Journal of Pre-Clinical and Clinical Research 2024, Vol 18, No 2, 162-167
www.jpccr.eu

REVIEW ARTICLE

Post-herpetic neuralgia: currently available oral and topical medications in the management of pain – a review

Damian Bęben[1,A,D]✉, Jan Kowalewski[2,A,D], Karolina Recka[3,B,F], Daria Michałka[4,B,F], Aleksandra Grzelak[5,C,E], Oliwia Jędrocha[4,C,F], Sara Godyńska[3,B,F], Ewa Obacz[3,A,E], Zuzanna Grodek[6,C-D], Joanna Miliwek[5,A-B]

[1] *Clinical Department of Internal Medicine, 4th Military Clinical Hospital, Wrocław, Poland*
[2] *Clinical Department of Endocrinology, Metabolic and Internal Medicine, University Clinical Hospital, Poznań Poland*
[3] *Internal Medicine Department, Rear Admiral Professor Wiesław Łasiński 7th Military Navy Hospital, Gdańsk, Poland*
[4] *SPZOZ of the Ministry of Internal Affairs and Administration, Department of Internal Medicine and Geriatrics, Krakow, Poland*
[5] *Department of Clinical Oncology, PCK Maritime Hospital, Gdynia, Poland*
[6] *Department of Gastroenterology and Internal Medicine, Autonomous Public Provincial Polyclinical Hospital, Szczecin, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Bęben D, Kowalewski J, Recka K, Michałka D, Grzelak A, Jędrocha O, Godyńska S, Obacz E, Grodek Z, Miliwek J. Postherpetic neuralgia: Currently available oral and topical medications in the management of pain – a review. J Pre-Clin Clin Res. 2024; 18(2): 162–167. doi: 10.26444/jpccr/189442

Abstract

Introduction. Post-herpetic neuralgia (PHN) is the most common chronic complication of herpes zoster and also one of the most troublesome. It is a prime example of typical neuropathic pain which in many cases contributes to a significant reduction in the patient's quality of life. Despite the emergence of a prophylactic method in the form of a vaccine, PHN continues to be a significant problem, particularly affecting the elderly and immunocompromised individuals.

Objective. The aim of this review is to summarize the knowledge contained in the current literature on the available oral and topical medications for the treatment of neuropathic pain in PHN. An area of particular focus was the effectiveness and safety of their use.

Review Methods. The review is based on 49 scientific publications found in PubMed, PubMedCentral, NCBI and Via Medica Journals databases published between 2008–2024.

Brief description of the state of knowledge. Current treatment of PHN is mainly based on pharmacological therapy. Both oral and topical drugs belonging to a variety of groups are used. Gabapentinoids, tricyclic anti-depressants and, in some circumstances, lidocaine 5% patches, are considered first-line medications. In contrast, capsaicin 8% and opioids are considered second-line medications. The use of multimodal therapy is becoming widespread due to the relatively frequent ineffectiveness of pain management during monotherapy.

Summary. Despite the wide range of methods available for use in the treatment of neuropathic pain, management of PHN continues to be a challenging task. Multimodal therapy using medications with different mechanisms of action and an individualized approach to drug selection based on the specific clinical case are crucial for treatment success.

Key words

postherpetic neuralgia, neuropathic pain, gabapentin, lidocaine, herpes zoster

INTRODUCTION

Definition and epidemiology. Post-herpetic neuralgia (PHN) is defined as unilateral chronic neuropathic pain within the dermatomes, usually of a burning, stabbing or throbbing nature that persists for at least three months after the development of herpes zoster (HZ) [1, 2]. PHN is the most common complication of herpes zoster, and the likelihood of developing it increases with age. It is estimated that about 20% of patients over the age of 65 and as many as 30% over the age of 80 who contract HZ will develop PHN [3, 4]. Groups at particular risk of developing post-herpetic neuralgia as a consequence of experiencing an episode of HZ are not only the elderly, but also immunocompromised patients, those burdened with chronic diseases, and pregnant women [2].

