

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

## Pain Management of Herpes Zoster

---

Hwa Young Jung and Hyun Jeong Park

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/62873>

---

### Abstract

Herpes zoster (HZ) is a disease triggered by the reactivation of latent varicella zoster virus (VZV) in spinal or cranial sensory ganglia, and is characterized by a painful vesicular eruption in the affected dermatome. Postherpetic neuralgia (PHN) is a chronic, neuropathic pain that can persist long beyond resolution of visible cutaneous manifestations which is often resistant to current analgesic treatments. The lifetime prevalence of herpes zoster is approximately 20–30% and about 9–34% of these patients develop PHN depending on its definition. Clinical experience has shown that PHN often develops in cases of inadequate initial pain management resulting in increased pain intensity. This review provides an overview of the treatment options for HZ and PHN, focusing on the therapeutic modalities of pain management. The primary objectives of management of HZ are to inhibit viral replication, relieve pain, and prevent associated complications, such as PHN. General treatments for acute HZ are combination of antiviral therapy with a short course of corticosteroids at the onset of the disease in conjunction with an effective control of acute pain, including nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, and anticonvulsants such as gabapentin or pregabalin. Treatment of PHN is often resistant to the current pharmacologic methods. Therefore, a multimodal analgesic treatment regimen including topical lidocaine and capsaicin, systemic therapies, and the interventional treatments is necessary to alleviate pain and its effect on quality of life. As the incidence of HZ increases with age, the number of patients with HZ and PHN may increase in the future considering the gradual aging of the general population. Appropriate management of HZ can reduce the duration and intensity of pain from HZ, and prevent the development of PHN. In addition, prophylactic zoster vaccination can prevent or reduce the incidence of HZ and PHN. Further efforts are needed to minimize pain of the patients suffering from HZ and PHN as it affects the quality of life in the aspect of both physical and psychological impairments.

**Keywords:** Herpes zoster, post-herpetic neuralgia, pain control, treatment of herpes zoster, management of post-herpetic neuralgia

---

## 1. Introduction

Herpes zoster (HZ) is caused by reactivation of latent varicella zoster virus (VZV) in sensory dorsal root ganglion cells, and is characterized by a painful, unilateral vesicular skin eruption in the affected dermatome. The lifetime risk of HZ is approximately 15–30% [1–3]. The incidence of herpes zoster is 1.5–3.0 per 1000 person-years in all ages and 7–11 per 1000 person-years in persons over 60 years of age in European and North American, according to studies [1–9]. Classically, the skin eruption is preceded by one to several days of stabbing, episodic or continuous pain in the affected area, although the pain may develop simultaneously or even following the skin eruption. Herpes zoster-associated pain tends to resolve over time, but approximately 10–50% of herpes zoster patients develop post-herpetic neuralgia (PHN) that can persist several years beyond resolution of visible cutaneous eruptions. The frequency of PHN has been reported to be from 10% to 50% depending on its definition [10]. PHN is typically defined as persistent pain 90 days after the acute onset of HZ [3, 11, 12]. The incidence of PHN by this definition is 10–20% [3, 12]. In approximately 15% of patients with PHN, the pain persists for up to two years [13]. Mechanism to cause PHN follows a classic paradigm of other forms of neuropathic pain. Sensitization of nociceptors occurs after inflammation of dorsal root ganglia by reactivation of varicella zoster virus, leading to hyperexcitability of sensory neurons. The spontaneous discharge and lower activation thresholds provoke exaggerated responses to stimuli, resulting in allodynia and hyperalgesia. The loss of function or death of dorsal horn neurons, contributes to a connectional state of central nervous system nociceptive pathways, after anatomic deafferentation. The central sensitization is initially temporary, but may become permanent [14, 15]. Clinical experiences have shown that immunocompromised patients and elderly individuals are at an increased risk of PHN, and early initiation of antiviral treatment may reduce the incidence of PHN [16]. This review focuses on the practical overview of the treatment options available for management of patients with acute HZ and PHN.

## 2. Treatment of acute herpes zoster

The management of acute HZ aims to inhibit ongoing viral replication and alleviate pain. Treatment modalities for acute HZ include antiviral agents, analgesics, corticosteroids, and neural blockade.

### 2.1. Antiviral agents

Acute HZ is treated with antiviral agents such as acyclovir, famciclovir, and valacyclovir [17–20].

These antiviral agents are nucleoside analogues which are phosphorylated by viral thymidine kinase and cellular kinases to a triphosphate form that inhibits viral DNA polymerase, leading to a decrease of viral replication. Other types of antiviral agents such as foscarnet, vidarabine, and cidofovir are not dependent on viral phosphorylation and noncompetitively block viral DNA polymerase. In general, famciclovir and valaciclovir are accepted to have higher and

