The time-honored adage that prevention is better than cure, as with all infectious diseases, is certainly true for herpes zoster. Commonly known as shingles, herpes zoster is caused by reactivation of the varicella-zoster virus (VZV) after a period of latency following the primary infection of varicella (i.e., chickenpox). The varicella-zoster virus remains dormant in dorsal root ganglia of the host during this latent period, which may last decades.

In 1965, R. Edgar Hope-Simpson, MD, recognized that as the human host of VZV ages, a gradual waning of cell-mediated immunity occurs. When the level of cell-mediated immunity drops below a critical threshold, VZV reemerges to cause a prodrome of tingling, burning, or itching pain that heralds the appearance of the red, vesicular, dermatomal rash of shingles.

Herpes zoster infection develops in approximately one million people in the United States every year, with approximately 40% to 50% of these cases occurring in the rapidly growing segment of the population older than age 60 years. More than 90% of adults are susceptible to herpes zoster, but there is no way to predict in whom the disease will develop. Of those individuals who reach age 85 years, approximately 50% will have had herpes zoster, and the lifetime risk of zoster is close to 30%.

The acute pain of herpes zoster infection has substantial effects on the lives of patients, resulting in reduced physical functioning, increased emotional distress, and decreased social functioning. Even more debilitating than the acute pain of shingles is the persistent pain known as postherpetic neuralgia (PHN), which is variously defined as pain that persists after the blistering rash of shingles has healed or as pain and discomfort that either persists or appears more than 90 to 120 days after the onset of rash. A recent study of 94 patients showed that 50% of patients with shingles reported at least some pain persisting for three months, and 32% of patients continued to report pain at six months.

Postherpetic neuralgia is difficult—if not impossible—to prevent once herpes zoster infection is manifested, because the nerve damage caused by VZV reactivation occurs before the rash is evident. Just as the incidence of herpes zoster infection increases with advancing age, the risk for PHN likewise increases with age. As noted by Bennett, if neuropathic low back pain is included, PHN cases would rank third in prevalence behind low back pain and painful diabetic peripheral neuropathy.

The pain of PHN may be spontaneous (i.e., with no apparent cause) or evoked, and it may be continuous or intermittent. A characteristic feature of PHN is allodynia, which is pain that is provoked by innocuous or normally nonpainful stimuli, such as a slight breeze. Allodynia is present in approximately 45% to 55% of patients with acute herpes zoster, but it may affect as many as 90% of patients with PHN. In addition to having pain characterized as aching, burning or boring, patients with PHN frequently experience other sensory abnormalities, such as dyesthesia, hyperalgesia and hyperesthesia. These uncomfortable sensations can also be spontaneous or evoked, and continuous or paroxysmal.

Haanpaa et al. evaluated the prognostic value of certain types of paresthesias associated with herpes zoster, concluding that mechanical allodynia and pinprick hyperalgesia were both strongly associated with the development of PHN. However, the authors cautioned that this association could not be used as a predictive rule for individual patients. The severity and duration of PHN represent the true burden of herpes zoster, because the pain and paresthesia of this condition can be so onerous as to make such routine daily tasks as bathing and dressing extremely difficult or even impossible.

Appropriate treatment of patients with
PHN is fraught with difficulty, requiring trials of different pharmacologic agents as well as cautious titration to avoid adverse effects of the drugs. Medications typically used for management of pain—such as acetaminophen, narcotic and non-narcotic analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and topical agents—may have limited efficacy in managing PHN pain.\(^8\)\(^9\)\(^,\)\(^20\) Because current treatment strategies for patients with PHN are only partially effective, consultation with a pain management specialist may be necessary.\(^8\)

Consider the following case, which illustrates diagnostic and treatment difficulties often seen with herpes zoster and PHN. In this case, various pharmacologic strategies are evaluated, and the importance of vaccination is highlighted.

**Case presentation**

Marion Powers is a generally healthy, pleasant and fit 67-year-old woman who is the sole guardian of her two young granddaughters. She was seen by her primary care physician for pain and tingling on the right side of her face, extending from the lateral margin of her eyebrow to her forehead and scalp. This unpleasant sensation had been present for two days before she saw the physician. She also told the physician that her right eye had been “twitching,” but she denied having visual loss or pain in the eye itself.

The physician thoroughly examined Marion but was unable to find any obvious cause for her discomfort, though a slight eye tic was noted. Since the patient’s reported pain was distributed along the right temporal artery, the physician was concerned that the pain might represent temporal arteritis. The physician ordered tests for complete blood count and erythrocyte sedimentation rate, and she referred Marion to a surgeon for temporal artery biopsy at the next available appointment, which was in three days. Marion was also given a prescription for high-dose prednisone with a taper, and she was instructed to phone the physician immediately if she experienced any changes in vision.

