SUPPLEMENT TO
MANAGED Care

Postherpetic Neuralgia
A Model for Treating Severe Pain

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Overview of Postherpetic Neuralgia

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SUMMARY

PHN is a disabling condition that impairs quality of life. Varying definitions of PHN have made it difficult to quantify its prevalence or qualify its severity. Undertreatment of PHN is common and can carry costly implications for third-party payers.

Postherpetic neuralgia (PHN) is a neuropathic pain syndrome. It is a consequence of neuronal damage that results from reactivation of latent varicella zoster virus (VZV) in neurons located in the dorsal root ganglia (DRG) or cranial nerve ganglia. The virus remains latent within cells of the ganglion after a primary varicella infection. Years later, VZV reactivation can result in herpes zoster (HZ, or shingles). PHN is the most common complication of HZ (Dworkin 1997).

RANDALL P. BREWER, MD

Definitions of PHN

Historically, numerous definitions of PHN have been proposed. Terms are applied relative to the time elapsed following viral reactivation. Pain associated with acute HZ typically resolves, along with healing of the skin lesions, within 3 weeks of the onset of the HZ rash.

The definition proposed by Dworkin and Portenoy is the one most commonly used in clinical research (Johnson 2001) and describes PHN as the presence of pain that persists for 4 months after onset of the skin manifestations of HZ (Dworkin 1994). Others have defined PHN in various ways (Table 1). Such diversity complicates the study of PHN.

Note that all of these definitions of PHN share a common characteristic: they fail to take severity of pain into account. Studies of PHN, therefore, become difficult to compare (Dworkin 1997). To address this inadequacy, it has been suggested that PHN definitions be revised to include only those patients with clinically meaningful neuropathic pain — pain severe enough to cause disability or that requires medical treatment. Taking into account functional deficits, sleep impairment, and level of treatment required would lead to more homogenous study populations.

Description of neuropathic pain

Pain is generally described in terms of *nociceptive* (inflammatory) pain or *neuropathic* pain (Backonja 2005a) and can be conceived of as proceeding along inflammatory and neuropathic axes (Figure 1). The International Association for the Study of Pain defines neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction of the nervous system" (Merskey 1994). However, this definition is overly broad, because *dysfunction* can result in ambiguities related to the generators of neuropathic pain (Backonja 2005a). Neuropathic pain can be described more precisely as pain stemming from disease or injury causing lesions in the peripheral or central nervous system. In contrast, the source of inflammatory pain is tissue destruction from a defined tissue injury resulting in inflammation. Although there is some evidence of an inflammatory component to PHN (Watson 1991a), this distinction helps to classify PHN pain as neuropathic.

Additional distinctions can be drawn between these two kinds of pain. In inflammatory pain, activated pain receptors (nociceptors) in the periphery generate pain signals. In neuropathic pain, the injured neuron is the source of signaling (Backonja 2005b). Inflammatory pain ends with the completion of the healing process, but neuropathic pain and sensory defects persist long after healing has occurred. A neurological evaluation of a pa-

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TABLE
Definitions of PHN

The most commonly accepted definition of PHN in clinical practice was proposed by Dworkin and Portenoy: pain that persists 4 months after rash onset (or 3 months after zoster healing).[a] Several other definitions are found in the literature; however, each has varying degrees of acceptance:

- Pain persisting or recurring at the site of shingles 3 or more months after the appearance of the HZ rash[b]
- Presence of pain more than 1 month after the onset of zoster eruption[c]
- Any subjective painful sensation that persists after the acute phase of the infection[d]
- Persistent or recurrent pain for at least 3 months after healing of skin lesions[e]

SOURCES: [a]DWORKIN 1994; [b]BOWSHER 1999; [c]ROGERS 1971; [d]BURGOON 1957; [e]ROWBOTHAM 1989

tient with inflammatory pain will be normal unless the nervous system has been affected by the disease or injury that caused the pain; a patient with neuropathic pain will be found to have positive and negative sensory phenomena with possible positive and negative motor phenomena or autonomic signs. Patients with inflammatory pain will likely respond to nonsteroidal anti-inflammatory drugs and acetaminophen. Neuropathic pain typically remains resistant to those agents and responds best to anticonvulsants, topical anesthetics, and antidepressants.

In addition to PHN, neuropathic pain also includes monoradiculopathies, trigeminal neuralgia, phantom limb pain, complex regional pain syndromes, and the various peripheral neuropathies.

Clinical manifestation of PHN

Phases of pain. In many patients, dermatomal pain precedes the onset of the characteristic rash of HZ. Prodromal pain that begins several days before the onset of a rash has been reported in more than 80 percent of patients (Beutner 1995).

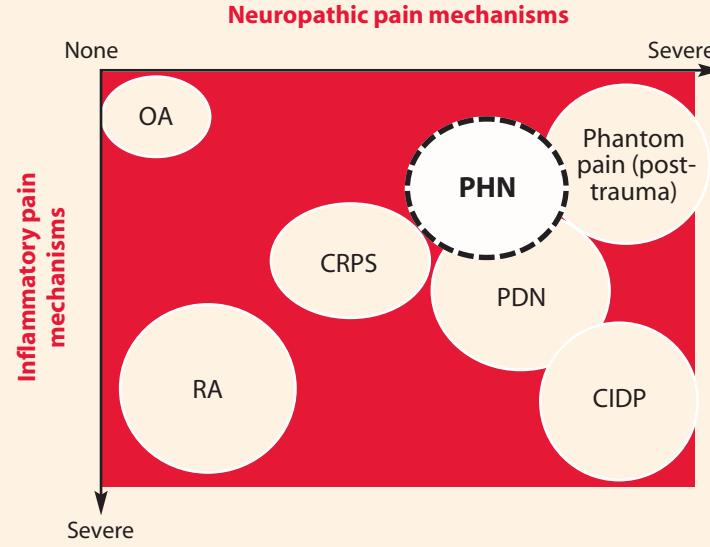
As for zoster-associated pain itself, Dworkin and Portenoy have suggested three phases of pain — acute, subacute, and PHN. The acute phase consists of pain associated with the HZ outbreak. Such pain usually subsides in 4 weeks or less (Dworkin 1994). The subacute phase encompasses pain persisting more than 30 days after rash onset but less than 4 months (Dworkin 1994). Pain persisting for 4 months or more after rash onset is regarded as PHN. Regardless of how PHN is defined, it would be imprudent to conceive of zoster-associated pain as a continuum, because PHN is a discrete disorder with a distinct pathophysiology involving long-term changes to pain processing within the nervous system (Bowsher 1995).

Signs and symptoms. The signs and symptoms of PHN may vary from patient to patient and within individual patients over time. Because some patients with PHN experience discontinuous pain (Watson 1991b), long-term follow-up is needed to ascertain that patients indeed are pain free.

Pain usually spreads along a single dermatome from the central dorsal line in a ventral direction, often remaining confined to that dermatome. The commonly described symptoms of PHN include a constant, usually deep-burning pain; a brief recurrent shooting or shock-like pain; and allodynia (Rowbotham 1989).

