lose their autonomy or end up institutionalized[22]. PHN patients fear recurrences of symptoms and are at greater risk of anxiety and depression, especially if the pain is intense[12,21]. The impact of PHN on QoL can be of such magnitude that some patients even became suicidal[23].

For such reasons, it is advisable to pursue a comprehensive pathway of care that values the physical, psychological and social components of pain and to evolve our mindset by targeting both pain and functional outcomes as complementary means to ensure adequate care[7]. Such an approach would align with the evolving notion of pain as a biopsychosocial issue[24]. Chronic pain is a complex multidimensional experience that goes beyond adaptations in the nervous, endocrine, and immune systems and comprises other factors facets severely compromising the HR-QoL.

Diagnosis, the Patient's Journey, and the Role of the Primary Care Physician and of the Pain Therapist

Compared to other forms of peripheral neuropathic pain (PNP), PHN may be one of the most

Table II. Diagnostic steps in postherpetic neuralgia.

Step	Diagnosis notes
1. Patient history	Routine questioning should identify the source of the patient's pain Pain is typically discrete and unilateral and displays an itching, burning, sharp, stabbing or throbbing quality Pain is intermittent and chronic in nature Pain is sufficiently intense to interfere with normal daily activities Pain following a documented episode of AHZ provides compelling evidence for a diagnosis of PHN
2. Physical examination	Areas of previous AHZ infection may manifest evidence of cutaneous scarring Affected area may display either hypersensitivity or hyposensitivity to pain Allodynia may occur in the pain-producing area Autonomic changes may also occur in the affected area, including increased sweating
3. Laboratory investigations	PHN diagnosis does not rely on laboratory evaluations Viral culture or immunofluorescent staining may be used to distinguish herpes simplex from herpes zoster Presence of antibodies to herpes zoster may help support diagnosis of subclinical herpes zoster infection, especially in the case of zoster sine herpete Other laboratory tests may be useful in confirming a herpes zoster infection, includin immunoperoxidase staining, histopathology and the Tzanck smear

AHZ: Acute herpes zoster; PHN: Postherpetic neuralgia. Source: Nalamachu et al[26] 2012. Reproduced from Springer Nature under the terms of the Creative Commons Attribution 2.0 International License.

straightforward conditions to diagnose and manage. Steps to properly diagnose PHN are presented in Table II. However, particular attention from the physician is required, given the variability of the clinical picture, the possible temporal distance between the onset of PHN and that of the HZ rash, and the fact that the patient may not recall being affected by the virus[25-27]. In the acute phase, neuropathy-related pain is easier to diagnose. The subacute and chronic phases are more difficult to frame from a diagnostic and therapeutic point of view. A superficial neuropathic pain, with dermatomal and persistent localization, without any plausible cause and/or explanation, should lead to a suspect of PHN even in the absence of a herpetic eruption in the medical history, especially in a patient with risk factors for HZ/PHN. Moreover, it should not be forgotten that there is a risk of underestimating the event, in particular in the subacute phase, since there is no structured flow for sending patients with PHN to the pain therapy network (at least in Italy)[7].

The PHN patient's journey is often long and troubled, and many issues must be solved to optimize the treatment pathway in clinical practice. The treatment goal is to relieve pain quickly. Despite numerous consultations and receiving multiple medications, most patients report being in pain 'most of the time' or 'all of the time'[17]. Moreover, with each treatment failure, patients become more frustrated and feel a lack of understanding, augmenting the already high burden of PHN on the HR-QoL. For example, it has been reported[28] that patients with PHN in a pain clinic sample had visited their general physicians an average of 19 times (range: 0-69 visits). In addition, nearly half of patients with comorbid conditions, such as rheumatoid arthritis, coeliac disease, osteoarthritis, heart failure, diabetes and asthma, reported some degree of deterioration in those conditions because of HZ/PHN[16]. Indeed, frustrated patients often seek specialist intervention to "recover from pain". This poses a problem to the pain specialist (PS): freedom from pain in neuropathic conditions is an unrealistic goal since it is often unattainable or would result in important downsides as aggressive dosing of pharmacological therapies may be required[29]. The role of the PS should thus not be limited to making the correct diagnosis and choosing the most suitable pain treatment, but also include a redefinition of therapeutic objectives (mitigation instead of healing) and strive to improve all facets of the HR-QoL rather than just reducing pain[7,24].

