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CONTINUING EDUCATION ACTIVITY

Treatment of Acute Herpes Zoster Pain and Postherpetic Neuralgia

Angela Starkweather, PhD, ACNP-BC, CNRN, FAAN

Learning Objectives/Outcomes: After participating in this CME/CNE activity, the provider should be better able to:

1. Describe the pathogenesis of herpes zoster and the risk factors for postherpetic neuralgia.
2. Identify the clinical characteristics of herpes zoster and postherpetic neuralgia.
3. Evaluate the treatment strategies for pain associated with acute herpes zoster and postherpetic neuralgia and preventative measures to reduce the occurrence of herpes zoster.

Key Words: Herpes Zoster, Postherpatic Neuralgia

With advancing age or immunocompromised states, the varicella zoster virus can reactivate, resulting in an eruption of acute herpes zoster (HZ), also known as shingles. More than 1 million Americans are diagnosed with acute HZ each year, and it is estimated that up to 20% of those who develop herpes zoster will subsequently develop postherpetic neuralgia (PHN). As the most common complication of HZ, PHN can cause significant suffering and reduced quality of life. Clinicians across all disciplines should be aware of the preventive measures for reducing the incidence of HZ and

In This Issue

Dr. Starkweather is Professor and Director of the Center for Advancement in Managing Pain, University of Connecticut School of Nursing, 231 Glenbrook Rd, Storrs, CT 06269; E-mail: angela.starkweather@uconn.edu.

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PHN through vaccination, and the strategies for treating PHN when it occurs.

As the most common complication of herpes zoster, postherpetic neuralgia can cause significant suffering and reduced quality of life.

Overview of Herpes Zoster

HZ, or shingles, is an infectious disease caused by reactivation of the varicella zoster virus (VZV), a highly contagious DNA virus.[1] After primary infection by human herpes virus-3, also known as VZV, the virus can lie dormant in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia of the entire neuraxis for decades.[2,3] One study suggests that over 95% of young adults in North America and Europe are seropositive for VZV.[4] Reactivation of VZV is associated with a decline in cell-mediated immunity that can occur with immunosuppression due to disease (such as HIV or cancer), immunotherapy (corticosteroids), or advanced age.[5] The annual incidence of HZ is estimated at 3.4 cases per 1000 persons and rises sharply after the age of 50 years to approximately 13 to 15 cases per 1000 by the ninth decade of life.[6] The risk of HZ is 2 to 10 times higher in immunocompromised people.[7] In

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addition, approximately 6% of individuals who have HZ will have a recurrence within 8 years.[8]

When VZV is reactivated, it travels along the sensory ganglion and propagates in the territory of the innervated epidermis, which typically results in a unilateral erythematous maculopapular rash (Figure 1). The dermatome affected by HZ is often described as being itchy, numb, and/or tender, with or without pain. Half of the people affected by HZ have a rash in the thoracic region; other most common sites are in the trigeminal (typically the ophthalmic branch), cervical, and lumbar regions.[9] Approximately 48 to 72 hours after, the rash erupts and progresses to clear vesicles, pustules form, ulcerate, and then scab over. In immunocompromised individuals, the rash can progress to a disseminated infection.[5] Usually, HZ is a self-limiting disease, and over the ensuing 2 to 3 weeks, the scabs fall off and the pain resolves.

> The pain associated with herpes zoster precedes the rash by several days in 75% of individuals.

Known as the prodromal phase, pain associated with HZ precedes the rash by several days in 75% of individuals, but it also can develop with the eruption of zoster vesicles.[9] VZV can also reactivate with only pain in a dermatomal distribution and without any rash, a condition known as zoster sine herpete.[10]

Affecting multiple levels of the nervous system, zoster sine herpete is considered to be a more complex manifestation, as lack of treatment can lead to the uncommon but serious complications of HZ, including cranial neuropathies, ophthalmicus retinitis, herpes oticus, polyneuritis, myelitis, and aseptic meningitis. These complications can lead to long-term disability, unilateral blindness, and/or deafness.

VZV reactivation can also manifest in facial palsy (Ramsay Hunt syndrome or Ramsay Hunt syndrome zoster sine herpete), which is associated with poor prognosis despite antivirals and corticosteroids.[11] Ramsay Hunt syndrome is also known as HZ oticus, geniculate neuralgia, and nervus intermedius neuralgia. Symptoms of Ramsay Hunt syndrome include cranial, cervical, or pharyngeal pain that can precede or accompany acute-onset dysphagia and dysphonia. Herpetic vesicles of the skin and/or mucosa may or may not occur.

