HHS Public Access

Author manuscript

Infect Dis Clin North Am. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Infect Dis Clin North Am. 2017 December ; 31(4): 811–826. doi:10.1016/j.idc.2017.07.016.

Herpes zoster in the older adult

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Synopsis

Herpes Zoster (HZ) is the result of reactivation of latent varicella zoster virus (VZV) and occurs most frequently in older adults. Generally, HZ presents as a unilateral, self-limited dermatomal rash. Postherpetic neuralgia (PHN) is a common sequela; presenting as severe pain that persists after the rash has resolved. It occurs more commonly in older age and can be very debilitating. Management of HZ in the elderly requires a prompt diagnosis, treatment with antivirals, and adequate pain control. A longer- term pain management strategy is required if PHN occurs. A modestly effective vaccine exists and is recommended for older individuals.

Keywords

Older adults; shingles; zoster; postherpetic neuralgia; vaccination

Introduction

Primary infection with varicella zoster virus (VZV) causes chicken pox, a self-limited disease that is characterized by disseminated skins lesions and occurs mostly in childhood. Herpes Zoster (HZ) which is also known as shingles, is the result of reactivation of latent varicella zoster virus and occurs more frequently in older adults and immunocompromised individuals.

Epidemiology

The incidence of HZ has been on the rise over the past several decades. Some studies indicate more than a 4-fold increase since the 1940s affecting elderly people and women

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Disclosure statement:

AJ: None

DHC: Seqirus, Merck, Sanofi Pasteur: Grant investigator/recipient.

disproportionately.[1] This is occurring globally and appears to be independent of demographic shifts seen with a growing elderly population and increased prevalence of immunocompromised individuals.[1–3]

North American database studies indicate that this rise in incidence of HZ started even prior to the introduction of the varicella vaccine, debunking the theory that the increase was due to older individuals no longer having the immunologic boosting from periodic community exposure to children with chickenpox (Hope-Simpson hypothesis).[2, 4, 5]

The lifetime risk of HZ in the general population ranges from 20–30% but the risk increases dramatically after 50 years of age with a lifetime risk of HZ reaching 50% at age 85 years. Current estimates point to more than 1 million cases of HZ in the United States every year, costing the United States Healthcare system 5 billion USD annually.[6–8] HZ, originally not thought to occur more than once in an individual, is now estimated to recur in approximately 6.4% of immunocompetent people. The recurrence rate is higher among the immunocompromised population.[2, 6, 9, 10]

Pathogenesis

VZV is a double stranded DNA human neurotrophic alphaherpes virus. The primary infection or chickenpox, might be subclinical or present with fever and vesicular lesions. At this time, VZV establishes a latent state in dorsal root ganglia of peripheral neurons, cranial nerve ganglia and autonomic nerve ganglia along the entire neuroaxis through retrograde axonal transport from the cutaneous lesions or by hematogenous spread during the viremic phase.[7, 11] Months to years later, reactivation of VZV manifests clinically as HZ, with the spectrum of disease ranging from disseminated zoster to the more commonly seen typical dermatomal HZ.

During the period of latency, VZV downregulates gene expression and in turn the production of major histocompatibility complex I antigen on the surface of infected cells.[12] Reactivation occurs when VZV is able to overpower immune controls and spreads through the affected ganglions and nerves to reach the skin and manifest as HZ.[7, 12, 13]

Risk factors for reactivation of VZV include older age and immunocompromised status from such conditions as HIV-1 infection, lymphoma, leukemia, bone marrow transplant, solid organ transplant, and immunosuppressive medications. One mechanism of reactivation from these risk factors is decreased VZV-specific cell mediated immunity.[14] There are data associating depression with development of HZ. Weight loss and sleep disturbances were also found to be associated with risk of VZV recurrence independent of depression as a risk factor. Other risk factors include Caucasian race, female sex, physical trauma, diabetes mellitus and a prior history of HZ. Finally, a family history of HZ increases risk in a dose-dependent manner; the greater the number of relatives affected, particularly first-degree relatives, the higher the risk of HZ for an individual in that family.[5, 6, 15]

Clinical Features

Classically, reactivation of VZV presents as a unilateral dermatomal rash (*i.e.*, does not cross the midline) which is initially maculopapular on an erythematous base, evolves into vesicular-pustular appearance which after 7–10 days begins to crust over and heals within 2–4 weeks. It can either be limited to a single dermatome or occur over adjacent dermatomes depending on the distribution of the sensory ganglia where reactivation occurs.[16] In older adults, the rash may have an atypical appearance and may be limited to a small patch within the dermatome, or have a maculopapular appearance without evolving into vesicles.[6] The onset of the rash is often preceded by neuropathic pain (aching, burning, lancinating) over the involved dermatome(s). This prodromal phase can result in a diagnostic dilemma for the physician as it may mimic other painful conditions in older adults such as migraine headaches, trigeminal neuralgia, myocardial infarction, biliary or renal colic, appendicitis, lumbosacral pain or muscle strain.

The presence of very sensitive skin could clue the physician that this is HZ. This prodromal phase may be associated with systemic symptoms of fever, fatigue, headache, malaise and photophobia. In some cases, the prodromal phase is not followed by the development of rash; this is termed zoster sine herpete.[16, 17]

Between 2.5 and 20% of people with HZ present as herpes zoster ophthalmicus (HZO) which occurs when the VZV reactivation involves the ophthalmic branch of the trigeminal nerve.[18, 19] Since the cranial nerve V1 also innervates the skin over the nose, the presence of a cutaneous lesion at the tip of the nose, referred to as Hutchinson sign, is highly predictive of ocular involvement.[7] Eye manifestations include periorbital cutaneous lesions, conjunctival injection and chemosis, keratitis, corneal ulceration, uveitis, scleritis, episcleritis, glaucoma, retinal necrosis and optic neuritis. Keratitis remains the most commonly seen complication. Acute retinal necrosis (ARN), however, is associated with greater morbidity and occurs in both immunocompetent and immunocompromised hosts. This is a full thickness patchy rapid necrosis of the retina presenting with periorbital pain, floaters, and almost always permanent peripheral vision loss. In the immunocompromised host, progressive outer retinal necrosis (PORN) occurs and, though similar to ARN, often presents as sudden onset of painless vision loss, floaters, and constricted visual fields with retinal detachment. This may be preceded by zoster ophthalmicus, retrobulbar neuritis, aseptic meningitis and/or central retinal artery occlusion. PORN may present concurrently with VZV vasculopathy, which is discussed in greater detail below[7, 19]