Allodynia can affect large areas of skin — up to 1,200 cm^2 (Choi 1997). In some patients, allodynia can be so severe that even a breeze wafting across the skin or the touch of clothing or bedding can cause pain, and it may be the most disabling symptom (Rowbotham 2001).

FIGURE 1
Position of PHN along neuropathic and inflammatory axes



CIDP=chronic inflammatory demyelinating polyneuropathy, CRPS=complex regional pain syndrome, OA=osteoarthritis, PDN=painful diabetic neuropathy, PHN=postherpetic neuralgia, RA=rheumatoid arthritis.

SOURCE: BACKONJA 2005B

Mechanical allodynia is subdivided into two types, *dynamic* and *static*. In dynamic allodynia, light stroking suffices to elicit pain, whereas in static allodynia, pain is induced by stretching or compressing the skin (Haanpää 2000).

Two distinct patterns of pain have been observed clinically in which the key variables are the severity of allodynia and the extent of sensory loss. These patterns have been described by Fields (1998) as the *irritable nociceptor* and *deafferentation* types of neuropathic pain. In the former, patients experience severe allodynia and have minimal or no sensory loss in the painful area. If an intradermal local anesthetic is applied, these patients experience marked pain relief. In contrast, patients with deafferentation have allodynia that varies in intensity, and their pain is greatest within a region of zoster scarring and extensive sensory loss. An intradermal local anesthetic provides no pain relief for these patients. In some patients, a mixture of these subtypes is said to occur.

Epidemiology

Established risk factors for PHN

Numerous risk factors for PHN have been described, but thus far most are not strong enough to have positive predictive value. Three risk factors for PHN, however, are undisputed: greater age at onset of HZ, greater pain severity during the acute phase of HZ, and greater severity of HZ rash (Haanpää 2000).

Greater age. Age is a well-established risk factor for PHN. The classic study by de Moragas (1957) confirmed this finding based on records of HZ- or PHN-diagnosed patients seen at the Mayo Clinic over a 14-year span. Numerous reports have confirmed the association between advanced age and PHN, even in the general population. In a retrospective study conducted in the United Kingdom involving 1,071 randomly selected elderly persons (Bowsher 1999), 24 percent (255/1,071) reported ever having had HZ, and of this group, 15 percent (39/255) went on to develop PHN. In this study, PHN was defined as pain persisting 3 or more months after the appearance of rash. The mean age of HZ onset for subjects who developed PHN was 65.6 years. Among the HZ subjects who did not develop PHN, the mean age of HZ onset was 54.9 years. Among those who were 80 years and older when they developed HZ, 40 percent developed PHN.

In a U.S. managed care population, the prevalence of PHN (defined as the documented presence of sensory symptoms more than 30 days after HZ onset) was 14.7 times higher after 30 days and 27.4 times higher after 60 days in patients aged 50 or older (Choo 1997).

Greater pain and **HZ severity.** Severe HZ attacks, in terms of rash or pain intensity, are well-established risk factors for PHN (Bowsher 1999, Jung 2004). In a study of subjects enrolled in two clinical trials of an antiviral agent for HZ patients, severe rash within 3 days after onset of HZ was found in 72 percent of subjects who developed PHN (defined as pain at 4 months after rash onset) versus 44 percent of subjects in whom PHN was absent ($P<.001$) (Jung 2004). In that same study, 49 percent of the subjects with PHN reported severe acute pain compared with 22 percent of subjects without PHN ($P<.001$).

Possible risk factors

Compromised immune system. A compromised immune system for reasons other than age (e.g., HIV, blood dyscrasias, or immunosuppression due to use of corticosteroids or chemotherapy) may be a risk factor for PHN (Choo 1997). Some studies, however, have suggested that the risks of PHN are similar in immunocompetent and immunocompromised patients (Dworkin 2001).

Prodrome. Evidence that prodromal symptoms are risk factors for PHN is inconsistent. Choo (1997) found that in a managed care population, PHN was 2.1 and 3.4 times more prevalent at 30 and 60 days, respectively, after HZ onset in patients with prodromal symptoms. Jung (2004) found that in subjects who participated in two clinical trials of an antiviral agent, prodrome was present in 94 percent of those who developed PHN versus 83 percent of those who did not ($P<.01$). However, prodromal pain was not found to be predictive of PHN in a Finnish study enrolling 113 immunocompetent patients with acute HZ (Haanpää 2000).

Psychosocial risk factors. Affective distress at zoster onset, as assessed by the Multidimensional Pain Inventory (MPI), has been found to be predictive of PHN at 6 months after onset ($P<.05$) (Thyregod 2007).

Allodynia. In the Haanpää (2000) study, allodynia of any kind noted during a patient's first visit for acute HZ was found to be a statistically significant risk factor for PHN, defined as any zoster-associated pain 3 months after HZ onset. In this study, dynamic allodynia was assessed through the light application of an electric toothbrush to the affected skin, and static allodynia was tested through gentle compression and lateral stretching of the skin. These test methods were selected because they are easily performed in a clinician's office. Brush-evoked allodynia was present in 41 percent (13/32) of patients who developed PHN, but of patients without brush-stroked allodynia, only 15 percent (11/73) developed PHN ($P=.005$). Compression-evoked or stretch-evoked allodynia was present in 43 percent (13/30; $P=.002$) and 47 percent (8/17; $P=.02$), respectively, of patients who developed PHN, whereas 14 percent (10/70) and 18 percent (15/82), respectively, of patients without these forms of static allodynia developed PHN ($P=.02$).

The low sensitivity and specificity of these tests preclude their use for predicting whether any given patient will develop PHN; however, if a patient lacks static allodynia at the first visit, the 94 percent negative predictive value of the

test could be useful to reassure a patient that the development of PHN is less likely (Haanpää 2000).

Pinprick hypesthesia. The Haanpää study (2000) also evaluated pinprick hypesthesia as a risk factor. This test involved pressing the point of a sharp wooden stick against the skin with moderate force to determine whether the patient experienced a reduced test of sharpness. Among patients who displayed pinprick hypesthesia at the first visit, 46 percent (12/26) developed PHN, whereas only 17 percent (13/77) of patients without pinprick hypesthesia at the first visit developed PHN (P=.002). Pinprick hypesthesia at the first visit also was associated with moderate or severe pain at 3 months (P=.02).

Rash duration. Longer duration of HZ rash before medical consultation has been associated with *reduced* risk of PHN (Opstelten 2007). Opstelten speculates that the delay in consultation could stem from lack of concern, or a different perception of pain, or both when compared with early consulters. It is possible that patients presenting with delayed onset of rash have a less severe form of HZ and, thus, are less likely to develop long-term neuronal dysfunction associated with PHN.

