Clinical Policy Bulletin:  
Post-Herpetic Neuralgia  

Number: 0725  

Policy  

I. Aetna considers the use of antivirals (oral), capsaicin patch, gabapentin, intrathecal corticosteroids, lidocaine patch, opioids (oral), pregabalin, and tricyclic antidepressants medically necessary for post-herpetic neuralgia (PHN). Refer to the pharmacy policies on our website for specific prior authorization requirements for the listed group of drugs.  

II. Aetna considers any of the following therapeutic modalities for PHN experimental and investigational because their effectiveness for this indication has not been established (not an all-inclusive list):  

   A. Acupuncture  
   B. Botulinum toxin  
   C. Cryocautery  
   D. Dorsal root entry zone lesions/dorsal root ganglion destruction  
   E. Epidural corticosteroid or morphine  
   F. Intercostal nerve block  
   G. Intralesional corticosteroid  
   H. Intravenous antiviral therapy  
      I. Intravenous ketamine  
      J. Intravenous lidocaine  
   K. Intravenous vitamin C  
   L. Iontophoresis of vincristine  
   M. Laser irradiation  
   N. Narrow-band ultraviolet light B  
   O. Peripheral nerve stimulation  
   P. Stellate ganglion blockade  
   Q. Sympathectomy  
   R. Topical ketamine  
   S. Topical piroxicam  
   T. Transcutaneous electrical nerve stimulation (TENS).  

For spinal cord stimulation for PHN, see CPB 0194 - Dorsal Column Stimulation.
III. Aetna considers the use of any of the following pharmacotherapies for the treatment of PHN experimental and investigational because their effectiveness for this indication has not been established (not an all inclusive list):

A. Biperiden
B. Carbamazepine
C. Chlorprothixene
D. Ganoderma lucidum extract
E. Nicardipine.

See also CPB 0011 - Electrical Stimulation for Pain, CPB 0113 - Botulinum Toxin, CPB 0115 - Varicella and Herpes Zoster Vaccines, CPB 0135 - Acupuncture, and CPB 0194 - Dorsal Column Stimulation.

Background

Herpes zoster (HZ) is the consequence of re-activation of the varicella zoster virus that remains latent since primary infection (varicella). The overall incidence of HZ is about 3 per 1000 of the population per year increasing to 10 per 1000 per year by age 80. Approximately half of persons reaching age 90 years will have had HZ. In approximately 6%, a second episode of HZ may occur; usually several decades after the first attack. The most common complication of HZ is post-herpetic neuralgia (PHN), defined as significant pain or dyseaesthesia present 3 months or more following HZ. More than 5% of the elderly have PHN at 1 year after acute HZ. Reduced cell-mediated immunity to HZ occurs with aging, which may be responsible for the increased incidence in the elderly and from other causes such as tumors, human immunodeficiency virus infection as well as immunosuppressant drugs. Diagnosis of PHN is usually clinical from typical unilateral dermatomal pain and rash. Prodromal symptoms, pain, itching and malaise, are common (Johnson and Whitton, 2004).

The observation that patients with PHN experience different types of pain (e.g., continuous burning or intense paroxysmal; most often with tactile allodynia) suggests that multiple pathophysiological mechanisms are involved, which may include the peripheral as well as the central nervous systems. Traditional treatments for PHN usually entail tricyclic antidepressants (TCA) such as amitriptyline, nortriptyline, desipramine and maprotiline; antiepileptic drugs such as gabapentin and pregabalin; topical 5% lidocaine patches (Lidoderm), which frequently reduce allodynia; as well as long-acting oral opioid preparations and tramadol (Ultra). Oral antiviral agents (aciclovir, famciclovir, valaciclovir) are used during an acute attack of herpes zoster to prevent postherpetic neuralgia (Wareham, 2006). There is evidence that intrathecal corticosteroids may be effective in patients who are refractory to conservative measures (Wu and Raja, 2008; Hempenstall et al, 2005), but the potential for neurological sequelae should prompt caution with their application (Christo et al, 2007). Epidural corticosteroids have not been shown to provide effective analgesia for PHN (Christo et al, 2007). Many alternative treatments for PHN such as cryocaucery, dorsal column (spinal cord) stimulation, iontophoresis of vincristine, intravenous administration of ketamine, an N-methyl-D-aspartate (NMDA) antagonist; laser; peripheral nerve stimulation as well as transcutaneous electrical nerve stimulation (TENS) have not been adequately studied.
Iontophoresis has been suggested to be effective in treating PHN (Ozawa et al, 1999). However, in a randomized controlled trial, Dowd et al (1999) reported that that iontophoresed vincristine is no better than iontophoresed saline in the treatment of this condition. Although TENS has been reported to benefit some patients with PHN (Milligan and Nash, 1985; Robertson and George, 1990), these findings have not been validated by randomized controlled studies. Furthermore, on behalf of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Reeve and Corabian (1995) evaluated the scientific evidence of the clinical effectiveness of TENS for the treatment of acute, chronic as well as labor and delivery pain. These researchers concluded that there is little evidence that TENS is effective in treating chronic pain.

