Each year, herpes zoster develops in approximately 1 million Americans, about half of whom are at least 50 years old. Postherpetic neuralgia (PHN), a neuropathic pain syndrome that is the most common complication of herpes zoster, subsequently develops in between 9% and 34% of individuals who have had herpes zoster.

Before the US Food and Drug Administration’s approval of the herpes zoster vaccine, there was no available method to prevent herpes zoster. Treatment focused instead on speeding the healing and easing the pain of the acute rash with antiviral agents and, in some cases, corticosteroids. Evidence suggests that antiviral agents may also shorten the duration of, but not prevent, PHN. Once PHN has developed, options are available to alleviate the pain. Anticonvulsants, tricyclic antidepressants, opioids, topical lidocaine patches, and topical capsaicin creams have all demonstrated some efficacy in alleviating the pain of PHN. However, these agents offer most patients little more than moderate pain relief, and some are associated with adverse events that limit their use.

Prevention of herpes zoster and PHN via prophylactic vaccination with the herpes zoster vaccine is the best strategy for alleviating the morbidity of this disease. However, because universal vaccination has not yet been attained, and because some individuals will have herpes zoster and PHN (albeit milder forms) will develop despite vaccination, these conditions will continue to occur. This review outlines evidence-based strategies for managing acute herpes zoster and attenuating the pain of PHN (Figure 1).

Acute Herpes Zoster

Antiviral Agents

When given within 72 hours after onset of rash, antiviral agents have been shown to speed healing and decrease the duration of pain. Some evidence also suggests that these agents may reduce the duration of PHN, though they do not prevent it.

- Acyclovir—Individuals aged 60 years or older with acute herpes zoster (N=209) of no greater than 72 hours’ duration were randomly assigned to receive either placebo or acyclovir, 800 mg, five times daily for 7 days in a blinded fashion. Patients who received acyclovir within 48 hours of onset of the rash had significantly faster rash healing than patients who received placebo; this difference was not statistically significant for patients who received acyclovir between 48 and 72 hours after onset of the rash. Acyclovir was also associated with a significant reduction in pain.

- Valacyclovir—An antiviral agent that may be even more effective than acyclovir at limiting the duration of pain, valacyclovir has a simpler dosing schedule (three times daily vs five times daily).
times daily).\textsuperscript{5} Patients aged 50 years or older with herpes zoster who sought treatment within 72 hours of the onset of rash were randomly assigned to receive valacyclovir, 1000 mg three times daily for 7 days (n=384); valacyclovir, 1000 mg three times daily for 14 days (n=381); or acyclovir, 800 mg five times daily for 7 days (n=376). Primary outcome measures included time to healing or crusting of at least 50% of rash, time to cessation of lesion formation, and time to pain cessation. Pain was assessed through week 24. There was no difference between the valacyclovir regimen and acyclovir in time to either cessation of lesion formation or at least 50% lesion crusting. Both valacyclovir regimens (7 days and 14 days) were associated with significantly shorter time to pain cessation (38 and 44 days, respectively, vs 51 days with acyclovir). The difference between the 7- and 14-day valacyclovir regimens was not significant.\textsuperscript{5}

Postherpetic neuralgia, defined as pain persisting for longer than 30 days after rash healing, affected 57% of patients receiving acyclovir, 49% of patients receiving 7-day valacyclovir, and 50% of patients receiving 14-day valacyclovir. Patients who received valacyclovir had a significantly shorter duration of PHN (30-35 days) than patients who received acyclovir (39 days).\textsuperscript{5}

\textbf{Famciclovir—}Famciclovir has also been shown to accelerate rash healing and shorten the duration of PHN. Patients aged 18 years or older with herpes zoster of less than 72 hours' duration were randomly assigned to receive either 500 mg (n=138) or 750 mg (n=135) of famciclovir or placebo (n=146) three times daily for 1 week. Famciclovir significantly speeded rash healing, but it had no effect on time to resolution of acute pain or the incidence of PHN; the duration of PHN was, however, shorter among patients who had received famciclovir than among those receiving placebo.\textsuperscript{9}

The safety and efficacy of valacyclovir and famciclovir were compared in a randomized, double-blind study.\textsuperscript{5} Patients aged 50 years or older with herpes zoster who saw a physician within 72 hours of onset of rash were assigned to receive either valacyclovir, 1 g three times daily (n=297) or famciclovir, 500 mg three times daily (n=300) for 7 days, and followed up for as long as 24 weeks. Outcome measures included time to cessation of pain and lesion dissemination, and time to rash healing.\textsuperscript{6}

When group differences in baseline characteristics, such as proportion of patients who had prodromal pain, were taken into account, no differences existed between the two agents in time to cessation of pain. Likewise, valacyclovir and famciclovir were associated with significant rates of rash healing, and no patients in either group had cutaneous disseminated zoster. Adverse events were also similar for the two agents, both in their incidence and type.\textsuperscript{6}