Overview of Postherpetic Neuralgia

PHN is most commonly defined as pain associated with HZ that lasts 3 months or longer from the onset of the HZ rash, although other definitions vary by duration or severity of pain.[9] The varying definitions of PHN can affect estimates of its incidence. However, a population-based study in the United States demonstrated that 18% of patients diagnosed with HZ reported pain for at least 30 days and 10% for at least 90 days.[12]

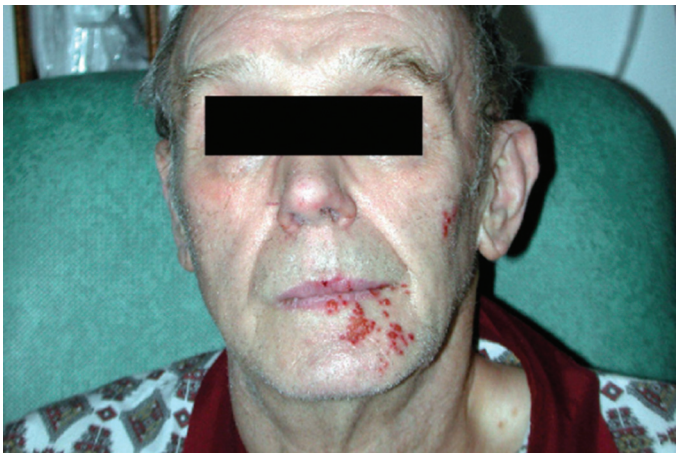

Figure 1. Facial herpes zoster infection precipitated by surgical manipulation of the trigeminal nerve during exploration of the posterior fossa. From *J Med Case Reports* 2009;3:7813.

The Shingles Prevention Study, a randomized, double-blind, placebo-controlled trial of live-attenuated Oka VZV vaccine, which included 38,546 people 60 years and older and defined PHN as pain intensity of 3/10 or more, demonstrated that 30% of patients who developed HZ had PHN at 30 days, 12% at 90 days, and 5% at 180 days in the placebo group.[13] Although it is apparent that the number of people affected by PHN decreases over time, the personal and societal costs are substantial for the 10% or more of individuals experiencing persistent pain for 90 days or longer.

The cost of HZ alone is significant when including the associated clinical visits, loss of productivity, and time away from work.[14,15] Dworkin et al[16] demonstrated that patients with PHN or subacute herpetic neuralgia assumed an additional annual cost of $4917 for those who were commercially insured, $2696 for those with Medicare, and $9310 for those with Medicaid. Immunocompromised individuals assumed double to triple times the amount of additional annual cost that immunocompetent people experienced.[17] More recently, a population-based study that compared the costs of HZ and PHN from 1997–1998 to 2013–2014 demonstrated a significant increase in the annual number of HZ cases, which was attributed to a larger percentage of older adults in the population; and a plateau in the costs, driven by higher expenses in prescription medicines but lower costs in hospitalization due to a decrease in hospital admissions.[18] With an increasing number of older adults, who make up the majority of those affected by PHN, the associated costs are expected to grow.

> Postherpetic neuralgia occurs in the same dermatome affected by the herpes zoster rash.

Table 1. Major Categories of Pain With Postherpetic Neuralgia

Intermittent pain evoked by normally innocuous sensory stimuli (allodynia)
Intermittent paroxysmal pain with lancinating quality (stabbing, shooting, shock-like)
Constant deep aching or burning pain (burning, aching, throbbing)

PHN occurs in the same dermatome affected by the HZ rash. The pain is thought to occur due to peripheral and central nerve damage during the inflammatory response resulting from VZV reactivation and migration,[19] including dorsal horn atrophy and peripheral axonal loss and sensory neuronal damage. Variability in the severity and duration of pain still remains unclear. In a recent study that compared interhemispheric connectivity between 18 patients with PHN and 18 well-matched healthy controls, patients with PHN had abnormally decreased homotopic connectivity in the dorsolateral prefrontal cortex and the precuneus and posterior cingulate cortex.[20] The changes in connectivity were associated with self-reported pain scores. The authors suggest that the alterations may be due to the presence of VZV. Another descriptive study showed significant differences in levels of microRNAs between patients with acute HZ and PHN that reflected mechanistic pathways related to host-virus interactions.[21]

Sensory disturbances of PHN include burning pain, itching, and dysesthesias, along with pathologic sensory amplifications such as allodynia and hyperalgesia.[1] Allodynia occurs in at least 70% of patients and can be particularly bothersome; it is typically mechanical but can also be thermal.[9] The major categories of PHN pain are described in Table 1.

Table 2. Risk Factors of Postherpetic Neuralgia After Acute Herpes Zoster

Advanced age
Presence of a prodrome (pain or abnormal sensations before rash onset)
Severe rash (>50 lesions—papules, vesicles, or crusted vesicles)
Severe pain during the acute phase
Ophthalmic involvement
Possible risk factors: family history, systemic lupus erythematosus, diabetes, recent trauma including traumatic brain injury

> Sensory disturbances of postherpetic neuralgia include burning pain, itching, and dysesthesias, along with pathologic sensory amplifications such as allodynia and hyperalgesia.

