

## POSTHERPETIC NEURALGIA

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**SUMMARY** – Postherpetic neuralgia is a chronic neuropathic pain syndrome that may complicate recovery from an acute attack of herpes zoster. About 20% of patients with herpes zoster develop persistent neuropathic pain. Evidence based medicine supports the use of tricyclic antidepressants, opioids and anticonvulsants in the management of postherpetic neuralgia. Other methods are topical therapy with lidocaine and capsaicin as well as intrathecal administration of methylprednisolone in some refractory cases of postherpetic neuralgia.

**Key words:** *Herpes zoster – drug therapy; Herpes zoster – physiopathology; Neuralgia – drug therapy; Neuralgia – etiology; Neuralgia – physiopathology; Pain – etiology*

### Introduction

Herpes zoster and postherpetic neuralgia (PHN) result from reactivation of the varicella-zoster virus acquired during the primary varicella infection, or chickenpox. Whereas varicella is generally a disease of childhood, herpes zoster and PHN become more common with increasing age<sup>1</sup>. Many conditions that decrease immune function, such as human immunodeficiency virus (HIV) infection, chemotherapy, malignancies and chronic corticosteroid use, may also increase the risk of developing herpes zoster. Reactivation of latent varicella-zoster virus from dorsal root ganglia is responsible for the classic dermatomal rash and pain that occur with herpes zoster. Burning pain typically precedes the rash by several days and can persist for several months after the rash has resolved<sup>2,3</sup>.

Acute herpetic neuralgia refers to pain preceding or accompanying the eruption of rash that persists for up to 30 days from its onset. Subacute form refers to pain that persists beyond healing of the rash, which resolves within four months of onset. PHN is defined as pain persisting beyond four months from the onset of rash<sup>4</sup>.

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Herpes zoster is a sporadic disease with an estimated lifetime incidence of 10 to 20 percent. The incidence of herpes zoster increases sharply with advancing age, roughly doubling in each decade past the age of 50 years. Herpes zoster is uncommon in persons less than 15 years of age. In HIV-infected patients, the incidence of herpes zoster is up to 15-fold that in uninfected persons, and as many as 25 percent of patients with Hodgkin's lymphoma develop herpes zoster<sup>5</sup>.

About 20 percent of patients with herpes zoster develop PHN. The best established risk factor is age. Other possible risk factors for the development of PHN are ophthalmic zoster, a history of prodromal pain before the appearance of skin lesions, and an immunocompromised state<sup>6</sup>.

### Pathogenesis

The infection with acute herpes zoster is caused by reactivation of varicella zoster virus. The virus persists for years in the dorsal root ganglia of cranial or spinal nerves after resolution of the original infection. In cases with decreased immunity the virus travels down the sensory nerve and is the cause of dermatomal distribution of pain and skin lesions.

The pathophysiology of PHN remains unclear. However, pathologic studies have demonstrated damage to the sensory nerves, sensory dorsal root ganglia and dorsal horns of the spinal cord in patients with this condition.

The pain in acute phase probably is produced by the inflammation and movement of viral particles from sensory nerves to the skin and subcutaneous tissues as well as by damage to nerve structures. The activity of primary afferent neurons that respond to tissue damage causes changes in dorsal horn neurons, sensitizing them to further input and resulting in spontaneous activity capable of maintaining pain in the absence of ongoing tissue damage. In cases of persistence of this response, the pain becomes postherpetic<sup>8</sup>.

### Clinical Manifestation

The pain associated with acute zoster infection is characterized by sharp or stabbing sensation. Affected patients usually report constant burning, lancinating pain that may be radicular in nature. Many patients complain of allodynia, defined as pain evoked by normally non-painful stimuli such as light touch. It has been suggested that allodynia is most prominent in the areas of relatively preserved sensation, while spontaneous pain is felt predominantly within the areas of lost or impaired sensation.

PHN is characterized by areas of anesthesia as well as deficits of thermal, tactile, pinprick and vibration sensation within affected dermatomes. Although any vertebral dermatome may be involved, T5 and T6 are most commonly affected. The most frequently involved cranial nerve dermatome is the ophthalmic division of the trigeminal nerve.

PHN is generally a self-limited disease. Symptoms tend to abate over time. Less than one quarter of patients still experience pain at six months of herpes zoster eruption, and fewer than one in 20 has pain at one year<sup>9</sup>.

### Treatment of Postherpetic Neuralgia

Although PHN is generally a self-limited condition, it can last indefinitely. Treatment is directed at pain control while waiting for the condition to resolve. Pain therapy may include multiple interventions, such as topical medications, over-the-counter analgesics, tricyclic antidepressants, anticonvulsants, and a number of non-medical modalities. Occasionally, narcotics may be required<sup>10</sup>.

#### *Analgesics*

Mild analgesics such as nonsteroidal anti-inflammatory drugs are of limited value in patients with acute or chronic pain. Opioids may be more effective. Because

of the addictive properties of narcotics, their chronic use is discouraged except for rare patients that do not adequately respond to other modalities.

#### *Capsaicin*

Capsaicin, an extract from hot chili peppers, is currently the only drug labeled by the U.S. Food and Drug Administration for the treatment of PHN<sup>11</sup>. Trials have shown the drug to be more efficacious than placebo but not necessarily more than other conventional treatments. It is thought to produce analgesia by enhancing the release of the nocigenic peptide substance P from C-fibers and then preventing reaccumulation. Topical application causes burning, stinging and erythema<sup>11</sup>.