more reliable levels of antiviral activity and bioavailability, although there is no systematic data proving superior efficacy of one antiviral agent over another. In addition, valacyclovir and famciclovir shows greater patient compliance than acyclovir with less frequent dosing [21]. The main benefits of administration of antiviral agents within 72 hours are to reduce the severity and duration of zoster-associated pain and the incidence of PHN [16]. Therefore, the use of antiviral agents is crucial in treatment of HZ, and should be prescribed for patients with HZ as soon as possible. In complicated cases, especially in ophthalmic zoster, disseminated zoster, or Ramsay Hunt syndrome, and in patients failing oral treatment, intravenous therapy should be considered. Many clinical trials suggest that antiviral agents should be started within 3 days of the cutaneous eruption [22–24]. In general, the recommended duration of systemic antiviral agents for uncomplicated HZ is a seven-day course [17]. However, there is no solid consensus about whether it is beneficial to extend the duration of the treatment for patients with new onset vesicles after the seventh day, or for patients with either neurologic or ocular complications [21]. In herpes zoster ophthalmicus, the ophthalmic division of the fifth cranial nerve is involved, and the antiviral treatment should always be prescribed even after 3 days of the disease onset [17]. In any case of ophthalmic herpes zoster, the patient should be seen by an ophthalmologist as soon as possible, especially when vesicles on the side and tip of the nose (Hutchinson’s sign) are present. In cases with the immunosuppressed patients, antiviral therapy should always be started earlier because of the increased risk of herpes zoster complications. The same doses as in immunocompetent patients are used in immunosuppressed patients. The dosing regimen of the antiviral agents used in acute herpes zoster is summarized in **Table 1**. Meanwhile, the efficacy of topical antiviral agents for acute HZ had been shown to lack evidence [21].

| Drug                           | Regimen                            |  |
|--------------------------------|------------------------------------|--|
|                                | Immunocompetent patient            | Immunocompromised patient  |
| Famciclovir                    | PO 500 mg every 8 hour for 7 days  | PO 500 mg every 8 hour for 7–10 days   |
| Valaciclovir                   | PO 1000 mg every 8 hour for 7 days | PO 1000 mg every 8 hour for 7–10 days  |
| Acyclovir                      | PO 800 mg 5 times a day for 7 days | PO 800 mg 5 times a day for 7–10 days or<br>IV 10 mg/kg every 8 hour for 7–10 days |
| PO, per oral, IV, intravenous. |                                    |  |

**Table 1.** Summary of antiviral agents for treatment of acute herpes zoster.

**2.2. Pain control**

Since pain is the most troublesome symptom of herpes zoster, adequate pain management is the mainstream of the treatment in conjunction with antiviral therapy. Most patients require additional analgesics, although antiviral treatment may reduce the acute pain from HZ. In addition, the effective relief of acute pain may reduce the risk of progression to PHN, because severe acute pain is a risk factor for PHN. Acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid analgesia may be used initially [25]. In patients experiencing

insufficient pain relief with these agents, adjuvant analgesics such as antidepressants and anticonvulsants are shown to be effective to alleviate acute pain from HZ [24]. If parts of the pain of acute HZ may have inflammatory component, corticosteroids have been used during the acute episode of HZ. In clinical trials with selected older individuals, corticosteroids accelerate healing of the cutaneous lesion, improve quality-of-life measures, aid to return to routine activities, and reduce analgesic use. Systemic steroids starting at about 1 mg/kg/day for about 1 week, followed by 0.5 mg/kg/day for 1 week, and 0.25 mg/kg/day for another 1 week regimen is proven to be adequate to achieve these benefits [21]. If pain is refractory to formerly discussed medications, nerve block or referral to a pain specialist for sympathetic and epidural neural blockade can be performed.

3. Treatment of postherpetic neuralgia

PHN is difficult to treat and often resistant to the current pharmacologic therapies. A multi-modal analgesic treatment approach should be performed achieving both the efficacy and the tolerability of the therapeutic regimen [26]. Currently, Food and Drug Administration (FDA)-approved therapies for the treatment of PHN are the transdermal lidocaine and capsaicin patches, gabapentin, and pregabalin. Therapies often use off-label or over-the-counter medications for PHN include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), opioids, antiepileptics, and nonsteroidal anti-inflammatory drugs (NSAIDs). The dosing regimen and adverse effects of treatment options for PHN are summarized in **Table 2**.

| Treatment                       | Regimen  | Adverse effects  |
|---------------------------------|--|--|
| Topical agent                   |  |  |
| Topical lidocaine               | Maximum of three 5% lidocaine patches for 12 hours a day           | Itching, burning sensation or erythema on the application site                                     |
| Topical capsaicin               | 0.025% or 0.075% capsaicin cream<br>8% capsaicin patch             |  |
| Anticonvulsants                 |  |  |
| Gabapentin                      | Starting dose of 300 mg a day to maximum dose of 3600 mg a day     | Somnolence, dizziness, peripheral edema  |
| Pregabalin                      | Starting dose of 100–150 mg a day to maximum dose of 600 mg a day  |  |
| Tricyclic antidepressant (TCAs) |  |  |
| Amitriptyline                   | Starting dose of 10 mg at night to maximum dose of 100 mg at night | Dry mouth, sedation, constipation, increased appetite, blurred vision, tinnitus, euphoria, urinary |
| Nortriptyline                   | Starting dose of 10–25 mg at night                                 |  |

| Treatment         | Regimen   | Adverse effects  |
|-------------------|---|--|
|                   | with maintenance dose of 30–75 mg a day in divided doses  | retention  |
| Desipramine       | Starting dose of 10–25 mg a day to maximum dose of 150 mg a day   |  |
| Opioid analgesics |   |  |
| Tramadol          | Starting dose of 50 mg every 4–6 hour (100–400 mg a day )   |  |
| Morphine          | PO controlled release morphine: Starting dose of 10 mg at night to maximum dose of 200 mg a day or divided dose of 10–30 mg every 12 hour<br>IV morphine: Target dose of 0.3 mg/kg over 1 hour to maximum dose of 25 mg with cardiopulmonary monitoring | Nausea, vomiting, constipation, drowsiness, dizziness, mood change, disorientation, somnolence, headache, seizures |
| Oxycodone         | PO controlled release oxycodone: Starting dose of 10 mg twice a day to maximum dose of 60 mg a day  |  |
| Methadone         | Starting dose of 5 mg at night escalating dosage till dose-limiting side effects  |  |

PO, per oral, IV, intravenous.