In a review on sympathectomy for neuropathic pain, Mailis and Furlan (2003) stated that the practice of surgical and chemical sympathectomy is based on poor quality evidence, uncontrolled studies and anecdotal experience. In addition, complications of the procedure may be significant, in terms of both worsening the pain or producing a new pain syndrome; and abnormal forms of sweating (e.g., compensatory hyperhidrosis and pathological gustatory sweating). The authors concluded that more clinical studies of sympathectomy are needed to establish the potential risks and overall effectiveness of this procedure.

In a pilot study (n = 10), Johnson and Burchiel (2004) found that peripheral nerve stimulation of the supra-orbital or infra-orbital branches of the trigeminal nerve is effective in relieving trigeminal neuropathic pain following facial trauma or herpetic infection. These investigators stated that a prospective clinical trial using this novel approach to treat these disorders is thus warranted. A recent Cochrane review (Mailis-Gagnon et al, 2004) on spinal cord stimulation (SCS) concluded that although there is limited evidence in favor of SCS for failed back surgery syndrome and complex regional pain syndrome (also known as reflex sympathetic dystrophy), more research is needed to confirm whether SCS is an effective treatment for other types of chronic pain. Gilden et al (2005) noted that because only a few studies have used antiviral therapy to manage PHN and with conflicting results, larger, double-blind studies, which give intravenous antiviral drug, are needed. Thus, well-designed, multi-center, controlled clinical trials are needed to ascertain the effectiveness of various alternative treatments in the treatment of PHN.

An earlier systematic review of randomized controlled trials on treatments for PHN (Volmink et al, 1996) reported that pooled analysis of the effect of TCA demonstrated statistically significant pain relief. Pooling of the results of the 3 studies comparing the effects of capsaicin and placebo could not be performed due to heterogeneity, which was mainly attributable to an unpublished trial which differed in terms of the dosage and duration of treatment. When this study was omitted, no heterogeneity was found and the pooled analysis revealed a statistically significant benefit. However, problems with blinding in patients using capsaicin may have accounted for the positive effect. One small study of iontophoresis of vincristine compared to placebo yielded a favorable result. Other therapies evaluated included lorazepam, acyclovir, topical benzydamine as well as acupuncture. There was no evidence that these treatments are effective in relieving pain associated with PHN. These investigators concluded that based on evidence from randomized trials, TCA appear to be the only agents of proven benefit for established PHN.
A more recent evidence-based report on treatment of PHN was developed by the Quality Standards Subcommittee of the American Academy of Neurology (Dubinsky et al, 2004) and it had the following recommendations:

1. Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E and zimelidine are not of benefit.
2. Aspirin cream or ointment is possibly effective in the relief of pain in patients with PHN but the magnitude of benefit is low, as is seen with topical capsaicin.
3. The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, Helium:Neon (He:Ne) laser irradiation, intralvesional triamcinolone, cryocautery, topical piroxicam, extract of Ganoderma lucidum, dorsal root entry zone lesions and stellate ganglion block are unproven in the treatment of PHN.
4. Tricyclic antidepressants, gabapentin, pregabalin, opioids and lidocaine patch are effective and should be used in the treatment of PHN.