Pathogenesis of postherpetic neuralgia. Under favourable conditions, when the host's immune mechanisms are impaired, the varicella zoster virus is reactivated [5]. The virus replicates in the dorsal root ganglia of the spinal nerves triggering an increase in pro-inflammatory cytokines [6]. As a result, pathological inflammatory changes develop, resulting in a strong local sympathetic response. It causes nerve ischaemia due to vaso-constriction and their progressive damage, resulting in neuropathic pain, affecting both the central and peripheral nerves [3, 7]. The described changes occurring during the acute phase of herpes zoster can disintegrate the nervous system and cause, over time,

✉ Address for correspondence: Damian Bęben, 4th Military Clinical Hospital, Clinical Department of Internal Medicine, Weigla 5 Street, 53-114 Wrocław, Poland
E-mail: damianbeben98@gmail.com

Received: 29.04.2024; accepted: 20.05.2024; first published: 14.06.2024

a decrease in the activity of descending pain inhibitory pathways in the central nervous system, enlargement of sensory areas or changes in the activity of genes that are responsible for the synthesis of neuropeptides. These changes are key to the occurrence of the peripheral and central sensitization phenomenon characteristic of PHN which results in the ability of spinal cord dorsal horn nerve cells to spontaneously discharge as a result of their hyperactivity [7].

These structural and functional changes within the nervous system lead to a range of symptoms that affect patient, such as, prolonged or intermittent pain of a burning, throbbing or electric shock-like nature that occurs without the presence of a stimulus, allodynia (a feeling of pain in response to a stimulus that does not normally cause it, hyperalgesia (excessive, disproportionate pain response to a stimulus), as well as paresthesias and dysesthesias [8].

Available oral and topical medications for pain management in PHN. Unfortunately, managing neuropathic pain in PHN is not easy and remains a major health care challenge. Because PHN primarily affects the elderly, the higher risk of adverse effects in this population group must be kept in mind when selecting an appropriate treatment regimen. This is related to the very common polypharmacotherapy in the elderly, chronic diseases and metabolic changes resulting from the aging process. These factors affect the pharmacokinetics of drugs, while implying therapeutic difficulties for healthcare professionals [9].

There is no single gold standard for the treatment of PHN, and the methods with the greatest effectiveness are characterized by a significant reduction in pain intensity of at least 50% in less than half of patients [1]. The lack of up-to-date guidelines strictly focused on post-herpetic neuralgia (the 2004 American Academy of Neurology [AAN] guidelines are considered outdated and have been withdrawn, and are no longer supported by the AAN), and long-term studies on sufficiently large groups of patients also do not facilitate the selection of an appropriate treatment pathway [4]. Nevertheless, multimodal therapy using at least two drugs with different mechanisms of action appears to be the best choice in the search for effective pain control as long as it is safe for the patient. Due to the chronic nature of a condition like PHN and the fact that it often negatively affects the patient's daily functioning, a multidisciplinary approach that includes psychological and social support is important [2, 7].

Pharmacological treatment of PHN uses medications belonging to several groups which differ in both mechanism of action and potential side-effects. Guidelines for the treatment of neuropathic pain unanimously recognize tricyclic anti-depressants (TCAs) and gabapentinoids as first-line drugs. [4, 10]. Although 5% lidocaine patches used to be widely recommended as a first-line drug for the treatment of PHN [2], at present, however, the various guidelines do not agree on its efficacy in the treatment of PHN or other types of neuropathic pain, thus making it difficult to currently assess whether it should be considered a first- or second-line pharmaceutical due to conflicting conclusions from various studies [11, 12]. Capsaicin 8% in a patch or cream, as well as opioids, are among second-line treatments [8].

Gabapentinoids. Two drugs belonging to the gabapentinoid group – gabapentin and pregabalin, originally used to treat epilepsy, are now recommended as first-line treatment in PHN and other types of neuropathic pain. Gabapentinoids, despite being analogs of gamma-aminobutyric acid (GABA), do not bind to its receptors [13, 14]. Their function is based on attachment to the α2δ-1 subunit of voltage-gated calcium channels. Studies suggest that several mechanisms underlie the analgesic activity of gabapentinoids in neuropathic pain. It is hypothesized that gabapentinoids inhibit α2δ-1 subunit-dependent excessive release of neurotransmitters that modulate pain conduction. They also reduce the accumulation of α2δ-1 in synaptic vesicles within the dorsal root ganglia of spinal nerves, and stimulate the descending noradrenergic inhibitory system-thereby suppressing nociceptive transmission [13]. Gabapentin and pregabalin do not bind to plasma proteins, are not metabolized by liver enzymes, and thus do not affect the concentrations of drugs metabolized by cytochrome CYP450. Both drugs are mainly eliminated in the urine, and their half-lives are very similar to each other, for gabapentin this is five to seven hours, depending on the dose, and for pregabalin – about 6.3 hours [13, 15].