HZ may manifest as cranial neuritis, with an array of clinical presentations depending on the cranial nerve affected. HZ neuritis involving cranial nerves III, IV and VI may present with ophthalmoplegia and/or ptosis; involvement of branches V2 and V3 of the trigeminal nerve may rarely present with osteonecrosis and spontaneous tooth loss. Ramsey-Hunt syndrome describes involvement of cranial nerve VII, which presents as an ipsilateral facial palsy with lesions in the external auditory meatus and tympanic membrane or on the ipsilateral anterior two-thirds of the tongue and hard palate. Involvement of cranial nerve VIII may occur simultaneously, with symptoms of nausea, vomiting, hearing loss, tinnitus, vertigo and nystagmus.[7, 13] HZ of cranial nerves XI, X and IX presents as odynophagia, dysphagia,

hoarseness, dysgeusia, hemilaryngeal or hemipharyngeal paresis.[20] HZ involving the cervical or lumbar nerve roots may result in radiculopathy. Rarely cervical zoster may result in diaphragmatic weakness and thoracic zoster can result in abdominal wall weakness and herniation.[7]

VZV myelitis, which is characterized by paresis of the extremities, bowel and/or bladder incontinence and sensory deficits, has two types of clinical presentation. In immunocompetent hosts it is usually self- limited and occurs days to weeks after acute varicella or zoster. In the immunocompromised host, VZV myelitis is more likely have a poor outcome associated with disability and even death.[7, 13]

VZV recurrence can also present as encephalitis and meningitis. Patients usually present with altered mental status and focal neurological deficits. Seizures are rarely seen and a third of patients may not have a rash. Even with effective treatment, the mortality rate ranges from 9–20% and survivors might be left with residual deficits such as slowing of cognitive processes, memory loss and emotional disturbances.[13]

There are also instances of VZV recurrence affecting viscera resulting in pancreatitis, hepatitis, and gastritis. Visceral zoster is thought to be due to reactivation in dorsal root and/or autonomic ganglia followed by transaxonal spread via post ganglionic fibers to the organ being supplied. It should be considered in persons with current or recent cutaneous zoster if their clinical or laboratory parameters suggest internal organ involvement and PCR in blood, histologic or culture data supports the presence of VZV.[11, 21–24]

Disseminated HZ is defined as the presence of 20 or more vesicles outside the area of the primary and adjacent dermatomes or the involvement of 3 or more dermatomes. Both disseminated and visceral zoster are more common in immunocompromised individuals, however there have been case reports of visceral VZV in the immunocompetent host as well.[22]

Post-zoster sequelae

One of the hallmarks of HZ is that following resolution of the vesicular rash, individuals may experience additional sequelae. For older adults in particular, these may have adverse effects on functional status, independence, and quality of life. The post-zoster sequelae are discussed below.

Postherpetic neuralgia (PHN)

A consensus definition for PHN is still to be determined, as definitions to date have been arbitrary ranging from 1 month to 6 months after rash onset. The conventional definition is ‘pain continuing 90 days past the diagnosis of HZ or rash onset’.[25] Due to this lack of a consensus definition and the varying age ranges of the populations being studied, the incidence of PHN after HZ ranges from 5–30% and occurs in 50% of HZ affected individuals greater than 85 years.[2, 3, 5, 26–28] It is considered the most debilitating sequelae of HZ since it impairs the affected individual’s quality of life across all 4 health domains: physical, psychological, functional and social.[27]

Risk factors for the development of PHN include prodromal symptoms, severity of pain and rash extent, older age, immunosuppression, diabetes and presence of zoster ophthalmicus. While PHN gradually resolves in most older adults, there is a subset of patients who are refractory to pain management and in whom the pain lingers or even continues to worsen over time. Some might have a temporary cessation of pain only to have it return weeks to months later.[29, 30]

The pain might be constant, intermittent or stimulus driven. Some describe it as burning, throbbing, stabbing, shooting. The most debilitating is allodynia which occurs when normal tactile experiences (clothes, wind *etc.*) cause severe pain. Besides suffering from the various subtypes of pain, the person may also develop anxiety, depression, weight loss, sleep disturbances, social isolation and have difficulty with their activities of daily living. The Zoster Brief Pain Inventory is a useful tool in the evaluation of PHN.[12, 31]

Secondary bacterial infection

This needs to be suspected if there is no resolution of clinical symptoms within 1–2 weeks and the rash appears to worsen. Secondary bacterial infection is often due to Staphylococcal or Streptococcal infection and if not diagnosed early can rarely lead to septicemia.[16, 32] In HZO, this may present with yellowish drainage and crusting from the eye.[33]

Other dermatologic complications

A wide range of benign and malignant lesions rarely can develop months to years later at the site of previous cutaneous HZ. These include post-zoster granulomatous dermatitis, granulomatous vasculitis, atypical lymphoid proliferation, dermatophytosis, lymphoplasmacytoid lymphoma, T-cell lymphoma, leukemia cutis, Kaposi sarcoma, and pseudolymphoma.[34]

Residual neurological manifestations of VZV

Neurologic signs and symptoms can present during the active phase of the VZV primary infection (chickenpox) or reactivation disease (HZ) and as chronic residual deficits following an episode of VZV encephalitis or meningitis. CNS manifestations of HZ in adults can result in outcomes ranging from complete recovery to deficits such as loss of memory, impaired executive functioning, learning difficulties with severe disability, and death. Transverse myelitis can occur either during the acute infection or as post-infectious sequelae. Mortality from transverse myelitis is reported at 23% and almost always occurs in the immunocompromised host. HZ can also result in polyneuropathy and in Guillian-Barre Syndrome.[13]

VZV Vasculopathy

Population studies indicate that for 3–12 months following an episode of HZ, individuals older than 50 years are at higher risk for stroke or myocardial infarction compared to the general population, even after adjusting for other variables. The presence of VZV in intracerebral and coronary arteries of these patients in post mortem studies provides histological support for this finding.[11, 13, 35, 36] Vasculopathy results from the transaxonal migration of reactivated VZV to the adventia of arteries where infection is established,

followed by transmural migration to the media and intima and vascular remodeling.[37] The presence of VZV in the arteries, in conjunction with the increased inflammatory response seen in infected individuals might result in disruption of atherosclerotic plaques.[7, 38] In some instances, VZV vasculopathy may result in cardiac dysfunction without any concomitant neurological manifestation.[11]