Incidence and prevalence of PHN

Largely because of the various definitions of PHN, along with demographic differences among populations studied, estimates of the incidence and prevalence of PHN vary widely. Estimates of the percentage of HZ patients who develop PHN range from 10 to 76 percent (Ragozzino 1982, de Moragas 1957). Schmader (2002) has estimated that 25 to 50 percent of HZ patients over 50 years of age will go on to develop PHN.

Without taking into account the effects of preventive measures, such as VZV vaccines to reduce the risk of primary varicella infection or the reactivation of latent VZV, the incidence of PHN is related in a rough sense to the incidence of HZ. The lifetime risk of HZ has been estimated at 22 to 30 percent in the United States, but 50 percent of persons who live until age 85 can be expected to develop HZ (Jung 2004). The annual incidence, or new occurrences, of HZ in the United States is thought to exceed one million cases (Oxman 2005). In immunocompetent populations, overall HZ incidence ranges from 1.2 to 3.4 cases per 1,000 person-years, but in persons aged 65 years and older, HZ incidence ranges from 3.9 to 11.8 cases per 1,000 person-years (Dworkin 2001).

PHN prevalence, or cases at a given time, among the elderly has been estimated "very conservatively" at 200,000 in the United Kingdom, and this figure has been extrapolated to create an estimate of 1 million prevalent PHN cases in the United States (Bowsher 1999). These estimates were based on a point prevalence of 25 PHN cases per 1,000 HZ cases, with PHN being defined as pain persisting 3 or more months after rash appearance.

In one managed care population, the prevalence of PHN 30 days after HZ onset was 8.0 per 100 cases, and at 60 days after HZ onset, 4.5 per 100 cases (Choo 1997). If there are 1 million new HZ cases in the United States each year, as Oxman (2005) estimates, then to apply the rates in Choo's findings, Oxman's estimates translate to 80,000 and 45,000 PHN cases at 30 and 60 days.

In another managed care population of 3 million people, patients with PHN represented 0.4 percent (244/55,686) of patients with painful neuropathic disorders in 1 year (Berger 2004). These findings were based solely on ICD-9 diagnosis coding, and a patient was required to have had at least two medical encounters with the appropriate code during the year counted. In this population, people aged 65 and older were overrepresented, accounting for 25 percent of patients, whereas people in the over-65 age group account for 16 percent of the total U.S. population. Extrapolating from this study to adults aged 18 years and older in the U.S. population, physicians nationwide might be expected to see fewer than 20,000 cases of PHN each year, though this methodology is conservative, owing to its reliance on proper identification and diagnosis.

The various definitions of PHN complicate the understanding of the extent of the clinical problem. In an Icelandic study, the point prevalence of PHN in a primary care population was assessed according to four degrees of pain severity at 1, 3, and 12 months after HZ onset (Helgason 2000). The study included all patients with a first episode of HZ who were seen at 62 general practices serving about 100,000 people. High percentages of the 421 HZ patients recruited were available for follow-up after 1 month (n=359), 3 months (n=391), and 12 months (n=417). Patients were asked to classify their discomfort as none, mild, moderate, or severe, and these categories also were assigned numerical values (0, 1–25, 26–75, 76–100, respectively). The percentage of patients reporting pain increased with age at each follow-up visit, but the majority of patients were pain free at all follow-up visits, and moderate or severe pain was infrequently reported (Figure 2, page 6).

Severity of pain also was assessed by Haanpää (2000), who defined PHN as any zoster-associated pain at 3 months from onset of HZ rash. By that definition, 25 percent (28/113) of HZ patients had PHN at 3 months, and 12 percent (14/113) had PHN at 6 months. Patients were asked to rate their pain intensity as none, mild, moderate, or severe. The majority of patients with PHN reported mild pain.

In a longitudinal study enrolling 94 HZ patients at high risk for developing PHN, 32 percent (30/94) had PHN, defined as average daily pain exceeding 0 on a 0–100 mm visual analog scale (VAS) during the previous 48 hours, 6 months after HZ onset (Thyregod 2007). This study also looked at the rate of *clinically meaningful* pain,

as defined above, except for requiring the average daily pain to be at least 30 mm on the VAS 6 months after HZ onset. When this measure was used, the percentage of HZ patients with PHN at 6 months dropped to 2 percent (2/94). The authors concluded that after 6 months, pain in PHN patients was mild compared with that reported by patients in trials of pain therapies, but added that moderate to severe pain not only lasts, but it can be devastating and may impair functioning, disrupt sleep, interfere with employment, and require daily medication and frequent physician visits.

Clinical and economic burdens of disease

The pain of PHN becomes more intractable with increasing age (Rogers 1971, Burgoon 1957). In one meta-analysis, pain lasting more than 1 year was reported in 22 percent of patients older than 55 years of age, but in 48 percent of patients beyond the age of 70 (Figure 3). The prognosis is often poor for patients with PHN of longer duration (Watson 1991b). Elderly patients can be refractory to multiple treatments because of age-related decline in cellular immunity to VZV (Oxman 2005).

Patients seen at pain clinics generally are very difficult to treat. In a Spanish study involving 119 patients seen at pain clinics at major hospitals in Catalonia, 88 percent reported that onset of their HZ rash had occurred more than 6 months ago. Most of these patients had moderate to severe pain, and some said their pain was unbearable; their mean score on the VAS was 47.3, with a range from 2 to 99. Despite pain of long-standing duration, 35 percent (41/119) had ceased treatment for pain (Lazaro 2003).

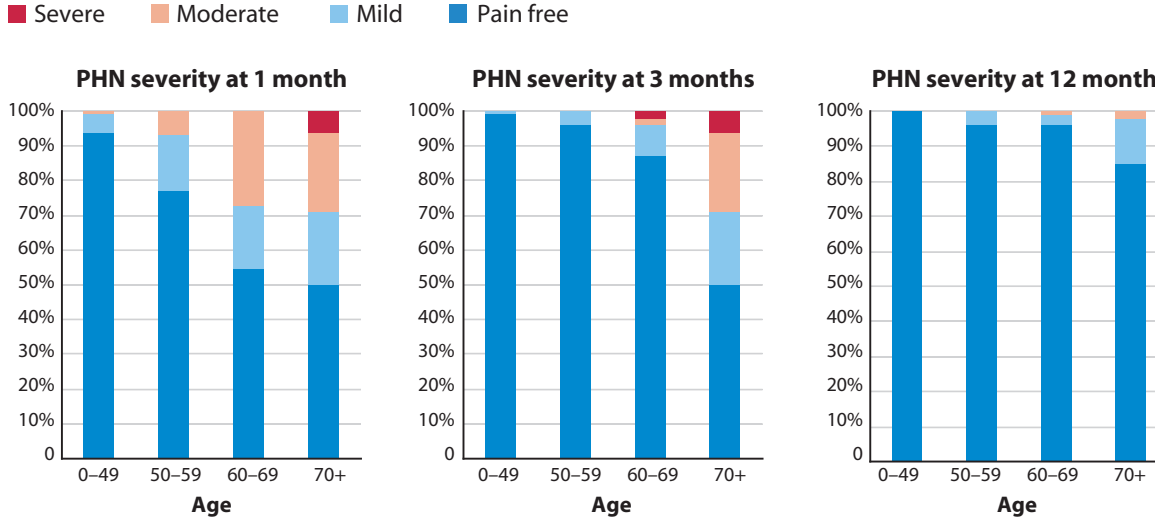
In another study enrolling patients who presented to a pain clinic with PHN, those with a pain duration of one year or longer prior to their first visit were more likely to have a poor outcome than those presenting with PHN of shorter duration (Watson 1991b). Unfortunately, no risk factors could be found to assist in identifying those patients in advance.