**Table 2.** Summary of treatment options for pain management of post-herpetic neuralgia.

**3.1. Pharmacological treatment**

*3.1.1. Topical agent*

Topical application of anesthetics and analgesics may reduce pain with convenient delivery of the pharmaceutical effect, improved patient adherence, and direct access to the target site leading to decreased risk for systemic side effects. For localized and relatively mild pain, topical agents may be a reasonable choice, especially in patients who cannot tolerate systemic therapy. Currently available topical therapies include lidocaine and capsaicin patches. In addition, in a small group of patients, topical application of a cannabinoid receptor agonist resulted in pain reduction by more than 80% [27, 28].



### 3.1.1.1. *Topical lidocaine*

Lidocaine relieves pain by reducing the ectopic activity of sensory nerves. The 5% lidocaine patch has been shown in controlled clinical trials to produce significant pain relief in patients with PHN and allodynia [29–32]. Often 7–10 days of treatment is required before efficacy is noted. It is easy to use and systemic toxicity is not considered a significant risk in adults. Side effects are usually limited to application site reaction, such as skin redness or rash, which may necessitate the discontinuation of treatment. Therefore, topical lidocaine is a good first-line treatment for elderly patients who have contraindications to systemic agents. The lidocaine patch contains 5% lidocaine base, adhesive, and other ingredients. In general, maximum of three patches are applied over the affected area for 12 hours a day. In addition, eutectic mixture of local anesthetics (EMLA) cream applied once a day on the affected skin with an occlusive dressing may perform as an adjuvant therapy [33].

### 3.1.1.2. *Topical capsaicin*

Capsaicin is an alkaloid derived from hot chili peppers and acts as a transient receptor potential cation channel, subfamily V, member 1 agonist that activates afferent nociceptor terminals [34–36]. Topical capsaicin has proven to effectively reduce pain than placebo in patients with both musculoskeletal and neuropathic pain [37, 38]. Topical capsaicin demonstrates analgesia via a counter-irritant mechanism in which the irritation of the affected area masks the pain sensation of the skin. Also, repeated use of capsaicin results in depletion of substance P and other neuropeptides from nociceptive fibers leading to desensitization of nociceptive terminals [39]. Adverse effects are often limited to local reaction such as itching, burning sensation, soreness, and erythema at the site of application, which may slowly disappear after continued use. The systemic absorption is minimal. Application of low concentration (0.025 and 0.075%) cream formulations for several weeks have shown efficacy in neuropathic pain. An 8% capsaicin patch is also available for use in patients with PHN and HIV neuropathic pain [40, 41]. A Cochrane review in 2009 analyzed six studies treating with either a capsaicin 0.075% cream or single application of 8% patch for chronic neuropathic pain. The authors concluded that both concentrations of capsaicin may relieve pain, but there were insufficient data to prove the degree of the benefit [42].

Although topical capsaicin monotherapy is generally not considered satisfactory for patients with chronic pain, it can be helpful as an adjuvant therapy.

### 3.1.2. *Systemic treatment*

PHN is typically difficult to treat due to both unsatisfactory pain relieving effects of pharmaceuticals and dose limitations related to intolerable side effects and drug-drug interactions.

Mainly, three classes of medication are used as standard therapies to manage PHN: anticonvulsants, antidepressants (TCAs), and opioid analgesics.

### 3.1.2.1. Anticonvulsants

Many anticonvulsants have been studied to treat chronic neuropathic pain disorders including trigeminal neuralgia and PHN. Gabapentin and pregabalin have been documented as safe and well tolerated anticonvulsant drugs helping to reduce zoster-associated pain. The mechanism of the analgesic action of gabapentin and pregabalin has not been fully described. Both gabapentin and pregabalin bind to the same receptor,  $\alpha 2\delta$  subunits of voltage-gated calcium channels in the central nervous system. Since gabapentin and pregabalin are both eliminated from the systemic circulation primarily by renal excretion as unchanged drugs, the dosage of these drugs should be adjusted based on the renal function of the patients.

#### 3.1.2.1.1. Gabapentin

Gabapentin has been shown to be superior in relieving pain in 41–43% of patients with PHN compared to 12–23% in patients receiving placebo [43, 44]. Gabapentin is absorbed slowly and reaches a peak level at 3–4 hours after administration. Gabapentin is initiated at 300 mg daily, escalating up to 3600 mg/day as needed for pain control. Pain relief occurs as early as one week after the initiation of the treatment. Frequent adverse effects of gabapentin are somnolence, dizziness, and peripheral edema. These adverse effects are usually short-lived, but they sometimes require dose adjustment [29, 43].

#### 3.1.2.1.2. Pregabalin

Pregabalin is a potent gabapentinoid and structural analog of  $\gamma$ -aminobutyric acid (GABA). It is an ion channel modulator that has rapid analgesic, anticonvulsive, and anxiolytic effects. Pregabalin has been shown to relieve pain by more than 50% in 50% of patients with PHN compared to 20% in placebo groups [45, 46]. Dizziness, somnolence, and peripheral edema were also the most often reported adverse effects for pregabalin, although pregabalin usually has fewer dose-related adverse events than gabapentin because of the lower doses used [45–47]. Pregabalin has improved pharmacokinetics with better absorption and steadier blood levels and a faster onset of action than gabapentin. Therefore, titration of pregabalin to the therapeutic dose range is more rapid [47]. Pregabalin can be given in two divided doses per day, offering greater convenience than gabapentin [47, 48]. In general, the starting dose is 100–150 mg/day in divided doses escalating to 300 mg/day within one week, considering tolerability and effectiveness. Further up regulation of the dose up to 600 mg/day in 2–4 weeks may be considered for patients who experience unsatisfactory effect.