Diagnosis of Postherpetic Neuralgia

Because of the unique characteristics of HZ, the clinical diagnosis of PHN is fairly straightforward among patients who are able to provide a history. The general principles for evaluation of peripheral neuropathic pain should be followed for patients who present with suspected PHN.[22] The region of the pain should be inspected for rash, color changes, and edema and scarring over the affected area.[9] Sensory abnormalities, including allodynia, hyperalgesia, and dysesthesia, should be assessed in the affected areas for sensitivity to touch and pinprick, thermal response, and response to vibration. The contralateral region of the body should also be assessed for comparison. Sufficient data for making a clinical diagnosis include acquiring information about the patient's medical and family history, medications and immunizations, and the physical examination.[1]

Typically, no laboratory work is necessary. In cases that are difficult to diagnose due to lack of history or unusual clinical presentation, the practitioner and laboratory can use viral culture or immunofluorescent staining. Both polymerase chain reaction–amplifiable VZV DNA and anti-VZV immunoglobulin G in cerebrospinal fluid can be measured to detect VZV reactivation in cases of suspected zoster sine herpete.[11,12]

The risk of PHN is associated with the site of HZ involvement, with lower risk in the areas of the jaw, neck, and lumbar or sacral areas, moderate risk in the thoracic area, which is the most common area affected, and highest risk in the trigeminal area particularly involving the ophthalmic division and brachial plexus.[9] Additional risk factors are shown in Table 2. Notably, the association between advanced age and PHN is significant. At age 60 years, approximately 60% of patients with shingles develop PHN, and at age 70 years, 75% develop PHN. Some studies suggest that family history may be a potential risk factor for HZ and PHN. In a study of 227 case patients and 678 matched controls, case patients were more likely to report a family history of HZ (odds ratio = 2.3, $P = 0.002$), whereas recurrences and painful HZ only showed a trend toward significance.[23]

The differential diagnoses of PHN include cavernous sinus syndromes, chronic paroxysmal hemicranias, cluster headache, hemifacial spasm, migraine headaches or migraine variants, persistent idiopathic facial pain, Tolosa-Hunt syndrome, traumatic peripheral nerve lesions, and trigeminal neuralgia.[5] Even when there is a clearly documented history of HZ followed by ongoing pain, it is important to consider other possible diagnoses and revisit the differential diagnosis list periodically, particularly when the pain is refractory to standard therapies.

Prevention of Herpes Zoster and Postherpetic Neuralgia

Before reviewing the common pharmacologic pain management strategies for acute HZ and PHN the importance of preventive measures is briefly discussed. The varicella vaccine was introduced in the United States in 1995, and is recommended for all children and adults who have never had chickenpox through a 2-dose schedule.[24] HZ can occur in people who have been vaccinated against varicella, due to reactivation of the vaccine-strain virus, but the risk is lower than after infection with wild-type varicella.[25]

Individuals who have a history of chickenpox or chickenpox vaccination and/or a history of HZ can be vaccinated to prevent shingles or its recurrence. The Advisory Committee on Immunization Practices (ACIP) recommends that immunocompetent persons 60 years or older should receive a single dose of the live-attenuated HZ vaccine subcutaneously.[26] Currently, the only shingles vaccine approved by the FDA is Zostavax.

Zostavax is approved for use in individuals 50 years and older, and it contains the live-attenuated Oka strain of VZV. The ACIP's recommendation on the age criteria for shingles vaccination stems from the lower risk of HZ in people younger than 60 years.[27]

The live-attenuated vaccine boosts VZV-specific cell-mediated immunity, preventing reactivation of the latent virus. Although people who are vaccinated can still have shingles, they are likely to experience a milder case than people who are not vaccinated.[28] Despite potentially reducing the risk of shingles by 50% and increasing awareness about the availability of the vaccine, a 2014 survey reported that less than 30% of adults 60 years and older had received it.[29]

For individuals with active HZ, it has been suggested to wait 6 to 12 months after the shingles resolves to achieve maximum efficacy of the vaccine in boosting immunity.[30] There are also a few important contraindications to the shingles vaccine, including a history of allergic reaction to any of the components of the vaccine, pregnancy, and immunosuppression or immunodeficiency (disease or treatment of disease).[24]

For immunocompetent patients who will be receiving immunosuppressive therapy (including chemotherapy), the vaccination should be administered at least 14 days before starting, and it is suggested that immunosuppressive therapy be delayed until 1 month after vaccination if possible. Patients receiving cancer chemotherapy should wait 3 months after therapy is discontinued before receiving the vaccination. Patients receiving high-dose corticosteroids, isoantibodies, immune-mediators, or immunomodulators should wait 1 month after therapy is discontinued, but waiting is unnecessary for those receiving low doses of methotrexate, azathioprine, or 6-mercaptopurine.[30]

An experimental vaccination for shingles that uses a weakened live virus to stimulate the immune response, HZ subunit vaccine (HZ/su) is currently being tested.[31] The vaccine uses a small piece of the surface of the shingles virus with the AS01B adjuvant system to boost the immune response. Clinical trials have shown that the vaccine protected 90% of adults 70 years and older, a much higher percentage than the current vaccine.