Impaired quality of life is suggested by clinical observations (Schmader 2002). PHN patients may experience chronic fatigue, anorexia, weight loss, physical inactivity, insomnia, depression, and difficulty in concentrating. They may curtail their social functioning, and may find it difficult to execute ordinary activities of daily living, such as bathing or dressing. Psychosocial stress also is evident in many patients.

Patients with PHN can consume substantial health care resources. In a sample of PHN patients at a United Kingdom pain clinic, Davies (1994) found that patients visited their physicians 19 times, on average, over the course of their lives. The same patients also required, on average, 16 visits by a home health aide.

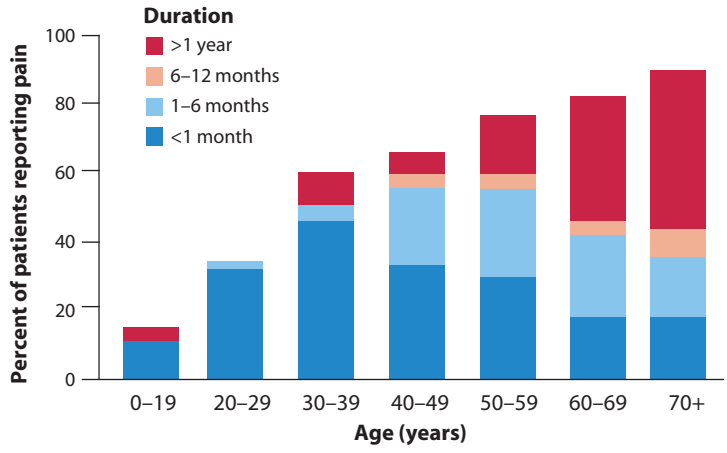
In the first assessment of the economic burdens of acute HZ pain and chronic PHN pain in the United States, Dworkin (2007) estimates that the total direct and indirect costs of diagnosed HZ and PHN in the United States are $1.7 billion annually. Average excess direct health care expenditures for Medicare beneficiaries diagnosed with HZ and PHN are estimated at $1,298 and $2,159, respectively ($P<.001$). In commercial health plans, excess costs are much higher: $1,313 for patients with HZ and $5,387 for patients with diagnosed PHN ($P<.001$). The reasons for the discrepancy between Medi-

FIGURE 2
Prevalence and severity of PHN in 4 age groups in a primary care population



ADAPTED FROM HELGASON 2000

FIGURE 3
Prevalence of PHN and duration of pain, by age



SOURCE: KOST 1996

care and commercial plans are unclear, but the authors speculate that the differences may be attributed to the effects of higher average out-of-pocket expenses in the Medicare cohort (Dworkin 2007).

Implications for third-party payers

Long-term efficacy of the live attenuated VZV vaccine will not be known for many years, and age-related decline in the cell-mediated immune system suggests that the vaccine might be less effective in older persons. Moreover, the cost-effectiveness of the VZV vaccine is uncertain (Hornberger 2006), whereas the cost-effectiveness of topical lidocaine patches and systemic agents has been studied (Smith 2007). For these reasons, it is probable that clinicians will be treating patients with PHN for many years.

Though yet to be proven, it may be prudent for clinicians to implement early, aggressive treatment of HZ and PHN to reduce the risk of the appearance of severe, intractable pain associated with central sensitization (Watson 2001). In their assessment of the economic burden of PHN, Dworkin and White postulate that a substantial amount of PHN is undiagnosed in the commercially insured population (Dworkin 2007). Yet, through case management, MCOs are positioned to be drivers in the process of referring patients for appropriate treatment. Claims data can help health plans identify patients with HZ who may be at risk for developing PHN. Commercial payers also can facilitate the identification and referral of people who may have undiagnosed PHN by offering health risk assessments to their employer clients.

Given the escalation of expenditures in the commercial segment as pain progresses from HZ to PHN, the estimated indirect costs to society, and the potential for substantial health care resource use, managed care payers should have an interest in careful identification, evaluation, and management of patients with PHN who could benefit from appropriate care.

Conclusions

PHN is a disabling condition that impairs quality of life. Undertreatment of PHN carries costly implications for third-party payers. It is important for MCOs to recognize that PHN is a chronic condition that may require multimodal therapy and ancillary assistance (e.g., from psychologists, psychiatrists, and physical therapists), which will lead to increased initial treatment expense.

The number of elderly Americans is increasing rapidly, and given that the incidence of HZ accelerates after age 50, clinicians and payers likely will be faced with many cases of PHN in the elderly in the years ahead.

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Scientific Understanding of PHN And MOA of Lidocaine Patch 5%

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SUMMARY

PHN is a consequence of reactivation of the VZV virus. The result of viral damage to the nervous system, PHN can be severe and intractable to therapy. Targeted analgesia may be useful in reducing the chronic discomfort of PHN caused by central sensitization.

The varicella-zoster virus (VZV) is responsible for varicella and herpes zoster (HZ), commonly known as shingles. Postherpetic neuralgia (PHN) is a neuropathic pain syndrome that is the most common complication of an HZ attack (Dworkin 1997). HZ arises after latent VZV (holdover from the initial chickenpox infection) becomes reactivated. In some patients, the reactivated VZV causes nerve damage that results in PHN, which may persist for many years (Bowsher 1992) and severely affect a person's quality of life.

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VZV and PHN pose interesting scientific questions. What changes does the reactivated VZV induce in the nervous system to cause some people to experience neuropathic pain long after the HZ rash has healed? What does knowledge of the pathophysiology of PHN at the molecular level contribute toward improved treatment of the condition?

During its latent period, VZV resides primarily in a dorsal root ganglion (DRG), a nodule containing the cell bodies (soma) of afferent neurons. It is believed that the virus may reach the DRG through axons extending to the periphery. Such conditions as age- or health-related impairment of immune response can cause the virus to become reactivated, resulting in ganglionitis, a severe inflammation of the DRG (Galer 2000). The virus then erupts from the DRG and moves distally along axons of afferent fibers extending to the skin and, sometimes, ventrally toward the spinal cord.

The prolonged, intense painful stimuli of acute HZ and the subsequent damage to the afferent nervous system lead to long-term functional and structural changes in the pain-processing system and the clinical phenomenon of neuropathic pain (Woolf 1983). Understanding the nature of these changes, the underlying pathophysiology, and the mechanism and site of analgesic action is useful in the rational selection of analgesics to treat patients with PHN.