Two days later, a visibly upset Marion returned to the physician’s office with her granddaughters in tow. She said she had awoken that morning with a terribly painful rash on the right side of her forehead (which fortunately spared her eye). She had immediately realized that the rash was shingles and rushed to the office to obtain treatment.

The physician, upon seeing evidence of herpes zoster infection, was apologetic. The surgical consult was cancelled. Marion was told to finish the steroid taper and was given a one-week prescription for the antiviral medication valacyclovir hydrochloride, along with directions for gentle cleansing and drying of the lesions. She was also given a prescription for tramadol hydrochloride (50 mg every eight hours) for pain. Medications prescribed for herpes zoster in the current case are:

- **y** High-dose prednisone with taper
- **y** Valacyclovir hydrochloride (for one week)
- **y** Tramadol hydrochloride (50 mg every eight hours, refillable).

At Marion’s next visit to the office, later that month, her shingles vesicles were crusted and drying, and the erythema and inflammation were almost gone. Postinflammatory hyperpigmentation, with minimal scarring, remained on her face.

Marion said that the tramadol had lessened the burning pain and tingling on her face and scalp, but she complained that light touch—even something as soft as a breeze from the window—seemed to cause searing pain. Her physician explained that this phenomenon, called allodynia, was common with shingles, and she noted that it should resolve over time. The physician then gave her a refillable prescription for the tramadol.

Three months later, Marion returned to the physician’s office. She had lost 7.3 kilograms (16 pounds) since her previous visit and was visibly distressed. Marion complained of excruciating pain across her scalp and forehead that was much worse than the tingling, burning pain that had preceded and accompanied the healing of the rash. She described the new pain as the sudden jolting sensation of a “hot poker being jabbed into my cheekbone,” with resulting searing, electric shock-like feelings running up her forehead and scalp. She indicated that an area of pain much larger than had been occupied by the rash extended from the top of her head to behind her ear and into her neck.

Having run out of tramadol, Marion said she had been taking over-the-counter ibuprofen and acetaminophen with codeine, which a friend had given her. Since she remembered that the tramadol had made her feel drowsy and “out of it” she decided not to seek another prescription. She said she was also applying ice packs to the affected area several times daily. She reported that she had obtained only minimal relief from these measures.

Marion told the physician that it was nearly impossible to perform her routine daily tasks, which included getting her granddaughters ready for school, meeting the girls after school for the walk home, preparing their meals, doing laundry and cleaning house, shopping, and paying bills. She confessed that she had been in so much pain that she had been unable to help the girls with their homework or to enjoy their nightly ritual of watching a favorite television program together.

During the office visit, Marion broke down, crying, “I can’t go on with this pain! I have to be able to provide for my granddaughters. I’m all they’ve got! It’s hard enough keeping up with them when I am feeling well, but this is the worst pain I’ve ever had. Oh, why didn’t you just give me the medicine for shingles when I saw you the first time? At least then I might not have gotten that horrible rash and this pain. Now, you’ve got to help me with this pain. Please, please help me!”

Marion was experiencing the dreaded consequence of herpes zoster infection—PHN. Her description of piercing, burning pain is the classic description of neuropathic pain, which is the clinical manifestation of destruction of nerve cell bodies by VZV. Because PHN involves the destruction of both spinal cord and peripheral nerves,\(^2\)\(^3\) the pain that is experienced is much greater than the apparent injury, and the affected area is more widespread than that occupied by the rash.\(^21\)

Marion was correct in identifying the
origin of her pain as shingles, but she was mistaken about the potential for antiviral medications to have aborted or reduced the development of PHN. Although corticosteroids have been shown to produce modest improvements in rash healing and acute pain,22-23 neither antiviral medications nor steroids have been shown to prevent PHN.24,25 Marion’s painful condition might have been avoided had she received herpes zoster immunization, but the clinical goal at the time of her presentation was to provide support, reassurance and as much pain relief as possible so that Marion could continue to perform her important activities of daily living. Marion’s physician asked her to rate her pain on the 11-point Numeric Pain Intensity Scale (NPIS), which ranges from 0 to 10, with 0 representing no pain and 10 representing the worst pain experienced by the individual.23 Marion rated her pain as 9, reiterating that the pain was so debilitating that she was unable to function. The physician wrote her a prescription for oxycodone hydrochloride (5 mg, one or two tablets every six hours, as needed for pain) and instructed her to return to the office in one week.

Three days later, Marion phoned the office to report that the medication relieved the pain, but she experienced nausea and sedation when she increased the dose to two tablets. She requested a drug for pain that had fewer adverse effects. The physician called in a prescription for pregabalin (50 mg twice daily, titrated to three times daily) and instructed Marion to continue taking oxycodone as needed for breakthrough pain.