Manifestations of VZV CNS vasculopathy range from transient ischemic attacks, stroke (ischemic or hemorrhagic), aneurysm, subarachnoid and intracerebral hemorrhage, spinal cord infarction, cerebral venous sinus thrombosis, vision loss, giant cell temporal arteritis, or other focal neurological deficits depending on the location of the infarction.[7, 13] The mortality rate of untreated VZV CNS vasculopathy approaches 25%; treatment with antivirals may be curative.[7, 35, 39] It is difficult to assess the incidence of stroke secondary to VZV vasculopathy since in most elderly patients, it is presumed to be due to atherosclerotic disease and CSF is not routinely analyzed.[13]

Diagnosis

In most patients, the history and classic dermatomal appearance of the rash permits a clinical diagnosis of HZ. Laboratory based diagnostic tools can be used for confirmation in patients with atypical clinical presentations for HZ.[40] Of all clinical specimens, the yield from early vesicular lesions is the greatest.[12, 41] If vesicular fluid cannot be obtained, other acceptable alternatives include lesion scrapings, crusts, tissue biopsy, saliva, cerebrospinal fluid(CSF) and blood.[6, 12]

VZV DNA PCR has the highest sensitivity and specificity and has become the gold standard for diagnosis. The RT-PCR assay used in the Shingles Prevention Study detected as few as 7 copies of the VZV-Wild Type or the VZV-Oka genome and had a sensitivity close to 100%.[42] Quantitative PCR is available in most commercial laboratories and provides a rapid and timely diagnostic test. A positive PCR in CSF is indicative of CNS HZ. A positive salivary VZV DNA PCR supports the diagnosis of enteric zoster.[43] Positive VZV DNA PCR from blood or from oropharyngeal samples is useful when patient has an atypical presentation and/or has zoster sine herpete.[44]

VZV culture is very specific but the result might take 1–2 weeks. Also, the sensitivity ranges from 30–75%.[40, 45] Serological tests may show a rise in antibody titers against VZV during an episode of HZ but it is not a sensitive or specific diagnostic method. Commercial ELISA tests for detection of VZV-specific serum antibody have a sensitivity of 66–97% and specificity of 82–99%.[45, 46]

For patients with potential neurological involvement, serologic studies of CSF may improve diagnostic accuracy. In active CNS HZ, CSF studies show elevated protein level with positive VZV DNA PCR and/or anti-VZV IgG. In VZV CNS vasculopathy, definitive diagnosis depends on detection of anti-VZV IgG in CSF, since VZV DNA PCR from CSF is often negative. A low serum/CSF ratio of anti-VZV IgG can also be supportive of ongoing CNS VZV infection and CNS vasculopathy.[13, 39] Presence of MRI or CT showing evidence

of infarction along with supporting CSF studies is essential for a diagnosis of VZV CNS vasculopathy.[45]

The Tzanck smear was one of the earliest diagnostic tools for VZV. Developed by a French dermatologist in 1947, it involves deroofing the vesicle, scraping the base with a sterile blade, and smearing the material onto a clean glass slide. The specimen is then air dried, fixed with methanol, stained with either methylene blue, Giemsa or Wright's stain, and examined for presence of multinucleated giant cells and intranuclear inclusions which might indicate the presence of VZV. However, these cannot be differentiated from herpes simplex virus (HSV).[47] The modified Tzanck technique allows for the staining of the smear with fluorescein conjugated monoclonal antibodies to differentiate between VZV and HSV. Antigen detection via immunofluorescence has almost entirely been replaced by PCR.[45]

Treatment

Treatment can be broken down into treatment of the virus with antivirals and treatment of the sequelae of infection with other agents. Table 1 lists the various classes of agents used to treat HZ and PHN that are discussed below.

Antiviral agents

Antiviral therapy for acute HZ [48] is indicated in patients fulfilling any of these criteria (1) age greater than 50 years (2) with moderate to severe rash or pain (3) those with non-truncal involvement and (4) immunocompromised patients.[40] Antivirals initiated within 72 hours of rash onset decrease the duration of viral shedding, new lesion formation, and the severity and duration of acute pain. Experts recommend initiating antiviral therapy more than 72 hours after rash onset if there is evidence of new lesion formation, or when there are motor, neurological or ocular complications.[6, 40] Hospitalization for closer monitoring and treatment with intravenous acyclovir should be considered in (1) allogenic stem cell transplant recipients; especially those within the first 4 months of transplant, (2) hematopoietic stem cell transplant recipients with moderate-severe graft-versus-host-disease, (3) transplant recipients on aggressive anti-rejection therapy (4) , any individual with suspected visceral dissemination (encephalitis/ pneumonitis)and (5) individuals with HZO or VZV retinitis.[13, 40, 45]

Also, closer monitoring for disease progression and response to therapy should be considered for frail elderly individuals since they have markedly diminished physiologic reserves to deal with stressors, and may be non-compliant with the prescribed oral therapy due to a combination of fatigue, pain, confusion, poor appetite and overall functional decline associated with the acute disease process.[16, 40]

Acyclovir, famciclovir and valacyclovir are guanosine analogs that are phosphorylated by viral thymidine kinase to a triphosphate form that inhibits VZV DNA polymerase. In head to head comparisons there is no difference among acyclovir, famciclovir and valacyclovir in treatment end points. They also have a similar side effect profile, however ease of dosing, bioavailability and cost need to be factored in when choosing an agent.[40] Valacyclovir has

greater oral bioavailability (around 55%) when compared to acyclovir (10–20%) and is more convenient to dose.[13]

Cases of acyclovir-resistant VZV have been reported in the immunocompromised host, so the possibility of resistance should be considered if the HZ lesions appear to be atypical in nature and are not showing response in spite of adequate antiviral therapy. If resistance is suspected, testing for mutations in thymidine kinase gene can be sent and the patient switched to intravenous foscarnet or cidofovir.[40]

Corticosteroids

Corticosteroids improve the pain associated with acute HZ and can be used for this purpose after consideration is given to relative contraindications such as hypertension, diabetes mellitus, glaucoma, osteoporosis, peptic ulcer disease.[40] However, a meta-analysis indicated that corticosteroids given during acute HZ neither reduce the incidence of PHN following an episode of HZ nor reduce the duration of PHN.[49] Some clinicians use steroids in cases of VZV-induced facial paralysis and cranial polyneuritis to decrease inflammation and swelling and reduce risk of residual peripheral nerve damage, a practice supported by minimal data.[50–52] If used, steroids should always be used in conjunction with antivirals.[6] Intrathecal methylprednisolone was effective in reducing the pain of PHN, however, because of the invasive nature and possible risk of arachnoiditis, it should be considered only after other less invasive options have failed.[53] Methylprednisolone is not approved for intrathecal administration by the US Food and Drug Administration (FDA) and preservative-free methylprednisolone is not currently available in the United States.