Pathophysiology of neuropathic pain

The nervous system is plastic — capable of being molded in response to various stimuli. Such neuroplasticity often is adaptive, enabling an organism to endure prolonged stimuli that might otherwise be overwhelming. In an undamaged nervous system, the perception of pain usually begins with the application of some painful stimulus. The stimulus interacts with a specialized cell, a *nociceptor*, and through *transduction* is converted into an electrical signal. The electrical signal is then transmitted via various nerve fibers to the DRG, and then proceeds to the dorsal horn, a region in the spinal cord where nociceptive afferent nerves terminate. In the dorsal horn, nerve signals are modulated by various stimuli, resulting in short- or long-term changes in neuronal firing patterns.

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In a patient with PHN, neuroplasticity is maladaptive. The progressive buildup in dorsal horn neuron response to input from C-nociceptors (nerve fibers) as a result of prolonged application of the same noxious stimuli is known as *wind-up*. Wind-up decreases the threshold as a result of repetitive application and leads to *central sensitization*, an exaggeration of subsequent input due to an increase in the size of the receptive field of dorsal horn neurons (Fields 1998, Woolf 1999). As a result of C fiber activity leading to central sensitization, nerve fibers that are normally sensitive to innocuous tactile stimuli begin activating the central nervous system (CNS) pain-signaling neurons, resulting in allodynia, hyperalgesia, and secondary hyperalgesia. The phenomenon of central sensitization is not restricted to PHN and other forms of neuralgia, but also is an aggravating feature of migraine (Yarnitsky 2003), fibromyalgia (Meeus 2007), and, possibly, gastrointestinal and noncardiac chest pain (Sarkar 2000).

At the molecular level, allodynia and other forms of hypersensitivity are believed to stem from an important change that occurs during central sensitization: NMDA receptors become more responsive, owing to a shift in their distribution patterns (Woolf 2004). NMDA receptors, which are activated by the neurotransmitter glutamate, control cation channels that permit the flow of potassium, sodium, and calcium ions. The heightened response to glutamate increases the excitability of a neuron and, thus, lowers its activation threshold. Allodynia, hyperalgesia, and secondary hyperalgesia are the clinical consequences (Woolf 2004).

In theory, the NMDA receptor antagonist ketamine could be used to combat the hypersensitivity associated with central sensitization, but NMDA receptors are so ubiquitous in the brain that the side effects (potential for intoxication and cognitive difficulties) would be unacceptable (Woolf 2004). Although commonly used analgesics work at the modulation stage of pain processing, their effectiveness is limited and they are associated with systemic side effects (Bridges 2001). An alternative strategy for addressing the pain of PHN is to block sodium channels in afferent peripheral nerves damaged by VZV reactivation, where the distribution and firing patterns of sodium channels are altered.

Nerve fiber types and ion channels

On the basis of their conduction velocity (CV), mammalian nerve fibers have been divided into three groups: A, B, and C (Table). B fibers are preganglionic sympathetic neurons that have no role in the sensation of pain.

TABLE
Types of nerve fibers

Fiber type	Anatomic location	Function	Diameter, µm	Conduction velocity, m/s	Clinical sensitivity to block
A fibers (myelinated)					
α	Afferent to and efferent from muscles and joints	Proprioception; somatic motor	12–20	70–120	+
β		Touch, pressure	5–12	30–70	++
γ	Efferent to muscle spindles	Motor to muscle spindles	3–6	15–30	++
δ	Sensory roots, afferent peripheral nerves	Pain, cold, touch	2–5	12–30	+++
B fibers (myelinated)					
Sympathetic	Preganglionic sympathetic	Preganglionic autonomic	<3	3–15	++++
C fibers (unmyelinated)					
Dorsal root	Sensory roots, afferent peripheral nerves	Pain, temperature, some mechanoreception, reflex responses	0.4–1.2	0.5–2	++++
Sympathetic	Postganglionic sympathetic	Postganglionic sympathetics	0.3–1.3	0.7–2.3	++++

SOURCES: GANONG 1999, CATTERALL 2006

This discussion focuses on the role of certain A and C fibers in PHN and, in particular, the voltage-gated sodium channels associated with these fibers. These channels are blocked by local anesthetics, such as lidocaine, which is contained in the lidocaine patch 5% (Galer 2000).

Pain transmission fibers in primary afferent nerves include both Aδ and Cδ fibers. Aδ fibers are relatively large-diameter myelinated fibers with high CV. C fibers are small unmyelinated fibers and are the most numerous of the nociceptive DRG fibers, mediating touch and warmth.The cell bodies of primary afferent neurons are located in the DRG or the ganglia of cranial nerves. The neurons terminate in the dorsal horns of the spinal cord.

Voltage-gated sodium channels

The plasma membrane provides cells with their basic integrity, enabling the intracellular milieu to differ from the exterior environment in terms of biochemical composition and electrical charge. Specialized protein molecules that span the bilayer provide a means for ions to cross the plasma membrane, establishing the charge differential essential for the membrane potential and the action potential.

In nerve cells, ion channels are the most important proteins for the transport of small inorganic ions across the plasma membrane (Catterall 2000). They are involved in the conduction of nerve signals from all external stimuli — light, touch, chemicals, and temperature. These dynamic molecules can change their shape to allow the selective passage of ions. Ion channels are selective on the basis of charge, admitting either anions or cations, but not both. The mechanisms for opening and closing these channels include neurotransmitters, hormones, and other substances that bind to receptors on the exterior of the channel; intracellular metabolites and enzymes; and changes in voltage across the plasma membrane.

Voltage-gated sodium channels are complex proteins embedded in the plasma membrane. They are widely expressed in excitable cells — nerve, muscle, and neuroendocrine — and are found at low levels in nonexcitable cells. Their general role in neurons is to generate inward currents in axons.

Voltage-gated sodium channels comprise an α subunit with four domains and two β subunits (Figure 1). The α subunit forms the pore and the pair of gates that regulate ion flux through it. The smaller β subunits modify kinetics and voltage dependence, and they facilitate interaction with cell adhesion molecules, the extracellular matrix, and the intracellular cytoskeleton (Catterall 2000).

Because of the presence of two gates — activation and inactivation — the sodium channel can be thought of as transiting through four different states: *closed* or *resting* (activation gate open, inactivation gate closed), *open* or *activated* (both gates open), *inactivated* (activation gate open, inactivation gate closed), and *deactivated* (both gates closed) (Figure 2, page 12). If the channel is in the resting transition and poised to open, segments of the molecule spiral outward in response to depolarization, opening the pore.

