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# Postherpetic neuralgia (PHN)

**Abstract**

Herpes zoster (shingles) is an infectious disease caused by the varicella-zoster virus. Following the active phase of chicken pox and the crusting of skin lesions the virus spreads to the spinal and cranial ganglia and the posterior horns of the spinal cord, where it can stay dormant for many years. In immunocompromised patients, especially cancer patients, the virus can undergo reactivation to produce herpes zoster. The average incidence of herpes zoster is 4 per 1000 cases and rapidly increases with age and the lifetime prevalence is estimated at 10–20%. The predominating symptom of the acute phase of the disease is burning pain accompanied by abnormal skin sensation. The skin lesions in the form of vesicles usually heal within 3–5 weeks, unless a secondary bacterial infection ensues. After the skin lesions have healed, the pain may persist in some patients (9–14%) in the form of a chronic pain syndrome of various severity, usually unilaterally within one or several spinal dermatomes or the trigeminal nerve area. The first part of the paper discusses the pathomechanism, epidemiology, location, clinical manifestations and management of the acute phase of the disease. The second part provides a detailed discussion of the pathomechanism, risk factors, prevention and management of persistent postherpetic neuralgia according to evidence-based medicine, presenting the current state of knowledge on herpes zoster and postherpetic neuralgia. Over the years, the effectiveness of treatment of persistent postherpetic neuralgia has been gradually improving, mainly as a result of the currently available medication (antidepressants + gabapentinoids + topical medication + opioids) and the increasing understanding of the pathomechanism of this condition.

**Key words:** herpes zoster, postherpetic neuralgia, PHN, epidemiology of herpes zoster and PHN, pathomechanism of herpes zoster and PHN, risk factors of PHN, neuropathic pain, treatment of PHN

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## Introduction

Postherpetic neuralgia (PHN) is a classic example of neuropathic pain. Neuropathic pain is a type of non-nociceptive, chronic, severe and debilitating pain. Compared to patients with nociceptive pain, patients with neuropathic pain:

— experience a greater severity of pain;
— report a considerably lower quality of life;
— use more analgesics;
— report less symptomatic relief with treatment;
— report a higher incidence of side effects;
— fewer than 50% of the patients achieve satisfactory, yet still partial symptomatic relief;
— drugs proved to be effective in neuropathic pain are not used in the treatment;
— the doses of drugs are usually too low to achieve a therapeutic effect;
— despite using recommended drugs the patients continue to suffer from moderate pain [1–3].

The similarity between the pathomechanisms of neuropathic pain, depression and epilepsy has made it possible to use tricyclic antidepressants (e.g. am-

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itriptyline) or selective serotonin and noradrenaline reuptake inhibitors (venlafaxine, duloxetine) and, less frequently, selective serotonin reuptake inhibitors (paroxetine, sertraline, citalopram) and antiepileptic agents (gabapentin, pregabalin, carbamazepine, lamotrigine, valproic acid). In many cases, however, these drugs demonstrate poor effectiveness and there is an ongoing search for novel substances which might prove useful in the treatment of neuropathic pain. We take advantage of the effects exerted by muscle relaxants (baclofen), NMDA receptor antagonists (ketamine, dextromethorphan, magnesium), antiarrhythmics, which block pathological sodium channels (lidocaine IV, lidocaine patches 5% topically), bisphosphonates, alpha$_2$-agonists (clonidine), cannabinoids, COX inhibitors, adenosine receptor agonists and glutamatergic receptor agonists. Substances acting via the TRPV1 vanilloid receptor (8% capsaicin) are the latest addition to this group [4, 5].