> Treatment of acute herpes zoster with antiviral medications within 72 hours of rash onset can reduce acute HZ symptoms, slow the production of the virus, and decrease viral load.

Treatment of Acute Herpes Zoster Pain and Postherpetic Neuralgia

Treatment of acute HZ with antiviral medications (acyclovir, famciclovir, or valacyclovir) within 72 hours of rash onset can reduce acute HZ symptoms, slow the production of the virus, and decrease viral load.[5,9] However, antiviral agents do not significantly reduce the incidence of PHN.[32] Patients who are immunocompromised or have neurologic complications may receive Iv antivirals for 7 to 10 days.[1]

Patients presenting with severe symptoms may be prescribed short-term corticosteroids in combination with antiviral treatment when there are no major contraindications. Although corticosteroids are associated with a number of adverse effects, in combination with an antiviral, they have been demonstrated to reduce pain and improve short-term quality of life in patients with HZ without additional risk compared with placebo. However, corticosteroids do not seem to reduce the incidence or duration of PHN.[33]

Very few high-quality studies have assessed optimal pain management for acute HZ; thus, the general principles of acute pain management can be useful in guiding therapy, and oftentimes a combination of approaches is most beneficial.[9,34] Analgesic medications should be prescribed on the basis of the severity of pain, patient comorbid conditions, and contraindications such as drug interactions (Table 3). As HZ often affects older adults, issues such as polypharmacy, inappropriate use, and poor adherence to prescribed medications can place them at higher risk of adverse events.[5]

In addition to oral analgesics, several other strategies may be used to treat acute HZ pain, including early treatment with amitriptyline or gabapentin, or paravertebral blockade.[9] A single epidural injection of local anesthetic and corticosteroid was shown to reduce HZ pain at 1 month but had no effect on incidence of PHN,[35] whereas a randomized controlled trial

Table 3. Treatment of Pain Associated With Acute Herpes Zoster

Pain Level	Treatment
Mild	Acetaminophen and/or nonsteroidal anti-inflammatory drugs
Moderate	Tramadol (consider adjuvant with gabapentin or tricyclic antidepressants)
Severe	Corticosteroids, opioid analgesics

(RCT) of repeated paravertebral blockades of a local anesthetic and corticosteroid in patients older than 50 years with HZ taking acyclovir reported effective pain relief and prevention of PHN at 1, 6, and 12 months.[36]

More recently, an RCT of a single paravertebral injection for acute thoracic HZ was conducted among 138 patients older than 50 years.[37] Participants were assigned to receive a paravertebral block using either 10 mL of saline (placebo) or 25 mg of bupivacaine plus 8 mg of dexamethasone to a total volume of 10 mL (active group). All participants received 150 mg of pregabalin daily and acetaminophen was available for rescue analgesia.

> As herpes zoster often affects older adults, polypharmacy, inappropriate use, and poor adherence to prescribed medications can place them at higher risk of adverse events.

The active group had significantly shorter duration of pain and herpetic eruption compared with the placebo group ($P = 0.013$ and $P < 0.001$, respectively), and a significantly lower pain score by visual analogue scale was reported by the active group by the third week.

Although the incidence of PHN was comparable in both groups at 3 months, there was significantly lower incidence in the active group at 6 months ($P = 0.048$).

Another RCT evaluated repetitive intracutaneous injections with local anesthetics and corticosteroids in 93 patients with acute thoracic HZ and reported a significant reduction in pain severity, duration of pain, and skin eruption compared with the standard treatment control group.[38] At 1 month posttherapy, 12.8% of patients in the intracutaneous injection group reported pain associated with HZ compared with 47.8% in the standard treatment group ($P < 0.001$). At 3 and 6 months, the incidence of PHN remained significantly lower in the intracutaneous injection group compared with standard control.

A systematic review and meta-analysis of 9 RCTs performed within 3 weeks onset of HZ was conducted to evaluate the efficacy of using nerve blocks to prevent PHN.[39] The authors concluded that nerve blocks during the acute phase of HZ shorten the duration of pain, and that somatic blocks, paravertebral blocks, and repeated/continuous epidural blocks can be used to prevent PHN.

Vitamin C is a plasma antioxidant that is important for virus-specific cellular immunity, and its effects on HZ were recently examined. In an RCT to evaluate the efficacy of IV administered vitamin C on acute pain and preventative effects on PHN in patients with HZ, 87 patients admitted to the hospital received normal saline infusion with or without 5 g of ascorbic acid on days 1, 3, and 5.[40] In the short-term follow, there was no difference between groups in severity or duration of pain. However, at week 8, both pain severity and the incidence of PHN were significantly lower in the treatment group compared with the control group ($P < 0.05$ and $P = 0.014$, respectively).

