CLINICAL PRACTICE

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Postherpetic Neuralgia

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

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A 73-year-old woman presents with persistent pain and itching in the right T10 dermatome from just above the thoracolumbar junction to the umbilicus since a documented episode of herpes zoster in the same region 1 year earlier. She describes a severe, continuous "burning" pain, unpredictable paroxysms of lancinating pain lasting a few seconds, and intense hypersensitivity to light tactile stimulation, such as clothing brushing against the skin. On physical examination, there are signs of cutaneous scarring throughout the right T10 dermatome, with areas of excoriation caused by scratching. She has patchy loss of tactile perception in this distribution as well as areas of pain provoked by a light brush. Acetaminophen did not help her pain. How would you manage this patient's condition?

THE CLINICAL PROBLEM

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Postherpetic neuralgia is the most frequent chronic complication of herpes zoster and the most common neuropathic pain resulting from infection. Herpes zoster results from reactivation of dormant varicella–zoster virus (VZV) in a sensory ganglion and is usually manifested as an acutely painful vesicular rash affecting a single dermatome, which generally resolves within a few weeks. VZV is a neurotropic herpes virus that typically gains access to sensory neurons during childhood infection with varicella (chickenpox). In North America and Europe, more than 95% of young adults are seropositive for VZV and thus are at risk for herpes zoster. The annual incidence of herpes zoster is approximately 3.4 cases per 1000 persons, and it rises sharply from the age of 50 years, to approximately 11 cases per 1000 by the ninth decade of life.[1] The rate of recurrence is less than 6% among immunocompetent persons.[2]

Postherpetic neuralgia is a complex neuropathic pain condition in which the pain is a direct consequence of the response to peripheral-nerve damage sustained during the herpes zoster attack.[3] Pathologic damage to nerve tissue from skin to spinal cord has been observed.[4,5] Postherpetic neuralgia is conventionally defined as dermatomal pain persisting at least 90 days after the appearance of the acute herpes zoster rash. A minimal threshold of clinically significant pain intensity, usually a score of 40 or higher (but sometimes ≥30) on a Likert scale ranging from 0 (no pain) to 100 (worst possible pain), is often used in the case definition for postherpetic neuralgia in clinical trials.[6,7]

The incidence and prevalence of postherpetic neuralgia vary depending on the definition used, but approximately a fifth of patients with herpes zoster report some pain at 3 months after the onset of symptoms, and 15% report pain at 2 years. Approximately 6% have a score for pain intensity of at least 30 out of 100 at both time points.[8] In a longitudinal study involving patients with herpes zoster who were followed for 4 years, the proportion of patients with spontaneous resolution of pain

KEY CLINICAL POINTS

POSTHERPETIC NEURALGIA

- The frequencies of both herpes zoster and postherpetic neuralgia increase with age.
- Postherpetic neuralgia results in suffering and reduced quality of life as well as individual and societal health care costs.
- Treatment may involve topical therapy (lidocaine or capsaicin) and systemic therapy, generally with gabapentin, pregabalin, or tricyclic antidepressants.
- Opioid analgesics are sometimes used, but there is uncertainty about their long-term benefits and concern about risks, including potential for abuse; if opioids are used, consultation with a specialist and close supervision and monitoring are warranted.
- In clinical trials of available therapies, fewer than half of patients with postherpetic neuralgia have a 50% or greater reduction in pain; adverse effects are common, particularly in older patients (among whom the disorder is most prevalent).
- Herpes zoster vaccination significantly reduces the incidence of both herpes zoster and postherpetic neuralgia.

decreased with increasing time since the onset of herpes zoster (Fig. 1).[9] Analysis of data from the United Kingdom General Practice Research Database showed that the incidence of postherpetic neuralgia (as defined by pain at 3 months) rose from 8% at 50 to 54 years of age to 21% at 80 to 84 years of age.[10] Risk factors for postherpetic neuralgia include older age and greater severity of the prodrome, rash, and pain during the acute phase.[11] The incidence is also increased among persons with chronic diseases such as respiratory disease and diabetes, and it may be increased among immunocompromised patients, although the evidence is sparse and inconsistent.[11,12]