Gabapentin is administered orally and is available in two forms – an extended-release or immediate-release formulation [16]. Immediate-release gabapentin has been confirmed in studies to be more effective than placebo in treating PHN symptoms at doses between 1,800mg and 3,600mg per day [16, 17]. Such a wide range of therapeutic dose is related to the non-linear absorption of this drug from the gastrointestinal tract – the higher the dose, the more its bioavailability decreases, making it difficult to adequately titrate the medication and efficiently achieve a therapeutic effect without causing adverse reactions [15]. The Cochrane Review also indicated that extended-release formulations of gabapentin – gastroretentive gabapentin and gabapentin enacarbil – are more effective than placebo in the treatment of PHN. They are easier to dose and have greater bioavailability. The drug in the gastroretentive formulation is absorbed up to 15h from the gastrointestinal tract, and is taken once daily [16]. The initial recommended dosage is 900mg per day, and the goal is to reach a therapeutic dose by gradually titrating the drug over two weeks [8]. At 1,800mg per day, its effectiveness in controlling neuropathic pain in PHN was demonstrated in an 11-week, double-blind, randomized, placebo-controlled phase three study [18]. Gabapentin enacarbil is a prodrug, requires less frequent dosing than the immediate-release formulation of gabapentin, and provides less variation in plasma drug concentration [19]. The minimum therapeutic dose of gabapentin enacarbil is 1,200mg per day, and is achieved by gradually dosing the drug over four days [8].

Pregabalin is a drug characterized not only by high bioavailability but also, unlike gabapentin, by linear absorption from the gastrointestinal tract which makes its pharmacokinetics more predictable. After oral administration, it reaches its maximum plasma concentration after only one hour [20]. Based on 14 randomized clinical trials, pregabalin was more effective than gabapentin in relieving pain in PHN; on the other hand, it was characterized by more frequent incidents of side-effects [21]. The recommended initial dosage is 150mg/day (in two or three divided doses) with gradual titration over about one week. In contrast, the maximum recommended and relatively well-tolerated therapeutic dose is 600mg/day [8, 16].

As for the adverse effects of gabapentinoids, among the most common are those affecting the central nervous system which include dizziness (19% when taking gabapentin), as well as balance disorders and drowsiness (incidence of 14% for gabapetin). For pregabalin, the incidence of dizziness is 24% and drowsiness 17%. Furthermore, gabapentinoids may induce moderate weight gain – up to 25% of patients taking pregabalin may be affected. However, it should be noted that in most patients treated with pregabalin, weight gain within a year of starting therapy does not exceed 7% of baseline weight. Gastrointestinal adverse effects, such as bloating, constipation, appetite disturbance or nausea, are relatively common [22].

Gabapentinoids can also cause withdrawal symptoms. In the available case reports, gabapentin withdrawal symptoms appeared between 12 hours and seven days after the last dose. The most common were agitation, confusion, tremor, insomnia, gastric symptoms and excessive sweating, although isolated cases of akathisia, as well as catatonia and convulsions, have been documented [23]. It is also important to keep in mind the risks of using gabapentinoids in patients with renal failure in the form of toxicity. This is related to the metabolism of the drugs of this group and their excretion in the urine. The risk is particularly high in dialysis patients. Symptoms of toxicity include sedation, confusion, imbalance, tremors, myoclonus or ataxia. It should be noted that cases of respiratory depression have also been described in patients who have been administered a combination of gabapentinoids and opioids. This makes it imperative that special care must be taken in the treatment of the elderly, as respiratory illnesses are very common in this population, as well as the use of opioid drugs [13].

Tricyclic ant-idepressants. As the name suggests, initially the main purpose of tricyclic anti-depressants (TCAs) was to treat depression. Today, despite the lack of approval by the *Food and Drug Administration (FDA), they are widely used off-label as first-line medications to treat PHN pain symptoms in the United States and many other countries [24, 25]. The mechanism of action of this group of drugs is based on inhibition of the re-uptake of two neurotransmitters from the post-synaptic gap – norepinephrine and serotonin. In this way, the noradrenergic and serotonergic descending inhibitory systems are likely to be stimulated. Furthermore, TCAs may also modulate the sensation of neuropathic pain by acting on alpha-adrenergic receptors and blocking sodium channels [26, 27].*

