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Journal of Pain & Palliative Care Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ippc20

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To cite this article: Edmundo Gónima Valero, Walter Antanas Sosa Mendoza, Diana A. Sarmiento & Sebastian Amaya (2023): Analgesic Treatment Approach for Postherpetic Neuralgia: A Narrative Review, Journal of Pain & Palliative Care Pharmacotherapy, DOI: 10.1080/15360288.2023.2174632

To link to this article: https://doi.org/10.1080/15360288.2023.2174632

Published online: 02 Feb 2023.

JOURNAL OF PAIN & PALLIATIVE CARE PHARMACOTHERAPY
https://doi.org/10.1080/15360288.2023.2174632

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REVIEW

Analgesic Treatment Approach for Postherpetic Neuralgia: A Narrative Review

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ABSTRACT

Post-herpetic neuralgia (PHN) is an entity derived from peripheral nerve damage that occurs during the reactivation of the Varicella Zoster Virus (VZV), which manifests itself through pain with neuropathic characteristics. This can prove to be very difficult to manage in the chronic stages of disease reappearance. There currently exists a multitude of treatment alternatives for PHN, however, prevention through the early initiation of antiviral regimens is vital. There are various pharmacological options available, but it is important to individualize each patient to maximize efficacy and minimize adverse effects. Interventional procedures have become a cornerstone in difficult-to-manage cases, and have shown promising outcomes when used in a multimodal approach by experienced specialists. It is necessary to make an objective diagnosis of PHN and start early treatment. Additionally there is current evidence that vouches for interventional therapies as well as individualization, with a clear establishment of therapeutic objectives according to the needs of each patient.

ARTICLE HISTORY
Received 14 May 2021
Revised 5 December 2022
Accepted 23 January 2023

KEYWORDS
Acute herpetic pain; herpes zoster; postherpetic neuralgia; Varicella zoster; interventional pain management; continuous analgesia

Introduction

PHN is known as neuropathic pain that persists for at least 90 days after the resolution of the eruptions caused by the VZV (1), which corresponds to peripheral nerve damage derived from viral reactivation. Regarding the panorama of the disease, each year in the United States 1 million cases of VZV infections are reported, of which approximately 5 to 20% develop PHN (2), with the female gender being the most affected (3). Similarly, it has been shown that the incidence and severity is closely related to increasing age, such that it occurs in 20% of adults aged 60 to 65 who have had acute VZV infection, and in more than 30% of those over 80 years of age (2). Additionally, the recurrence rate has been reported to be less than 6% in immunocompetent patients (4). This condition significantly impacts the quality of life of patients, making pain management essential. With the existence of multiple invasive and noninvasive treatments, however, choosing a treatment option can become a challenge for health professionals. The purpose of this article is to explore the current pharmacological and interventional treatment options for PHN and briefly describe the pathophysiology, clinical presentation, and diagnosis.

Methods

A narrative literature review was carried out, using MEDLINE and PUBMED to search for articles in English between 2010 and 2022, with the keywords "acute herpetic pain," "herpes zoster," "postherpetic neuralgia," "Varicella Zoster," "interventional pain management," and "continuous analgesia." Articles that describe the pathophysiological considerations, current treatment options, as well as risks and advantages were

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chosen after a screening process completed by the authors

Pathophysiology

Regarding the pathophysiology of this entity, the starting point is the VZV, which is a double-stranded DNA virus that can enter via the respiratory tract, mucosa and/or hematogenously, leading to the generation of primary and secondary viremia. This viremia manifests as a fever and rash characteristic of the entity known as herpes zoster, and after the initial period resolves, the virus remains latent in the dorsal root ganglion, and can be reactivated in moments of immunosuppression (2). This reactivation leads to an inflammatory response capable of damaging central and peripheral neurons, leading to generalized neuronal necrosis, neuritis, demyelination, and ultimately the loss of the ability to inhibit painful nociceptive signals. This, in turn, leads to the lowering of the threshold for the activation of nociceptive pain, producing spontaneous ectopic discharges and generating disproportionate pain when faced with non-painful stimuli (2).