Analgesics

Mild pain of HZ can be treated with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDS). Acetaminophen and NSAIDS are unlikely to provide pain relief in PHN although they are first line agents for pain control in acute HZ. Severe pain of acute HZ might benefit from opioid analgesics. Opioids while used for PHN are not approved by the FDA for this indication, and at present are considered third line agents for symptom relief in PHN along with tramadol.[6, 31] For more severe acute HZ consider initiating control with short acting opioid agents. Once an effective dose is achieved then switch to a long acting opioid agent for more consistent pain relief and dosing convenience. A provision for short acting agents for breakthrough pain should be in place alongside the long acting agents. Tramadol is an alternative agent that is a weak μ-opioid antagonist which can be used in the treatment of PHN and HZ. However, it is associated with an increased seizure risk and needs to be avoided in those with history of seizures and in people who are on medication that lowers their seizure threshold. It also can cause serotonin syndrome in patients on selective serotonin reuptake inhibitor antidepressants.[6, 40]

Tricyclic antidepressants (TCAs)

TCAs have a role in pain control in both acute HZ and PHN.[24] While several studies indicate that amitriptyline significantly reduces the pain of PHN, nortriptyline and desipramine are preferred due to their better anticholinergic side effect.[6] Prior to initiation of therapy with TCAs, an electrocardiogram can screen for prolonged QTc interval .[40] There

are some data to suggest that those unable to tolerate the side effects of TCAs could use the selective serotonin and norepinephrine reuptake inhibitor antidepressants such as venlafaxine and duloxetine for management of pain and depression that is associated with chronic PHN.[40, 54]

Gabapentin/Pregabalin

Classified as anticonvulsants, gabapentin and pregabalin have a role in neuropathic pain relief in both acute HZ and PHN.[40] If acute HZ pain persists even after treatment with antivirals, analgesics and corticosteroids, gabapentin or pregabalin may help. In PHN, gabapentin or pregabalin is preferred to the use of TCAs or opioids, especially in the elderly. Administering these medications in the evening may reduce some of the side effects including somnolence, dizziness, ataxia. The dose can subsequently be increased in frequency and/or amount to achieve pain control. There is the possibility that increasing doses of gabapentin or pregabalin may lead to cognitive impairment among the frail elderly and in this situation it is advisable to discontinue the medication.[6] There is currently a randomized placebo controlled trial to evaluate the effectiveness of gabapentin in the prevention of PHN.[27]

Topical therapy

Topical lidocaine is one of the best tolerated options for pain control in PHN. It is easily administered and has minimal systemic absorption. Up to 3 patches can be applied locally over a 12-hour period.[6, 31] There are few studies on the use of topical lidocaine in the treatment of acute pain of HZ, primarily because of concerns of further local damage to the area with the rash and risk of increased systemic toxicity. A randomized controlled trial has shown that the lidocaine patch can provide significant pain relief in acute HZ but care should to taken to ensure that it is applied only to the area of intact skin.[24, 55] Topical capsaicin is an effective backup alternative in the treatment of PHN.[31] Unfortunately, most patients find the burning sensation from capsaicin intolerable so it is not recommended for acute pain from HZ.[45]

Regional or local anesthetic nerve blocks

A meta-analysis by the International Association for the Study of Pain (IASP) and the Special Interest Group on Neuropathic Pain (NeuPSIG) gave a weak recommendation to use for epidural or paravertebral local anesthetic and steroid nerve blocks as a symptomatic treatment for relief of acute pain associated with HZ.[56] The absence of rigorous randomized controlled trials in the area of interventional management of neuropathic pain associated with HZ and PHN make it difficult to provide a strong evidence-based recommendation. When used to treat PHN, very few elderly patients achieved sustained pain relief. [6, 56] Accordingly, nerve blocks tend to be used only when acute HZ pain is not relieved in spite of the use of antivirals, oral analgesics, steroids and all adjuvant agents mentioned above.

Herpes zoster ophthalmicus therapy

When HZO is suspected, ophthalmology should be involved in the care of the patient. The standard duration of treatment with antivirals remains 7–10 days, however in elderly patients

VZV DNA persists on the cornea for up to 30 days. Accordingly, older adults and immunocompromised hosts may need a longer course of treatment although there are no clinical trials done in this regard.[19] If corneal involvement is noted, artificial tears may improve lubrication and erythromycin ointment may prevent secondary infection. Topical steroids must be used judiciously and only in consultation with an ophthalmologist. While they have utility in management of stromal keratitis, uveitis, scleritis/episcleritis, imprudent use of topical steroids can worsen corneal disease and result in corneal ulceration and perforation.[19]

Prevention

HZ with vesicular lesions can be contagious leading to chickenpox in the seronegative, non-immune persons via direct contact as well as airborne and droplet nuclei. The risk for transmission is greatest when the lesions are still in the maculopapular/vesicular phase and disappears once they have crusted over.[6] Covering the lesions until they have crusted over can be a primary prevention measure to non- immune or immunocompromised contacts.

Currently, there is one commercially available live attenuated vaccine (Zostavax®, Merck) for the prevention of shingles. It is the same strain as the vaccine used for primary prevention of chickenpox but at a 14 times higher dose.[13] In large study of persons over age 60, the live attenuated zoster vaccine reduced the incidence of HZ by 51% and PHN by 66%.[57] Since 2008, the United States Advisory Committee on Immunization Practices (ACIP) recommends Zostavax for immunocompetent people older than 60 years. The FDA initially approved the vaccine for those older than 60 years and later licensed it to include those aged 50 and older.[1, 5, 58] Longitudinal studies of older adults indicate that 7–10 years after the vaccine is administered, its efficacy declines to 21% for the prevention of HZ, 35% for the prevention of PHN and 37% for HZ Burden of Illness. This had led to concerns that if given to early that individuals may not be protected at the age when the incidence of HZ is the highest.[58, 59] A booster dose given 10 years after the first dose of Zostavax enhanced VZV-specific cell mediated immunity.[58, 60] There is currently however no recommendation to boost the vaccine. Perhaps there will be a future recommendation after obtaining more data about the timing and potential benefits of boosting.