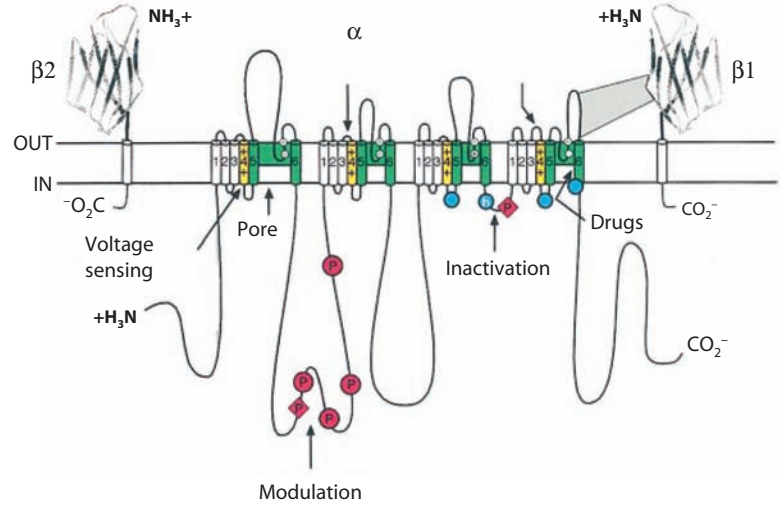
A few milliseconds after opening, the sodium channel becomes inactivated (Catterall 2000). The same depolarization that caused the activation gate to open also causes the inactivation gate to close (Levitan 1997).

During the interval when both gates are closed, no current can flow, even upon depolarization, because even

FIGURE 1

Sodium channel diagram

The primary structures of the subunits α and β are shown as transmembrane folding diagrams. Cylinders represent probable α-helical segments. Green cylinders line pores; white circles are rings of amino residues that form the ion selectivity filter; yellow cylinders are voltage sensors. Red shows sites of protein phosphorylation. Blue circles are sites implicated in forming the inactivation gate receptor; the white h in blue circle indicates an inactivation particle in the inactivation gate loop.



SOURCE: CATTERALL 2000

though depolarization would open the activation gate, the inactivation gate would remain closed. The inactivation gate must be removed to return the channel to the resting state for current to flow upon depolarization (Levitan 1997).

Drugs that block voltage-gated sodium channels have much greater affinity for inactivated states of the channel than for its resting states (Hille 1977). This would permit the drugs to suppress nerve impulses generated during pain sensation without affecting the generation of normal impulses, and it would shift the population of sodium channels toward the inactivated state.

Four kinds of voltage-gated sodium channels are found in DRG neurons (Garry 2005, Djouhri 2003). These are the isoforms of greatest interest in pain sensation, and are identified as $Na_v1.3$, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$. $Na_v1.7$ is almost exclusively expressed in DRG — in small C fiber nociceptors, and also in some A cells. $Na_v1.8$ is expressed in small- and medium-sized DRG neurons, and $Na_v1.9$ is expressed within nociceptive C fiber neurons and some nociceptive A fibers (Fang 2002). Under normal conditions, sodium channels are not uniformly distributed along an axon, but concentrated in the nodes of Ranvier (Ganong 1999).

Consequences of neuronal damage

After injury to peripheral afferent axons — perhaps mimicking the injury that sometimes is produced by VZV reactivation — increased excitability is found in motor and sensory neurons. At the tips of the injured axons, sodium channels accumulate in excessive numbers. Also, after axonal injury, there is a change in the type of sodium channels, possibly due to the loss of access to neurotrophins. Axonal injury appears to result in upregulation of the previously silent gene for $Na_v1.3$. In numerous models of neuropathic pain, including PHN, there is up to a 30-fold upregulation of $Na_v1.3$ expression in adult DRG (Rogers 2006).

These changes subsequent to axonal injury dispose DRG neurons to spontaneous firing or firing at an abnormally high frequency. The increased density of sodium channels after axonal injury is associated with abnormal excitability of DRG neurons, owing to a lowering of the threshold (Waxman 1999).

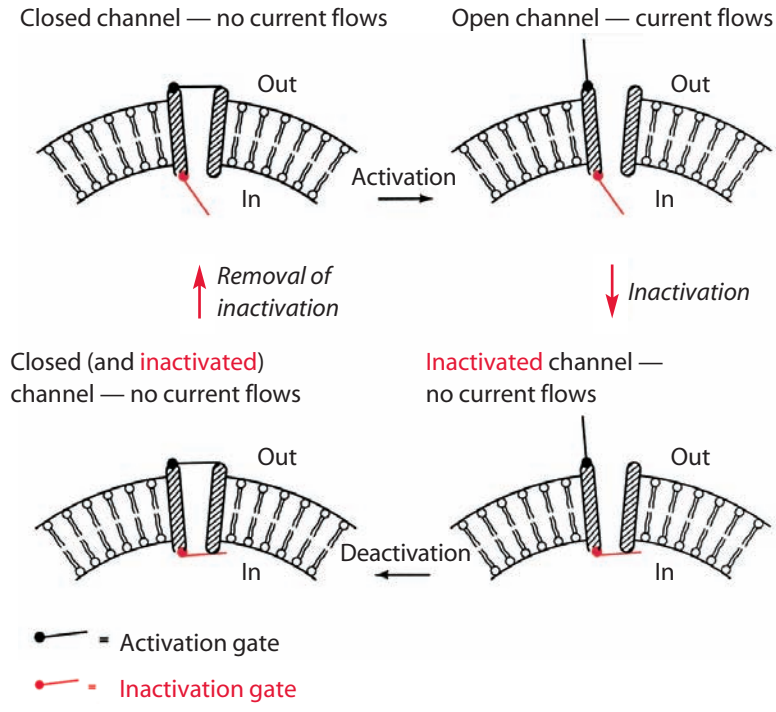
Topical treatment

Targeted peripheral analgesics

Local anesthetics are believed to modify axonal conduction by blocking voltage-gated sodium channels and by binding nonselectively to a site within the pore lining (Catterall 2006). This site is accessible only when the pore is open. When the sodium channel becomes inactivated, the anesthetic bonds more tightly, stabilizing the inactivated state. Because the currently available antagonists of voltage-gated sodium channels are not selective for a single isoform, local anesthetics have a narrow therapeutic index. Their potential to cause neurologic adverse effects and, to a lesser extent, cardiac adverse effects at high systemic concentrations (Catterall 2006), may limit their usefulness for PHN when used systemically.

Other commonly used analgesics for neuropathic pain, such as anticonvulsants, antidepressants, and opioids, work primarily by altering synaptic transmission, not axonal conduction. Gabapentin, for instance, works at the axon terminal by modulating calcium flux at the $\alpha 2\delta$ subunit of N-type calcium channels. Tricyclic antidepressants modulate neurotransmitter release, primarily that of norepinephrine and serotonin. An American Academy of Neurology consensus panel determined that these drugs can be effective in reducing PHN pain (Dubinsky 2004), but others have noted that in some cases

FIGURE 2
Operation of sodium channel



SOURCE: LEVITAN 1997

the effectiveness of these agents may be limited by their systemic side effects (Neurontin 2007, Leipzig 1999, Hempenstall 2005). The same AAN panel, on the basis of strong clinical evidence, found that topical lidocaine is effective in reducing the pain of postherpetic neuralgia (Dubinsky 2004).