## Herpes zoster

### Pathomechanism

Herpes zoster is an infectious disease caused by the varicella-zoster virus (VZV) [6]. Once an episode of chickenpox in childhood has resolved and the skin lesions have healed, the virus travels to dorsal root ganglia (DRG), cranial nerve ganglia and the dorsal horns of the spinal cord, where it can remain inactive for many years. In certain clinical situations (e.g. cancer) the virus reactivates causing inflammation of the nerve called herpes zoster (or shingles). The mechanism of virus reactivation is unclear. Immunocompromised patients (patients with cancer, tuberculosis, HIV infection, patients treated with glucocorticosteroids or immunosuppressant drugs, patients with renal failure, patients with liver failure) and the elderly are known to be at an increased risk of virus reactivation. Reactivation of the virus results in its rapid proliferation in DRG, cranial nerve ganglia and dorsal horns of the spinal cord. In these areas inflammatory, haemorrhagic and necrotic lesions develop. In the nerves of one or several dermatomes affected, demyelination, fibrosis and cellular inflammatory reactions ensue. In the affected dermatomes, painful lesions in the form of fluid-filled vesicles develop. In the affected skin, ulcers and necrotic foci may develop [7–9]. Examinations of skin sections collected in patients during the active phase of the disease show that a "secondary" viraemia is present in the skin, where the virus spreads from cell to cell. In the case of herpes zoster, the virus spreads via axonal transport, following reactivation in DRG, to keratinocytes and dermal cells. The diagnosis of herpes zoster is generally straight-forward due to the characteristic appearance of the skin lesions that are localised unilaterally within one or several dermatomes and take the form of an erythematous rash with vesicles [7, 8].

### Epidemiology

The incidence rate of herpes zoster averages between 3 and 4.5 per 1000 per year. The incidence increases with age, and this increase is particularly rapid in patients over the age of 60 years (6.8 per 1000 per year) with the incidence rate exceeding 10 per 1000 per year in patients over the age of 80 years [9–11]. The VZV is an extremely contagious pathogen belonging to the *Herpesviridae* family (*herpeton* in ancient Greek meant 'reptile'). Its contagiousness is strictly associated with the cell, outside of which the virus virtually immediately loses its ability to infect [12, 13].

### Location

The infection may affect sensory nerves of the trunk, extremities or cranial nerves. In more than 50% of the cases the disease affects intercostal nerves. Of the cranial nerves, the first division of the trigeminal nerve (herpes zoster ophthalmicus) is the most commonly affected (10–25% of the cases). The pain in herpes zoster localised in the head is generally more persistent and of longer duration [7–9].

### Signs and symptoms

The onset of pain in herpes zoster usually precedes the appearance of skin lesions, although these two manifestations may develop concurrently. There are, however, reports of prodromal periods of pain of 100 and more days' duration. Reactivation of the VZV may manifest as pain unaccompanied by skin lesions (zoster sine herpete), which makes the diagnosis difficult and delays treatment. Some patients, in addition to pain, complain of such symptoms as paraesthesia in the affected dermatome, i.e. numbness and tingling. Headache, fatigue and elevated body temperature may also be present. These three manifestations, due to the lack of precise data, should be regarded as accompanying manifestations. In immunocompromised patients, the course of the disease may be untypical, the symptomatic period longer and the lesions irreversible and present within a higher number of dermatomes. Pain is the nearly inseparable and in most cases the most troublesome symptom of herpes zoster. Due to its varied nature, four qualitative categories of pain in herpes zoster may be distinguished:

— spontaneous constant pain independent of the stimulus;
— spontaneous intermittent pain independent of the stimulus;
— pain evoked by the stimulus, e.g. dynamic allodynia;
— increased sensitivity to pain in the form of paraesthesia (numbness, pruritus) or dysaesthesia (burning sensation).

Patients most commonly describe spontaneous pain in herpes zoster as burning, throbbing or sharp, shooting, stabbing pain. Spontaneous intermittent pain described as shooting, stabbing or electric-shock-like pain is characteristic of the prodromal symptoms of herpes zoster. Pain described as burning pain is the most worrying type of pain, as it is characteristic of neuropathic pain. The burning nature of the pain is most likely a reflection of the important neurogenic pathomechanism of subsequent postherpetic neuralgia [1, 2]. Pain is usually severe. On the 11-point numeric rating scale (NRS), where 0 refers to 'no pain' and 10 to 'worst pain imaginable', pain in herpes zoster is usually rated at 4–10 points. The severity of pain generally increases in the evening and at night. The vesicular skin lesions heal within 3–5 weeks. During this period a secondary bacterial infection may develop, which — if the first division of the trigeminal nerve is affected — leads to keratitis and iritis and may result in vision loss. The pain accompanies the skin lesions throughout their presence on the skin and should resolve upon healing of the rash. In rare cases, accompanying signs and symptoms are present, such as elevated body temperature, enlarged lymph nodes, nuchal rigidity, headache and nausea [7–9].