There has been a poor uptake of this vaccine, with only 24% of US adults older than 60 years having had Zostavax in 2013.[13, 57, 59, 61, 62] Although the proportion of population vaccinated for HZ has increased from 2007, it is still below the goal of 30% of the target population from Healthy People 2020. Females, those above 65 years, and non-Hispanic whites were all more likely to be vaccinated for HZ.[63] Also the chances of being vaccinated were directly proportional to the frequency of outpatient hospital/ physician/pharmacy visits and inversely proportional to the number of emergency room and/or inpatient visits. Costs of the vaccine and reimbursement remains one of the top barriers in the uptake of this vaccine.[58, 63]

Current developments

The herpes zoster subunit vaccine (HZ/su) is under review at the FDA for potential licensure after finishing two large phase 3 trials. It contains recombinant VZV glycoprotein E and liposome based $AS01_B$ adjuvant. The vaccine is a 2-dose series with a booster at 2 months after the primary dose. It was studied in a double blinded randomized placebo-controlled trial in adults above the age of 70 years in 18 different countries. Unlike the currently available live attenuated vaccine, the efficacy of the HZ/su vaccine was 97% for HZ and 89% for PHN, and it was similar across all age groups showing no significant decline in protection in those aged 70 and above.[64–66] There are no data available yet for this vaccine on longer term protection beyond the 3.7-year analysis in those studies. The subunit vaccine is also immunogenic and safe in people that have had a previous episode of HZ.[67]

The subunit vaccine is also showing considerable promise in immunocompromised populations such as HIV-infected individuals and adults following autologous hematopoietic stem-cell transplant. Prior to the era of highly active antiretroviral therapy (HAART), HIV-infected people were 10–20 times more likely to develop HZ than aged matched HIV-uninfected cohorts, and even after the introduction of HAART they continued to be 3–4 times more likely to develop HZ.[68–70] In 2013, an estimated 6% of all individuals diagnosed with HIV were older than 65 years, and this number is expected to increase in the future.[71] There are limited data that giving Zostavax to virologically suppressed HIV-infected persons with CD4>200/μL is safe but it is still contraindicated in those with CD4<200/μL.[72, 73] The HZ/su vaccine has been studied in a phase 1/2, randomized, placebo-controlled study and found to be immunogenic with an acceptable safety profile when given as 3 doses of HZ/su vaccine at months 0, 2, and 6 to three separate cohorts of HIV-infected individuals with varying CD4 counts (50-199 while on HAART, >200 while on HAART, >500 but HAART naive). The third dose did not produce any considerable benefit in terms of humoral or cell mediated immunity.[70]

Similarly, hematopoietic stem cell transplant recipients are at increased risk for developing HZ especially in the first year post-transplantation when the rates are at 15–30%. At present, patients are placed on prophylaxis with acyclovir or a similar antiviral, however there are no clear guidelines on dose and duration of therapy. The HZ/su vaccine has been studied in a phase 1/2, randomized, observer-blind, placebo-controlled study in this population of adults with conditions ranging from with multiple myeloma, non-Hodgkin lymphoma (B- or T-cell), Hodgkin lymphoma, or acute myeloid leukemia who had undergone autologous hematopoietic stem-cell transplant 50 to 70 days prior. The study involved 2 different formulations of the HZ/su delivered in 2 different schedules. They were found to be comparable in terms of immunogenicity and safety profile. Again in those group receiving 3 doses of the vaccine instead of 2, the additional increase in immunity after the third dose was minimal.[74] A phase 3 trial is ongoing evaluating the safety and immunogenicity of HZ/su in adults with hematologic malignancies (ClinicalTrials.gov Identifier: NCT01767467). Understanding the safety and efficacy of this vaccine in oncology patients would be imperative before the vaccine would be used in oncology patients.

Valnivudine hydrochloride (FV-100) is a novel nucleoside analog now in phase 3 trials that compare it to valacyclovir. The primary endpoint is PHN incidence following 7 days treatment with valnivudine versus valacyclovir (NCT02412917).[75] In phase 2 trials, while it showed no significant difference when compared to valacyclovir with relation to disease severity at 30 days, it did show decreased burden of illness with a decreased incidence and severity of PHN at 90 days.[26, 75] Other novel nucleoside analogs in development include valomaciclovir stearate (EPB-348), N-methanocarbathymidine (N-MCT, NN-001), as well as non-nucleoside helicase-primase inhibitor amenamevir (ASP2151, M5220).[75]