Postherpetic neuralgia causes considerable suffering and results in a health care burden at both the individual and societal levels. The disorder predominantly affects the elderly and may be an important factor in the change from independent functioning to dependent care. Patients with postherpetic neuralgia have reduced quality of life, physical functioning, and psychological well-being.[13,14]

STRATEGIES AND EVIDENCE

ASSESSMENT OF THE PATIENT WITH POSTHERPETIC NEURALGIA

Although a history of herpes zoster often cannot be confirmed with absolute certainty, the disorder has a characteristic clinical presentation, and thus postherpetic neuralgia rarely presents a diagnostic challenge. Clinical assessment of the patient with postherpetic neuralgia should follow the general principles of assessment of patients with peripheral neuropathic pain.[15] Features of pain and associated sensory perturbations (e.g., numbness, itching, and paresthesias) should be assessed.[16-18] Pain associated with postherpetic neuralgia occurs in three broad categories: spontaneous pain that is ongoing (e.g., continuous burning pain), paroxysmal shooting or electric shock–like pains, and evoked sensations that are pathologic amplifications of responses to light touch and other innocuous stimuli (mechanical allodynia) or to noxious stimuli (mechanical hyperalgesia). Diaries in which patients record pain type and intensity, effects of pain on activities of daily living, and their fluctuations over time are useful. The Zoster Brief Pain Inventory is a validated and convenient tool for this purpose[19] (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Other validated questionnaires are available to assess the effect of postherpetic neuralgia on quality of life and sleep but are not generally used in nonspecialist clinical practice.[15] The physical examination should include a comparison of sensory function in the affected dermatome with that on the contralateral side.[15] Loss of sensory function in response to both mechanical and thermal stimuli is common in patients with postherpetic neuralgia, as are pathologic sensory amplifications (e.g., allodynia and hyperalgesia). In most cases, no addi-

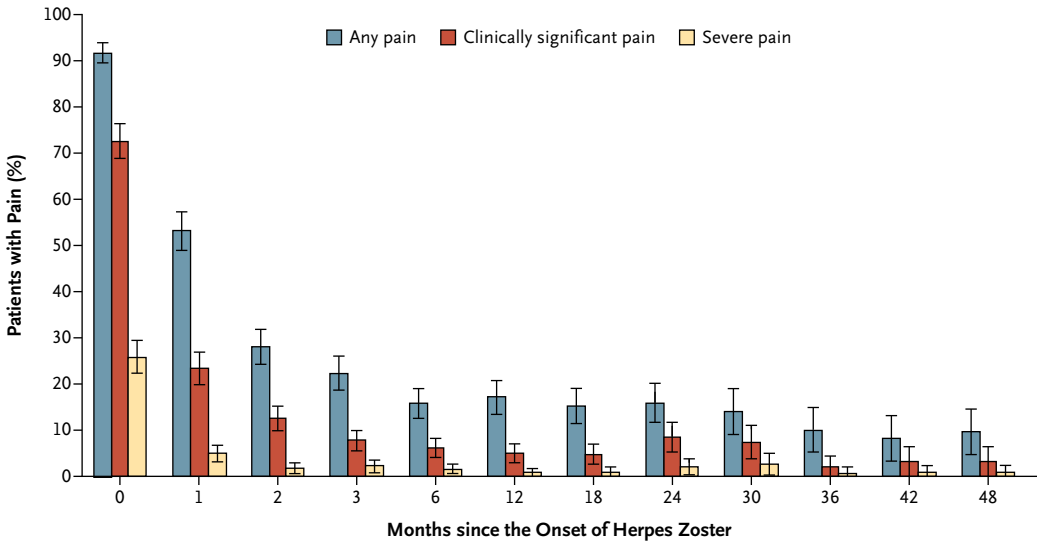

Figure 1. Incidence of Pain over Time after the Onset of Herpes Zoster.

Shown are the proportions of patients with any pain, clinically significant pain, and severe pain in a study involving 566 patients with a mean age of 66 years (range, 58 to 75). Clinically significant pain was defined by a score of more than 30 on a visual-analogue scale that ranged from 0 to 100, with 100 indicating maximal pain. Severe pain was defined by a score of more than 70 on the same scale. I bars denote 95% confidence intervals. Data are from van Wijck.[9]

tional evaluation is needed beyond the history taking (with concomitant disease and medications noted) and physical examination.