The most popular classification of pain in herpes zoster is based on 3 phases:
— acute pain — pain that is present for up to 30 days after the onset of the rash;
— subacute postherpetic neuralgia — pain of more than 30 days' duration but resolves before the diagnosis of PHN is made;
— postherpetic neuralgia — pain that persists beyond 120 days after the onset of the rash. The lack of a unified and unequivocal definition of PHN that would specify a universal timeframe makes it difficult to interpret many studies of postherpetic pain [14].

### Management

In the acute stage of the disease, antiviral treatment, prevention of secondary bacterial infection and pain relief are recommended. The combination treatment is particularly important in patients at a high risk of PHN (see below).
— antiviral treatment: acyclovir 800 mg five times daily for 7 days (to be started immediately after the onset of the rash);
— prevention of secondary bacterial infection;
— Topical treatment: ointments, skin powder;
— Pain relief: NSAIDs + paracetamol + tramadol. In severe pain: potent opioids;
— nervous system blocks: infiltrative blocks, nerve trunk blocks, sympathetic nervous system blocks, central blocks. These interventions provide pain relief and may reduce the risk of PHN;
— intravenous infusions of lidocaine — 3 mg/kg body weight over 30 minutes twice weekly until pain relief is achieved (prevention of the formation of pathological sodium channels — reduction of the risk of PHN);
— antidepressants: amitriptyline 10–75 mg/day — reduction of the risk of PHN;
— anticonvulsants: gabapentin/pregabalin — reduction of the risk of PHN.

## Postherpetic neuralgia (PHN)

Postherpetic neuralgia (PHN) refers to pain localised within dermatomes affected by the viral infection that persists (or recurs) after the infection and the healing of the skin lesions for more than 3 months. The viral infection may cause injury to both sensory and motor nerve fibres with subsequent cicatrisation of a peripheral nerve trunk, spinal ganglion, nerve root and posterior horns of the spinal cord. Within the area of the healed skin lesions pain is described as burning, stinging, piercing, shooting or throbbing. The pain may be constant or intermittent. A cold rainy weather and stress may increase the severity of the pain. The pain is also more severe in the evening and at night. The patient also develops sensation abnormalities in the form of allodynia (pain evoked by non-nociceptive stimuli, e.g. touch), hyperalgesia (exaggerated pain response to mechanical and thermal stimuli, e.g. to contact of the affected skin with clothing) and hypoaesthesia (impaired touch and temperature sensation). In addition, sleep disorders and reduced activity are present in more than a half of the patients with PHN [7–9, 15]. Two non-mutually exclusive theories are currently most popular among researchers investigating PHN. The first theory suggests a role of decreased excitability of nerves within the ganglia and even within the spinal cord. The other theory suggests a chronic or smouldering viral infection within the nerve ganglia,

where infiltrates of cells characteristic of chronic inflammation have been documented [14]. The cause of PHN is unclear. Pain and abnormal sensation in the affected area are a result of inflammation, extravasation, necrosis and degeneration that develop in the peripheral nerve, sympathetic ganglia, DRG, posterior roots of the spinal cord and ascending tracts of the spinal cord during the activation of the virus. The inflammation causes disintegration of the nervous system (peripheral sensitisation, impulse formation in pathological ectopic pacemakers of the nerve, central sensitisation, central reorganisation of A-beta fibres, functional impairment of the descending pain control pathways) [7–9, 16, 17].