References

1. Kawai K, Yawn BP, Wollan P, Harpaz R. Increasing Incidence of Herpes Zoster Over a 60-year Period From a Population-based Study. Clinical infectious diseases. 2016; 63(2):221–226. [PubMed: 27161774]
2. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open. 2014; 4(6):e004833.
3. Friesen KJ, Chateau D, Falk J, Alessi-Severini S, Bugden S. Cost of shingles: population based burden of disease analysis of herpes zoster and postherpetic neuralgia. BMC infectious diseases. 2017; 17(1):69. [PubMed: 28086817]
4. Hales CMHR, Joesoef MR, Bialek SR. Examination of Links Between Herpes Zoster Incidence and Childhood Varicella Vaccination. Ann Intern Med. 2013 Dec 3; 159(11):739–45. [PubMed: 24297190]
5. Marra F, Chong M, Najafzadeh M. Increasing incidence associated with herpes zoster infection in British Columbia, Canada. BMC infectious diseases. 2016; 16(1):589. [PubMed: 27765026]
6. Schmader K. Herpes Zoster. Clin Geriatr Med. 2016; 32(3):539–553. [PubMed: 27394022]
7. Mueller NH, Gilden DH, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus infection: clinical features, molecular pathogenesis of disease, and latency. Neurol Clin. 2008; 26(3):675–697. viii. [PubMed: 18657721]
8. McLaughlin JM, McGinnis JJ, Tan L, Mercatante A, Fortuna J. Estimated Human and Economic Burden of Four Major Adult Vaccine-Preventable Diseases in the United States, 2013. J Prim Prev. 2015; 36(4):259–273. [PubMed: 26032932]
9. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. Herpes zoster recurrences more frequent than previously reported. Mayo Clinic proceedings. 2011; 86(2):88–93. [PubMed: 21220354]
10. Shiraki K, Toyama N, Daikoku T, Yajima M, Miyazaki Dermatologist S. Herpes Zoster and Recurrent Herpes Zoster. Open Forum Infect Dis. 2017; 4(1) ofx007.
11. Nagel MA, Lenggenhager D, White T, et al. Disseminated VZV infection and asymptomatic VZV vasculopathy after steroid abuse. J Clin Virol. 2015; 66:72–75. [PubMed: 25866342]
12. Schmader K. Herpes zoster in older adults. Clinical infectious diseases. 2001; 32(10):1481–1486. [PubMed: 11317250]
13. Grahn A, Studahl M. Varicella-zoster virus infections of the central nervous system - Prognosis, diagnostics and treatment. J Infect. 2015; 71(3):281–293. [PubMed: 26073188]
14. Yawn BP GD. The global epidemiology of herpes zoster. 2013
15. Marin M, Harpaz R, Zhang J, Wollan PC, Bialek SR, Yawn BP. Risk Factors for Herpes Zoster Among Adults. Open Forum Infect Dis. 2016; 3(3) ofw119.
16. Sengupta S. Cutaneous herpes zoster. Curr Infect Dis Rep. 2013; 15(5):432–439. [PubMed: 23901015]
17. Wareham DW, Breuer J. Herpes zoster. BMJ. 2007; 334(7605):1211–1215. [PubMed: 17556477]
18. Yawn BP, Wollan PC, St Sauver JL, Butterfield LC. Herpes zoster eye complications: rates and trends. Mayo Clinic proceedings. 2013; 88(6):562–570. [PubMed: 23664666]
19. Vrcek I, Choudhury E, Durairaj V. Herpes Zoster Ophthalmicus: A Review for the Internist. Am J Med. 2017; 130(1):21–26. [PubMed: 27644149]

20. Nisa L, Landis BN, Giger R, Leuchter I. Pharyngolaryngeal involvement by varicella-zoster virus. J Voice. 2013; 27(5):636–641. [PubMed: 23769009]
21. Wang Z, Ye J, Han YH. Acute pancreatitis associated with herpes zoster: case report and literature review. World J Gastroenterol. 2014; 20(47):18053–18056. [PubMed: 25548507]
22. Bookhout C, Moylan V, Thorne LB. Two fatal herpesvirus cases: Treatable but easily missed diagnoses. IDCases. 2016; 6:65–67. [PubMed: 27747159]
23. de Jong MD, Weel JFL, van Oers MHJ, Boom R, Dillen PMEW-v. Molecular diagnosis of visceral herpes zoster. The Lancet. 2001; 357(9274):2101–2102.
24. Cohen JI. Clinical practice: Herpes zoster. N Engl J Med. 2013; 369(3):255–263. [PubMed: 23863052]
25. Watson P. Postherpetic neuralgia. American family physician. 2011; 84(6):690–692. [PubMed: 21916395]
26. Tyring SK, Lee P, Hill GT Jr, et al. FV-100 versus valacyclovir for the prevention of post-herpetic neuralgia and the treatment of acute herpes zoster-associated pain: A randomized-controlled trial. J Med Virol. 2016
27. Rullan M, Bulilete O, Leiva A, et al. Efficacy of gabapentin for prevention of postherpetic neuralgia: study protocol for a randomized controlled clinical trial. Trials. 2017; 18(1):24. [PubMed: 28088231]
28. Gater A, Uhart M, McCool R, Preaud E. The humanistic, economic and societal burden of herpes zoster in Europe: a critical review. BMC Public Health. 2015; 15:193. [PubMed: 25880058]
29. Watson CP, Watt VR, Chipman M, Birkett N, Evans RJ. The prognosis with postherpetic neuralgia. Pain. 1991; 46(2):195–199. [PubMed: 1749643]
30. Kost RG, Straus SE. Postherpetic Neuralgia — Pathogenesis, Treatment, and Prevention. New England Journal of Medicine. 1996; 335(1):32–42. [PubMed: 8637540]
31. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. N Engl J Med. 2014; 371(16): 1526–1533. [PubMed: 25317872]
32. Woznowski M, Quack I, Bolke E, et al. Fulminant staphylococcus lugdunensis septicaemia following a pelvic varicella-zoster virus infection in an immune-deficient patient: a case report. European journal of medical research. 2010; 15(9):410–414. [PubMed: 20952351]
33. Saad Shaikh MD, Christopher N, Ta MD. Evaluation and Management of Herpes Zoster Ophthalmicus. American Famly Physician. 2002; 66(9):1723–1730.
34. Ferenczi K, Rosenberg AS, McCalmont TH, Kwon EJ, Elenitsas R, Somach SC. Herpes zoster granulomatous dermatitis: histopathologic findings in a case series. J Cutan Pathol. 2015; 42(10): 739–745. [PubMed: 25970643]
35. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. Clinical infectious diseases. 2014; 58(11):1497–1503. [PubMed: 24700656]
36. Breuer JPM, Gautier A, Brown MM. Herpes zoster as a risk factor for stroke and TIA. Neurology. 2014 Jul 8; 83(2):e27–33. [PubMed: 25002574]
37. Nagel M, Gilden D. Editorial commentary: varicella zoster virus infection: generally benign in kids, bad in grown-ups. Clinical infectious diseases. 2014; 58(11):1504–1506. [PubMed: 24700655]
38. Yawn BP, Wollan PC, Nagel MA, Gilden D. Risk of Stroke and Myocardial Infarction After Herpes Zoster in Older Adults in a US Community Population. Mayo Clinic proceedings. 2016; 91(1):33–44. [PubMed: 26704438]
39. Nagel MA, Gilden D. The relationship between herpes zoster and stroke. Curr Neurol Neurosci Rep. 2015; 15(4):16. [PubMed: 25712420]
40. Dworkin RHJR, Breuer J, Gnann JW, Levin MJ, Backonja M, Betts RF, Gershon AA, Haanpaa ML, McKendrick MW, Nurmikko TJ, Oaklander AL, Oxman MN, Pavan-Langston D, Petersen KL, Rowbotham MC, Schmader KE, Stacey BR, Tyring SK, van Wijck AJ, Wallace MS, Wassilew SW, Whitley RJ. Recommendations for the management of herpes zoster. Clinical infectious diseases. 2007; 1(44 Suppl 1):S1–26.
41. Wilson DA, Yen-Lieberman B, Schindler S, Asamoto K, Schold JD, Procop GW. Should varicella-zoster virus culture be eliminated? A comparison of direct immunofluorescence antigen detection,

culture, and PCR, with a historical review. J Clin Microbiol. 2012; 50(12):4120–4122. [PubMed: 23035203]