#### 3.1.2.2. Tricyclic antidepressant

The TCAs work by blocking neuronal uptake of noradrenaline and serotonin, thereby potentiating inhibition of spinal neurons involved in nociceptive perception. Since the TCAs also block  $\alpha$ -adrenergic receptors and sodium channels, they are known to be useful in PHN in which damaged primary afferent neurons develop adrenergic sensitivity and generate ectopic impulses closely related to sodium-channel blockade. In several randomized, control-



led trials, the TCAs have been shown to relieve pain in 44–67% of elderly patients with PHN [26, 49–51].

The reported adverse effects of the TCAs include excessive sedation, cognitive impairment, dry mouth, constipation, sexual dysfunction, and orthostatic dizziness. The contraindications of the TCAs are patients with cardiovascular disease, glaucoma, and urinary retention. In addition, the patients with high risk of suicide are administered with caution. In general, the starting dose of TCAs is 10–25 mg/night for elderly patients. The dose may be increased by 25 mg nightly up to maximal dose. TCAs such as amitriptyline, nortriptyline, desipramine are well studied and documented as effective managements of PHN.

#### 3.1.2.2.1. *Amitriptyline*

Amitriptyline is a tricyclic antidepressant that is widely used to treat various chronic neuropathic pains including PHN. However, there is insufficient evidence to recommend amitriptyline as a first-line agent for neuropathic pain with an overestimation of treatment effect. A Cochrane review in 2015 analyzed 17 studies involving 1342 oral amitriptyline-treated participants. The authors concluded that amitriptyline should continue to be used as part of the treatment of neuropathic pain, but only a minority of people will achieve satisfactory pain relief [52]. Amitriptyline is started at a low dose of 10 mg/night, with gradual dose increase up to 100 mg/night [11].

#### 3.1.2.2.2. *Nortriptyline*

Nortriptyline, along with desipramine, is a preferred alternative treatment to amitriptyline because of its lesser adverse effects for the elderly such as cardiac problems, sedation, cognitive impairment, orthostatic hypotension, and constipation [53]. A recent Cochrane review in 2015 analyzed six studies treating 310 participants with various neuropathic pain conditions. The authors concluded that little evidence supports the use of nortriptyline as effective treatment for neuropathic pain [54]. The starting dose is 10–25 mg/night and the dosage may be increased by 25 mg/day with 1 week interval. In general, maintenance dose is 30–75 mg daily in divided doses, or a single night dose [11]. The most common side effects include dry mouth, sedation, constipation, increased appetite, mild blurred vision, tinnitus, and often euphoria and mania [55].

In a double-blind, randomized controlled trials, patients with diabetic polyneuropathy or PHN were randomized to receive nortriptyline and gabapentin, alone or in combination [56]. Combination regimen of gabapentin and nortriptyline produced greater pain relief than either agent alone. Therefore, combination therapy may benefit patients with PHN, but with higher risk of adverse effects than with either drug alone.

#### 3.1.2.2.3. *Desipramine*

A Cochrane review in 2014 analyzed five studies treating 177 participants with painful diabetic neuropathy or PHN. The authors concluded that this review found little evidence to support the use of desipramine as effective treatment for neuropathic pain, although there was very

low quality evidence of benefit and harm [57]. In randomized, placebo-controlled, double-blind, crossover studies, amitriptyline and desipramine have been shown to be effective for the treatment of PHN [58, 59]. Results from these studies showed that 67% of patients taking amitriptyline rated their pain relief as good to excellent, and 63% of patients taking desipramine rated their pain relief as moderate or better. Typically, the initial dose of desipramine for treatment of PHN is 10–25 mg/day with a maximum dose of 150 mg/day [11].

#### 3.1.2.3. *Opioid analgesics*

Pain management with opioids may also alleviate PHN. Although effective in treating PHN, the issue of tolerance and concerns of misuse and abuse often tends to prevent opioids from being used as first-line agents. Opioids regulate pain binding to the opioid receptors such as  $\mu$ ,  $\kappa$ ,  $\delta$  and nociceptors present in both central and peripheral nervous system. The opioid receptors are activated by binding to inhibitory G-proteins, resulting in closure of voltage-gated calcium channels. This process leads to a cascade of potassium efflux causing hyperpolarization and reduced cyclic adenosine monophosphate level, hence decreasing the neuronal excitability. Additionally, opioids are capable of diverse and complex pharmacologic effects because they may function with various potencies acting as an agonist, partial agonist, or an antagonist binding to more than one receptor subtype. Side effects of opioids include constipation, cardiorespiratory dysfunction, sedation, nausea/vomiting, and histamine release [11]. Since constipation is a major side effect in elderly persons, bulk laxatives should be recommended. Additionally, the fact that many patients with PHN are elderly and have other underlying diseases for which they are taking medication emphasizes the need for close monitoring of adverse effects [11, 30, 60].

##### 3.1.2.3.1. *Tramadol*

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine and acts as an analgesic with both opioid and non-opioid analgesic activity. Besides the opioid analgesic activity, it works via inhibition of noradrenaline reuptake and stimulation of serotonin release at the spinal level. Thus, it has properties of both an opioid and a TCA. In a randomized clinical trial, tramadol was proven to be an agent that significantly improve quality of life and alleviate pain in patients with PHN [61]. Adverse effects of tramadol include nausea, vomiting, constipation, drowsiness, dizziness, somnolence, headache, and seizures. Concomitant use of SSRIs, selective serotonin-and norepinephrine-reuptake inhibitor (SSNRIs), or TCAs should be avoided and drug interactions should be monitored [24]. It is generally dosed at 100–400 mg/day, in divided doses. The starting dose is 50 mg every 4–6 hours [26, 49].