In a multi-center, randomized controlled study, van Wijck and colleagues (2006) reported that a single epidural injection of 80 mg methylprednisolone and 10 mg bupivacaine within the first days of herpes zoster has a modest effect in reducing zoster-associated pain for one month; however there were no significant differences in pain level between the two groups at subsequent follow-ups. At 1 month, 137 (48 %) patients in the epidural group (plus standard therapy given to the control group) reported pain compared with 164 (58 %) in the control group (oral antivirals and analgesics). After 3 months these values were 58 (21 %) and 63 (24 %) respectively, and at 6 months, 39 (15 %) and 44 (17 %). The main drawback of this study was that it was neither double-blinded nor placebo-controlled, which decreased the validity of the already modest anti-nociceptive effects of the treatment within the first month. Moreover, this treatment is ineffective in preventing the development of long-term PHN. Furthermore, Baron and Wasner (2006) stated that large, well-designed prospective studies are needed to estimate the preemptive effect of neuropathic pain treatment on PHN.

In a Cochrane review, Khaliq et al (2007) examined the safety and effectiveness of topical lidocaine in the treatment of PHN. The investigators identified three trials meeting inclusion criteria, involving 182 topical lidocaine treated participants and 132 control participants. Two trials gave data on pain relief, and the remaining study provided data on secondary outcome measures. The largest trial compared topical lidocaine patch to a placebo patch and accounted for 150 of the 314 patients included in the analysis. A meta-analysis combining two of the three studies identified a significant difference between the topical lidocaine and control groups for the primary outcome measure -- a mean improvement in pain relief according to a pain relief scale. Topical lidocaine relieved pain better than placebo (p = 0.003). The investigators also found a statistical difference between the groups for the secondary outcome measure of mean visual analog scale (VAS) score reduction (p = 0.03), but only for a single small trial. In the selected studies, there were a similar number of adverse skin reactions in both treatment and placebo groups. The investigators reported that the highest recorded blood lidocaine concentration varied between 59 ng/ml and 431 ng/ml between trials. The investigators noted that the latter figure is high and posited that it may have been due to contamination of the sample during the assay procedure.

Christo et al (2007) stated that epidural corticosteroids have not been shown to provide effective analgesia for PHN. Furthermore, Wu and Raja (2008) stated that the majority of
Interventional therapies show equivocal analgesic efficacy although some data indicate that intrathecal methylprednisolone may be effective. The author stated that further randomized, controlled trials will be needed to confirm the analgesic efficacy of analgesic and interventional therapies (e.g., sympathetic nerve blocks/other nerve blocks, intrathecal methylprednisolone, and spinal cord stimulation) to determine their role in the overall treatment of patients with PHN.

In a Cochrane review, He et al (2008) examined the effectiveness of corticosteroids in preventing PHN. People of all ages with herpes zoster of all degrees of severity within 7 days after onset were included. Interventions include corticosteroids given by oral, intramuscular or intravenous routes during the acute stage (starting within 1 week of onset of the rash) compared with no treatment or placebo, but not with other treatments. Primary outcome measure was the presence of PHN 6 months after the onset of the acute herpetic rash. Secondary outcome measure was pain severity measured by a validated VAS or numerical descriptive scale after 3, 6 and 12 months; quality of life measured with the Short Form 36 questionnaire after 6 months; adverse events during or within 2 weeks after stopping treatment. Five trials were included with altogether 787 participants. All were randomized, double-blind, placebo-controlled parallel group studies. There was no significant difference between the corticosteroid and control groups for the primary outcome (risk ratio [RR] 1.27, 95% confidence interval [CI]: 0.20 to 7.97). There was also no significant difference between the corticosteroid plus anti-viral agents and placebo plus anti-viral agents groups for the primary outcome (RR 0.90, 95% CI: 0.40 to 2.03). No included trials evaluated pain severity with a validated VAS or numerical descriptive scale and also no trials measured quality of life with the Short Form 36 questionnaire. Adverse events during or within 2 weeks after stopping treatment were reported by all 5 included trials, but after meta-analysis, there was no significant difference in any serious adverse event (e.g., death, acute cardiac insufficiency, rash dissemination, bacterial pneumonia or hematemesis) or non-serious adverse event (e.g., dizziness, nausea, vomiting, hypertension or hyperglycemia). The authors concluded that there was insufficient evidence that corticosteroids are safe or effective in the prevention of PHN. They stated that more randomized controlled trials with a greater number of participants are needed to determine reliably whether there is real benefit (or harm) from the use of corticosteroid therapy to prevent PHN; and that future trials should measure function and quality of life.