42. Harbecke R, Oxman MN, Arnold BA, et al. A real-time PCR assay to identify and discriminate among wild-type and vaccine strains of varicella-zoster virus and herpes simplex virus in clinical specimens, and comparison with the clinical diagnoses. J Med Virol. 2009; 81(7):1310–1322. [PubMed: 19475609]
43. Gershon AA, Chen J, Gershon MD. Use of Saliva to Identify Varicella Zoster Virus Infection of the Gut. Clinical infectious diseases. 2015; 61(4):536–544. [PubMed: 25882301]
44. Levin MJ. Varicella-zoster virus and virus DNA in the blood and oropharynx of people with latent or active varicella-zoster virus infections. J Clin Virol. 2014; 61(4):487–495. [PubMed: 25453570]
45. Wilson JF. In the clinic. Herpes zoster. Ann Intern Med. 2011; 154(5):ITC31–15. quiz ITC316. [PubMed: 21357905]
46. Breuer J, Schmid DS, Gershon AA. Use and limitations of varicella-zoster virus-specific serological testing to evaluate breakthrough disease in vaccinees and to screen for susceptibility to varicella. J Infect Dis. 2008; 197(Suppl 2):S147–151. [PubMed: 18419389]
47. Arnold P, Oranje MD, Elzo Folkers MD. The Tzanck Smear Old but Still of Inestimable Value. Pediatric Dermatology. 5(2):127–129.
48. Arvin AM. Varicella-zoster virus. Clinical microbiology reviews. 1996; 9(3):361–381. [PubMed: 8809466]
49. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2013; (3):CD005582. [PubMed: 23543541]
50. Uscategui T, Doree C, Chamberlain IJ, Burton MJ. Corticosteroids as adjuvant to antiviral treatment in Ramsay Hunt syndrome (herpes zoster oticus with facial palsy) in adults. Cochrane Database of Systematic Reviews. 2008; (3)
51. Gagyor I, Madhok VB, Daly F, et al. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev. 2015; (11):CD001869.
52. Duda JF, Castro JG. Bilateral Retrobulbar Optic Neuritis Caused by Varicella Zoster Virus in a Patient with AIDS. Br J Med Med Res. 2015; 5(11):1381–1386. [PubMed: 26740936]
53. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2004; 63(6):959–965. [PubMed: 15452284]
54. Sampathkumar P, Drage LA, Martin DP. Herpes Zoster (Shingles) and Postherpetic Neuralgia. Mayo Clinic proceedings. 2009; 84(3):274–280. [PubMed: 19252116]
55. Lin PL, Fan SZ, Huang CH, et al. Analgesic effect of lidocaine patch 5% in the treatment of acute herpes zoster: a double-blind and vehicle-controlled study. Regional anesthesia and pain medicine. 2008; 33(4):320–325. [PubMed: 18675742]
56. Dworkin RH, O'Connor AB, Kent J, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain. 2013; 154(11):2249–2261. [PubMed: 23748119]
57. Oxman MNLM, Johnson GR, Schmader KE, Straus SE, Gelb LD, Arbeit RD, Simberkoff MS, Gershon AA, Davis LE, Weinberg A, Boardman KD, Williams HM, Zhang JH, Peduzzi PN, Beisel CE, Morrison VA, Guatelli JC, Brooks PA, Kauffman CA, Pachucki CT, Neuzil KM, Betts RF, Wright PF, Griffin MR, Brunell P, Soto NE, Marques AR, Keay SK, Goodman RP, Cotton DJ, Gnann JW Jr, Loutit J, Holodniy M, Keitel WA, Crawford GE, Yeh SS, Lobo Z, Toney JF, Greenberg RN, Keller PM, Harbecke R, Hayward AR, Irwin MR, Kyriakides TC, Chan CY, Chan IS, Wang WW, Annunziato PW, Silber JL. Shingles Prevention Study Group. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. N Engl J Med. 2005 Jun 2; 352(22): 2271–84. [PubMed: 15930418]
58. Van Epps PS KE, Canaday DH. Herpes Zoster Vaccination: Controversies and Common Clinical Questions.pdf. Gerontology. 2016; 62(2):150–154. [PubMed: 26184711]
59. Morrison VA, Johnson GR, Schmader KE, et al. Long-term persistence of zoster vaccine efficacy. Clinical infectious diseases. 2015; 60(6):900–909. [PubMed: 25416754]
60. Levin MJ, Schmader KE, Pang L, et al. Cellular and Humoral Responses to a Second Dose of Herpes Zoster Vaccine Administered 10 Years After the First Dose Among Older Adults. J Infect Dis. 2016; 213(1):14–22. [PubMed: 26452397]