##### 3.1.2.3.2. *Morphine*

In a crossover trial with patients suffering PHN, both controlled release morphine and TCAs provided significant pain relief compared to placebo group [62]. In this report, patients preferred treatment with opioid analgesics to either TCAs or placebo, despite a higher incidence of adverse effects and more dropout patients during opioid treatment. In another crossover trial, patients with diabetic polyneuropathy or PHN were randomized to daily active

placebo, sustained-release morphine, gabapentin, and a combination of gabapentin and morphine [63]. Combination regimen with morphine and gabapentin showed superior effect in pain relief than either agent alone or the active placebo, but with increased adverse effects. The starting dose of oral controlled release morphine is 10 mg/night and the dose is increased twice weekly till maximal dose of 200 mg/day. Also, it can be given at divided dose of 10–30 mg every 12 hours as needed [62]. For intravenous morphine, the target dose is 0.3 mg/kg over 1 hour, up to a maximum of 25 mg with cardiorespiratory monitoring in inpatient setting [64]. The adverse effects include nausea, vomiting, constipation, drowsiness, dizziness, mood change, and disorientation [26, 49].

#### 3.1.2.3.3. Oxycodone

A Cochrane review in 2014 analyzed three studies treating 254 participants with painful diabetic neuropathy or PHN. In all three studies, controlled release oxycodone was used with doses titrated up to a maximum of 60–120 mg daily. The authors concluded that no convincing, unbiased evidence suggesting oxycodone is of value in treating patients with painful diabetic neuropathy or PHN exists [65]. However, other randomized, placebo-controlled crossover trials suggest greater efficacy of controlled release oxycodone over placebo [66]. The dose is 10 mg twice daily, up to a maximum of 60 mg/day. Adverse effects are typical of other opioids [30].

#### 3.1.2.3.4. Methadone

Methadone is a synthetic opioid agonist that exhibits a potent antagonist effect on glutamate N-methyl-D-aspartate (NMDA) receptors. Although there is a great paucity of clinical evidence regarding the treatment effect of methadone on PHN, methadone may be tried as an adjunctive treatment for PHN. In a recent double blind and placebo controlled study, methadone, when compared to placebo, did not significantly affect the intensity of spontaneous pain, as measured by the visual analogue scale [67]. However, the intensity of spontaneous pain was significantly decreased after the methadone treatment, compared to placebo by the category verbal scale (50% improved after the methadone treatment, none after the placebo,  $p=0.031$ ). Evoked pain was reduced under methadone compared to placebo (50% improved after the methadone treatment, none after the placebo,  $p=0.031$ ). The starting dose is 5 mg/night and is increased till maximal pain relief is achieved or occurrence of dose-limiting side effects. Methadone has a high intestinal absorption, and most of the drug is excreted in feces with no significant renal elimination, hence this drug is safe for patients with renal failure [68].

### 3.2. Non-pharmacological treatment

As a general rule, non-pharmacological, interventional pain management is frequently used in acute settings or in patients who have failed the standard therapies.

### 3.2.1. Nerve block

The interventional treatments including sublesional anesthesia, epidural blocks, intrathecal injection, and sympathetic nerve blocks with and without corticosteroids have been reported in large series, but rarely studied in a controlled manner. They have limited evidence of effective treatment of PHN [29]. Epidural block with local anesthetics and steroids is not effective in providing long-term pain relief in patients with PHN. Sympathetic nerve blocks have shown beneficial effects in patients with acute HZ, but with insufficient effect in providing long-term pain alleviation in patients with PHN [69]. Long-term pain relief by peripheral nerve block using local anesthetics has been reported, but with limited quality of the evidence [70].

### 3.2.2. Spinal cord stimulation

Spinal cord stimulation (SCS) has been used for the management of chronic neuropathic pain disorders [71, 72]. However, no randomized controlled study supports the usefulness of SCS. Studies on SCS were all case series with a small number of cases [73–75]. Therefore, SCS should be used only as a next resort after intrathecal steroid injections or nerve blocks in patient's refractory to pharmacological treatments of PHN.

### 3.2.3. Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is the use of electric current produced by a device to stimulate the nerves at a strong but nonpainful intensity that can produce pain relief [76]. TENS is an adjunctive therapy that has shown efficacy in transiently relieving neuropathic pain [77, 78]. In a study of TENS for patients with chronic pain, approximately 30% of patients with PHN fail to respond to TENS and among patients who respond initially, only a third continue to obtain pain relief after 2 years [77]. In a recent pilot randomized study of patients who were refractory to previous pharmacological therapy, the patients were treated with TENS with a biofeedback capability [79]. After every two treatments with the sham and true device, the patients were required to fill out a standard neuropathic pain scale score. The patients had choices to select the other device after three consecutive treatments if they felt an insufficient relief in their pain. The true device was chosen over the sham device by all patients. The majority of these patients treated by the true device reported a significant decrease in pain scores.