**Risk factors of PHN**

The factors increasing the risk of PHN include: age, female sex, severe pain preceding the appearance of the rash, involvement of the first division of the trigeminal nerve, involvement of non-neighbouring dermatomes, diabetes, cancer or other immunocompromising conditions and a very severe course of the acute phase of the disease with severe pain and involvement of multiple dermatomes. However, PHN may also develop in patients with a very mild course of herpes zoster [7–10, 18]. The risk of PHN increases with age reaching 50%, 75% and nearly 100% in patients over the age of 50, 65 and 80 years, respectively. The pain may resolve spontaneously within several months but in some patients it persists for years or even a lifetime [7].

**Can herpes zoster and postherpetic neuralgia be prevented?**

Multicentre randomised double-blind studies of a total of 38.5 thousand patients over the age of 60 years immunised with the antiviral vaccine Zostavax composed of live attenuated viruses demonstrated, over 3 years of follow-up, a statistically significant reduction in the incidence of herpes zoster following immunisation of 61% [6, 19]. The incidence rate of herpes zoster was 11.1 per 1000 in the placebo group versus 5.4 per 1000 in the immunised group. Similarly, there was a statistically significant reduction in the incidence of PHN following immunisation of 66.5% [9, 19]. Many studies have been conducted on the treatment of the active phase of herpes zoster with acyclovir. This antiviral drug, if used sufficiently early (within 48 hours of the onset of the skin lesions), is aimed to limit proliferation of the virus in DRG, cranial nerve ganglia and posterior horns of the spinal cord. Results of the analyses are, however, ambiguous and the confirmation of the role of early antiviral treatment in reducing the risk of PHN requires further, well-planned studies. Several studies in which various dosages of acyclovir were used negates the efficacy of antiviral therapy in the treatment of herpes zoster and the prevention of PHN. Other studies, however, confirm the efficacy of acyclovir at the dose of 800 mg five times daily. Studies confirming the efficacy of other antiviral agents, such as famciclovir and valaciclovir, have also been published. A study showing superiority of intravenous over oral acyclovir has also been published. Studies to assess acyclovir concentrations with oral and intravenous administration are, however, lacking [8, 9, 14]. The following measures are recommended in the prevention of PHN (particularly in high-risk patients): effective pain relief in the acute phase of the disease, sympathetic nervous system blocks, intravenous infusions of lidocaine and treatment with antidepressants and anticonvulsive agents [8, 9].

**Management of PHN**

The management of PHN depends on the duration and type of pain reported by the patient. If the patient is suffering from allodynia or hyperalgesia to stimuli the following are recommended:

— topically, lidocaine patches 5%;
— topically, 8% capsaicin;
— topically, EMLA cream;
— topically, acetylsalicylic acid;
— topically, doxepin cream;
— infiltrative blocks with 1% lidocaine;
— sympathetic blocks;
— epidural blocks [7–9].

***Topical agents***

*EMLA cream*

EMLA cream is an oil-in-water emulsion containing lidocaine and prilocaine in the ratio 1:1. This is a unique local anaesthetic formulation, as thanks to the high water content it is readily absorbed by the skin and thanks to the fact that the active substances are not present in the dissociated form but in the form of more active basic compounds contained in fine droplets of fat suspended in water it is possible to achieve effective skin anaesthesia at the depth of about 5 mm. EMLA cream is an eutectic mixture, which means that the melting point of the mixture differs from the melting points of its individual components. At the human skin temperature, the formulation maintains a liquid form thanks to which it has a chance of being absorbed by the skin and of evoking its anaesthesia,

even over extensive areas of skin exceeding 400 $cm^2$, with a single dose of 30–50 g (1 g of the cream contains 25 mg of lidocaine and 25 mg of prilocaine). EMLA cream is indicated for skin anaesthesia to eliminate acute pain during procedures limited to the depth of the skin of about 5 mm (excision of small skin lesions, intravenous cannulation, painful punctures). EMLA cream is also indicated for the treatment of peripheral neuropathic pain, e.g. postherpetic neuralgia, especially in patients in whom blocks are contraindicated. When applying EMLA cream on a large area of the skin, the patient requires haemodynamic monitoring and monitoring the levels of lidocaine and methaemoglobin, whose formation may be induced by prilocaine metabolites. The high price is a considerable factor that limits the use of EMLA cream in Poland and when the product needs to be applied on large areas of skin, another important limiting factor if the need for monitoring that requires hospitalisation of the patient [20, 21].