Guidelines and Treatments

Several treatments can reduce neuropathic pain and PHN[30-34]. Nearly all current guidelines[29,31,33,35,36] recommend calcium channel α2-δ ligands (i.e., anticonvulsants), such as gabapentin

and pregabalin, and antidepressants (with both norepinephrine and serotonin reuptake inhibition), such as amitriptyline, nortriptyline and desipramine, as first-line treatment for neuropathic pain. However, these systemic treatments have only been effective in 30-40% of the treated patients. They are often associated with tolerability problems and side effects[37], which will be further discussed in the following section. The French recommendations[36] and guidelines from the German Society of Neurology[29], published in 2020 and thus appearing to be the most up to date, recommend lidocaine patches as first-line treatment in all kinds of patients suffering from PHN. Other guidelines, such as those from the European Federation of Neurological Societies (EFNS)[33] and the Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP[35], although not recommending LMP as first-line treatment, recommend it as first-line treatment for frail and/or elderly patients, especially when other concomitant medications are being used. This recommendation is based on LMP's low systemic absorption, which results in excellent safety and tolerability compared to systemic treatments. Interestingly, Japan guidelines[38] acknowledge the effectiveness of LMP but have not added it to the recommended therapies, as it hasn't been approved in the country yet.

As reported in the German guidelines[29], drug therapy of neuropathic pain should set realistic treatment goals. Although many drugs are available, there is a remaining issue that some patients do not respond appropriately or suffer from intolerable side effects. Complete freedom from pain is often not achievable. Suggested realistic treatment goals could be: pain reduction by ≥ 30%, improvement of quality of sleep, improvement of QoL, preservation of relationships and social activity, maintaining the ability to work and improved functionality. Considering these treatment goals, LMP could be considered the most suitable option for PHN treatment, as discussed in the next paragraph.

The Lidocaine Medicated Plaster – Rationale for Use in PHN

The LMP (Versatis®) was first registered in 1999 in the USA. It has been approved and used to relieve neuropathic pain associated with PHN in adults in Italy. The patch consists of a soft polyethylene terephthalate fabric base on which an adhesive hydrogel is placed. These two components act in synergy: the polyethylene terephthalate fabric confers physical protection against mechanical stresses and is very much appreciated in the case of allodynia or hyperalgesia; lidocaine is released from the hydrogel base and reaches the skin layers of the epidermis and dermis, where it exerts its mechanism of action[37].

Pharmacological Profile

As outlined in the section "Physiopathology of LNP and PHN", pain in PHN may be caused by discharges at ectopic pacemaker sites in the PNS[9]. Consequently, suppression of the ectopic electrogenesis at a peripherical level by stabilizing membranes would result in a therapeutic effect. This may explain why the currently used systemic drugs (systemic local anesthetics, membrane-acting antidepressants, and anticonvulsants) may fail as they are membrane-stabilizing drugs, suppressing neuronal hyperexcitability not only in the PNS, but also in the CNS[9]. Lidocaine can also act in the same way, but it is administered topically; thus, it does not interfere with the CNS and possesses a more targeted effect.

Mechanism of Action

Lidocaine is a well-known local anesthetic that acts through a selective sodium channel blockade. The presumed mechanism of action of LMP is the suppression of ectopic stimuli by reversibly inhibiting the conduction of neuronal impulses and stabilizing neuronal membranes of abnormally excitable Aδ and C fibers through the blockade of sensitized Nav1.7 and Nav1.8 sodium channels. It also regulates T-cell activity and suppresses nitric oxide production, inhibiting inflammatory processes. It may also reduce firing in transient receptor potential (TRP)-containing nerves (with subsequent analgesia by membrane depolarization) through the activation of the TRP channels TRPV1, and TRPA1 expressed in nociceptive sensory neurons[39-47]. However, skin penetration and concentration are far too low to block impulses propagating along with dermal axon bundles; indeed, LMP has an analgesic, and not anesthetic effect, and thus, the skin does not get numbed[9,48,49]. In practice, there would be a peripheral action whereby ectopic impulses are turned off, with a consequent central effect of containment of the central sensitization caused and maintained by the continuous firing arriving from the peripheral neurons. Reduced inputs from the PNS (counteracting the central sensitization) and a smaller nerve fiber density in the epidermis thus seem to play a key role in LMP's long-term pain relief action[50].