### 3.2.4. Botulinum toxin

BTX-A may play an adjunctive role as a promising therapeutic modality for PHN with its proven efficacy, safety, and tolerability. Botulinum toxin A (BTX-A) blocks acetylcholine by cleaving synaptosomal-associated protein of 25 kDa (SNAP25), which participates in the formation of the exocytic soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex (SNARE) that is essential for the fusion of acetylcholine-containing vesicles with the presynaptic membrane [80, 81]. Therefore, the local peripheral BTX-A injection may result in anti-nociceptive effect associated with the inhibition of formalin-induced glutamate

release, substance P and calcitonin gene-related peptide, which participates in the neurogenic inflammation [82]. There are several case series and randomized controlled trials supporting both therapeutic benefit and safety of BTX-A on PHN patients [83–88]. In these studies, no significant safety issues including local or systemic adverse effects was raised except the pain during injections. A possible consideration to BTX-A use is that, unlike other therapeutic modalities for PHN, it may induce antitoxin antibodies that could probably limit the long-term repetitive use of the treatment [89].

#### 4. Vaccination against herpes zoster

In a randomized trial with elderly patients, adult vaccination reduced the incidence of herpes zoster by 51% and the incidence of postherpetic neuralgia by 66%. In patients 70 years of age or older as compared with patients 60 to 69 years of age, the vaccine was less effective in reducing the risk of herpes zoster (38% reduction) but demonstrated similar protection against PHN (67% reduction) [90]. A live attenuated VZV vaccine has been available since 2006. It is a one-dose, high-potency vaccine originally approved for immunocompetent persons 60 years of age or older, but in 2011, it was approved to include persons aged 50–59 years [91]. This live attenuated vaccine is contraindicated in pregnant women and immunocompromised individuals. The reported side effects of the vaccine are minor, such as erythema, pain, and an itching sensation at the injection site, and fever [90]. Regarding the persistence of vaccine efficacy, the Shingles Prevention Study demonstrated the proven efficacy of the vaccine through four years post-vaccination. Additionally, the Short-Term Persistence Substudy subsequently demonstrated the persistence of vaccine efficacy through five years post-vaccination, although the efficacy beyond five years is uncertain [92]. Overall, the zoster vaccination can be used as the first line management for the prevention of HZ and PHN.

#### 5. Conclusion

As the general population ages, the number of patients suffering from HZ and PHN may increase gradually in the future. Diverse and comprehensive efforts are necessary as patients suffering from acute HZ and PHN are burdened by a worse quality of life due to both physical and psychological impairments [11]. We summarized the management of acute HZ and PHN to shorten the duration and intensity of pain. In order to choose the optimal treatment, clinicians should consider issues related to efficacy, safety, and tolerability in conjunction with individuals' goals of therapy, preferences, and adherence issues. Finally, regardless of the agents chosen, the adverse effects and drug interactions should always be considered to provide safe and effective management of pain.



## Acknowledgements

This work was supported by the Basic Science Research program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Education, Science and Technology (2015R1C1A2A01055073).

## Author details

Hwa Young Jung and Hyun Jeong Park\*

\*Address all correspondence to: [hjpark@catholic.ac.kr](mailto:hjpark@catholic.ac.kr)

Department of Dermatology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

## Reference

- [1] Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. *Journal of General Internal Medicine*. 2005;20(8):748–53.
- [2] Vazquez M, Shapiro ED. Varicella vaccine and infection with varicella-zoster virus. *The New England Journal of Medicine*. 2005;352(5):439–40.
- [3] Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clinic Proceedings*. 2007;82(11):1341–9.
- [4] Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Archives of Internal Medicine*. 1995;155(15):1605–9.
- [5] Gauthier A, Breuer J, Carrington D, Martin M, Remy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. *Epidemiology and Infection*. 2009;137(1):38–47.
- [6] Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997–2002. *Epidemiology and Infection*. 2005;133(2):245–53.
- [7] Schmader K, George LK, Burchett BM, Pieper CF, Hamilton JD. Racial differences in the occurrence of herpes zoster. *The Journal of Infectious Diseases*. 1995;171(3):701–4.
- [8] Schmader K, Gnann JW, Jr., Watson CP. The epidemiological, clinical, and pathological rationale for the herpes zoster vaccine. *The Journal of Infectious Diseases*. 2008;197 Suppl 2:S207-15.



- [9] Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? *The Lancet Infectious Diseases*. 2004;4(1):26–33.
- [10] Cohen JL. Clinical practice: Herpes zoster. *The New England Journal of Medicine*. 2013;369(3):255–63.
- [11] Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *The New England Journal of Medicine*. 2014;371(16):1526–33.
- [12] Arvin A. Aging, immunity, and the varicella-zoster virus. *The New England Journal of Medicine*. 2005;352(22):2266–7.
- [13] Zin CS, Nissen LM, Smith MT, O'Callaghan JP, Moore BJ. An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy. *CNS Drugs*. 2008;22(5):417–42.
- [14] Bennett GJ. Hypotheses on the pathogenesis of herpes zoster-associated pain. *Annals of Neurology*. 1994;35 Suppl:S38–41.
- [15] Cervero F, Laird JM. Mechanisms of touch-evoked pain (allodynia): a new model. *Pain*. 1996;68(1):13–23.
- [16] Panlilio LM, Christo PJ, Raja SN. Current management of postherpetic neuralgia. *The Neurologist*. 2002;8(6):339–50.
- [17] Bruxelle J, Pinchinat S. Effectiveness of antiviral treatment on acute phase of herpes zoster and development of post herpetic neuralgia: review of international publications. *Medecine et Maladies Infectieuses*. 2012;42(2):53–8.
- [18] Jackson JL, Gibbons R, Meyer G, Inouye L. The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia. A meta-analysis. *Archives of Internal Medicine*. 1997;157(8):909–12.
- [19] Tyring S, Barbarash RA, Nahlik JE, Cunningham A, Marley J, Heng M, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. *Annals of Internal Medicine*. 1995;123(2):89–96.
- [20] Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL, Wood MJ. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrobial Agents and Chemotherapy*. 1995;39(7):1546–53.
- [21] Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2007;44 Suppl 1:S1–26.
- [22] Shafran SD, Tyring SK, Ashton R, Decroix J, Forszpaniak C, Wade A, et al. Once, twice, or three times daily famciclovir compared with aciclovir for the oral treatment of herpes