The best-studied and best-studied representative of the tricyclic antidepressant group is amitriptyline, and its impact in controlling neuropathic pain can be observed at doses lower than those required to achieve an antidepressant effect [11]. A meta-analysis of placebo-controlled studies of TCAs using primarily amitriptyline showed good effects in the treatment of neuropathic pain (with a Number Needed to Treat of 3.6) [25]. Desipramine and nortriptyline are two other drugs belonging to the group of tricyclic antidepressants, but the evaluation of their effectiveness in the treatment of neuropathic pain syndromes is inconclusive due to conflicting conclusions from various clinical trials and meta-analyses. [25, 27–29, 30]. Nevertheless, it should be noted that the studies conducted often included too small groups of patients and lasted too short a time to provide high-quality data [29, 30]. The use of TCAs in the treatment of PHN should be started with low doses (10–25mg/day) and possibly gradually titrated up to 75–100mg/day depending on the individual patient's sensitivity to potential adverse effects [3].

Tricyclic anti-depressants are metabolized in the liver by enzymes of the cytochrome P450 family, and the half-life for drugs in this group ranges from 10 – 28 hours [31].

Due to the multitude of receptor interactions, the use of TCAs is associated with the risk of various side-effects. By blocking muscarinic receptors and acting cholinergically, their use can lead to visual disturbances, dry mouth, tachycardia or constipation. In turn, the consequence of blocking alpha-adrenergic receptors is the possibility of orthostatic hypotension or dizziness. In addition, drugs in this group can also lead to excessive appetite and weight gain due to their interaction with histamine receptors [31, 32].

Caution should be exercised when using TCAs in cardiac patients, as they can cause arrhythmias and prolong the QTc interval. Another group particularly vulnerable to the side- effects of TCAs are geriatric patients. This is a result of both the frequent multidrug use in these patients and age-related changes in metabolism, which can affect the pharmacokinetics of tricyclic anti-depressants. Additionally, elderly patients are more sensitive to the cholinolytic impact of these medications. It is worth considering the use of desipramine or nortriptyline in this group – their pharmacokinetics are more linear than amitriptyline, and they have less cholinolytic activity [32].

Opioids. The first representative of the opioid group of medications used in the treatment of pain was morphine. It was isolated from opium as long ago as the early 19th century. Over time, other substances belonging to the opioid group were developed, such as tramadol, buprenorphine and oxycodone. The mechanism of action of these drugs is based on their effects on opioid receptors. There are three main types of opioid receptors: MOP – to which most exogenous opioids have the highest affinity, KOP and DOP. They are located in the brain and spinal cord as well as peripherally. The anti-nociceptive effect of opioids is achieved by stimulating the above receptors – primarily MOP – and inhibiting the conduction of pain stimuli [33].

In neuropathic pain, the effectiveness of opioid medications is reduced. It is likely that one of the underlying mechanisms is a decrease in MOP receptor protein expression in the dorsal horns of the spinal cord and an increase in the activity of neuropeptides responsible for transmitting pain stimuli, such as substance P, in response to nerve tissue damage [33, 34]

Currently, due to the risks they involve, as well as their low efficacy in managing neuropathic pain, opioids are considered second-line drugs, and sometimes only third-line treatment. Opiods can be used in combination therapy with other drugs and for pain relief in PHN before the intended therapeutic effect is achieved during titration of TCAs and gabapentinoids [4, 8]. In PHN, opioid drugs are mainly administered in oral form, although there are studies and case reports showing that in certain patients administering them in transdermal form can provide effective pain control. In one study, transdermal oxycodone proved effective in a group of severe paresthesia sufferers and had fewer gastrointestinal side- effects than the oral form of the drug. Along with this, opioids in this form can sometimes be more effective in patients who are prone to non-compliance with dosage recommendations and oral medications intake [35, 36].

Opioid treatment, especially long-term, is fraught with a number of potentially dangerous or life-diminishing implications. Chronic use of drugs in this group is also associated with a high risk of psychological and physical dependence. Among the most common side-effects of opioid use are constipation and nausea, the first of these disorders is extremely common and can occur after just a single dose. Constipation after opioids is a significant problem, prompting patients to reduce the dosage or discontinue the drug in order to avoid unwanted discomfort, and this leads to inadequate analgesia. Other very common adverse effects include dizziness (which, especially in the elderly, increases the risk of falls and serious fractures), vomiting, myoclonus or muscle rigidity. Opiods also depress the respiratory centre within the brainstem, and therefore should not be used in patients with respiratory failure.

The above side-effects and the risk of developing dependence make it clear that drugs of this group should be used more as a second or even third line of PHN treatment, or as part of multimodal therapy [8, 37 38].