Systemic Uptake

Lidocaine patches have shown a very low systemic uptake (3%), with blood concentrations around 0.06 mg/l. A population kinetics analysis[37,44,51-53] revealed that after the simultaneous application of three plasters for 12 hours/day for up to 1 year, a mean maximum lidocaine plasma concentration of 45 ng/ml could be reached, i.e., a concentration much lower than therapeutic antiarrhythmic (2-5 mg/l) or toxic (> 6 mg/l) concentration. Based on this low systemic exposure, pharmacological interactions are unlikely.

In conclusion, the use of LMP is in line with the aforementioned ectopic pacemaker hypothesis, which stresses the importance of "focusing on suppression of ectopic electrogenesis using nonblocking concentrations of membrane-stabilizing drugs[9]".

Clinical Profile

Adherence rates to the prescribed pain medications in patients suffering from chronic pain vary, ranging between 8% and 62%[54]. Multiple factors impact adherence, including tolerability, dosing frequency, comorbidities, such as depression, and a perceived benefit from treatments[55]. In patients with PHN, therapeutic compliance is difficult to achieve since treatment dissatisfaction is often high. In one study[12], only 14% of patients were satisfied with their medication. Almost half of them did not discuss their symptoms with physicians regularly, and around 10% was considerably troubled by the treatments' side effects[12,22]. Personalized management of chronic pain must be based on goals agreed with the patient according to his/her own, family and work needs, sports potential, and lifestyle habits. Considering the