- zoster in immunocompetent adults: a randomized, multicenter, double-blind clinical trial. *Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology*. 2004;29(4):248–53.
- [23] Shen MC, Lin HH, Lee SS, Chen YS, Chiang PC, Liu YC. Double-blind, randomized, acyclovir-controlled, parallel-group trial comparing the safety and efficacy of famciclovir and acyclovir in patients with uncomplicated herpes zoster. *Journal of Microbiology, Immunology, and Infection = Wei mian yu gan ran za zhi*. 2004;37(2):75–81.
- [24] Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. *Mayo Clinic Proceedings*. 2009;84(3):274–80.
- [25] Dworkin RH, Barbano RL, Tyring SK, Betts RF, McDermott MP, Pennella-Vaughan J, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain*. 2009;142(3):209–17.
- [26] Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. *PLoS Medicine*. 2005;2(7):e164.
- [27] Beiteke U, Bigge S, Reichenberger C, Gralow I. Pain and pain management in dermatology. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG*. 2015;13(10):967–87.
- [28] Phan NQ, Siepmann D, Gralow I, Stander S. Adjuvant topical therapy with a cannabinoid receptor agonist in facial postherpetic neuralgia. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG*. 2010;8(2):88–91.
- [29] Jeon YH. Herpes Zoster and Postherpetic Neuralgia: Practical Consideration for Prevention and Treatment. *The Korean Journal of Pain*. 2015;28(3):177–84.
- [30] Gan EY, Tian EA, Tey HL. Management of herpes zoster and post-herpetic neuralgia. *American Journal of Clinical Dermatology*. 2013;14(2):77–85.
- [31] Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain*. 1996;65(1):39–44.
- [32] Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. *The Clinical Journal of Pain*. 2002;18(5):297–301.
- [33] Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*. 1999;80(3):533–8.

- [34] Enamandram M, Rathmell JP, Kimball AB. Chronic pain management in dermatology: a guide to assessment and nonopioid pharmacotherapy. *Journal of the American Academy of Dermatology*. 2015;73(4):563–73; quiz 73–4.
- [35] Irving GA, Backonja MM, Duntzman E, Blonsky ER, Vanhove GF, Lu SP, et al. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *Pain Medicine* (Malden, Mass). 2011;12(1):99–109.
- [36] Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *The Cochrane Database of Systematic Reviews*. 2013;2:Cd007393.
- [37] Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ* (Clinical research ed). 2004;328(7446):991.
- [38] Casanueva B, Rodero B, Quintial C, Llorca J, Gonzalez-Gay MA. Short-term efficacy of topical capsaicin therapy in severely affected fibromyalgia patients. *Rheumatology International*. 2013;33(10):2665–70.
- [39] Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clinical Therapeutics*. 1993;15(3):510–26.
- [40] Sawynok J. Topical and peripherally acting analgesics. *Pharmacological Reviews*. 2003;55(1):1–20.
- [41] Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A meta-analysis. *European Journal of Clinical Pharmacology*. 1994;46(6):517–22.
- [42] Derry S, Lloyd R, Moore RA, McQuay HJ. Topical capsaicin for chronic neuropathic pain in adults. *The Cochrane Database of Systematic Reviews*. 2009(4):Cd007393.
- [43] Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *Jama*. 1998;280(21):1837–42.
- [44] Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. *Pain*. 2001;94(2):215–24.
- [45] Dworkin RH, Corbin AE, Young JP, Jr., Sharma U, LaMoreaux L, Bockbrader H, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology*. 2003;60(8):1274–83.
- [46] Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *The Cochrane Database of Systematic Reviews*. 2009(3):Cd007076.
- [47] Sabatowski R, Galvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic

neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain*. 2004;109(1-2):26-35.

- [48] Christo PJ, Hobelmann G, Maine DN. Post-herpetic neuralgia in older adults: evidence-based approaches to clinical management. *Drugs & Aging*. 2007;24(1):1-19.
- [49] Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132(3):237-51.
- [50] Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004;63(6):959-65.
- [51] Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2010;81(12):1372-3.
- [52] Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. *The Cochrane Database of Systematic Reviews*. 2015;7:Cd008242.
- [53] Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology*. 1998;51(4):1166-71.
- [54] Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. *The Cochrane Database of Systematic Reviews*. 2015;1:Cd011209.
- [55] Liu WQ, Kanungo A, Toth C. Equivalency of tricyclic antidepressants in open-label neuropathic pain study. *Acta Neurologica Scandinavica*. 2014;129(2):132-41.
- [56] Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet (London, England)*. 2009;374(9697):1252-61.
- [57] Hearn L, Moore RA, Derry S, Wiffen PJ, Phillips T. Desipramine for neuropathic pain in adults. *The Cochrane Database of Systematic Reviews*. 2014;9:Cd011003.
- [58] Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology*. 1982;32(6):671-3.
- [59] Kishore-Kumar R, Max MB, Schafer SC, Gaughan AM, Smoller B, Gracely RH, et al. Desipramine relieves postherpetic neuralgia. *Clinical Pharmacology and Therapeutics*. 1990;47(3):305-12.
- [60] Khadem T, Stevens V. Therapeutic options for the treatment of postherpetic neuralgia: a systematic review. *Journal of Pain & Palliative Care Pharmacotherapy*. 2013;27(3):268-83.
- [61] Boureau F, Legallier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain*. 2003;104(1-2):323-31.