A Clinical Evidence systematic evidence review concluded that corticosteroids for post-herpetic neuralgia are likely to be ineffective or harmful in preventing post-herpetic neuralgia (Wareham, 2006). The evidence review noted that, not only have corticosteroids not been proven to be effective for this indication, but they may cause dissemination of herpes zoster.

Chau et al (2007) evaluated the outcome of pain treatment for the elderly patients with PHN. A total of 58 elderly outpatients with PHN were studied. The pain intensity before and after treatment were assessed by patients themselves with numeric pain scale (NPS). The pain treatment included (i) medication with anti-convulsants, opioids and non-steroidal anti-inflammatory drugs (NSAIDs); (ii) nerve block with 0.25% bupivacaine or 1% lidocaine twice-weekly at the beginning of the treatment. The therapeutic outcome was expressed by pain relief. The reduction of pain and residual pain intensity were evaluated subjectively by the patients themselves with patients’ global impression and NPS, respectively, after treatment for 1 and 3 months (or last visit). The adverse events throughout the treatment course were analyzed. The mean age of the patients was 75.1 years. The number of female PHN sufferers was higher than that of male in all aged

http://qawww.aetna.com/cpb/medical/data/700_799/0725_draft.html

11/03/2014
groups and the highest incidence was found in the age group of 70 to 79 (65.5 %). The most commonly involved dermatomes were in the thoracic region (82.7 %). All patients suffered from severe pain (NPS 8 to 10) before treatment. The pain management was a combination of medication and nerve block at the beginning of the treatment. Among the medications, gabapentin was prescribed to all the patients and almost all of them (98.3 %) required opioids simultaneously and some of them needed additional NSAIDs at the beginning of the treatment. The most common adverse event was somnolence (24.1 %). Among the sympathetic blocks, the intercostal nerve block was performed commonly (84.5 %). The therapeutic outcome was expressed by pain relief. As to the reduction of pain, 46 cases (79.3 %) and 57 cases (98.3 %) felt moderate and much improvement after treatment for 1 and 3 months (or last visit), respectively. As to residual pain intensity, although none of them got complete pain relief, there were 12 cases (20.7 %) and 45 cases (77.6 %) felt the pain intensity was mild (NPS 1 to 3) after treatment for 1 and 3 months respectively. There was a statistically significant decrease in the pain intensity between before treatment and after treatment for 1 month and 3 months. The authors concluded that these findings showed that the concurrent combination therapy with proper medications and appropriate nerve blocks could offer satisfactory pain relief in the majority of elderly patients with PHN. The effect of intercostal nerve block is confounded by the concomitant use of pain medications.

Schencking and associates (2010) reported the findings of intravenous administration of vitamin C in the treatment of 2 patients with PHN. These 2 subjects (females aged 67 and 53 years) were from an average and unselected patient group of a general practice with confirmed acute herpetic neuralgia who were observed in the course of their illness. They received the basic analgesic (according to the WHO step scheme) and viral-static therapy. Furthermore, 15-g of vitamin C was administered intravenously every second day over a period of 2 weeks. Sudden and total remission of the neuropathic pain (measured on the basis of VAS) could be observed. Remission of the cutaneous lesions was noted within 10 days. The use of the vitamin C appears to be an interesting component of alternative therapeutic strategies in the treatment of HZ. Especially for therapy-resistant cases of PHN, vitamin C administration should be examined as an additional option. The authors concluded that to test and confirm these clinical findings, randomized clinical trials regarding the use of vitamin C in the concomitant treatment of zoster-associated neuralgia should be performed.