Altogether, this leads to the death of peripheral neurons and changes in the central nervous system, inducing an abnormal reorganization of the painful stimulus transmission system and a disorganized innervation pattern that generates spontaneous pain in PHN (5). Within the course of the disease there are 2 major mechanisms involved; the first being the irritable nociceptor that leads to mechanical, thermal and tactile allodynia, sensitization of fibers and a decrease in the threshold for action potentials, as well as increase in the discharge rate and its magnitude, which results in spontaneous pain and allodynia. The second mechanism refers to the damage in afferent nerves that translates into allodynia, as well as sensory loss of the dermatomes involved and the reorganization of the dorsal horn (6).

As mentioned above, one of the main manifestations in this syndrome is allodynia, which occurs through various mechanisms. These mechanisms include a decrease in C fibers in the affected area (7), the increase in A-beta fibers from mechanical stimuli, and the production of connections with spinothalamic tracts that previously transmitted pain through the synapse with type C fibers, leading to the generation of interaction with spinothalamic tracts and peripheral pressure stimuli. Additionally, there are other mechanisms described such as the positive regulation of TRPV1 receptors, an increase in the proportion of voltage-gated sodium and potassium channels, and the loss of GABA inhibitory interneurons in the dorsal horn, all of which must be taken into account (8).

Presentation and diagnosis

In order to arrive at a correct diagnosis, it is essential to carry out a complete clinical history, adequately characterizing the pain and looking for elements of neuropathic pain and risk factors. Prodromal pain, severe skin rash, unilateral dermatomal distribution, and ophthalmic symptoms in patients with severe immunosuppression are manifestations that are classically described in PHN (7). Likewise, it is necessary to perform a physical examination in search of areas previously affected by VZV that can be evidenced as scars, rash, discoloration, edema (2), as well as areas of sensory alteration with findings such as hyperalgesia, allodynia and dysesthesia. One must also keep in mind that it is essential to evaluate the impact of the disease on the quality of life of patients. To accomplish this, it is recommended to use scales to identify the presence of neuropathic pain such as DN4 and LANSS, which allows a more objective diagnosis (9).

Treatment

The initial objective of treatment should be to prevent the emergence of PHN, for which the initial approach with antiviral drugs is the only therapy that has proven to be effective for this purpose. Acyclovir 800 mg 5 times a day, with a duration of 7 to 10 days, has shown to have an impact in the acute phase of the disease, making it essential to start treatment in the first 72 hours after diagnosis, however dosing may need to be adjusted in patients with renal disease (10). Additionally, studies with a similar antiviral, Amenamevir (a helicase-primase inhibitor), have

shown to potently suppress the development of acute herpetic pain and the development of PHN, however this medication is currently only used in Japan (11).

The approach to herpes zoster pain should be based on the management algorithm for neuropathic pain, which is divided based on lines of treatment and supported by current evidence (9). On the other hand, alternate management schemes with famciclovir and corticosteroids have been proposed, however these do not have sufficient support nor degree of evidence to be currently recommended (12). Another highly debated but important issue regarding preventive treatment is vaccination, which has shown to be effective and safe in preventing herpes zoster and thus reducing the incidence of PHN in adults over 60 years of age (13).

The different therapeutic approaches for PHN can be divided into systemic, topical and interventional therapies. Regarding the different pharmacological groups, among the most used in daily practice are those of the first line of treatment; tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentinoids, topical management (lidocaine and capsaicin) and transdermal substances (9).

Gabapentin has shown to reduce PHN pain for up to 14 weeks, and can be safely used for up to 24 weeks. It has also been described that it presents lower rates of medication abandonment by patients, without finding differences between single or divided doses (14). Its use is recommended from the onset of symptoms; decreasing allodynia and severity of symptoms of neuropathic pain, which is also seen with pregabalin (15). In a 2019 systematic review done by *Derry et al.* including 45 studies with 11,906 patients, it was found that more participants had at least a 30%-50% reduction in neuropathic pain intensity when using 300 mg and 600 mg of pregabalin versus placebo, however, somnolence was seen in 16% and 25%, respectively (16). Clinical studies have shown dosage efficacy of immediate-release formulation of gabapentin in PHN between 1,800 milligrams per day to 3,600 milligrams per day. However, no additional benefit was seen when using doses greater than 1,800 milligrams per day, the reason for which current dosing regimens reach 2,400 milligrams (2). Taking into account the efficacy seen with this medication, gastroretentive gabapentin and gabapentin enacarbil were introduced to the market. These developments lead to improved drug absorption and bioavailability, as well as simplified dosing regimens and titration (2).