Treatment of Postherpetic Neuralgia

First-line pharmacologic agents used to treat PHN include calcium channel α2-δ ligands (gabapentin and pregabalin), tricyclic antidepressants (amitriptyline, nortriptyline, or desipramine), and topical lidocaine patches. The titration of calcium channel α2-δ ligands and tricyclics should be done slowly, particularly among older adults, and patients should be informed that it may take up to 2 months or longer to effectively reduce pain. Each class of medication is discussed separately in this article along with current studies, and a brief description are listed in Table 4.

Calcium Channel α2-δ Ligands

Calcium channel α2-δ ligands bind to the α2-δ subunit of voltage-dependent calcium channels, leading to a reduction of the influx of calcium in neurons and reducing release of glutamate, norepinephrine, and substance P. As they are not metabolized by the cytochrome P450 system drug-metabolizing enzymes, there is a low risk of drug-drug interactions.[5] However, they are excreted by the kidneys and for that reason require dosage adjustments for patients with reduced renal function.[9] Common adverse effects include somnolence, dizziness, and peripheral edema, and as with all central nervous system agents, patients and families should be warned about increased risk of suicidal thoughts and/or behaviors.[5] The dosage of gabapentin differs according to preparation.

Immediate-release gabapentin is dosed 3 times daily due to its short half-life. Gabapentin enacarbil is a prodrug, providing more efficient drug absorption and bioavailability. It is dosed twice daily. Gastroretentive gabapentin uses a polymer-based technology that causes the tablet to swell upon exposure to gastric fluid, which allows it to remain in the stomach for 8 to 10 hours where it gradually releases gabapentin to the site of absorption in the upper small intestine.[5] It is dosed once a day and taken with food.

Table 4. Pharmacologic Therapy for Postherpetic Neuralgia

Class	Medication	Dose
Tricyclic antidepressants	Amitriptyline Nortriptyline Desipramine	Starting dose 10–25 mg at bedtime. Increase dose by 10–25 mg/d every 3–7 d as tolerated up to a maximum of 150 mg/d
Calcium channel α2-δ ligands	Gabapentin	Start at 100–300 mg at bedtime or 100 mg 3 times daily. Increase dose by 100–300 mg 3 times every 1–7 d as tolerated up to a maximum of 1800 mg/d
	Gabapentin enacarbil	Start at 600 mg in the morning. Increase dose to 600 mg twice daily on day 4
	Gastroretentive gabapentin	Starting dose 300 mg/d. Increase dose by 300 mg/d on days 2, 3, 7, 11, and 15 up to a maximum dose of 1,800 mg/d
	Pregabalin	Starting dose 50 mg 3 times daily or 75 mg twice daily as tolerated. Increase dose to 300 mg/d after 3–7 d, and then by 150 mg/d every 3–7 d as tolerated up to a maximum of 600 mg/d
Topical agents	Lidocaine 5% patch	Apply every 4–12 h; up to 3 patches per day
	Prescription capsaicin 8% patch/plaster	Up to 4 patches for 1 h every 3 mo or longer; needs to be administered by trained personnel; a topical anesthetic is applied to the affected area 1 h before capsaicin patch

A meta-analysis of 7 RCTs including 2041 randomized participants evaluated the efficacy and safety of extended-release gabapentin and gabapentin enacarbil for PHN.[41] The authors concluded that higher gabapentin dosage does not necessarily offer better outcomes, as there are increased risks of adverse events. Suggested dosages include extended-release gabapentin 1800 mg/d twice daily, which showed no significant difference in efficacy and safety compared with placebo, whereas once-daily dosing increased the incidence of adverse events. They demonstrated that gabapentin enacarbil at 1200 mg/d and 2400 mg/d doses are more effective and safe for PHN treatment compared with 3600 mg/d.

Pregabalin causes calcium channel α2-δ binding, thereby reducing release of presynaptic neurotransmitters. It has a quicker titration schedule, recommended over 1 week to reach the effective dose. As with gabapentin, dosage reduction may be required if there is renal damage, and patients should be warned of the potential for increased risk of suicidal thoughts or behaviors.

> Tricyclic antidepressants are used for postherpetic neuralgia off label and at a much lower dose than required to treat depression.

Tricyclic Antidepressants

Tricyclic antidepressants are used for PHN off label and at a much lower dose than required to treat depression.[5] Common adverse effects include dry mouth, weight gain, urinary retention, and drowsiness. They should be used cautiously in patients with heart disease, epilepsy, or glaucoma. A pretreatment cardiac conduction screening with rescreening at higher doses should be considered.[9] Patients and families should be informed that it can take several weeks for the medication to effectively reduce pain.

Topical Lidocaine

Topical lidocaine blocks voltage-dependent sodium channels to reduce pain. The patch should be applied only to intact skin and may be used along with systemic treatments or as a first-line treatment in individuals who cannot tolerate oral medications. Lidocaine gel or cream (5%) can also be used and is applied 3 times daily. A recent subgroup analysis from 3 open-label clinical trials (all lacking a placebo control group) was performed to evaluate the short- and long-term effectiveness and safety of 5% lidocaine medicated plaster for patients 70 years or older with PHN.[42] The authors reported significant reductions in allodynia severity and minimal adverse events, which were mostly skin-related, occurring in less than 15% of the participants.