If a local anesthetic is employed in the treatment of PHN, the formulation that may be most advantageous is what Argoff (2003) calls a "targeted peripheral analgesic," such as the lidocaine patch 5%. Targeted peripheral analgesics are topically administered agents that direct pharmacologic action at peripheral sites instead of central sites of pain generation, without causing clinically significant increases in serum drug levels. This characteristic gives them several advantages over systemic agents such as opiates, anticonvulsants, and antidepressants: 1) any adverse effects are generally mild and transient; 2) there is minimal systemic accumulation of the drug with regular use (Rowbotham 1996); 3) the risk of drug-drug interactions is minimal (Galer 1999); and 4) a targeted topical peripheral analgesic is easy to use because no titration is required.

The lidocaine patch 5% is believed to address both peripheral and central pain mechanisms involved in PHN (Figure 3) and to be a peripherally acting medication. It has been proposed that reducing the peripheral afferent impulses helps attenuate central sensitization (Endo 2007).

The lidocaine patch 5% is composed of an adhesive material containing the drug applied to a nonwoven polyester felt backing and covered with a polyethylene terephthalate film release liner, which is removed before application (Lidoderm 2006). The patch measures 10 cm x 14 cm, but can be cut with a scissors to fit the dimensions of the painful skin area prior to removal of the liner. Up to three patches may be applied for up to 12 hours within a 24-hour period, covering up to 420 cm^2 of sensitive skin. While being worn, the patch provides a sufficient amount of medication to produce an analgesic effect, but less than the amount needed to produce a complete sensory block (Lidoderm 2006). Further, the patch shields the skin from mechanical stimulation (Rowbotham 1996).

The lidocaine patch 5% should be applied only to intact skin. The reason for this precaution is that local anesthetics are absorbed rapidly into the circulation following application to denuded skin (or mucous membranes), which increases the risk of systemic effects (Cat-

FIGURE 3

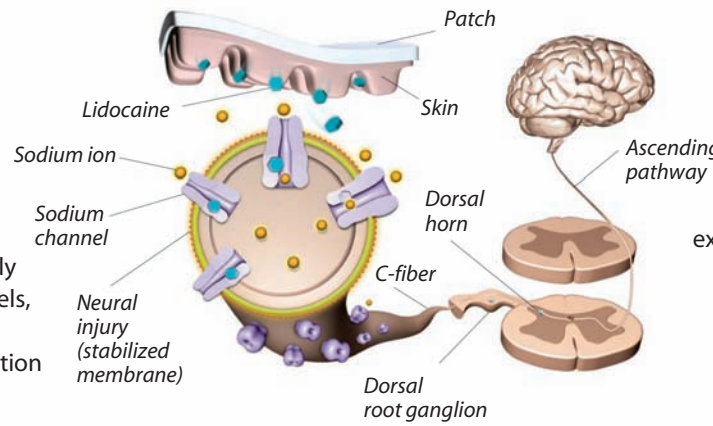
Theoretical representation of lidocaine patch 5% and its effect on PHN pain

Acting locally, lidocaine molecules bind to a site within the pore of voltage-gated sodium channels found in the plasma membrane of peripheral afferent neurons in the dermis, preventing the influx of sodium ions. The resulting blockade of abnormally firing sodium channels causes a reduction in peripheral afferent impulses, which is believed to help attenuate central sensitization in the dorsal horn. Note, however, that the exact mechanism of action of the lidocaine patch 5% is not known.

A targeted peripheral analgesic

1 Peripheral sodium channel blockade plays a primary role in mechanism-based treatment of PHN.

2 The mechanism of action depicted represents the lidocaine patch 5% acting locally in the dermis on abnormally firing sodium channels, which are primarily involved in the initiation and maintenance of PHN.



3 Reducing the peripheral afferent impulses helps attenuate central sensitization. This is an example of a drug, in this case lidocaine, having more than one site and mechanism of action.

SOURCE: ENDO 2007

Theoretical representation specific to the lidocaine patch 5% and its effect on PHN pain. The mechanism of action of the patch, however, is not known.

terall 2006). The risk of systemic absorption or toxicity, however, appears to be minimal. When used as directed, the lidocaine patch 5% presents a low risk of systemic adverse effects because approximately 3 percent of the applied dosed is absorbed. Care should be taken to avoid excessive dosing resulting from the application of the lidocaine patch 5% to larger areas or for longer than the recommended wearing time, as these actions could result in increased absorption of the drug and lead to serious adverse effects (Lidoderm 2006). Used patches or remaining unused portions of cut patches should be discarded immediately in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.

Clinical trials of lidocaine patch 5%

Results of clinical trials of the lidocaine patch 5% have been published. Although limited in number and conducted with small and sometimes selected populations, they demonstrate its efficacy and tolerability.

Patch versus placebo and observation. One randomized (2:1:1), double-blind, 4-way crossover trial (Rowbotham 1996) evaluated the efficacy and tolerability of the lidocaine patch 5% in patients with established allodynic PHN. In this trial, allodynic patients (N=35; 20 men, 15 women) had a mean age of 75 years (range, 50–90) and PHN with a mean duration of 48 months. Patients participated in four 12-hour sessions. During two sessions they received up to three lidocaine patches, during one session they received a placebo patch, and during another session they were observed without treatment. Subjects were permitted to use oral medications, including "as needed" analgesics for control of PHN pain, but were not allowed to start new oral medications during the study. A 100 mm visual analog scale (VAS) was used to assess pain intensity (0=no pain, 100=worst pain imaginable) and a 6-point scale to assess pain relief (0=worse, 1=no pain relief, 2=slight relief, 3=moderate relief, 4=a lot of relief, 5=complete relief). Patients indicated the change in pain relief after patch application at seven time points (30 minutes and 1, 2, 4, 6, 9, and 12 hours).

Compared with observation, lidocaine utilization was associated with a statistically significant reduction in pain at all time points versus observation (P=.0001 to P=.021); compared with placebo patch, the lidocaine patch was associated with a statistically significant reduction in pain at 4, 6, 9, and 12 hours (P<.001 to P=.038). In contrast, the placebo patch was associated with a statistically significant pain reduction in comparison with observation at only 2 and 6 hours. Limitations of this study included the short treatment duration and the small number of subjects.

Enriched enrollment study. The lidocaine patch 5% has been evaluated in a randomized, enriched enrollment, double-blind, placebo-controlled crossover study (Galer 1999). It was enriched in the sense that all subjects were known responders to the lidocaine patch 5%, having previously used the topical lidocaine patch for at least 1 month with success in a compassionate use protocol (mean duration of use of open-label lidocaine patch, 3.3 years). Subjects were enrolled and randomly assigned (1:1) to initial treatment with either the lidocaine patch or a placebo patch, and 32 subjects (18 men, 14 women) completed the protocol. Their mean age was 77.4 years (range, 62.1–96.6) and the mean duration of their PHN was 7.3 years (range, 0.7–24.9 years). Patients were permitted concomitant use of analgesics as needed for control of pain.