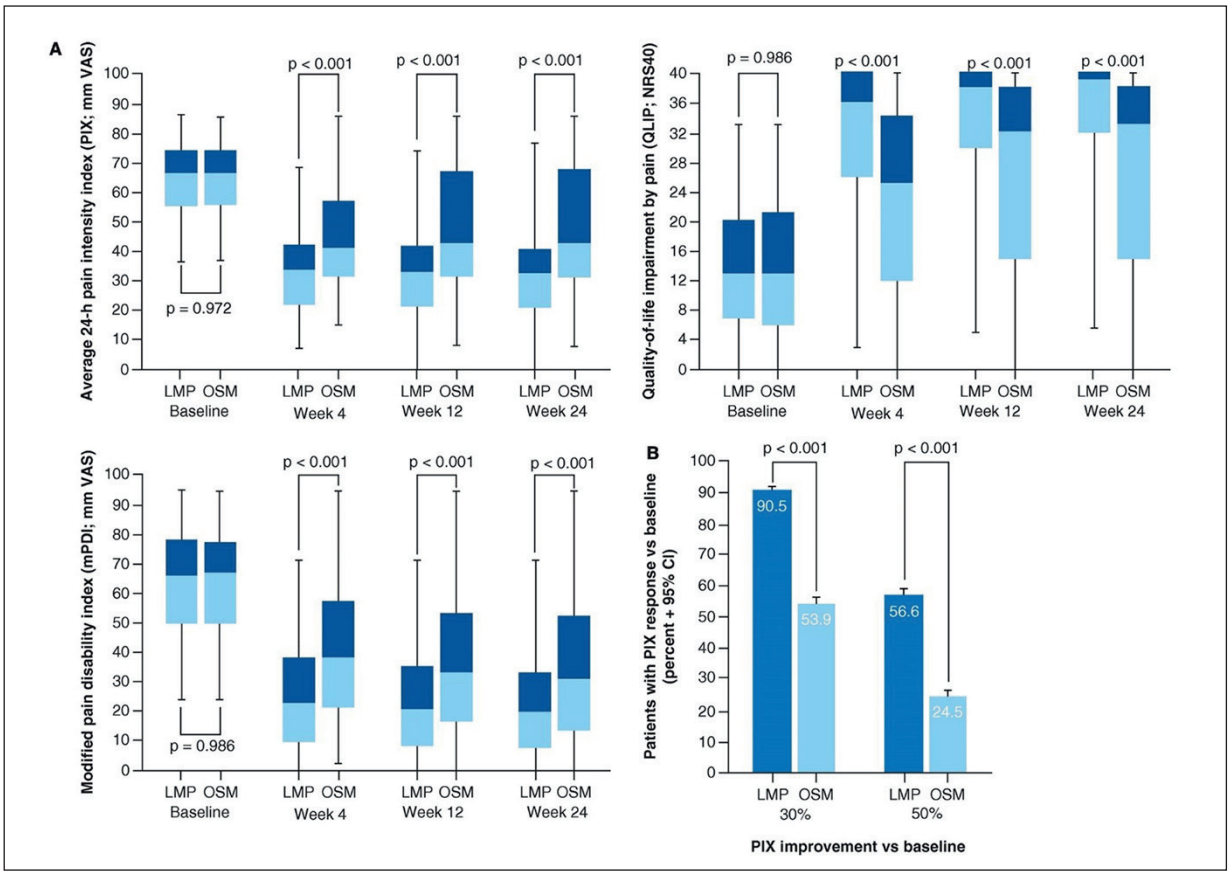

Figure 3. Change in pain intensity index, pain-related impairments, and quality of life. **A**, Change from baseline over the observation period. Boxplots show median (middle horizontal line in the box), 25 and 75% quartiles (bottom and top lines of the box), and 5% and 95% percentiles (whiskers). Improvement is shown by reductions in Pain Intensity Index and Modified Pain Disability Index, and by increases in quality-of-life impairment by pain. **B**, Improvement *vs.* baseline in pain intensity index at end of observation. LMP: Lidocaine 700 mg medicated plaster; NRS: Numerical rating scale; OSM: Oral systemic medication; PIX: Pain intensity index; VAS: Visual analogue scale. Source: Überall et al[47] 2021. Reproduced from Future Medicine Ltd. under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License.

needs of patients (pain reduction and improvements in QoL) and clinicians (safety, tolerability, practicality, and personalization of therapy), LMP may help addressing the objectives of both patients and clinicians.

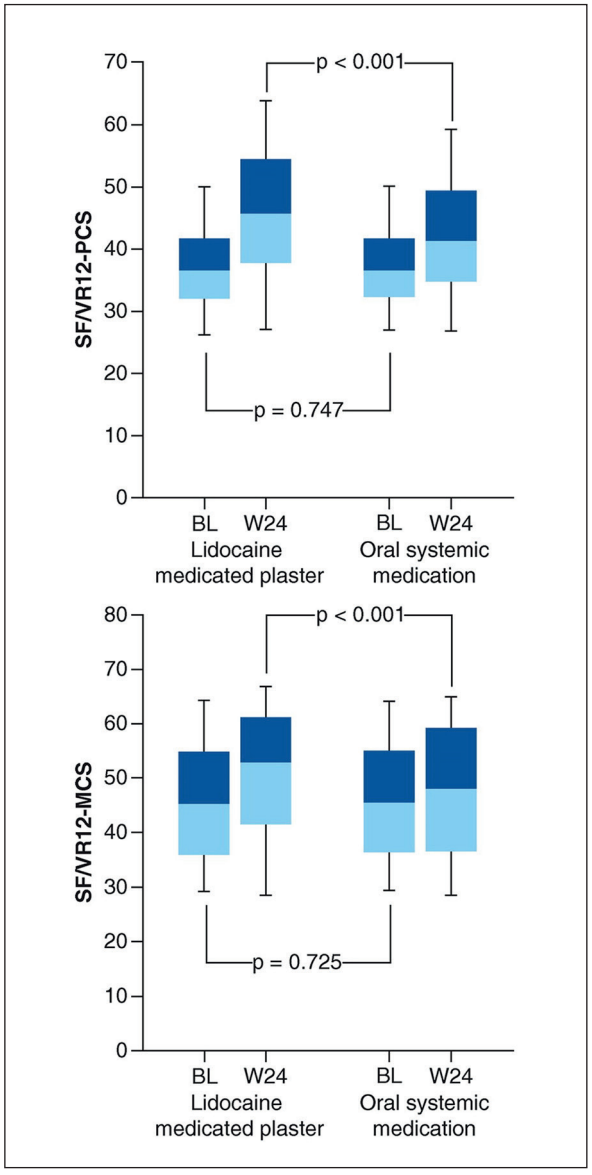

Figure 4. Change in overall quality of life over the observation period (Short Form 12 questionnaire). Boxplots show median (middle horizontal line in the box), 25% and 75% quartiles (bottom and top lines of the box), and 5% and 95% percentiles (whiskers). BL: Baseline; MCS: Mental component score; PCS: Physical component score; SF/VR12: Short form/Veterans RAND 12. W24: Week 24. Source: Überall et al[47] 2021. Reproduced from Future Medicine Ltd. under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License.