In a randomized, double-blind study, Backonja et al (2008) examined the safety and effectiveness of one application of NGX-4010, a high-concentration (8 %) capsaicin dermal patch, in the treatment of patients with PHN. A total of 402 patients were randomly assigned to one 60-min application of NGX-4010 (640 microg/cm(2) or a low-concentration capsaicin control patch (3.2 microg/cm(2) [0.04 % capsaicin]). Patients were aged 18 to 90 years, had had PHN for at least 6 months, and had an average baseline numeric pain rating scale (NPRS) score of 3 to 9. The primary efficacy end point was percentage change in NPRS score from baseline to weeks 2 to 8. Analysis was by intention-to-treat. Patients who were randomly assigned to NGX-4010 (n = 206) had a significantly greater reduction in pain during weeks 2 to 8 than did patients who had the control patch (n = 196). The mean changes in NPRS score were -29.6 % versus -19.9 % (difference -9.7 %, 95 % CI: -15.47 to -3.95; p = 0.001). A total of 87 (42 %) patients who received NGX-4010 and 63 (32 %) controls had a 30 % or greater reduction in mean NPRS score (odds ratio [OR] 1.56, 95 % CI: 1.03 to 2.37; p = 0.03). Patients who had NGX-4010 had significant improvements in pain during weeks 2 to 12 (mean change in NPRS score -29.9 % versus -20.4 %, difference -9.5, -15.39 to -3.61; p = 0.002).
Transient blood pressure changes associated with changes in pain level were recorded on the day of treatment, and short-lasting erythema and pain at the site of application were common, self-limited, and generally mild-to-moderate in the NGX-4010 group and less frequent and severe in the controls. The authors concluded that one 60-min application of NGX-4010 provided rapid and sustained pain relief in patients with PHN. No adverse events were associated with treatment except for local reactions at the site of application and those related to treatment-associated pain.

In a Cochrane review, Derry et al (2009) reviewed the evidence from controlled trials on the efficacy and tolerability of topically applied capsaicin in chronic neuropathic pain in adults. Randomized, double-blind, placebo-controlled studies of at least 6 weeks' duration, using topical capsaicin to treat neuropathic pain were included in this analysis. A total of 6 studies (389 participants in total) compared regular application of low dose (0.075 %) capsaicin cream with placebo cream; the numbers needed to treat to benefit (NNT) for any pain relief over 6 to 8 weeks was 6.6 (4.1 to 17). Two studies (709 participants in total) compared a single application of high dose (8 %) capsaicin patch with placebo patch; the NNT for greater than or equal to 30 % pain relief over 12 weeks was 12 (6.4 to 70). Local skin reactions were more common with capsaicin, usually tolerable, and attenuated with time; the numbers needed to treat to harm (NNH) for repeated low dose application was 2.5 (2.1 to 3.1). There were insufficient data to analyse either data set by condition or outcome definition. All studies satisfied minimum criteria for quality and validity, but maintenance of blinding remains a potential problem. The authors concluded that capsaicin, either as repeated application of a low dose (0.075 %) cream, or a single application of a high dose (8 %) patch may provide a degree of pain relief to some patients with painful neuropathic conditions. Local skin irritation, which is often mild and transient but may lead to withdrawal, is common. Systemic adverse effects are rare. Estimates of benefit and harm are not robust due to limited amounts of data for different neuropathic conditions and inconsistent outcome definition.