*Lidocaine patches 5%*

In contrast to EMLA cream, patches containing 5% lidocaine exert their action mainly topically on pathological voltage-gated sodium channels (VGSCs) that are formed in the injured nerve. VGSCs accumulate at sites of injury and generate repetitive ectopic impulses. These channels are resistant to tetrodotoxin (TTR-R VGSCs) and are characterised by a high ability to bind lidocaine. Dissociation of lidocaine from TTR-R VGSCs is slow. After being released from the patch lidocaine penetrates the skin and only trace amounts (5%) enter the circulation, which is why it does not cause cardiovascular complications but binds with the internal wall of pathological VGSCs which are formed in nerve endings and keratinocytes.

As a result of the blocking of pathological sodium channels ectopic impulses are suppressed, although this is not accompanied by the blocking of afferent nerve conduction (numbness does not develop). The other mechanism of action of lidocaine involves inhibition of the release of nociception mediators by keratinocytes, which account for 95% of the cells in the epidermis and are closely associated with nerve fibres. Keratinocytes are involved in the process of signalling and their activation induces sensitisation and depolarisation of primary sensory nerve endings through P2X receptors and increased expression of NK1 receptors in keratinocytes, which increases the release of substance P and leads to activation of the primary nociceptive sensory nerve endings [21, 22]. In addition, lidocaine patches exert a skin cooling effect and provide a mechanical protection of the affected skin.

In contrast to EMLA cream, lidocaine in the form of patches is only minimally absorbed to the circulation (less than 5% enters the circulation) and the number needed to harm (NNH, the number of patients who need to be given a drug in order to cause clinically relevant adverse reactions in one of them) is very high (about 28). Topical lidocaine is recommended as the first-line treatment in localised peripheral neuropathic pain alone or in combination with another first-line drugs, which in the case of PHN may include antidepressants or gabapentinoids. The use of topical agents, such as lidocaine patches, may be preferred to systemic treatment, as the former are intended for local treatment of pain with minimum systemic absorption. Adverse reactions, such as somnolence or vertigo, which often accompany systemic treatment, may be problematic, particularly in the elderly, in whom they increase the risk of falls. Lidocaine patches may also increase patient adherence to long-term treatment thanks to the ease of use: they are applied on the skin once daily or every 12 hours, which is in line with the approved label (up to 4 patches at a time), in contrast to creams or oral agents, which often have to be dosed several times over the 24-hour period. Dosing every 12 hours provides a good analgesic effect throughout the entire 24 hours and the relatively long intervals between patch applications protect the skin from chafing. A metaanalysis performed in 2009 that included 6 databases (32 studies, 38 publications) showed that 5% lidocaine was effective in the treatment of PHN (EBM level I evidence). The number needed to treat (NNT, the number of patients who need to be given a drug in order to obtain a positive treatment effect in one of them) is 2 and in the case of painful diabetic neuropathy its efficacy is comparable to that of amitriptyline, capsaicin, gabapentin and pregabalin, although the use of 5% lidocaine is associated with fewer and less severe adverse reactions. The most common adverse reaction to lidocaine patches 5% is local skin irritation. A drawback for Polish patients is the high price, which limits the widespread use of this formulation despite the fact that international guidelines recommend initiating treatment from lidocaine patches 5%, especially in patients with allodynia [21, 23–28].

*Capsaicin*

Capsaicin, or *N*-[(4-hydroxy-3-methoxyphenyl) methyl]-8-methylnon-6-enamide, is a highly selective agonist of the transient receptor potential vanilloid-1

(TRPV1). The initial effect of capsaicin involves the activation of TPRV1 nociceptors in the skin, which leads to irritation and the development of erythema caused by the release of vasoactive neuropeptides, principally substance P. Following exposure to capsaicin skin nociceptors become less sensitive to various stimuli, hence the "late" action of capsaicin is often referred to as "anaesthesia" and is believed to be responsible for the resolution of pain. Sensations from skin nerves that do not express TPRV1 are unchanged, including touch and vibration sensation. Capsaicin-induced changes in skin nociceptors are reversible, as shown by studies in healthy volunteers which demonstrated normalisation of receptor function within several weeks. The mechanism of action of capsaicin, in addition to vanilloid receptor inactivation, also involves the removal of substance P from nerve endings.