MANAGEMENT OF POSTHERPETIC NEURALGIA

There is currently no disease-modifying therapy for postherpetic neuralgia[8]; thus, treatment is based on symptom control. Because pain may persist for years or for life, medication is often required over prolonged periods. It is important to monitor the effect of interventions on pain intensity (with the methods described above) and to modify or discontinue treatments that do not result in appreciable pain relief or that have adverse effects in excess of the benefit. Randomized, placebo-controlled trials support the effectiveness of several topical and oral agents. Table 1 provides information on dosing, efficacy, and adverse effects of these agents.

Topical Treatment

Topical therapy alone is reasonable to consider as first-line treatment for mild pain. It is sometimes used in combination with systemic drugs when pain is moderate or severe, although data are lacking from randomized trials comparing combination topical and systemic therapy with either therapy alone. Patches containing 5% lidocaine are approved for the treatment of postherpetic neuralgia in Europe and the United States. However, evidence in support of their efficacy is limited. A meta-analysis of small placebo-controlled trials suggested that the number needed to treat for one person to obtain at least 50% pain relief is 2.[20] However, a subsequent double-blind, placebo-controlled trial, in which the primary end point was the time to study discontinuation owing to insufficient pain relief, showed no significant difference between lidocaine and placebo, although a per-protocol analysis suggested some potential benefit of lidocaine.[26]

Capsaicin 0.075% cream may be helpful.[27] However, its use is limited because it must be applied four times daily and it causes a short-term burning or stinging sensation and erythema when applied. A meta-analysis of four randomized, controlled trials (involving a total of 1272 participants) showed that a high-concentration (8%) capsaicin patch, when applied for 30 to 90 minutes (after application of topical anesthesia), provides significantly greater pain relief than a low-concentration capsaicin patch for up to 12 weeks (the number needed to treat for one person to benefit was estimated at 7.0 to 8.8).[22] This treatment is

Table 1. Pharmacologic Therapies for Postherpetic Neuralgia.*

Agent	Average Effective Dose in Clinical Trials	Starting Dose	Dose Adjustment	Number Needed to Treat (95% CI)†	Side Effects	Precautions
Topical treatments						
Lidocaine patch	5%; up to 3 patches/day	Maximum of 3 patches/day for a maximum of 12 hr		2.0 (1.4–3.3)[20]	Local erythema	
Capsaicin cream	0.075%; 4 applications/day	NA		3.3 (2.3–5.8)[20]	Pain on application, local erythema, rash	Avoid eyes and nose
Capsaicin patch	8%; application time of 30–90 min	NA		11.0 (6.1–62.0)[22]	Pain on application, local erythema, rash; systemic adverse events in <5% of study participants‡	
Oral treatments						
Gabapentin	2572 mg/day	100 mg 3 times daily	Increase each of the 3 daily doses by 100–300 mg every 3–7 days as tolerated; maximum dose is 1800 mg/day, but unlicensed dose of up to 3600 mg/day is used by some clinicians	4.4 (3.3–6.1)[20]	Sedation, dizziness, peripheral edema	Avoid in patients with renal insufficiency
Pregabalin	398 mg/day	50–75 mg twice daily	Increase to 300 mg daily after 3–7 days, then by an additional 150 mg daily every 3–7 days as tolerated, to a maximum dose of 600 mg daily	4.2 (3.4–5.4)[20,23]	Same as with gabapentin	Same as with gabapentin
Tricyclic antidepressants (off-label use)	Amitriptyline, 95 mg/day; or nortriptyline, 122 mg/day	10–25 mg at bedtime	Increase by 10–25 mg every 3–7 days as tolerated to 75–150 mg/day with caution as side effects permit; if blood level of active drug and its metabolite is >100 ng/ml, continue dose adjustment very cautiously	2.6 (2.1–3.5)[20]	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Avoid in patients with cardiac disease, glaucoma, or seizure disorder; avoid concomitant use of tramadol
Morphine and oxycodone	Morphine, 90 mg/day; oxycodone, 45 mg/day	5–15 mg every 4 hr as needed	After 1–2 wk, convert total daily dose to long-acting opioid and continue short-acting formulation as rescue medication	Morphine, 2.8 (2.0–4.6)[20]; oxycodone, 2.5 (1.7–4.4)[20]	Nausea, vomiting, constipation, drowsiness, dizziness, mood change, disorientation	There is risk of abuse and uncertainty over long-term effectiveness and safety§
Tramadol	298 mg/day	50 mg every 4–6 hr	Increase by 50–100 mg/day in divided doses every 3–7 days as tolerated, to maximum dose of 400 mg/day (300 mg/day in patients >75 yr of age)	4.8 (2.6–27.0)[20]	Nausea, vomiting, constipation, drowsiness, dizziness, seizures	Same as with morphine and oxycodone; also, avoid concomitant use of SSRIs, SSNRIs, tricyclic antidepressants