Pain Reduction, Patient Satisfaction and QoL

Some of the most important treatment goals for neuropathic pain are pain control and improvement in function[29]. There are several studies[32,39,47,52,56-59] supporting the superiority of the treatment with LMP. A network meta-analysis of randomized controlled trials suggested lower effectiveness for pregabalin, or high-dose capsaicin compared with LMP in treating PHN[56]. One study of particular importance is the large, retrospective study from Überall et al[47]. It collected real-world data from the German Pain e-Registry of adult PHN patients with pain lasting ≥ 3 months and refractory to treatment with at least one systemic oral first-line drug. It compared two cohorts of 1,711 patients treated with either LMP or oral systemic medications (OSM). Analysis revealed a greater reduction in pain intensity in the group treated with LMP *vs.* OSM at 4, 12 and 24 weeks (Figure 3)[47]. There were also improvements in daily activities and higher quality of life in the group treated with LMP *vs.* OSM, measured with different parameters (SF-12, Pain disability index, quality of life impairment by pain) (Figure 4). After 24 weeks of treatment, significantly more LMP patients than OSM patients (76.5 *vs.* 45.7%, $p < 0.001$) reported 'much better' and 0'very much better' improvements. Considerable improvements for the outcome measure pain-related QoL were significantly greater than improvements under OSM treatment. Data from this retrospective chart review are consistent with that of the first randomized, controlled clinical trial comparing LMP with pregabalin for 4 weeks by Baron et al[39], which showed that, while both treatments reduced allodynia severity, more patients better responded to LMP treatment than to pregabalin. This response was not limited to a greater pain reduction but also included greater improvements in patient satisfaction and QoL and a more favorable efficacy/safety profile[39]. Another study showed a patient-rated pain relief between "moderate" and "a lot" and, most importantly, at the final visit, LMP was rated at least to be good by 91% of physicians and 89% of patients[52]. LMP was also shown to improve the QoL by maintaining cognitive integrity better than OSM (namely antidepressants, anticonvulsants, and opiates)[57]. Finally, treatment with LMP could also reduce the size of the allodynic area[58,59]. In a case series by Casale et al[59], a reduction in the painful area of more than 50% was recorded in PHN patients, including those with PHN lasting months or even years.

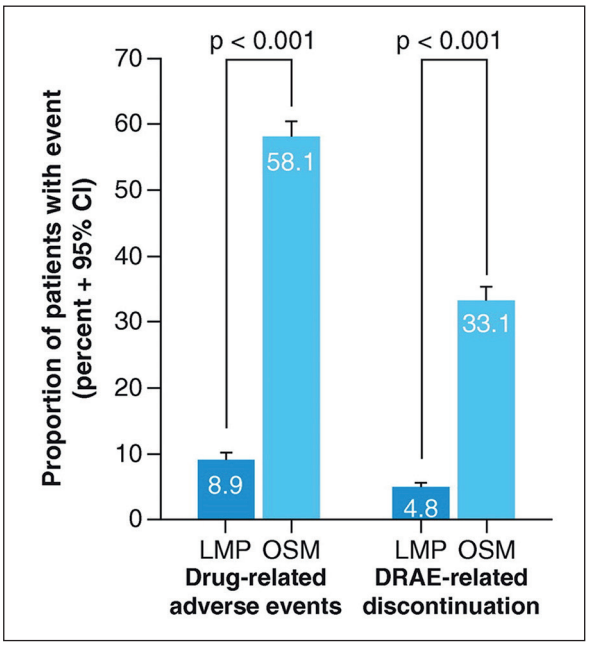

Figure 5. Drug-related adverse events over the observation period. DRAE: Drug-related adverse event; LMP: Lidocaine 700 mg medicated plaster; OSM: Oral systemic medication. Source: Überall et al[47] 2021. Reproduced from Future Medicine Ltd. under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License.