Topical Capsaicin

Topical capsaicin is an agonist of the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor expressed by primary sensory neurons. Application to the affected area initially causes burning, itching, and prickling sensations with cutaneous vasodilation.[9] A persistent desensitization phase follows, which can significantly reduce pain. The capsaicin 0.0075% cream formulation has shown inconsistent results in patients with PHN; however, 8% patch or plaster has been shown to be effective for PHN.[5,9] It is only applied under supervision by a licensed

health care provider, and a local anesthetic is applied to the area 1 hour before the procedure to reduce discomfort.

In a recent systematic review and meta-analysis that included 6 RCTs (1449 participants) to evaluate topical capsaicin for PHN, the authors reported a difference in mean percentage change in the numeric pain rating scale ranging from −31 to −4.3.[43] Topical capsaicin demonstrated high efficacy across studies for reducing pain. However, all studies reported more adverse effects in the treatment group.

Opioids

To address moderate to severe pain, opioids may be required, and can include tramadol, oxycodone, morphine, or methadone to reduce pain and improve functioning. Because of their abuse potential and adverse effects, including nausea, constipation, and itching, opioids are not recommended as first-line agents.[9] Although nonopioid medications are considered as first-line therapies, a recent study showed that these agents are not being fully used. A review of medical and pharmacy claims (≥65 years n = 20 million, <65 years n = 212 million) from 2010 to 2014 compared health care use in adults with PHN of which 0.4% of patients younger than 65 years and 1.3% 65 years and older were diagnosed with HZ.[44] The authors reported that approximately 36% of patients diagnosed with PHN were prescribed an opioid agonist, 21% received gabapentin, 4% lidocaine patch, 4% pregabalin, and 4% a tricyclic antidepressant.

Pulsed Radiofrequency

Two recent studies evaluating pulsed radiofrequency (PRF) for PHN were reported.[44,45] The first was conducted as an RCT with 33 patients who were admitted to the hospital with severe pain after HZ for 3 months.[45] The control group received pharmacologic treatment for 10 days (n = 18), whereas the experimental group received PRF and pharmacologic therapy (n = 15). Pain scores, measured by the McGill Pain Scale present pain intensity, were significantly lower in the PRF group (31.67 + 4.08) compared with the control group (43.06 + 8.25) at 10 days ($P < .001$).

The second study involved a retrospective investigation of 58 patients who underwent PRF to the dorsal root ganglion due to HZ-related pain, with the first group receiving early PRF within 90 days and the second group receiving PRF for HZ pain for more than 90 days.[46] All patients received a transforaminal epidural block before PRF (n = 58). Patients who received early PRF had significantly lower scores on the numeric rating scale through 8-week postprocedure ($P < 0.05$).

Botulinum Toxin

Botulinum toxin (BoTN-A) treatment in PHN must be performed in the office setting by a licensed health care provider. Although it is currently considered only for refractory cases,[9] a recent meta-analysis that included 6 studies showed a pooled difference in posttreatment pain intensity of −3.009 (95% confidence interval −4.566 to −1.453; $P < 0.001$) in favor of BoTN-A versus placebo in patients with PHN.[47]

Conclusions

Reactivation of VZV results in acute HZ that is typically accompanied by a vesicular rash, itching, and pain. Antiviral medications administered within 72 hours from onset of rash can significantly reduce HZ symptoms. However, some patients may require oral analgesics or other strategies such as paravertebral blockade to reduce pain. A small percentage of patients affected by HZ develop PHN, characterized by allodynia and hyperalgesia. Strategies to reduce the severity of PHN include the use of calcium channel α2-δ ligands, tricyclic antidepressants, and topical agents. Prevention of HZ through vaccination can help reduce the occurrence of PHN, and current recommendations include administration of shingles vaccine for adults 60 years or older. ■

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ICYMI: IN CASE YOU MISSED IT

Notes from recent studies related to pain management, compiled by Elizabeth A.M. Frost, MD

Pain Management After Total Knee Arthroplasty

The authors' objective in this meta-analysis was to identify the optimal modality in terms of best balanced pain scores, opioid consumption, and range of motion in the initial 72 postoperative hours after total knee arthroscopy. They searched multiple databases through July 2016 using random-effects network meta-analysis. Pain scores, opioid consumption, rehabilitation profile, quality of recovery, and complications were the outcomes.

A total of 170 trials (12,530 patients) assessed 17 treatment modalities. The best 5 modalities for pain at rest were femoral/obturator, femoral/sciatic/obturator, lumbar plexus/sciatic, femoral/sciatic, and fascia iliaca compartment blocks. Opioid consumption was reduced best by femoral/sciatic/obturator, femoral/obturator, lumbar plexus/sciatic, lumbar plexus, and femoral/sciatic blocks. Range of motion was improved most by femoral/sciatic blocks. Femoral/sciatic and femoral/obturator blocks best met the criteria for optimal performance.