Similarly, **amitriptyline**, a tricyclic antidepressant (TCA), has been shown to be effective in the management of both peripheral and central neuropathic pain, including PHN, however little evidence exists specifically for its use in PHN (9, 15, 17). Dosing can be initiated with 10 to 25 milligrams orally before bed, and increased by 10 to 25 milligrams per week to reach a target dose of 75 to 150 milligrams per day (18). TCAs should be used with caution in the elderly, as well as those with heart disease, epilepsy or glaucoma. The physician should reassure the patient that treatment with TCAs may take weeks to become fully effective, and that TCAs are notorious for certain systemic side effects (Anticholinergic and cardiotoxic effects) (2). In a randomized blinded trial, the TCAs desipramine and amitriptyline were compared to the serotonin-selective antidepressant fluoxetine, and showed that all 3 drugs reduced PHN pain, with desipramine providing the greatest relief in 80% of those treated (19). Dosing for nortriptyline and desipramine can be given at a starting dose of 25 milligrams at bedtime, with an increase of 25 milligrams per day every 3-7 days as tolerated by the patient, and a maximum dose of 150 milligrams per day can be reached (20). Additionally, a double-blind placebo controlled study done by Bowsher showed that early treatment with low-dose (25 mg) amitriptyline reduced pain prevalence in elderly patients with acute herpes zoster (21).

Duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, presents the same level of evidence as amitriptyline, however it has benefits in relation to a lower risk of associated cardiovascular effects (15). A recent systematic review for neuropathic pain in adults found that there is much high quality evidence for the use of serotonin-norepinephrine reuptake inhibitors (SNRI), such as duloxetine and venlafaxine, as first-line agents in general neuropathic pain (22).

However, other guidelines recommend the use of SNRI only for painful diabetic neuropathy, but not for PHN (23).

Topical therapies can be considered as the first line for patients with mild post-herpetic pain, highlighting 5% lidocaine patches and 8% capsaicin, which tend to be the most frequently used. However, these are usually managed in combination with oral therapy to increase their efficiency (24).

5% **Lidocaine** patches have been used for neuropathic pain relief, considering the fact that it has been shown to reduce pain intensity and improve quality of life in this scenario. In the literature, the maximum dose described is 3 patches per 12 hours, yielding a decrease in pain intensity of approximately 50% in ⅓ of patients with PHN (2). Additionally, it is an attractive pharmacological alternative given the absence of deleterious systemic effects (25, 26). Data from PHN studies have shown that patients using lidocaine patches can achieve pain relief as early as 30 minutes into treatment (27).

It is important to recall that lidocaine absorption is affected by the thickness and surface area of the skin (specifically, the stratum corneum), as well as local vascularity. The maximal penetration depth of lidocaine when applied to the skin is approximately 8-10 millimeters (28). Topical lidocaine is classically regarded as a safe medication, however some mild dose-related adverse reactions can arise, such as mild and transient skin irritation (27).

When considering treatment with **capsaicin** it must be remembered that it acts by the agonism of vanilloid receptors, and that this results in depletion of substance P from nerve terminals over time. For this reason, capsaicin must be applied regularly over an extended period of time (2, 15).

As mentioned above, capsaicin is an agonist for the transient receptor potential vanilloid 1 receptor (TRPV1), which causes a decrease in sensitivity to various stimuli leading to an end effect considered as desensitization (29). Capsaicin topical cream comes in many presentations, each with its respective degree of effectiveness and support in the medical literature. For example, *Lynn et al.* tested the effectiveness of 8% capsaicin patches in 24 patients with PHN, finding pain reduction throughout the 12 week interval in which the study was conducted, as well as adequate toleration when lidocaine 2.5% was used as a pretreatment (30)

Similarly, *Bernstein et al* found 0.075% capsaicin cream to be effective when being applied 3-5 times daily in patients with PHN; and various other studies have shown benefits from the lowest dose (0.025%) cream, however this requires more time in order to see improvement in pain (29, 31, 32). Typical dosing for capsaicin is up to four 8% patches for 1 hour every 3 months or longer; however this needs to be administered by a physician or trained personnel, and .075% cream can be applied three to five times per day (2). In the second line of treatment of neuropathic pain, combination therapy is recommended, and **tramadol** and/or tapentadol should be considered. Tramadol, thanks to its dual mechanism (SNRI as well as a very weak opioid agonist effect), has a favorable profile for the management of neuropathic pain, and in some guidelines it is also considered a third line of management (15). Recommended starting dose for neuropathic pain is 50 milligrams one to two times per day, with titration between 50–100 milligrams in divided doses every 3–7 days, with a maximum dose of 400 milligrams per day (maximum dose for elderly patients of 300 milligrams per day) (20).