Topical drugs. Lidocaine and capsaicin are used in the topical treatment of neuropathic pain in PHN. Lidocaine 5% patch is an FDA-approved treatment for PHN in the United States. In Europe, it is recommended as a first-line drug, especially for non-severe pain, over a limited area of the body, and as part of combination therapy with other drugs. The mechanism of action of Lidocaine in neuropathic pain is based on stabilizing the membrane potential of neurons by blocking voltage-gated sodium channels, and inhibiting ectopic excitations in damaged nerves. Numerous studies on the effects of lidocaine administered topically in the form of a patch have conflicting conclusions about its efficacy in PHN or other neuropathic pain syndromes. Some show significant pain reduction compared to placebo [1, 3, 8, 39]. One retrospective review, although though including only eight patients, showed a noticeable reduction in pain as well as a reduction in the area of pain experienced by an average of 66% after three months of therapy [40]. On the other hand, one double-blind placebo-controlled clinical trial showed no significant difference in pain control between the 5% lidocaine patch and placebo – no less; however, the analysis noted that such therapy is relatively safe due to its low risk of side-effects [41]. The 2020 S2k guidelines for the diagnosis and treatment of herpes zoster and post-herpetic neuralgia, recommend regarding 5% lidocaine as a second-choice drug for the treatment of PHN [11].

The advantage of the 5% lidocaine patch is that when administered in this form, the drug penetrates the bloodstream in small amounts and is therefore relatively safe. Side-effects are mainly skin reactions in the area of patch application – redness, swelling or itching. Systemic reactions after the use of lidocaine in the form of patches are extremely rare, and include dizziness, a metallic taste in the mouth, drowsiness, hypotension, bradycardia and, in extreme cases – respiratory and cardiac disturbances [42, 43].

Capsaicin 8% patches are currently considered a second-line medication for post-herpetic neuralgia. Like 5% lidocaine patches, they are an FDA-approved form of treatment for this complication of herpes zoster. They can also be used as one component of combination therapy [8, 27].

Capsaicin is a TRPV1 receptor agonist. After attaching to these receptors and activating them, there is a release of vasoactive neuropeptides, among which the main role is played by substance P. Subsequently, there is an influx of calcium ions into the interior of nerve cells which disrupts the functioning of their mitochondria. As a result, nerve endings become dysfunctional and, consequently, there will be no nociceptive stimulation in a specific area of capsaicin action. Such a condition can last from several weeks to as long as three months, and the dose contained in a single patch is already sufficient to achieve the desired analgesia [39].

In a meta-analysis of four randomized trials involving 1,272 PHN patients, a single application of an 8% capsaicin patch to the skin was found to be significantly more effective in treating neuropathic pain than 0.014% topical capsaicin [8]. In contrast, one observational study described the successful impact of 8% capsaicin patches on peripheral neuropathic pain in the short and medium term, in addition to a reduction in the area that the pain covered [44].

Although the use of 8% capsaicin in the form described above is generally well tolerated, it is also associated with local adverse effects that cause some patients to discontinue treatment, mainly pain of a burning nature, pruritus and erythema. Temporary elevation of blood pressure may also occur. Due to minimal absorption into the bloodstream when applied to the skin, the risk of systemic effects is very low [45].

Combination therapy. When monotherapy proves ineffective and fails to provide adequate analgesia, or side-effects fail to achieve an effective dose with TCAs or gabapentinoids, combination, therapy may be an appropriate option for a patient with PHN. Several studies indicate numerous benefits and advantages of using a combination of oral and topical medications to treat postherpetic neuralgia over monotherapy. By using different mechanisms of action it is possible to achieve the desired therapeutic result with the use of two drugs from different groups at lower doses, while minimizing the risk of adverse effects [7, 8, 24, 46].

The combination of gabapentin and morphine in one study proved more effective in controlling neuropathic pain in PHN than using these medications alone. However, the combination of the two drugs was also associated with a high incidence of adverse events, such as sedation, constipation, dry mouth, or nausea and vomiting [3, 8]. The concomitant use of gabapentinoids and topical medications seems particularly noteworthy because of the low risk of interactions with other drugs. The combination of pregabalin and lidocaine 5% has been shown to be efficient in PHN sufferers in whom other single-drug treatment options have failed to provide sufficient pain relief [24].