Capsaicin applied topically in the form of a cream (0.025% or 0.075%) evoked a significant effect in diabetic neuropathy and NNT for this disease entity was 2.5–4.9. Capsaicin is also used in PHN (NNT 5.3) and following nerve injury (NNT 3.5). NNH for capsaicin used for the treatment of neuropathic pain is 11.5 (range: 8.1–19.8) [28–32].

A randomised study of a patch containing 8% capsaicin in 299 patients with PHN versus a patch containing 0.04% capsaicin (control group) applied for 30, 60 or 90 minutes showed the greatest percentage of pain reduction in the group in whom a patch containing 8% capsaicin was applied for 60 minutes with symptomatic relief being maintained from weeks 2 to 12 of follow-up. Controlled clinical studies also showed the efficacy of a patch containing 8% capsaicin with a single application onto painful areas of the skin (following a one-hour local anaesthesia of the skin with EMLA cream). In 307 patients with neuropathy in the course of VZV infection, a pain reduction of 22.8% was already observed after a week and was maintained for 12 weeks. Capsaicin patches were used alone and in combination with other drugs used in neuropathic pain. The use of patches containing 8% capsaicin in patients with diabetic neuropathy is poorly investigated and requires further studies. A patch containing 8% capsaicin is approved and available in Poland.

Capsaicin contained in the patch must be "delivered" to the skin and it is estimated that during the one-hour application, 1% of capsaicin is absorbed into the layers of the epidermis and dermis. Given the fact that the quantity of capsaicin released from the patch is proportional to the application area, the estimated possible total maximum dose for a surface area of 1000 $cm^2$ is about 7 g. Assuming that a patch whose surface area is 1000 $cm^2$ delivers about 1% of capsaicin for a patient weighing 60 kg, the maximum dose of capsaicin possible to use will be 0.12 mg/kg for 3 months (up to 4 patches per application). Each capsaicin patch measures 14 ´ 20 cm (280 $cm^2$) and contains 179 mg of capsaicin (640 $\mu$g of capsaicin per $cm^2$). The patch is applied on painful areas of the skin, which should be precisely marked and previously anaesthetised with a local anaesthetic, in line with the label. Many experts question the requirement to anaesthetise the skin before patch application. They argue that this requirement considerably protracts the procedure, it is difficult to properly dry the skin following application of the local anaesthetic, which may negatively affect the adhesiveness of the capsaicin patch, and despite the use of EMLA cream most patients still require an additional analgesic medication to relieve the acute pain accompanying patch application. At our facility, we always anaesthetise the skin with EMLA cream. We meticulously apply the cream on the skin area and then we apply the patch keeping a 1-cm safety margin. EMLA cream is applied for 60 minutes. The patch can only be applied on an intact and dry skin without signs of irritation (the skin must not be shaved, if hairs are present, they should be trimmed). The patch should be cut precisely to the area of the skin affected by pain. The patch is applied for 30–60 minutes. Throughout the procedure the patient's blood pressure should be monitored (transient blood pressure surges may be observed, especially in hypertensive patients). If the pain persists or recurs, treatment may be repeated every 90 days. Statistically, the time to recurrence of pain and subsequent application of the patch ranges from 10–12 weeks to 8 months and increases with subsequent applications. If during or after patch application the patient complains of severe pain, oral analgesics may be used (e.g. short-acting opioids: morphine, tramadol, tramadol plus paracetamol and/or rapid-onset NSAIDs: lornoxicam, nimesulide). The patch is removed by inward rolling. After removing the patch a thick layer of a cleansing gel should be applied for about 1 minute, the gel should then be removed and the skin washed with soap and water. The pain that appears directly after removal of the patch is best relieved by application of the cleansing gel and local cooling of the skin. No capsaicin dose adjustments are necessary in patients with renal or liver insufficiency. The drug is not recommended for patients below 18 years of age. The use of the drug on the skin of the head is not recommended due to