61. Levin MJ, Oxman MN, Zhang JH, et al. Varicella-Zoster Virus–Specific Immune Responses in Elderly Recipients of a Herpes Zoster Vaccine. The Journal of Infectious Diseases. 2008; 197(6): 825–835. [PubMed: 18419349]
62. Williams WW, Lu PJ, O'Halloran A, et al. Vaccination coverage among adults, excluding influenza vaccination - United States, 2013. MMWR Morbidity and mortality weekly report. 2015; 64(4): 95–102. [PubMed: 25654611]
63. Zhang D, Johnson K, Newransky C, Acosta CJ. Herpes Zoster Vaccine Coverage in Older Adults in the U.S., 2007–2013. Am J Prev Med. 2017; 52(1):e17–e23. [PubMed: 28340974]
64. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster Subunit Vaccine in Adults 70 Years of Age or Older. N Engl J Med. 2016; 375(11):1019–1032. [PubMed: 27626517]
65. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015; 372(22):2087–2096. [PubMed: 25916341]
66. Sacks HS. In adults >/= 70 years of age, an adjuvanted herpes zoster subunit vaccine reduced herpes zoster at a mean 3.7 years. Ann Intern Med. 2017; 166(2):JC5. [PubMed: 28114461]
67. Godeaux O, Kovac M, Shu D, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit candidate vaccine in adults >/= 50 years of age with a prior history of herpes zoster: A phase III, non-randomized, open-label clinical trial. Hum Vaccin Immunother. 2017:1–8.
68. Moanna A, Rimland D. Decreasing incidence of herpes zoster in the highly active antiretroviral therapy era. Clinical infectious diseases. 2013; 57(1):122–125. [PubMed: 23487391]
69. Blank LJ, Polydefkis MJ, Moore RD, Gebo KA. Herpes zoster among persons living with HIV in the current antiretroviral therapy era. J Acquir Immune Defic Syndr. 2012; 61(2):203–207. [PubMed: 22766968]
70. Berkowitz EM, Moyle G, Stellbrink HJ, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. J Infect Dis. 2015; 211(8):1279–1287. [PubMed: 25371534]
71. Centers for Disease Control and Prevention. [Accessed June 03, 2017] HIV/AIDS. Feb 03. 2017 https://www.cdc.gov/hiv/group/age/olderamericans
72. Benson, CA., Hua, L., Jiang, JH., et al. The 19th Conference on Retroviruses and Opportunistic Infections. Seattle, Washington: 2012. ZOSTAVAX is generally safe and immunogenic in HIV+ adults virologically suppressed on ART: results of a phase 2, randomized, double-blind, placebo-controlled trial.
73. Centers for Disease Control and Prevention. [Accessed June 03, 2017] Immunization Schedules. 2017. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html
74. Stadtmauer EA, Sullivan KM, Marty FM, et al. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. Blood. 2014; 124(19): 2921–2929. [PubMed: 25237196]
75. Birkmann A, Zimmermann H. Drugs in development for herpes simplex and varicella zoster virus. Clin Pharmacol Ther. 2017
76. De Clercq E. Clinical potential of the acyclic nucleoside phosphonates cidofovir, adefovir, and tenofovir in treatment of DNA virus and retrovirus infections. Clin Microbiol Rev. 2003; 16(4): 569–596. [PubMed: 14557287]

Herpes Zoster

- The incidence of Herpes Zoster has been on the rise over the past several decades, with older adults disproportionately affected.
- While postherpetic neuralgia gradually resolves in most older adults, there is a subset of patients who are refractory to pain management and in whom the pain continues to worsen over time.
- For 3–12 months following an episode of herpes zoster, individuals older than 50 years are at higher risk for stroke or myocardial infarction compared to the general population.
- Antiviral therapy is indicated in patients greater than 50 years of age
- The current commercially available live attenuated vaccine for the prevention of shingles shows significant declines in efficacy 7–10 years following vaccination.

Table 1

Pharmacologic therapies used in the treatment of Herpes Zoster and Postherpetic neuralgia

Antiviral agents	**HZ**	**PHN**	**Recommended dose**
Acyclovir (oral)	+	−	800 mg 5 times daily for 7–10 days.
Famiciclovir (oral)	+	−	500 mg every 8 hours for 7 days.
Valacyclovir (oral)	+	−	1 gm every 8 hours for 7 days.
Brivudine (oral)	+	−	125 mg once daily for 7 days. Product licensed in various countries; *not currently available in the United States*
Acyclovir (IV)	+	−	10 to 15 mg/kg every 8 hours until clinical improvement; switch to oral regimen to complete a 10 to 14 day course when formation of new lesions has ceased and signs/symptoms of visceral infection areimproving.
Foscarnet (IV)	+	−	40 mg/kg every 8 hours for 7–10 days.[24] *Not approved for this indication by the FDA*
Cidofovir (IV)	+	−	5 mg/kg every week for 2 weeks, followed by or 5mg/kg every other week.[76] To be used if patient fails or relapses aftertherapy with foscarnet. *Not approved for this indication by the FDA*
Anti-inflammatory agents			
Prednisone (PO)	+	−	60 mg daily for 7 days, followed by 30 mgdaily for 7 days, then 15 mg daily for 7 days.
Intrathecal methylprednisone	-	±	Reserved for intractable PHN due to risk profile. *Not currently available in the United States.*
Analgesic agents			
Acetaminophen	+	−	Used for mild pain
NSAIDS	+	−	Used for mild pain
Oxycodone	1st line	3rd line	5 mg every 4 hours as needed, carefully titrate upwards by 5 mg 4 times daily every 2 days for pain control. Dosage needs to be converted to a long-acting opioid analgesic and combined with a short acting medicationfor breakthrough pain.
Tramadol	±	3rd line	50 mg once or twice daily, increase by 50–100 mg daily in divided doses every 2 days as tolerated. Maximum dose of 400 mg daily or 300 mg daily if older than 75 years.
Gabapentin	2nd line	2nd line	300 mg at bedtime or 100–300 mg 3 times daily, increase by 100–300 mg 3 times daily every 2 days as tolerated. Maximum dose of 3,600 mg daily.
Pregabalin	2nd line	2nd line	75 mg at bedtime or 75 mg twice daily, increase by 75 mg twice daily every 3 days astolerated. Maximum dose is 600 mg daily.
Nortryptyline	3rd line	2nd line	25 mg at bedtime, increase by 25 mg daily every 2–3 days as tolerated. Maximum dose 150 mg daily. * TCAs have similar efficacy to gabapentin orpregabalin, but cause more serious adverse events.[31]

Antiviral agents	HZ	PHN	Recommended dose
Venlafaxine	±	±	37.5 mg daily, titrate upwards by 75 mg each week over a 4–6 week period. Maximum dose of 225 mg/day * Used if unable to tolerate TCA side effect profile, however not as well studied as TCAs. *Not approved for this indication by the FDA*[54]
Duloxetine	±	±	20 mg at bedtime, increase dose by 20 mg every 5 days. Maximum dose 60 mg daily * Used if unable to tolerate TCA side effect profile, however not as well studied as TCAs. *Not approved for this indication by the FDA*[54]
Topical analgesic agents			
Lidocaine 5% patch	±	1st line	One patch can be applied to the location ofpain. Up to 3 patches can be used at the same time for a maximum of 12 hours.
Capsaicin 0.075% cream	−	±	Apply 4 times per day
Capsaicin 8% patch	−	±	Application time of 30–90 minutes.

+ Definitely can be used for this indication.

± May be used for this indication if no other alternative is present, minimal supportive data present.

− Avoid using for this indication, no supportive data present.