Future directions in the treatment of post-herpetic neuralgia. Despite the availability of drugs from different groups that rely on diverse mechanisms of action, the treatment of neuropathic pain associated with post-herpetic neuralgia can be difficult in many patients, sometimes without satisfactory results. Nevertheless, development is still underway and research is being conducted on new pharmaceuticals that may prove effective in the treatment of PHN in the future [36].

Ketamine is one drug that has manifested effectiveness in relieving neuropathic pain in several studies on small groups of patients. Yet more thorough studies on larger groups are needed to confirm these reports and assess the risk of side-effects during chronic use [2, 47].

A group of drugs that may prove effective in the treatment of neuropathic pain syndromes such as PHN, are type 2 receptor antagonists for Angiotensin II. A formulation called Olodanrigan (EMA401) seems particularly interesting. This is a highly selective antagonist of the aforementioned receptor for Angiotensin II which has shown promising results, and a good safety profile in PHN patients in two phase II trials [36, 48, 49]. However, one of the studies was stopped prematurely due to hepatotoxicity detected in preclinical studies with long-term use of Olodanrigan, although it was not observed in the aforementioned study itself [36, 48].

Other potential future drugs worth mentioning and currently under research include the adaptor-related kinase 1 inhibitor LX9211, which is presently in Phase II clinical trials, and LAT8881 which is a fragment of human growth hormone the action of which is dependent on the peptide-modifying enzymes LANCL1 and LANCL2 [36].

SUMMARY

Treating pain in post-herpetic neuralgia remains an extremely challenging task for health care professionals, and despite the many oral as well as topical medications available, adequate pain control is relatively often not achieved. The prevalence of this complication of post-herpetic neuralgia in the elderly, often burdened with multiple additional diseases and already taking other medications, makes it important to adequately know and understand the available treatments, together with their mechanism of action and potential side-effects. Currently, oral medications are considered the first-line treatment – gabapentinoids or tricyclic antidepressants – appear to be the most appropriate, either in monotherapy or in combination with topical 5% lidocaine or 8% capsaicin. Further studies are needed to assess the efficacy and risks of using specific drugs or combinations of drugs in specific groups of patients with PHN. This will enable the development of therapies more tailored to individual cases. Ongoing research and clinical trials of new drugs give hope for the emergence of new, safe and effective treatments for postherpetic neuralgia in the future.

Table 1. Medications used to treat postherpetic neuralgia and their adverse effects

Line of treatment	Medication group	Adverse effects
First-line treatment medications	Gabapentinoids – Pregabalin – Gabapentin	Dizziness, balance disorders, drowsiness, weight gain, constipation, nausea, appetite disturbance
	Tricyclic antidepressants – Amitriptyline – Desipramine – Nortriptyline	Visual disturbances, dry mouth, tachycardia, constipation, orthostatic hypotension, dizziness, arrhythmia, QT prolongation, weight gain
Second-line treatment medications	Opioids: – Morphine – Tramadol – Buprenorphine – Oxycodone	Constipation, nausea, dizziness, vomiting, myoclonus, muscle rigidity, respiratory disorders
	Topical Lidocaine	Mainly skin reactions: redness, swelling, itching
	Topical Capsaicin	Pain of a burning nature, pruritus, erythema – in the area of patch application