On the other hand, **tapentadol** is an opioid with dual effect, (mu agonist and norepinephrine reuptake inhibitor) however it does not inhibit serotonin reuptake. It has a greater potency compared to tramadol, but unfortunately evidence is still insufficient considering it is a relatively new opiod that requires more studies, but can possibly be considered in the second or third line of management (9). It should be noted that although tapentadol does not affect serotonin uptake, it has been implicated in some cases of serotonin syndrome when combined with serotoninergic drugs. Selective serotonin reuptake inhibitors and anticonvulsants can be seen in the third line of management, which have insufficient evidence, however, they are used as part of the multimodal strategy.

Combination therapy is considered a significant part of management of neuropathic pain in most guidelines, however there is limited evidence on effective strategies (9). A Cochrane

review aimed at combination therapy for neuropathic pain showed that gabapentin and opioids provide better pain relief than both of the agents on their own, however this was associated with increased risk of adverse events (33). Patients who reach this line of therapy should begin consideration for interventional therapies after consultation with a pain specialist (9). It is also worth noting that some synthetic opioids such as tramadol, tapentadol, methadone and dextromethorphan can contribute to serotonin syndrome, therefore it is important to take into account possible drug interactions to avoid this complication (34).

As mentioned previously, interventional therapy enters the third line of management, along with selective serotonin reuptake inhibitors, anticonvulsants and NMDA antagonists. Unfortunately, there exist cases where these strategies are not sufficient and further management with potent opioids is required (9). With regard to potent opioids; buprenorphine, methadone and oxycodone have shown the best performance for the control of neuropathic pain; however, their use should be limited as much as possible given their multiple adverse effects in the short and long term, as well as the risk of dependence (9, 15, 16). Many may disregard the use of non steroidal anti-inflammatory drugs in these cases, but paracetamol deserves special mention given that it is widely used as a co-analgesic and opioid sparing agent in chronic pain, including neuropathic pain, however the evidence is controversial (26).

Interventional management

Interventional management is recommended for use in the third step and this should be indicated as part of multimodal management once the patient is referred to a pain specialist (9). Within the therapeutic arsenal, the use of interfascial blocks, peripheral nerve blocks, ganglion blocks, application of steroids and/or epidural local anesthetics is recommended; while the use of sympathetic blocks, and the application of subarachnoid corticosteroids is not currently recommended (35). In the fourth line of management, electrical spinal stimulation can be implemented as a therapy for the management of neuropathic pain (9), however in PHN the evidence does not yet allow a clear recommendation to be made (35). In the last step of management, after management with potent systemic opioids, the administration of intrathecal drugs (ziconotide and/or opioids) can be implemented, however this approach has inconclusive evidence (9, 35, 36).

Botulinum toxin A

In two randomized, double-blind, placebo-controlled studies by *Xiao et al.* and *Apalla et al.*, Botulinum toxin A (BTA) of 100-200 UI was injected subcutaneously within 2 centimeters of the painful region, finding improved visual analogue scale (VAS) scores, an improvement in sleep quality, and a decrease in opioid use. These effects were seen after 7 days post-injection and lasted approximately for 3 months (37, 38). The fundamental behind this treatment is that BTA is a neurotoxic protein which has activity that inhibits the release of neurotransmitters such as acetylcholine and substance P from neurons, as well as decreasing nociceptive afference via the inhibition of glutamate (39–41).

Transcutaneous electrical nerve stimulation

Two studies evaluated the efficacy of transcutaneous electrical nerve stimulation (TENS) in combination with adjunct therapies for management of PHN, with one study using oral pregabalin as an adjunct, and the other using subcutaneous injection of cobalamin alone or with lidocaine. The TENS was applied 30 minutes per day through 4-8 weeks, and showed improvement in VAS scores, sleep quality, and an overall decrease in pain (42, 43). The way TENS functions is due to the production of segmental inhibition within the dorsal horn combined with stimulation of the release of endogenous opioids (44–47). Additionally, TENS has also been utilized in the prevention of PHN in patients who are within the acute stage of herpes zoster infection (48).