* Data are primarily from Hempenstall et al.[20] and Dworkin et al.[21] NA denotes not available, SSNRIs selective serotonin- and norepinephrine-reuptake inhibitors, and SSRIs selective serotonin-reuptake inhibitors.
† This is the number needed to treat for one person to have at least 50% pain relief.
‡ Systemic adverse events include diarrhea, nausea, vomiting, fatigue, infections, musculoskeletal disorders, hypertension, dizziness, and headache.
§ See also national guidelines on opioid use for chronic pain.[24,25]

suited to specialist clinics because of the complex logistics of administration.

Systemic Treatment

There is evidence to support the use of tricyclic antidepressants (off-label use) and the antiepileptic drugs gabapentin and pregabalin (Food and Drug Administration–approved) for the treatment of postherpetic neuralgia.[28,29] Meta-analyses of four placebo-controlled trials of tricyclic antidepressants have estimated that the number needed to treat for one patient to obtain meaningful pain relief with amitriptyline, desipramine, or nortriptyline is 3; the estimated number needed to harm (i.e., to result in adverse effects sufficiently bothersome that one person stops using the medication) is 16.[20,21] Meta-analyses of trials of gabapentin or pregabalin have estimated that the number needed to treat is 3 to 8 and the number needed to harm is 7 to 32.[20,21,23]

Although some clinical trial data have suggested that opioids (morphine and oxycodone) are effective in postherpetic neuralgia,[20,30] a more recent Cochrane review concluded that there was not convincing, unbiased evidence of a benefit of oxycodone in treating the disorder.[31] Opioids, including tramadol, should generally be considered as third-line drugs for postherpetic neuralgia after consultation with a specialist and should be prescribed only with appropriate goals and close monitoring.

Because many patients with postherpetic neuralgia are elderly and have other diseases for which they are taking medication, particular caution is needed when prescribing medications for these patients.[32] The oral agents used to manage postherpetic neuralgia have systemic and cognitive adverse effects, which may be amplified in older adults. Such agents should be initiated at low doses, and the dose can then be adjusted as needed, with close monitoring for adverse effects. Physicians should discuss with patients the possible effects of medication on their capacity to drive safely.

Acetaminophen and nonsteroidal antiinflammatory drugs are generally considered to be ineffective for neuropathic pain, although they have not been comprehensively evaluated in randomized, controlled trials.[33] Antiviral drugs and *N*-methyl-D-aspartate (NMDA) receptor antagonists are not effective in relieving postherpetic neuralgia.[20]

Other Treatments

Rigorous evidence is lacking that local anesthetic or neurolytic blocks of the sympathetic nervous system are beneficial in the treatment of postherpetic neuralgia.[34] A trial of acupuncture did not show efficacy, as compared with placebo, for relief of postherpetic neuralgia.[35] The use of repeated spinal intrathecal injections of methylprednisolone was reported to be effective in one randomized, controlled trial,[36] but concern was raised about the safety of this intervention (e.g., a risk of arachnoiditis or fungal meningitis)[37]; a subsequent trial did not replicate the findings and was terminated early for reasons of questionable safety and futility.[38] Although an initial case report suggested that surgical excision of skin affected by postherpetic neuralgia might be an effective treatment for the disorder, longer-term follow-up showed this approach to be ineffective.[39]