#### *Local and topical anesthetics*

Patches containing 5% lidocaine have also been used to treat PHN. One study found that compared with no treatment, lidocaine patches reduced pain intensity, with minimal systemic absorption. Although lidocaine was efficacious in relieving pain, the effect was temporary, lasting for only 4-12 hours with each application<sup>12</sup>. By the end of 2007, lidocaine patches will be available in Croatia.

#### *Tricyclic antidepressants*

Tricyclic antidepressants can be effective adjuncts in reducing neuropathic pain of PHN. These drugs inhibit the reuptake of serotonin and norepinephrine neurotransmitters. They are thought to increase the inhibition of nociceptive signals from the periphery. Tricyclic antidepressants commonly used in the treatment of PHN include amitriptyline, nortriptyline, imipramine and desipramine. These drugs are best tolerated when started at a low dosage (10-20 mg) and given at bedtime. The dosage is increased every two to four weeks to achieve an effective dose (a mean amitriptyline dose of 65 mg).

The side effects of tricyclic antidepressants are sedation, dry mouth, postural hypotension, blurred vision and urinary retention. Nortriptyline and amitriptyline appear to have equal efficacy; however, nortriptyline tends to produce fewer anticholinergic effects and is therefore better tolerated. Treatment with tricyclic antidepressants can occasionally lead to cardiac conduction abnormalities or liver toxicity. The potential for these problems should be considered in elderly patients and patients with cardiac or liver disease<sup>13</sup>.

### Anticonvulsants

Anticonvulsant medications are useful in the treatment of neuropathic pain, especially in reducing the lancinating component of painful syndromes like trigeminal neuralgia<sup>14</sup>. Gabapentin and pregabalin are most often used to control pain. A recent double-blind, placebo-controlled study showed gabapentin to be effective in treating PHN pain as well as the often associated sleep disturbance<sup>15</sup>. Pregabalin is similar to gabapentin. Randomized studies in PHN patients showed improvement in sleep and decrease in pain at doses of 150 to 600 mg daily<sup>16</sup>.

Anticonvulsants are associated with a variety of side effects including sedation, memory disturbances, electrolyte abnormalities, liver toxicity and thrombocytopenia. Side effects may be reduced or eliminated by initiating treatment in a low dosage, which can then be slowly titrated upward. There are no specific contraindications to using anticonvulsants in combination with antidepressants or analgesics. However, the risk of side effects increases when multiple medications are used<sup>14</sup>.

### Antagonists of N-methyl-D-aspartate receptor

Antagonists of N-methyl-D-aspartate (NMDA) receptor relieved neuropathic pain in some studies. The most

often used NMDA receptor antagonists are ketamine and dextromethorphan. Unfortunately, ketamine has many side effects when administered parenterally<sup>17</sup>.

### Surgery

Surgical procedures include anterolateral cordotomy, electrical stimulation of the thalamus, and electrocoagulation of the dorsal root. All surgical interventions are connected with the risk of permanent neurologic deficits. The results of these procedures are not satisfactory.

### Other methods

Sympathetic blocks with bupivacaine showed benefit for PHN in one study. Intravenous therapy with lidocaine may provide benefit in patients refractory to other therapies<sup>18</sup>. Acupuncture and transcutaneous electrical nerve stimulation (TENS) are widely used in therapy of PHN but the effectiveness has not been proven in studies. Effective treatment of PHN often requires multiple treatment approaches. The American Academy of Neurology recommends tricyclic antidepressants, gabapentin, pregabalin, strong opioids, and topical lidocaine patches as first-line therapies<sup>13</sup>.

Table 1. Medications for postherpetic neuralgia

Medication	Dosage
<b>Topical agents</b>	
Capsaicin cream (0.075%)	Three to five times daily on affected areas.
Lidocaine (Xylocaine) patch (5%)	Apply to affected area every 4 to 12 hours as needed.
<b>Tricyclic antidepressants</b>	
Amitriptyline	0 to 25 mg orally at bedtime; increase dosage by 25 mg every 2 to 4 weeks until response is adequate, or to maximum dosage of 150 mg per day.
Nortriptyline	0 to 25 mg orally at bedtime; increase dosage by 25 mg every 2 to 4 weeks until response is adequate, or to maximum dosage of 125 mg per day.
Imipramine	25 mg orally at bedtime; increase dosage by 25 mg every 2 to 4 weeks until response is adequate, or to maximum dosage of 150 mg per day.
<b>Anticonvulsant medications</b>	
Gabapentin	100 to 300 mg orally at bedtime; increase dosage by 100 to 300 mg every 3 days until dosage is 1800 to 2400 mg three times daily or response is adequate.
Pregabalin	Starting dose is 150 mg, divided into two or three doses daily, and increased to total daily dose of 300 mg.

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## Sažetak

## POSTHERPETIČNA NEURALGIJA

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Postherpetična neuralgija je kronični neuropatski bolni sindrom koji nastaje kao posljedica infekcije virusom herpes zoster. Nakon infekcije herpes virusom oko 20% bolesnika razvije postherpetičnu neuralgiju s trajnom neuropatskom boli. Temeljem medicine zasnovane na dokazima u terapiji postherpetične neuralgije rabe se triciklični antidepresivi, opiodi, antikonvulzivni lijekovi. Ostale metode uključuju lokalnu primjenu lidokainskih i kapscainskih gelova te intratekalnu primjenu metilprednizolona u nekim refraktornim slučajevima postherpetične neuralgije.

**Ključne riječi:** *Herpes zoster – terapija; Herpes zoster – patofiziologija; Neuralgija – terapija; Neuralgija – patofiziologija; Bol – etiologija*