- [62] Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology*. 2002;59(7):1015–21.
- [63] Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *The New England Journal of Medicine*. 2005;352(13):1324–34.
- [64] Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology*. 1991;41(7):1024–8.
- [65] Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for neuropathic pain and fibromyalgia in adults. *The Cochrane Database of Systematic Reviews*. 2014;6:CD010692.
- [66] Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology*. 1998;50(6):1837–41.
- [67] Teixeira MJ, Okada M, Moscoso AS, Puerta MY, Yeng LT, Galhardoni R, et al. Methadone in post-herpetic neuralgia: A pilot proof-of-concept study. *Clinics (Sao Paulo, Brazil)*. 2013;68(7):1057–60.
- [68] Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2004;22(1):185–92.
- [69] Kumar V, Krone K, Mathieu A. Neuraxial and sympathetic blocks in herpes zoster and postherpetic neuralgia: an appraisal of current evidence. *Regional Anesthesia and Pain Medicine*. 2004;29(5):454–61.
- [70] Doi K, Nikai T, Sakura S, Saito Y. Intercostal nerve block with 5% tetracaine for chronic pain syndromes. *Journal of Clinical Anesthesia*. 2002;14(1):39–41.
- [71] Moriyama K. Effect of temporary spinal cord stimulation on postherpetic neuralgia in the thoracic nerve area. *Neuromodulation: Journal of the International Neuromodulation Society*. 2009;12(1):39–43.
- [72] Benzon HT, Chekka K, Darnule A, Chung B, Wille O, Malik K. Evidence-based case report: the prevention and management of postherpetic neuralgia with emphasis on interventional procedures. *Regional Anesthesia and Pain Medicine*. 2009;34(5):514–21.
- [73] Meglio M, Cioni B, Prezioso A, Talamonti G. Spinal cord stimulation (SCS) in the treatment of postherpetic pain. *Acta Neurochirurgica Supplementum*. 1989;46:65–6.
- [74] Sanchez-Ledesma MJ, Garcia-March G, Diaz-Cascajo P, Gomez-Moreta J, Broseta J. Spinal cord stimulation in deafferentation pain. *Stereotactic and Functional Neurosurgery*. 1989;53(1):40–5.



- [75] Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery*. 2006;58(3):481–96; discussion–96.
- [76] Xu G, Xu G, Feng Y, Tang WZ, Lv ZW. Transcutaneous electrical nerve stimulation in combination with cobalamin injection for postherpetic neuralgia: a single-center randomized controlled trial. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists*. 2014;93(4):287–98.
- [77] Bates JA, Nathan PW. Transcutaneous electrical nerve stimulation for chronic pain. *Anaesthesia*. 1980;35(8):817–22.
- [78] Barbarisi M, Pace MC, Passavanti MB, Maisto M, Mazzariello L, Pota V, et al. Pregabalin and transcutaneous electrical nerve stimulation for postherpetic neuralgia treatment. *The Clinical Journal of Pain*. 2010;26(7):567–72.
- [79] Ing MR, Hellreich PD, Johnson DW, Chen JJ. Transcutaneous electrical nerve stimulation for chronic post-herpetic neuralgia. *International journal of dermatology*. 2015;54(4):476–80.
- [80] Blasi J, Chapman ER, Link E, Binz T, Yamasaki S, De Camilli P, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. *Nature*. 1993;365(6442):160–3.
- [81] Hay JC. SNARE complex structure and function. *Experimental Cell Research*. 2001;271(1):10–21.
- [82] Cui M, Khanijou S, Rubino J, Aoki KR. Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. *Pain*. 2004;107(1–2):125–33.
- [83] Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin A in postherpetic neuralgia: a parallel, randomized, double-blind, single-dose, placebo-controlled trial. *The Clinical Journal of Pain*. 2013;29(10):857–64.
- [84] Sotiriou E, Apalla Z, Panagiotidou D, Ioannidis D. Severe post-herpetic neuralgia successfully treated with botulinum toxin A: three case reports. *Acta Dermatovenereologica*. 2009;89(2):214–5.
- [85] Liu HT, Tsai SK, Kao MC, Hu JS. Botulinum toxin A relieved neuropathic pain in a case of post-herpetic neuralgia. *Pain Medicine (Malden, Mass)*. 2006;7(1):89–91.
- [86] Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. *Annals of Neurology*. 2008;64(3):274–83.
- [87] Yuan RY, Sheu JJ, Yu JM, Chen WT, Tseng IJ, Chang HH, et al. Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. *Neurology*. 2009;72(17):1473–8.



- [88] Xiao L, Mackey S, Hui H, Xong D, Zhang Q, Zhang D. Subcutaneous injection of botulinum toxin a is beneficial in postherpetic neuralgia. *Pain Medicine* (Malden, Mass). 2010;11(12):1827–33.
- [89] Naumann M, Carruthers A, Carruthers J, Aurora SK, Zafonte R, Abu-Shakra S, et al. Meta-analysis of neutralizing antibody conversion with onabotulinumtoxinA (BO-TOX(R)) across multiple indications. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2010;25(13):2211–8.
- [90] Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *The New England Journal of Medicine*. 2005;352(22):2271–84.
- [91] Voelker R. FDA expands age range for shingles vaccine. *Jama*. 2011;305(15):1526.
- [92] Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2012;55(10):1320–8.