PREVENTION OF POSTHERPETIC NEURALGIA

Placebo-controlled trials of antiviral drugs for acute herpes zoster have shown that they reduce the severity of acute pain and rash, hasten rash resolution, and reduce the duration of pain. These trials were not designed to assess the subsequent incidence of postherpetic neuralgia.[40] Two randomized trials have shown that the addition of systemic glucocorticoids to antiviral drugs during the acute phase of herpes zoster does not reduce the incidence of postherpetic neuralgia.[41,42] Another randomized trial showed no significant reduction in the risk of postherpetic neuralgia after an epidural injection of methylprednisolone and bupivacaine, administered in addition to standard treatment (antiviral and analgesic agents) for acute herpes zoster.[8] In one placebo-controlled trial, low-dose amitriptyline, started soon after the diagnosis of herpes zoster and continued for 90 days, significantly reduced the incidence of pain at 6 months. Further studies are required to confirm this finding.[43]

The only well-documented means of preventing postherpetic neuralgia is the prevention of herpes zoster. A live attenuated VZV vaccine has been available since 2006; it was initially licensed for immunocompetent persons 60 years of age or older but now is approved for persons 50 years of age or older. In a randomized trial in the older age group, its use 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 those 60 to 69 years of age, the vaccine was less effective in reducing the risk of herpes zoster (38% reduction) but conferred similar protection against postherpetic neuralgia (67% reduction).[7] A similar study involving persons 50 to 59 years of age showed that vaccination reduced the incidence of herpes zoster by 70%.[44]

AREAS OF UNCERTAINTY

Data from clinical trials assessing the use of any therapy do not extend beyond treatment periods of a few weeks, and there is a need for more randomized, controlled trials comparing active drugs and also randomized, controlled trials of combinations of drugs. In general, effects of treatment tend to be suboptimal; even the most effective treatments result in clinically significant analgesia (e.g., ≥50% pain relief) in fewer than half of patients.[20,30] Further study is needed to identify more effective therapies and the effects of long-term treatment. A recent clinical trial of oxcarbazepine involving patients with neuropathic pain, including a small number with postherpetic neuralgia, indicated that treatment response varied significantly according to pain phenotype (as determined by quantitative sensory testing).[45] The relevance of this finding for this and other therapies in postherpetic neuralgia needs to be determined. The use of potent opioids and tramadol in postherpetic neuralgia is controversial. Their long-term efficacy and safety in the treatment of this condition have not been established. When opioids are prescribed, appropriate goals must be established and monitoring and specialist supervision are required.[24,25,46] It remains unclear whether extended-release preparations of gabapentin have a lower risk–benefit ratio than normal-release preparations.[47] Combined therapy with topical lidocaine and oral medications requires investigation. Data from rigorous studies of nonpharmacologic therapies for postherpetic neuralgia are lacking.[34]

PROFESSIONAL GUIDELINES

Guidelines are available that address the use of strong opioids for chronic pain,[24,25] assessment of neuropathic pain,[15] and management of neuropathic pain, including postherpetic neuralgia.[48-51] Our recommendations are broadly in line with recent guidelines and emphasize consideration of opioids as third-line therapy, given the uncertainty regarding long-term efficacy and concern about safety. Although some guidelines classify topical lidocaine as second-line treatment,[48,49] we agree with other guidelines that recommend topical lidocaine for first-line use,[50,51] usually in combination with oral drugs (except in frail patients[50]).

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has typical manifestations of postherpetic neuralgia, including a clear history of herpes zoster, dermatomal continuous and paroxysmal pain, and allodynia. After an assessment of baseline pain (e.g., with the Zoster Brief Pain Inventory), we would start treatment with 5% lidocaine patches (on the basis of clinical experience, some clinical-trial evidence of efficacy, and a very low risk of adverse events). If an adequate benefit is not achieved, we would add pregabalin or gabapentin; these agents have an efficacy similar to that of tricyclic antidepressant drugs but pose lower risks of serious adverse events. On the basis of our experience, patients should be encouraged to return to normal physical and social activities as soon as possible. If joint movement is impeded by pain, physiotherapy and early mobilization are indicated.

Patients should be informed of both the benefits and the potential adverse effects of treatment, and they should understand that pain relief will not be immediate and that frequent reassessment will be needed. If pain relief is inadequate, doses should be increased. Regular follow-up is needed to assess pain relief, side effects, satisfaction with treatment, and activities of daily living. If a patient has an inadequate response to therapy or bothersome side effects, we would consider changing to a tricyclic antidepressant. Referral to a pain specialist should also be considered. It is unfortunate that the patient in the vignette did not receive herpes zoster vaccination, which significantly reduces the risk of postherpetic neuralgia.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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