REFERENCES

1. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. N Engl J Med. 2014;371(16):1526–1533. doi:10.1056/NEJMcp1403062
2. Gruver C, Guthmiller KB. Postherpetic Neuralgia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; April 17, 2023.
3. Philip A, Thakur R. Post herpetic neuralgia. J Palliat Med. 2011;14(6):765–773. doi:10.1089/jpm.2011.9685
4. Schutzer-Weissmann J, Farquhar-Smith P. Post-herpetic neuralgia – a review of current management and future directions. Expert Opin Pharmacother. 2017;18(16):1739–1750. doi:10.1080/14656566.2017.1392508
5. Nair PA, Patel BC. Herpes Zoster. In: StatPearls. Treasure Island (FL): StatPearls Publishing; September 4, 2023.
6. Niemeyer CS, Harlander-Locke M, Bubak AN, et al. Trigeminal Postherpetic Neuralgia: From Pathophysiology to Treatment. Curr Pain Headache Rep. 2024;28(4):295–306. doi:10.1007/s11916-023-01209-z
7. Feller L, Khammissa RAG, Fourie J, et al. Postherpetic Neuralgia and Trigeminal Neuralgia. Pain Res Treat. 2017;2017:1681765. doi:10.1155/2017/1681765
8. Mallick-Searle T, Snodgrass B, Brant JM. Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. J Multidiscip Healthc. 2016;9:447–454. Published 2016 Sep 21. doi:10.2147/JMDH.S106340
9. Andres TM, McGrane T, McEvoy MD, et al. Geriatric Pharmacology: An Update. Anesthesiol Clin. 2019;37(3):475–492. doi:10.1016/j.anclin.2019.04.007
10. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113-e88. doi:10.1111/j.1468-1331.2010.02999.x
11. Gross GE, Eisert L, Doerr HW, et al. S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia. J Dtsch Dermatol Ges. 2020;18(1):55–78. doi:10.1111/ddg.14013
12. Liu X, Wei L, Zeng Q, et al. The Treatment of Topical Drugs for Postherpetic Neuralgia: A Network Meta-Analysis. Pain Physician. 2020;23(6):541–551.
13. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. Br J Pain. 2020;14(2):104–114. doi:10.1177/2049463720912496
14. Athavale A, Murnion B. Gabapentinoids: a therapeutic review. Aust Prescr. 2023;46(4):80–85. doi:10.18773/austprescr.2023.025
15. Bockbrader HN, Wesche D, Miller R, et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin Pharmacokinet. 2010;49(10):661–669. doi:10.2165/11536200-000000000-00000
16. Hadley GR, Gayle JA, Ripoll J, et al. Post-herpetic Neuralgia: a Review [published correction appears in Curr Pain Headache Rep. 2016 Apr;20(4):28]. Curr Pain Headache Rep. 2016;20(3):17. doi:10.1007/s11916-016-0548-x
17. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6(6):CD007938. Published 2017 Jun 9. doi:10.1002/14651858.CD007938.pub4
18. Sang CN, Sathyanarayana R, Sweeney M; DM-1796 Study Investigators. Gastroretentive gabapentin (G-GR) formulation reduces intensity of pain associated with postherpetic neuralgia (PHN). Clin J Pain. 2013;29(4):281–288. doi:10.1097/AJP.0b013e318258993e
19. Swearingen D, Aronoff GM, Ciric S, et al. Pharmacokinetics of immediate release, extended release, and gastric retentive gabapentin formulations in healthy adults. Int J Clin Pharmacol Ther. 2018;56(5):231–238. doi:10.5414/CP203166
20. Schulze-Bonhage A. Pharmacokinetic and pharmacodynamic profile of pregabalin and its role in the treatment of epilepsy. Expert Opin Drug Metab Toxicol. 2013;9(1):105–115. doi:10.1517/17425255.2013.749239
21. Cao X, Shen Z, Wang X, et al. A Meta-analysis of Randomized Controlled Trials Comparing the Efficacy and Safety of Pregabalin and Gabapentin in the Treatment of Postherpetic Neuralgia. Pain Ther. 2023;12(1):1–18. doi:10.1007/s40122-022-00451-4
22. Mathieson S, Lin CC, Underwood M, et al. Pregabalin and gabapentin for pain. BMJ. 2020;369:m1315. Published 2020 Apr 28. doi:10.1136/bmj.m1315
23. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. Ann Pharmacother. 2016;50(3):229–233. doi:10.1177/1060028015620800
24. Massengill JS, Kittredge JL. Practical considerations in the pharmacological treatment of postherpetic neuralgia for the primary care provider. J Pain Res. 2014;7:125–132. Published 2014 Mar 10. doi:10.2147/JPR.S57242