Safety, Tolerability, Adverse Events, and Duration of Treatment

The aforementioned low systemic exposure to lidocaine results in a low number of systemic adverse events (AEs), known to be one of the main drawbacks of first-line oral treatments[39,51,60,61]. European general practice data for neuropathic pain treatment also show a better safety profile for LMP compared with gabapentin, pregabalin, duloxetine, and amitriptyline[62]. Data from the Überall study[47] show how patients in the OSM group reported nervous, psychiatric, and gastrointestinal disorders, with somnolence, dizziness, nausea and hyperidrosis being the most common drug-related AEs (DRAEs). The percentage of patients treated with LMP and experiencing DRAEs was significantly lower (8.9 *vs.* 58.1% for OSM patients; $p < 0.001$), as was the proportion of LMP patients discontinuing treatments because of DRAEs (4.8 *vs.* 33.1% for OSM patients; $p < 0.001$) (Figure 5). LMP-related AEs were limited to localized skin reactions.

LMP has a good tolerability profile in long-term treatments[51]. A study from Sabatowski et al[63] investigated the efficacy of LMP treatments for up to 4 years. It reported no serious AEs, while DRAEs were limited to application site reactions that were reported in only 18.8% of patients. There was also no visible tolerance to the analgesic effect at the end of the trial. The other three studies[44,64,65], which assessed long-term LMP treatment (from 5 to 7 years) found few side effects, a high degree of patient satisfaction, and no development of tolerance.

Having in mind the above-presented efficacy and safety profile of LMP in the treatment of PHN, it is not surprising that a recent benefit-risk analysis according to current guidance shows a more favorable benefit-risk ratio of LMP com-

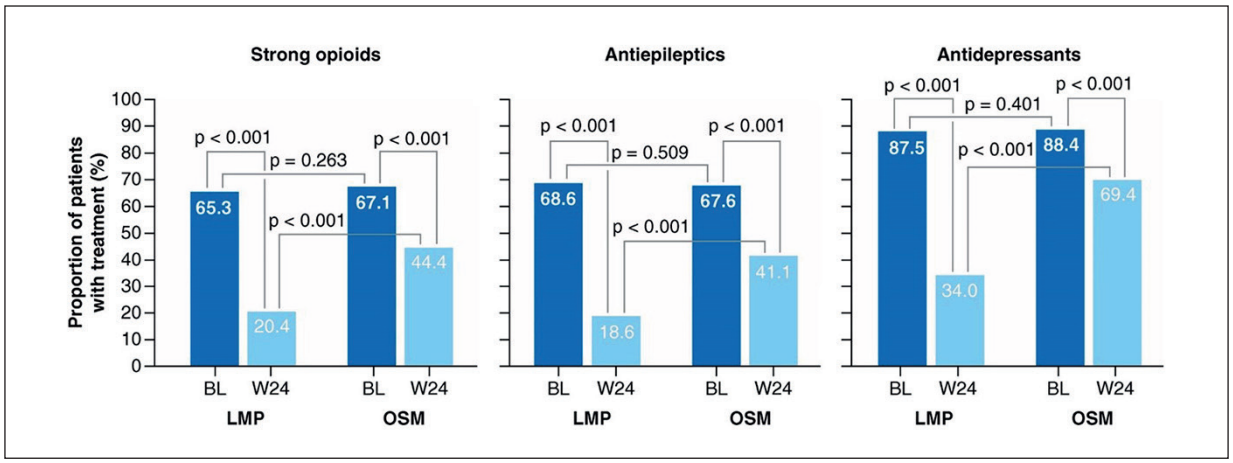

Figure 6. Changes in concomitant analgesic medications (taken by >60% of patients at baseline) over the observation period. Strong opioids included morphine, hydromorphone, oxycodone ± naloxone, fentanyl, buprenorphine, tapentadol and others. BL: Baseline; LMP: Lidocaine 700 mg medicated plaster; OSM: Oral systemic medication; W24: Week 24. Source: Überall et al[47] 2021. Reproduced from Future Medicine Ltd. under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License.

pared to the first-line treatment pregabalin not only in the treatment of PHN but also in other peripheral neuropathic pain conditions[66].