Triamcinolone

Pain relief was seen in 100% of the population within a RCT that treated patients with PHN with 3 local intralesional injections of triamcinolone combined with lidocaine over the course of 2 week intervals, with pain relief being reported after 3 months (49). It is believed that local triamcinolone injections play a role in the peripheral sensitization pathway, decreasing the inflammatory process (50).

Stellate ganglion block

One study showed that the stellate ganglion block significantly reduced incidence of PHN and led to decreased VAS scores as well as decreased dosage required with adjunct therapy such as pregabalin (51). This blockade plays a role considering that sympathetic terminals can contribute to sensitization, however this mechanism is poorly understood and evidence is currently limited to case reports (52, 53).

Pulsed radiofrequency

4 RCT used pulsed radiofrequency, a minimally invasive option, for PHN management, either via the angulus costae, paravertebral puncture or the intercostal nerves; and all the studies showed an improvement in the VAS, a decrease in rescue medication dosage, and improvement in the Pittsburgh Sleep Quality Index scale, after 2 or 3 days post-treatment, with the effects persisting approximately 2–6 months (54–57). Additionally, another study found that bipolar high voltage pulsed radiofrequency that targeted the cervical sympathetic chain can effectively relieve acute herpetic neuralgic in the oral, maxilofacial neck and upper limb regions, as well as aiding in reducing the incidence of PHN (53).

Spinal cord stimulation

Various studies have shown certain success with spinal cord stimulation in the presence of severe PHN in both subacute and chronic stage, with temporary stimulation from 7–10 days to 2.5 months showing immediate pain relief lasting for more than 1 year (58, 59). Spinal stimulation is considered invasive as it includes the insertion of percutaneous leads in the epidural space. The current theory behind how the spinal stimulation mechanism functions in pain modulation is its effect on A-beta fibers which inhibit the transmission of nociceptive signals carried by C-fibers, however the exact mechanism is still unclear and various other theories exist (60, 61).

Peripheral nerve stimulation

A systematic review of the literature done by *Chia-Siang et al.* found various case reports that have shown success with the use of peripheral nerve stimulation in the supraorbital and thoracic regions (53). Of these case reports, only 1 experienced a technical complication, and the rest benefited from the treatment with minimal or no need for adjunct medications, improved sleep quality as well as better functional status. However, this management approach does not have any RCTs that support its use, thus requiring further research in order to form adequate recommendations.

Paravertebral blocks

2 RCTs found that paravertebral blocks alone or combined with adjunct therapy were able to reduce pain as well as reduce the consumption of additional medications seen in PHN (61, 62). It is also important to note that a separate study concluded that the efficacy of this intervention varies with the course of the zoster-related pain (the shorter the time of onset, the greater the efficacy) (63).

Erector spinae plane block

A multicentric retrospective observational study with 34 patients concluded that the erector spinae plane block (ESP) provided adequate analgesia in patients with acute herpetic pain, and additionally provided effective analgesia within the 3 month period after the block, when combined with adjuncts such as pregabalin and tramadol (64). The ESP block is a relatively new interventional

management that is slowly coming to light within the treatment of PHN, however more studies must be done before a recommendation can be made.

Dorsal Root ganglion stimulation

Dorsal root ganglion stimulation (DRGS) is a treatment option currently supported in the literature considering that this structure is damaged in PHN. A consensus done by the Neuromodulation Appropriateness Consensus Committee reports a moderate strength recommendation for efficacy of DRGS in PHN, citing 4 recent studies. Similarly, the same consensus reports a strong recommendation for safety of DRGS in PHN. (65). In these cases it is vital to individualize the patient's situation with the goal of selecting the most adequate management strategy in order to achieve optimal analgesia and improve quality of life.

Conclusion

PHN is a frequent and preventable condition, which has a significant negative impact on the quality of life. The approach and diagnosis must be objective, with utilization of the tools and questionnaires/scales designed by various different authors. Similarly, it is necessary to recognize the multiple pharmacological and interventional treatments that currently exist in literature to correctly individualize the treatment in each of the patients in order to improve their quality of life and diminish their pain.

Acknowledgments

None.

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethical approval

Not applicable.

Funding

None.

Informed consent

Not applicable.

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