25. Schneider J, Patterson M, Jimenez XF. Beyond depression: Other uses for tricyclic antidepressants. Cleve Clin J Med. 2019;86(12):807–814. doi:10.3949/ccjm.86a.19005
26. Hiroki T, Suto T, Saito S, et al. Repeated Administration of Amitriptyline in Neuropathic Pain: Modulation of the Noradrenergic Descending Inhibitory System. Anesth Analg. 2017;125(4):1281–1288. doi:10.1213/ANE.0000000000002352
27. Shrestha M, Chen A. Modalities in managing postherpetic neuralgia. Korean J Pain. 2018;31(4):235–243. doi:10.3344/kjp.2018.31.4.235
28. Birkinshaw H, Friedrich CM, Cole P, et al. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. Cochrane Database Syst Rev. 2023;5(5):CD014682. Published 2023 May 10. doi:10.1002/14651858.CD014682.pub2
29. Hearn L, Moore RA, Derry S, et al. Desipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014;2014(9):CD011003. Published 2014 Sep 23. doi:10.1002/14651858.CD011003.pub2
30. Derry S, Wiffen PJ, Aldington D, et al. Nortriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;1(1):CD011209. Published 2015 Jan 8. doi:10.1002/14651858.CD011209.pub2
31. Thour A, Marwaha R. Amitriptyline. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 18, 2023.
32. Moraczewski J, Awosika AO, Aedma KK. Tricyclic Antidepressants. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 17, 2023.
33. Przewlocka B. Basic mechanisms of analgesic effects of opioids. Palliat Med Pract. 2017;11(2):48–54.
34. Smith HS. Opioids and neuropathic pain. Pain Physician. 2012;15(3 Suppl):ES93-ES110.
35. Tsoleridis T. The Use of Transdermal Buprenorphine for Acute Postherpetic Neuralgia: A Case Report. Cureus. 2023;15(2):e34886. Published 2023 Feb 12. doi:10.7759/cureus.34886
36. Huerta MÁ, Garcia MM, García-Parra B, et al. Investigational Drugs for the Treatment of Postherpetic Neuralgia: Systematic Review of Randomized Controlled Trials. Int J Mol Sci. 2023;24(16):12987. Published 2023 Aug 20. doi:10.3390/ijms241612987
37. Zaporowska-Stachowiak I, Oduah MT, Celichowska M, et al. Opioids in clinical practice. Palliat Med Pract. 2020;13(4):221–228. doi:10.5603/pmpi.2019.0024
38. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105–S120.
39. Wordliczek J, Zajączkowska R, Leppert W. Pharmacotherapy of neuropathic pain. Palliat Med Pract. 2017;11(2):61–73. doi:10.5603/PMPI.2020.0020
40. Casale R, Di Matteo M, Minella CE, et al. Reduction of painful area as new possible therapeutic target in post-herpetic neuropathic pain treated with 5% lidocaine medicated plaster: a case series. J Pain Res. 2014;7:353–357. Published 2014 Jun 23. doi:10.2147/JPR.S65398
41. Binder A, Bruxelle J, Rogers P, et al. Topical 5% lidocaine (lignocaine) medicated plaster treatment for post-herpetic neuralgia: results of a double-blind, placebo-controlled, multinational efficacy and safety trial. Clin Drug Investig. 2009;29(6):393–408. doi:10.2165/00044011-200929060-00003
42. Voute M, Morel V, Pickering G. Topical Lidocaine for Chronic Pain Treatment. Drug Des Devel Ther. 2021;15:4091–4103. Published 2021 Sep 29. doi:10.2147/DDDT.S328228
43. Baron R, Allegri M, Correa-Illanes G, et al. The 5% Lidocaine-Medicated Plaster: Its Inclusion in International Treatment Guidelines for Treating Localized Neuropathic Pain, and Clinical Evidence Supporting its Use. Pain Ther. 2016;5(2):149–169. doi:10.1007/s40122-016-0060-3
44. Goncalves D, Rebelo V, Barbosa P, et al. 8% Capsaicin Patch in Treatment of Peripheral Neuropathic Pain. Pain Physician. 2020;23(5):E541–E548.
45. Santos MP, Lemos F, Gomes J, et al. Topical capsaicin 8% patch in peripheral neuropathic pain: Efficacy and quality of life. Br J Pain. 2024;18(1):42–56. doi:10.1177/20494637231201502
46. Boccella S, De Filippis L, Giorgio C, et al. Combination Drug Therapy for the Management of Chronic Neuropathic Pain. Biomolecules. 2023;13(12):1802. Published 2023 Dec 16. doi:10.3390/biom13121802
47. Guimarães Pereira JE, Ferreira Gomes Pereira L, Mercante Linhares R, et al. Efficacy and Safety of Ketamine in the Treatment of Neuropathic Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Pain Res. 2022;15:1011–1037. Published 2022 Apr 9. doi:10.2147/JPR.S358070
48. Rice ASC, Dworkin RH, Finnerup NB, et al. Efficacy and safety of EMA401 in peripheral neuropathic pain: results of 2 randomised, double-blind, phase 2 studies in patients with postherpetic neuralgia and painful diabetic neuropathy. Pain. 2021;162(10):2578–2589. doi:10.1097/j.pain.0000000000002252
49. Keppel Hesselink JM, Schatman ME. EMA401: an old antagonist of the AT2R for a new indication in neuropathic pain. J Pain Res. 2017;10:439–443. Published 2017 Feb 20. doi:10.2147/JPR.S128520