Concomitant Medications and Therapy Personalization

The low systemic absorption of LMP results in minimal risk for pharmacological interactions. This is of particular relevance in clinical practice since most patients affected by PHN are elderly, with frequent comorbidities and/or are taking several other medications[33,52,67,68]. Most patients required more than one PHN medication, and symptomatic relief is achieved in only a fraction of them[12,22,69]. The advantage of the very low risk of drug-drug interactions allows LMP to be used as a background medication combinable with other treatments, if necessary[63]. In a study evaluating a combination therapy of pregabalin and LMP[39], the authors concluded that the combination therapy was safe, well-tolerated, and provided additional clinically relevant pain relief. Interestingly, LMP is also effective in reducing the number of concomitant analgesic medications patients take. In the study by Überall et al[47], all participants took concomitant medications, and almost two-thirds received up to two concomitant treatments. After 24 weeks, there was a reduction in the percentage of patients taking auxiliary medications, which was significantly greater in the LMP group than the OSM one (94.1 *vs.* 70.9%; $p < 0.001$) (Figure 6).

LMP also allows for a more precise personalization of therapy. The low systemic lidocaine exposure following LMP administration and its safety profile allow for easy addition, removal, or switching medications. The use of the plaster allows for precise localization of treatment in the affected skin area in contrast to OSM. The plaster can be cut and shaped to cover the painful area and if this is larger than the plaster's surface, more plasters can be applied simultaneously. The dosage involves the application of up to three patches for a maximum of 12 hours a day; this allows the patient to undergo therapy during the day or night, according to their preference[37,53]. This flexibility may enhance the patient's compliance.

Expert Opinion

The chronicity of PHN and its devastating impact on the HR-QoL frame this condition as a model of chronic pain with biopsychosocial consequences. Patients have their own level of acceptance of pain, needs related to their lifestyle, age, general health status, and psychological structure: adequate analgesia therapy must consider all of these to be truly effective and beneficial. In the approach to chronic pain syndromes, the total suppression of painful symptoms may be an unrealistic goal. Thus, it is essential to find a balance between pain control and the minimization of adverse events to improve the level of functioning. Moreover, treating PHN means counteracting pain and preventing it from becoming chronic. This should also be considered in the primary care setting. The incorrect treatment of HZ frequently leads to PHN, and the incorrect treatment of PHN often leads to chronic pain. In this perspective, GPs have an important role, as they are the first ones being consulted by patients with HZ or PHN – and thus able to treat early. The LMP represents a simple and safe therapy that can be used since the onset of the first PHN symptoms. Moreover, chronic pain from PHN requires medium- to long-term treatment and therefore, not only efficacy but also good tolerability, manageability, practicality (ease of dosing), and compliance play are very important. Both pharmacological and clinical features of the LMP allow considering these aspects. Data from a recent, large, real-world study[47] have shown that LMP, compared to systemic treatments, has superior effectiveness in reducing pain and improving the QoL and is associated with a tolerability profile that is mainly limited to localized skin reactions. LMP has also shown the possibility of personalizing therapy and adding concomitant medications when needed.

Conclusions

LMP is one of the best available treatment options for all patients suffering from HZ and PHN and should be considered for use as a first-line treatment. Polytherapy with systemic treatments can be of use in the case of refractory patients. In short, LMP provides GPs with a powerful tool that allows them to establish a safe and often efficacious therapy while waiting for the pain specialist's visit, if required.

Conflict of Interest

In the last 2 years, DF has received fees as consultant or speaker from the following companies: Alfasigma, Bayer, Daiichi, Grünenthal, IBSA, Lundbeck, Molteni, SPA. In the

last 2 years, AM has received fees as consultant or speaker from the following companies: Angelini, Alpha Sigma, Grünenthal, Pfizer, Sandoz. TP is an employee of Grünenthal Italia SRL. All the authors have no conflicts of interests to declare.

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Authors' Contribution
All authors contributed equally to the conception and design of this review, collection and interpretation of data from literature, manuscript editing. All authors gave their approval to submit.

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