\textbf{Combination Therapy}

In some cases, corticosteroids may be combined with antiviral agents. Two trials have investigated the results of adding prednisone/prednisolone to acyclovir. In the first trial,\textsuperscript{7} patients (N=400) aged 18 years or older with herpes zoster of no greater than 72 hours’ duration that was associated with moderate or greater pain were randomly assigned to receive 7 or 21 days of 600 mg of acyclovir five times daily with either prednisolone or placebo. Prednisolone was administered on the following schedule:
40 mg/d, days 0 to 6; 30 mg/d, days 7 to 10; 20 mg/d, days 11 to 14; 10 mg/d, days 15 through 18; and 5 mg/d, days 19 to 21. Progression of rash and intensity and duration of pain were assessed; pain was assessed for 6 months post herpes zoster.7

In this study by Wood et al,7 no significant differences existed between the groups in rash progression. When results were pooled across groups, patients who received prednisolone were found to have had more healing early, at days 7 and 14, but this early healing had no significant effect on time to rash resolution.

Treatment did, however, have an effect on pain: patients who received the longer course of acyclovir in combination had much efficacy against PHN; this finding is further substantiated by the lack of difference between the groups in time to complete cessation of pain (assessed during 6 months’ follow-up).7

In the second trial,10 patients were randomly assigned to receive acyclovir or placebo in conjunction with prednisone or placebo; thus, in this trial, patients could receive prednisone alone or no medication at all. Patients older than 50 years (N=208) with herpes zoster of less than 72 hours’ duration were randomly assigned to receive either oral acyclovir, 800 mg, five times daily for 21 days or placebo and either prednisone, 60 mg/d for days 1 to 7; 30 mg/d for days 8 to 14; and 15 mg/d for days 15 to 21; or placebo. Study end points included duration of pain and quality of life during 6 months’ follow-up (primary end points), and rash healing and medication toxicity (secondary end points).10

In terms of time to rash healing, acyclovir plus prednisone was significantly better than placebo plus prednisone (P=.008), but not to placebo plus placebo (P=.06). Acyclovir plus prednisone was superior to placebo plus prednisone, approaching statistical significance (P=.05).10

Prednisone offered some advantages in pain reduction in the short term, but these disappeared over the long term. Prednisone increased the likelihood that patients would have resolution of pain during the first month (relative risk, 2.28), regardless of whether the patient was receiving acyclovir. However, no active treatment showed a significant advantage over placebo in terms of time to resolution of PHN, and no significant differences existed between the four groups in the proportion of patients who had pain at 3 and 6 months after herpes zoster.10

Both acyclovir and prednisone had significant effects on time to resumption of usual activities (P<.01), a measure of quality of life. Patients who received prednisone were 1.74 times more likely than those not receiving prednisone to return to 100% activity.
during the course of the study, whereas acyclovir recipients were 1.90 times more likely than those not receiving acyclovir to return to 100% activity.10

Postherpetic Neuralgia
Although the treatment modalities discussed in the previous section offer considerable relief to many individuals with acute herpes zoster, none of them prevent PHN. Once PHN develops, there is no cure, but a variety of medications exists, including anticonvulsants, tricyclic antidepressants (TCAs), opioids, and topical treatment modalities, that may provide some pain relief.11-15

Commonly used treatments for PHN include all the previously mentioned; however, only gabapentin, pregabalin, and lidocaine-containing patch 5% are FDA-approved treatments for neuropathic pain. Capsaicin cream is available for topical use as an over-the-counter medication and is indicated for the treatment of neuropathic pain. Antidepressants have been used for many years for the treatment of neuropathic pain, though they lack the specific indication. Opioid analogs are indicated for the treatment of moderate to severe pain and are routinely used to treat patients for PHN.

Anticonvulsants
• Gabapentin—Gabapentin decreases severity of pain by approximately a third, though it is associated with significant adverse effects.11 Individuals aged 18 years or older with PHN that had lasted more than 3 months after healing of the initial herpes zoster rash were randomly assigned to receive either gabapentin (n=113) or placebo (n=116).11

Gabapentin was uptitrated from 300 mg/d to 3600 mg/d (divided into three daily doses) in 4 weeks; patients who could not tolerate the higher doses were permitted to step down to doses as low as 1200 mg/d. During the course of the study, the average daily pain score decreased by 33.3% in patients receiving gabapentin and 7.7% in those receiving placebo; 43.2% of patients receiving gabapentin had “much” or “moderate” pain relief, compared with 12.1% of patients receiving placebo (Figure 2). Gabapentin did not relieve pain in all patients, however: more than one in five (22.9%) reported no change in the severity of their pain.