The first treatment phase lasted 2 to 14 days, based on the patient's pain relief as self-rated on the 6-point VAS scale. If, for any 2 consecutive days, a patient's score decreased by two or more categories from that which the patient had reported prior to the start of the study, the patient exited that phase and began using the other treatment, again for 2 to 14 days. During the use of either treatment, patients were instructed to use them exactly as they had during the compassionate use protocol.

The primary efficacy variable was median time to exit, (more than 14 days during lidocaine treatment versus 3.8 days during placebo treatment; P<.001). In addition, 91 percent of patients (29/32) reported moderate or greater pain relief with the lidocaine patch 5% versus 41 percent of patients (13/32) with the placebo patch. The treatment phase employing lidocaine was preferred by 78 percent (25/32) of subjects. Nine percent of patients during the lidocaine phase and 12 percent during the placebo phase used rescue medications. Twenty-eight percent (9/32) of patients during the lidocaine phase and 34 percent (11/32) during the placebo phase reported skin redness or rash.

A limitation of this study was the enrollment of only those patients who had prior positive experiences with the lidocaine patch 5%, making results inapplicable to the general population. Further, subjects in such studies may be able to distinguish the active drug from placebo on the basis of nontherapeutic features of the treatments. On the other hand, the study provides some evidence that long-term use of the lidocaine patch 5% is effective and well tolerated, given the subjects' open-label use of the patch for a mean duration of 3.3 years immediately prior to this study.

No systemic side effects or serious adverse events believed to be related to the study medication were reported in the trials described.

Conclusion

The pathophysiology of PHN is now better understood. In particular, there is a greater scientific understanding of the role of voltage-gated sodium channels.

The nerve damage associated with PHN is characterized by changes in the type and concentration of voltage-gated sodium channels in peripheral neurons, which is believed to result in their spontaneous firing or firing at an abnormally high frequency. In addition to populating neurons involved in PHN, voltage-gated sodium channels are distributed throughout the body, being found in the CNS, heart, and skeletal muscle.

Lidocaine is capable of blocking the sodium channels in peripheral neurons — and in all voltage-gated sodium channels at other sites; therefore, it must be used with care in the treatment of PHN to avoid systemic adverse effects. The lidocaine patch 5% provides a means for applying lidocaine to intact sensitive skin with negligible systemic effects, because only a small amount of lidocaine is absorbed through the skin. This also precludes significant drug-drug interactions. Because of these characteristics, especially the low risk of systemic side effects, the lidocaine patch 5% is suited to serve as first-line monotherapy or as an adjunctive treatment for PHN.

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Glossary

Aα-fibers — Thinly myelinated nerve fibers that transmit pain signals.

Aβ-fibers — Large-diameter, myelinated nerve fibers that normally respond to innocuous tactile stimuli. Can activate central nervous system (CNS) pain-signaling neurons once *central sensitization* has occurred.

Action potential — A nerve impulse, or spike in voltage, that travels along an *axon.*

Afferent nerves — Nerves containing fibers that transmit sensory signals from the periphery to the CNS.

Allodynia — Painful response from a stimulus that normally is innocuous.

Anion — Ion with a negative charge.

Autonomic nervous system — Regulates functions that occur without conscious control. Also known as the involuntary, vegetative, or visceral nervous system.

Axons — Thin tube-like structures that extend from the *soma* for distances of a few μm (within the CNS) to up to 1 m (extending from the CNS to the periphery). Axons also vary in diameter, from 1 μm to 1 mm.

C fibers — Small-diameter, unmyelinated nerve fibers that normally are silent but respond to potentially noxious stimuli. C fibers become sensitized after acute tissue injury or during persistent inflammation.

Cation — Ion with a positive charge.

Central sensitization — Enhanced response of *dorsal horn* neurons to *afferent* input. A normal physiological response of the nervous system to any tissue damage involving prolonged or massive input from *C fibers.*

Conduction — The passage of an impulse along an *axon.*

Deafferentation — Loss of the sensory input from a portion of the body, usually caused by the interruption of peripheral sensory fibers.

Dermatome — Area of skin served by a single sensory spinal or cranial nerve.

Dorsal horn — Site in gray matter of spinal cord where primary *nociceptive afferents* terminate.

Dorsal root ganglion — A nodule containing the cell bodies of *afferent* spinal neurons.

Dysesthesia — Intermittent occurrence of abnormal sensations that are unpleasant and sometimes described as pain.

Efferent nerves — Nerves containing fibers that transmit motor signals from the CNS to the periphery. Consists of the somatic (voluntary) nervous system that enables conscious control of skeletal muscles and the autonomic (involuntary) nervous system that transmits motor impulses to cardiac muscle, visceral smooth muscle, and glandular epithelium.

Hypalgesia — *Hyperalgesia.*

Hyperalgesia — Heightened sensitivity to stimuli that cause pain.

Hyperesthsia — Increased sensitivity to stimuli that normally are painless.

Hyperpathia — Exaggerated response to stimuli that are normally painful.

Hypesthesia — *Hypoesthesia.*

Hypoesthesia — Abnormally decreased sensitivity, especially to touch.

Lamina — Layers of the *dorsal horn.* Lamina I is the outermost, lamina VI the deepest.

Mechanoreceptor — Sensory cells (neurons) that respond to movement. The peripheral end of the mechanoreceptor is in or under the skin and its cell body is in the *dorsal root ganglion.*

Membrane potential — A voltage difference exhibited by neurons (and all other cells) across the plasma membrane.

Myelin — A protein-lipid complex formed by glial cells that serves as an insulator for some axons.

NMDA receptor — A class of glutamate receptor. So named because it is most effectively activated by the agonist NMDA (N-methyl-D-aspartic acid).

Nociceptive — Pertaining to pain receptors.

Nociceptor — Receptor for pain caused by tissue injury or noxious stimuli. Abundant in skin, viscera.

Parasympathetic nervous system — A division of the autonomic nervous system.

Paresthesia — An abnormal sensation, often in the absence of an external stimulus.

Pilomotor — Pertaining to nerves that induce contraction of the erector muscles that cause hairs in the skin.

Prodrome — Premonitory symptom(s) indicating the onset of a disease. Prodromal pain precedes onset of rash in most herpes zoster patients.

Proprioception — Unconscious perception of movement and spatial orientation.

Soma — Cell body of a neuron.

Sudomotor — Pertaining to nerves that stimulate sweat glands.

Sympathetic nervous system — A division of the autonomic nervous system.

Transduction — Conversion of a chemical signal into an electrical signal.

Transmission — The passage of an impulse across a junction.

Vasomotor — Pertaining to nerves that stimulate blood vessels to dilate or contract.

Visceromotor — Pertaining to nerves that regulate movements of the viscera.

Wind-up — Progressive buildup in the response of dorsal horn neurons to input from C-nociceptors as the result of prolonged application of noxious stimuli; precedes *central sensitization.*