Two weeks later, Marion rated her pain as 6 on the NPIS and reported that her discomfort had lessened. She said she was also sleeping better, but she complained of some sedation from the pregabalin. Marion was surprised to see that her weight had returned to its pre-shingles level, though she noted that she did not have much of an appetite.

Marion continued to complain of episodes of stabbing pain in her face and scalp that was exacerbated by touch, heat, or water—making it difficult to shower and brush her hair. Thus, the physician prescribed the lidocaine patch 5%, to be applied to the temporal area every eight hours. Three days later, however, Marion brought a half-empty box of the patches to the office stating, “Please show me how you expect me to go out in public with this big patch covering the side of my face!”

The physician, realizing that the patch therapy was indeed impractical, prescribed duloxetine hydrochloride (20 mg daily) and recommended that Marion obtain over-the-counter capsaicin cream and apply it sparingly to the affected area two or three times daily as needed. Medications prescribed for PHN in the current case are:

- Oxycodone hydrochloride (5 mg, one or two tablets every six hours, as needed)
- Pregabalin (50 mg twice daily, titrated to three times daily)
- Lidocaine patch 5% (applied to temporal area every eight hours)
- Duloxetine hydrochloride (20 mg daily)
- Capsaicin cream

At the following office visit, one month later, Marion stated that her pain had further diminished with the two new medications (pregabalin and duloxetine), but the capsaicin cream caused redness and stinging. She reported that she was using the oxycodone less than twice daily, usually at night to help her sleep. Rating her pain as 4 on the NPIS, she thanked the physician for helping her get to a point where she was “more like myself again.”

**Discussion**

Marion’s case illustrates the inherent difficulty in diagnosing herpes zoster, which has presenting complaints that can mimic numerous other diseases. In Marion’s case, temporal arteritis was believed to be a major concern. Incipient shingles has been mistakenly diagnosed as acute cholecystitis, herniated nucleus pulposus, and myocardial infarction—among other conditions—depending on the location. Although the diagnosis of herpes zoster becomes evident once the rash presents itself, management of the long-term sequelae of PHN remains a clinical “trial-and-error” scenario.

It is useful to consider the course of Marion’s treatment, the medications that were initially prescribed as treatment for her acute pain of shingles and the medications that were later prescribed as treatment for her ongoing PHN pain.

Marion’s physician appropriately used the NPIS to rate her pain and to measure her response to ongoing treatment. Because careful titration of pain medications is vital for patients with PHN—especially for elderly individuals, who are at greatest risk for adverse drug reactions—an accurate assessment of pain using a validated pain scale is strongly recommended.5,26-29 Numerous pain scales are available in addition to the NPIS, including the Wong-Baker FACES Pain Rating Scale30 and the Visual Analog Scale.29 Well-validated pain-rating scales should be used for all patients who have chronic pain in order to assist in the titration of medications to achieve the desired response, which is analgesia.

Like other types of neuropathic pain, PHN cannot be reliably relieved with medications commonly used to treat most pain.3 Instead, the armamentarium against PHN includes ligands (eg, gabapentin, pregabalin); anticonvulsants (eg, carbamazepine); opioid analgesics (eg, oxycodone, tramadol); serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, duloxetine); tricyclic antidepressants (eg, amitriptyline hydrochloride); and topical agents, including anaesthetic and nonsteroidal anti-inflammatory creams, gels, or patches (eg, capsaicin, diclofenac sodium, lidocaine).31-33 Marion’s prescribed use of the antiviral medication valacyclovir and the tapering dose of the oral steroid prednisone may have contributed to a swift resolution of the shingles rash and acute pain. However, as previously noted, neither of these treat-
appropriate antiviral therapy.6,22,23 Herpes zoster infection in the absence of steroids in treatment of patients with acute herpes zoster infection is not indicated.6 The use of NSAIDs in elderly patients is risky not only because of their potential for causing gastrointestinal bleeding, but also because of their adverse effects on renal function.12 Recently, NSAID patches and gels have become available, but there is only limited data on their usefulness for patients with PHN. Although oral NSAIDs are typically used for pain management, these medications have limited use in cases of PHN. The use of NSAIDs in elderly patients is risky not only because of their potential for causing gastrointestinal bleeding, but also because of their adverse effects on renal function.12 Recently, NSAID patches and gels have become available, but there is only limited data on their usefulness for patients with PHN.