the risk of eye irritation. No clinical data are available on the use of capsaicin patches in pregnant or breastfeeding women. The most common adverse reactions have included transient burning sensation, pain, erythema and pruritus at the application site and have been mild to moderate. Apart from the warmth sensation at the site of patch application no other limitations of neurologic function have been observed. The efficacy of capsaicin should not only be assessed in terms of pain relief on the 11-point NRS but also in terms of changes in the nature of the pain, improvement of the quality of sleep and improvement of the quality of life. The high price is a disadvantage that limits the use of capsaicin patches in Poland [28–32].

***Sympathetic nervous system blocks***

The use of local anaesthetics in the treatment of early postherpetic pain was first reported in 1938 and since that time they have become an element of management standards in this type of pain. The blocks are performed at intervals of one or two days in the total number of 3 to 10. The sooner this treatment is initiated, the higher the efficacy and the lower the number of blocks that yield satisfactory outcomes. The efficacy of the blocks in the early period of 4 to 12 weeks is very high (85–98%) and during the period between 3 and 6 months is still good. The efficacy in the later period between 6 to 12 months is low and beyond 12 months is minimal. According to Winnie, blocks should be used as a preventive measure before the onset of neuralgia in each patient over the age of 50 years (after [33]). Winnie supported his opinion on early initiation of sympathetic blocks with a very convincing explanation of the pathophysiology of the changes which develop in herpes zoster. The VZV shows a high affinity for nerves and elicits inflammatory changes in them which are responsible for primary pain and the characteristic skin lesions. The inflammation causes a potent stimulation of the sympathetic nervous system leading to a very considerable reduction in blood supply to the nerve (up to 93%). The persistent ischaemia leads to changes in the endothelium of intraneural capillaries which leads to albumin leaks and oedema. The persistent oedema, by increasing intracapillary pressure, worsens the already present ischaemia and causes irreversible changes in the nerve. In addition, as a result of circulatory abnormalities, metabolic changes develop, which mainly manifest by reduced glucose levels. All these changes lead to degeneration of A-delta fibres.

Animal studies demonstrated that the thin type C nerve fibres are much more resistant to metabolic changes and the existing ischaemia, thanks to which they retain their function for a longer time under pathological conditions. In the normal nerve, A-delta fibres predominate over C fibres. In their theory of pain, the so-called gate control theory, Melzack and Wall [33, 34] pointed to the significance of impulses conducted by both types of nerve fibres in the process of nociception. At the level f the posterior horn of the spinal cord impulses from A-delta fibres close the path to impulses conducted by the thin type C nerve fibres. Microscopic studies of the nerves affected by herpes zoster showed numerous type C fibres, while most of the thick A-delta fibres were destroyed and replaced by connective tissue. This phenomenon was described as the so-called fibre dissociation. Nerves altered in this way generate nociceptive stimuli without the possibility of being suppressed as they are transmitted to the CNS. Based on the results of neurophysiologic studies that prove the existence of the so-called antinociception, Melzac also suggests that the primary neuronal dysfunction has its source not only in the spinal cord but also in higher-level structures, mainly in a part of the reticular formation of the brainstem. Under normal conditions, modulation or inhibition occurs at all levels of the ascending nervous system. The partial lack of sensory fibres as a result of injury to the peripheral nerve leads to a decrease of general afferentation from the periphery and the resulting decrease of the inhibitory influence on the function of the nociception system. In conclusion, sympathetic pain syndromes may be characterised by an abnormal activity of the neurons in all parts of the nervous system. The role of individual parts of this system depends on a series of interconnected factors that include, among others, the degree and type of nervous system injury, individual psychological traits of the patient and, most importantly, duration of the chronic pain syndrome. The pathomechanism of pain in the early period is most likely localised in a more peripheral part of the nervous system. This is confirmed by clinical studies, as at this stage the efficacy of various methods that exclude the peripheral nervous system is the highest. It seems that one of the more important peripheral mechanisms present in all the forms of chronic pain syndromes is hypersensitivity of injured axons or axonal endings to noradrenaline, which is released form sympathetic nervous system endings. Suppression of this mechanism by sympathetic blockade is considered the most effective treatment. Of particular significance is also the fact that this is also the least expensive treatment of postherpetic pain. It is therefore impor-