In addition, gabapentin was associated with a higher incidences of somnolence (27.4% vs 5.2%), dizziness (23.9% vs 5.2%), ataxia (7.1% vs 0%), peripheral edema (9.7% vs 3.4%), and infection (8.0% vs 2.6%) than placebo. Dizziness and somnolence caused some patients to withdraw from the study: 5.3% of the patients receiving gabapentin versus 0% of placebo recipients withdrew because of dizziness, and 4.4% of patients receiving gabapentin versus 1.7% of placebo recipients withdrew because of somnolence.11

• Pregabalin—Pregabalin also provides moderate pain relief to some patients with PHN. Patients aged 18 years and older who had PHN, regarded as pain lasting more than 3 months after healing of the herpes zoster rash, were randomly assigned to receive pregabalin (n=89) or placebo (n=84).12

The dose of pregabalin was determined based on creatinine clearance rates: those with a clearance rate greater than 60 mL/min received 200 mg three times daily, while those with a clearance rate greater than 30 mL/min but no greater than 60 mL/min received 100 mg three times daily. All patients were initially given 50 mg three times daily for 3 days, and then advanced to 100 mg three times daily. Patients with higher creatinine clearance rates were titrated up to 200 mg three times daily at the beginning of week 2.12

Nearly two thirds (P=.001) of the patients receiving pregabalin and a fourth of the patients receiving placebo had “clinically important” reduction in pain severity, regarded as 30% or greater reduction in pain. Half of the patients receiving pregabalin had 50% or greater decrease in pain severity (P=.0001), as opposed to 20% of patients receiving placebo. Both of these differences were statistically significant. Pregabalin was associated with adverse events similar to those found in patients using gabapentin, with somnolence leading to discontinuation of 11.2% of patients receiving pregabalin. Adverse events led to discontinuation of 32% of pregabalin recipients and 5% of placebo recipients.12

Tricyclic Antidepressants and Opioids
Neither tricyclic antidepressants (TCAs) nor opioids are indicated for the treatment of PHN, but both are widely used and have demonstrated efficacy in clinical trials. Head-to-head trials of TCAs and opioids failed to show significant differences in pain relief, though patients did prefer opioids over TCAs.13 Patients older than 18 years with pain lasting at least 3 months after resolution of rash (N=76) were randomly assigned to receive one of six treatments, each of which included 8-week periods of a TCA, an opioid, and placebo, with 1-week drug-free washout periods between the test periods.

The TCA studied was nortriptyline hydrochloride, 10 mg to 160 mg (average dose, 89 mg), with an option of desipramine hydrochloride (average dose, 63 mg) if nortriptyline was not tolerated. The study opioid was controlled-release morphine sulfate, 15 mg/d to 240 mg/d (average dose, 91 mg/d), with an option for methadone hydrochloride (average dose, 15 mg/d) if morphine was not tolerated. The study drugs were uptitrated from starting (lowest) dose via biweekly dose increases until the patient had maximal pain relief or dose-limiting adverse events.13

Both TCAs and opioids offered significantly greater pain relief than placebo; there was a nonsignificant (P=.06) tendency for the reduction in pain ratings to be greater with an opioid than with a TCA. Patients receiving an opioid had an average 38.2% reduction in pain, whereas patients receiving a TCA had a 31.9% reduction and patients receiving placebo had an 11.2% reduction (Figure 3). Commensurate with the greater reduction in pain, more patients preferred opioids (54%) than TCAs (30%; P=.02); the remainder pre-
ferred placebo. The preference for TCAs over placebo was not significant ($P=0.08$). Once dose levels were established, opioids were associated with a significantly greater incidence of constipation, nausea, and drowsiness than placebo; the first two were also significantly more common with opioids than with TCAs ($P<0.01$, opioids vs TCAs). Tricyclic antidepressants were associated with more dizziness than placebo. The strong patient preference for opioids over TCAs suggests that even though opioids are associated with a greater incidence of certain adverse events than TCAs, the pain relief they offer is such that this benefit outweighs the adverse events.

**Topical Treatment**

- **Lidocaine-Containing Patch 5%**—In a study by Rowbotham et al, in which PHN was defined as pain lasting more than a month after the herpes zoster rash healed, patients (N=35) with a well-defined region of allodynia underwent four sessions. They had two sessions of placement of a lidocaine-containing patch, one session of application of a vehicle patch, and one session of no patch placement (observation only) in randomized order. Lidocaine-containing patches were applied to the area of greatest pain.

  Vehicle patch placebo offered significant pain reduction relative to no patch at 2- and 6-hour points ($P=0.016$ and $P=0.041$, respectively), but lidocaine-containing patches offered significant pain relief relative to both no patch (all time points, $P<0.03$) and to vehicle patch (4-, 6-, 9-, and 12-hour points, $P<0.05$). Topical reactions to the patch and patch removal were generally mild.

- **Capsaicin Cream**—Patients (N=143) aged 18 years or older with PHN of at least 6 months’ duration were given either 0.075% capsaicin cream or a vehicle cream and instructed to apply the cream to the painful area four times daily for 6 weeks. Patients who received capsaicin cream had significantly greater pain relief than did patients who received vehicle cream only. Unfortunately, topical adverse events are quite common with capsaicin cream: 60% of participants had burning, stinging, or erythema at the application site, and these topical reactions were a leading reason among capsaicin recipients for discontinuing the study.

**Comment**

Prevention of herpes zoster and PHN via prophylactic vaccination with the herpes zoster vaccine is the best strategy to prevent or reduce the morbidity of these conditions. Treatment modalities are available, however, that may shorten the duration and severity of acute herpes zoster and alleviate the pain of PHN.

**References**