Opioids, the backbone of the armamentarium against moderate-to-severe pain, are likewise often inadequate for managing PHN. It is not surprising that ibuprofen and acetaminophen/codeine were inadequate to manage Marion’s PHN pain. Oxydoloxone, which—like tramadol—has been shown to provide relief for moderate-to-severe pain, was poorly tolerated by Marion, who complained of drowsiness, sedation, and nausea at higher doses. Opioid analgesics are less well-tolerated in elderly patients than in younger patients as a result of adverse effects. Opioid analgesics may also cause constipation, delirium, myoclonus and pruritus.19,35,36

Tricyclic antidepressants, such as amitriptyline and nortriptyline hydrochloride, have been used for decades to manage certain types of neuropathic pain, and they may be efficacious in management of PHN. Their usefulness in elderly patients, however, is limited because of their anticholinergic adverse effects—such as blurred vision, dry mouth, constipation and urinary retention—which may become worse during the titration phase. An alternative to tricyclic antidepressants is provided by the SNRI class of antidepressants, of which duloxetine is approved by the US Food and Drug Administration (FDA) for treating patients with neuropathic pain.37,38

Anticonvulsant medications have long had a role in treatment for neuropathic pain (eg, carbamazepine for trigeminal neuralgia).39-41 Recently, however, their use has been eclipsed by the a2d ligands (ie, the “gabapentenoids”) gabapentin and pregabalin, which have a different mechanism of action. Approved by the FDA for PHN, these medications bind to the a2d subunit of calcium channels, where they reduce neurotransmitter release, resulting in both antinociceptive and antiseizure effects.

Gabapentin and pregabalin both require uptitration to a therapeutic dose, with pregabalin having greater bioavailability and, thus, being more easily titrated to effect. Both gabapentin and pregabalin can produce the adverse effects of sedation and weight gain, but tolerance to these effects usually develops by the maintenance phase.19,42

Lidocaine patch 5% and lidocaine gel 5% are useful in treatment of patients with PHN, especially when the area of pain or paresthesia is amenable to patch placement. The obvious advantage to this mode of treatment is that the anaesthetic agent is placed at the site of pain, where it takes effect. Few adverse effects have been reported with lidocaine in either the patch or gel form.43 Another topical agent, capsicain, is thought to work by causing depletion of “substance P” (a neurotransmitter associated with inflammatory processes and pain syndromes) at the localized area of pain. Capsicain was the first agent to be approved by the FDA for treatment of patients with PHN.44 Available as an over-the-counter cream, capsicain, which is derived from hot chili pepper, must be applied in small amounts directly to the painful area several times daily. Care must be taken to thoroughly cleanse the hands after application and to avoid contact with the eyes, mucous membranes, or broken skin, because capsicain can cause burning or redness, as experienced by Marion.

The European Commission has approved a high-concentration capsicain dermal patch, called NGX-4010, for use in PHN management. The FDA has not yet approved NGX-4010 for use in the United States, but the patch has been accepted for filing by the FDA.45 No single treatment has been shown to be completely effective for treatment of patients with PHN. In clinical practice,
combinations of medications are commonly used to control the pain and discomfort associated with PHN. In a meta-analysis published in 2005 of available medications for PHN, Hempenstall et al19 searched databases for studies of PHN and found 65 studies for potential inclusion. Of that number, 31 studies were randomized, placebo-controlled clinical trials, and 25 of these trials included dichotomous data extraction appropriate for meta-analysis. After careful review and analysis of these 25 trials, the investigators found that sufficient evidence existed to support the use of gabapentin, pregabalin, tramadol, tricyclic antidepressants and certain opioid analgesics (morphine, oxycodone) as effective oral agents for PHN. Hempenstall et al19 further noted that topical therapies showing evidence for efficacy were capsaicin and lidocaine patch 5%

Hempenstall et al19 found that medications not associated with efficacy for PHN included acyclovir, codeine, ibuprofen, lorazepam, N-methyl-D-aspartate receptor antagonists and certain 5HT1 receptor agonists.

Final notes

Marion's physician quickly recognized her painful syndrome as PHN, validating the symptoms that she was experiencing. The physician also demonstrated a willingness to try different approaches to managing Marion's PHN pain, and she was responsive to Marion's concerns and problems with adverse effects. This case provides an example of the importance of the patient-physician relationship in achieving optimum pain control, which also requires accurate assessment of pain, trials of different treatment approaches, and possible use of combinations of medications. Clearly, the tangible benefits of an effective patient-physician relationship are achieved through communication, trust, reassurance and a willingness to “be there” for the patient.

Stated at the beginning of the current article was the adage that, as always, prevention is superior to cure. With this adage in mind, vaccination is the most effective method of managing herpes zoster and its debilitating complication of PHN. Thus, it is important that all individuals aged 60 years or older receive the herpes zoster vaccine. It is also important that all clinicians—especially primary care physicians—collaborate to overcome any and all logistical barriers to immunization of patients.

References