Therefore, the authors concluded that blocking multiple nerves was preferable to blocking any single nerve, periarticular infiltration, or epidural analgesia. The combination of femoral and sciatic nerve block seems to be the overall best approach. (See: Terkawi AS, Mavridis D, Sessler DI, et al. Pain management modalities after total knee arthroplasty: a network meta-analysis of 170 randomized controlled trials [published online ahead of print March 13, 2017]. *Anesthesiology*. doi:10.1097/ALN.0000000000001607.)

Efficacy of Acceptance and Commitment Therapy for Management of Chronic Pain: A Systematic Review

Acceptance and commitment therapy (often pronounced by its acronym, ACT) aims to increase valued action in painful situations, and has been suggested as an alternative approach in the management of chronic pain. To determine the clinical effectiveness of ACT, the authors performed a systematic review using the Cochrane library, MEDLINE, EMBASE, CINAHL Plus (EBSCO), and PsycINFO.

In the 11 trials included, ACT was found superior to controls (ie, no alternative intervention or treatment as usual). Significant, medium to large effect sizes were demonstrated for measures of pain acceptance and psychological flexibility, typically considered processes of ACT. Significant small to medium effect sizes were found for measures of functioning, anxiety, and depression. However, estimation of pain intensity and quality of life were not significantly improved. Moreover, improvements were generally less at follow-up.

Thus, ACT seems promising in the overall management of chronic pain in adults, but larger, more robust trials are needed. (See: Hughes LS, Clark J, Colclough JA, et al. Acceptance and commitment therapy (ACT) for chronic pain: a systematic review and meta-analyses. *Clin J Pain*. 2017;33(6):552-568. doi:10.1097/AJP.0000000000000425.)

Short-Term Consequences of Oral Corticosteroids

A retrospective cohort study examined data from 1.548 million adult patients, ages 18 to 64 years, enrolled in a commercially insured plan over a 3-year period. Short-term use of corticosteroids, defined as less than 30 days' duration, occurred in 21.1%, and more in older patients, women, and white adults, but with marked regional variation and prescribed from a diverse range of specialties.

The most common indications for use were upper respiratory tract infections, spinal conditions, and allergies. Rates of sepsis increased within 30 days of drug initiation (incidence rate ratio 5.30, 95% confidence interval 3.80–7.41). Moreover, risk of venous thromboembolism and fracture also increased (3.33, 2.78–3.99, and 1.87, 1.69–2.07, respectively).

Adverse events diminished over the subsequent 31 to 90 days. The increased risk persisted at prednisone-equivalent doses of less than 20 mg/d (incidence rate ratio 4.02 for sepsis, 3.61 for venous thromboembolism, and 1.83 for fracture; $P < 0.001$).

Given that practitioners frequently prescribe Dosepaks, these significant risks should be recognized and patients so informed. (See: Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ*. 2017;357:j1415. doi:10.1136/bmj.j1415.)

(*Continued on page 12*)

Topics in Pain Management CE Quiz

To earn CME credit using the enclosed form, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **July 31, 2018**. Only two entries will be considered for credit.

Online CME quiz instructions: Go to **http://cme.lww.com** and click on "Newsletters," then select *Topics in Pain Management*. Enter your ***username*** and ***password.*** First-time users must register. After log-in, follow the instructions on the quiz site. You may print your official certificate ***immediately.*** **Please note:** Lippincott CME Institute, Inc., ***will not*** mail certificates to online participants. **Online quizzes expire on the due date.**

To earn nursing CNE credit, you must take the quiz online. Go to **www.nursingcenter.com**, click on CE Connection on the toolbar at the top, and select Browse Newsletters and select *Topics in Pain Management.*

Log-in (upper right hand corner) to enter your ***username*** and ***password.*** First-time users must register. As a subscriber benefit, nurses can earn contact hours when taking CE activities from *Topics in Pain Management* for free. You must enter your subscription number in your registration profile where there is a field for **Link to my subscription**. The 100% discount is applied when payment is requested. Non-subscribers pay a $49.00 fee to earn ANCC contact hours for this activity.

After log-in, locate and click on the CE activity in which you are interested. There is only one correct answer for each question. A passing score for this test is 7 correct answers. If you fail, you have the option of taking the test again. When you pass, you can print your certificate of earned contact hours and access the answer key. For questions, contact Lippincott Williams & Wilkins: 1-800-787-8985. The registration deadline for CNE credit is **August 31, 2019**.