tant for the clinician to know whether sympathetic blockade in a given period of the disease is likely to result in a relevant therapeutic benefit and to prevent the development of a persistent pain syndrome. The persistence of pain for weeks, months and years results in a gradual involvement of higher levels of the CNS. Due to the complicated pathomechanism of neuropathic pain and most of all due to the lack of detailed studies of the CNS, they are still a great unknown despite the appearance of new hypotheses, which will, however, remain mere hypotheses until they have been proved [33–37].

***Systemic treatment***

*Anticonvulsive drugs*

Gabapentin acts by inhibiting the alpha$_2$ subunit of the G protein in the voltage-gated calcium channel. The starting dose is 100 mg daily. The full, therapeutically effective dose, which varies widely from 600 mg to 3600 mg daily, is achieved within about 30 days. NNT for gabapentin is 3.2 [7–9]. This wide range of doses results from the pharmacokinetic profile of gabapentin absorption, which is non-linear. This means that the higher the dose, the poorer the absorption, so that any deficiency of the drug is made up for by a high dose.

Another anticonvulsive drug shown to be effective in the treatment of PHN in clinical studies is pregabalin, a derivative of gabapentin. The drug is used at doses from 150 mg to 600 mg daily in two or three divided doses. Both drugs differ in two respects: the onset of action and the pharmacokinetic profile of absorption, which affects the level of the therapeutic dose. Absorption of oral pregabalin is linear which means that the absorption of the drug does not depend on the dose. Thanks to this the maximum dose of pregabalin is six times lower than that of gabapentin. The full analgesic effect of pregabalin is observed within only 7 days, while in the case of gabapentin the full effect takes 4 weeks to develop. Both drugs cause similar adverse reactions: vertigo, imbalance, somnolence, peripheral oedema [38].

*Intravenous lidocaine*

Intravenous lidocaine at the dose of 3 mg/kg (NNT 2.3) blocks the pathological sodium channels.

*Tricyclic antidepressants (TCAs)*

Tricyclic antidepressants are useful in the treatment of PHN and are characterised by the NNT of 2.4 for the entire class. TCAs are effective in relieving spontaneous pain with burning sensation and paraesthesia. Amitriptyline is the most commonly used TCA. It is used at doses ranging from 25 mg to 75 mg daily. TCAs is a group of drugs that cause numerous adverse reactions. Caution is therefore recommended in the elderly, patients with serious cardiovascular co-morbidities, benign prostatic hyperplasia and glaucoma. Controlled studies show the efficacy of the selective serotonin and noradrenaline reuptake inhibitors duloxetine and venlafaxine in the treatment of PHN. Duloxetine is given at doses from 60 mg to 120 mg daily and venlafaxine at doses from 75 mg to 150 mg daily.

*Opioids*

Tramadol is given at doses of up to 400 mg daily. Due to the fact that neuropathic pain is relatively resistant to opioids the initiation of potent opioids, such as fentanyl, morphine, buprenorphine or oxycodone, is recommended after performing tests of pharmacological analysis showing that this treatment is effective [7–9].

***Non-pharmacological treatments***

Non-pharmacological treatments include:

— TENS;
— acupuncture;
— laser therapy;
— local cooling;
— spinal cord stimulation [7–9].

## Conclusions

The current standard in the treatment of PHN is combination treatment with an antidepressant, a topically-acting gabapentinoid (5% lidocaine and/or 8% capsaicin) and an opioid. Of these drugs, gabapentin, pregabalin, TCA and lidocaine patches 5% are considered first-line treatments, and capsaicin and opioids are considered second-line treatments. As regards opioids, the greatest number of studies have been conducted with tramadol and oxycodone. It is recommendable to start treatment with lidocaine patches and gradually add other classes of drugs, if necessary [5, 24, 25, 27, 31, 32, 39, 40].

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