1. **Which one of the following is associated with varicella zoster virus reactivation?**
   A. Young age
   B. Female sex
   C. Immunotherapy
   D. Vitamin C supplementation
2. **Which one of the following is the most common body region of HZ rash?**
   A. Lumbar
   B. Thoracic
   C. Trigeminal
   D. Cervical
3. **A condition in which varicella zoster virus reactivates, causing pain in a dermatomal pattern without a rash being present, is known as which one of the following?**
   A. Chickenpox
   B. Trigeminal neuralgia
   C. Cervi
   D. Zoster sine herpete
4. **Definitions of PHN vary according to which one of the following?**
   A. Duration and severity of pain
   B. Age of the individual
   C. Severity of the rash
   D. Level of functional disability
5. **What percentage of people with PHN experience allodynia?**
   A. 40%
   B. 50%
   C. 60%
   D. 70%
6. **Which one of the following statements regarding the administration of antiviral medications for acute HZ within 72 hours of onset is *true*?**
   A. They can significantly reduce the incidence of PHN.
   B. They can reduce acute HZ symptoms.
   C. They increase the production of the virus.
   D. They increase the viral load.
7. **Which one of the following is a risk factor for PHN?**
   A. Younger age
   B. Mild rash
   C. Presence of a prodrome
   D. Painless lesions
8. **The shingles vaccine can reduce the incidence of HZ by at least.**
   A. 20%
   B. 30%
   C. 40%
   D. 50%
9. **Which one of the following agents used to treat PHN blocks voltage-dependent sodium channels to reduce pain?**
   A. Gabapentin enacarbil
   B. Amitriptyline
   C. Topical lidocaine
   D. Pregabalin
10. **Contraindications to the use of tricyclic antidepressants for treatment of pain include which one of the following conditions?**
    A. Glaucoma
    B. Diabetes
    C. Arthritis
    D. Obesity

(*Continued from page 10*)

Chondroitin Sulfate as Effective as Celecoxib in Management of Knee Osteoarthritis: The CONCEPT Trial

The authors of the CONCEPT Trial compared the effectiveness of pharmaceutical-grade chondroitin sulfate 800 mg/d against celecoxib 200 mg/d and placebo in 604 patients, recruited from 5 European countries for this prospective, randomized, 6-month, 3-arm, double-blind, placebo trial.

Changes in pain were assessed using a visual analog scale (VAS) and the Lequesne index (LI). Minimally important clinical improvement and patient-acceptable symptoms state were used as secondary end points.

Chondroitin and celecoxib resulted in greater pain reduction according to the VAS than did placebo (−42.6/mm, −39.5/mm, and −33.3/mm). A similar trend was demonstrated in the LI (−4.7, −4.6, and −3.7). Secondary end points improved at day 182 for both drugs.

The authors concluded that pharmaceutical-grade chondroitin 800 mg/d is superior to placebo and similar to celecoxib in reducing pain and improving function over a 6-month period for patients with symptomatic osteoarthritis. (It should be noted that this study was industry funded.) (See: Reginster JY, Dudler J, Blicharski T, et al. Pharmaceutical-grade chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT) published online ahead of print May 22, 2017. *Ann Rheum Dis*. doi:10.1136/annrheumdis-2016-210860.)

Long-Term Opioid Use May Decrease Functional Status

Patients with polyneuropathies are often prescribed opioids. A recent study indicates that such therapy may actually further decrease functional status.

Hoffman et al[1] conducted a retrospective population-based cohort study of prescriptions given to patients with polyneuropathy (n = 2892; 47% women; mean age, 67.5 years) and to control patients (n = 14,435; 47% women, mean age, 67.5 years) in ambulatory care between January 2006 and December 2010.

Patients with polyneuropathy were prescribed long-term opioids (≥90 days) more than were control patients (18.8% vs 5.4%; $P < 0.001$). Opioids most often prescribed to patients with and without neuropathy included oxycodone hydrochloride (45.9% and 41.7%, respectively), hydrocodone bitartrate (16.4% and 20.8%, respectively), and tramadol hydrochloride (14.3% and 16.7%, respectively).

Patients with polyneuropathy who were taking long-term versus short-term opioids had several functional status markers that worsened, including pain [adjusted odds ratio (OR), 2.5; 95% confidence interval (CI), 1.9–3.4], increased need for walking aids (adjusted OR, 1.9; 95% CI, 1.4–2.6), and inability to work (adjusted OR, 1.3; 95% CI, 0.8–2.0).

Depression also increased [adjusted hazard ratio (HR), 1.53; 95% CI, 1.29–1.82], and did opioid dependence (adjusted HR, 2.85; 95% CI, 1.54–5.47) and opioid overdose (adjusted HR, 5.12; 95% CI, 1.63–19.62).

Other studies have also demonstrated that long-term opioid use is associated with disability among those with chronic back pain and other forms of chronic noncancer pain.[2,3]

Pain physicians and neurologists were less likely to prescribe long-term opioids (about 4%), a finding that is consistent with national trends.[4] The majority of prescribers were primary care physicians, but other specialists, including authors of guidelines and policy statements, should be aware of these adverse and unintended outcomes.

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Coming Soon:

- Cannabinoids in the Management of Pain
- Pain Management for Patients with Opioid Use Disorder