In a randomized, double-blind, controlled study with an open-label extension, Backonja et al (2010) evaluated the safety, effectiveness and tolerability of NGX-4010 in patients with PHN. Patients were randomized to receive NGX-4010 or control patch in a 4-week, double-blind study. This was followed by an open-label extension phase (up to 48 weeks total) where patients could receive up to 3 additional treatments no sooner than 12 weeks after initial treatment. The primary efficacy variable was mean change from baseline in mean morning and evening NPRS scores. During days 8 to 28 after the double-blind treatment, NGX-4010 patients had a mean change in NPRS scores from baseline of -32.7 % compared with -4.4 % for control patients (p = 0.003). Mean NPRS scores decreased from baseline during week 1 in both treatment groups, remained relatively stable through week 12 in NXG-4010 patients, but returned to near baseline during weeks 2 to 4 in controls. Mean change in NPRS scores from baseline during weeks 2 to 12 was -33.8 % for NGX-4010 and +4.9 % for control recipients. A similar decrease in NPRS scores from baseline was maintained with subsequent NGX-4010 treatments, regardless of the number of treatments received. Transient increases in application site pain were adequately managed with analgesics. No increases in application site reactions or adverse events were observed with repeated treatments. No patients discontinued the study due to an adverse event. The authors concluded that NGX-4010 is a promising topical treatment for PHN patients, which appears to be tolerable, generally safe, and effective.

In an open-label study, Simpson and associates (2010) assessed the safety of repeated applications of NGX-4010 over 1 year in patients with moderate to severe PHN or human
immunodeficiency virus-associated distal sensory polyneuropathy (HIV-DSP). Patients had successfully completed a previous NGX-4010 study and had a pain level appropriate for further treatment. Eligible patients had not been treated with NGX-4010 within 12 weeks of study initiation. Patients received pre-treatment with a topical local anesthetic (lidocaine 4 %) for 60 minutes followed by either a 60-minute (PHN and HIV-DSP patients) or a 90-minute (HIV-DSP patients) treatment with NGX-4010. Patients could receive up to 3 additional treatments at intervals of greater than or equal to 12 weeks. Regardless of the number of treatments received, all patients were followed-up for 48 weeks except for those withdrawing early. A total of 106 patients were enrolled and received a total of 293 NGX-4010 treatments. The most frequently reported treatment-emergent adverse events were transient, mild-to-moderate application site erythema, pain, edema, and papules. Small, transient pain-related increases in blood pressure during and immediately after NGX-4010 application were observed. There was no evidence of an increased incidence of adverse events, dermal irritation, intolerability, or impaired neurological function with repeated treatments. The authors concluded that repeated treatments with NGX-4010 administered over a 1-year period are generally safe and well-tolerated.

McCormack (2010) stated that capsaicin dermal patch is an adhesive patch containing a high concentration (8 % w/w) of synthetic capsaicin. It is indicated in the European Union for the treatment of peripheral neuropathic pain in non-diabetic adults using a single 30- or 60-minute application repeated every 90 days, as required, and in the United States for the treatment of neuropathic pain associated with PHN. In pivotal, randomized, double-blind, multi-center trials in adults with PHN, a single 60-minute application of capsaicin dermal patch reduced the mean NPRS scores from baseline to a significantly greater extent than a low-concentration (0.04 % w/w capsaicin) control patch during weeks 2 to 8. In randomized, double-blind, multi-center trials in patients with HIV-associated neuropathy, capsaicin dermal patch reduced the mean NPRS scores from baseline significantly more than control in 1 study for the 30- and 90-minute, but not the 60-minute, application during weeks 2 to 12. In another study, the differences between capsaicin (30- and 60-minute applications) and control did not reach statistical significance. An integrated analysis of both studies showed that the 30-minute application of capsaicin dermal patch was significantly better than control for the reduction from baseline in mean NPRS scores during weeks 2 to 12. The efficacy of capsaicin dermal patch was maintained for up to 1 year in extension studies in which patients could receive up to 3 or 3 repeat treatments. Capsaicin dermal patch was generally well-tolerated in clinical trials. The most common adverse events were transient, mostly mild-to-moderate, application-site reactions.

On November 16, 2009, the Food and Drug Administration approved Qutenza (capsaicin, 8 % patch) for the treatment of the pain associated with PHN. Qutenza must be applied to the skin by a health care professional since placement of the patch can be quite painful, requiring use of a local topical anesthetic, as well as additional pain relief such as ice or use of opioid pain relievers. The patient must also be monitored for at least 1 hour since there is a risk of a significant rise in blood pressure following patch placement. The product insert of Qutenza states that the patches should be applied to the most painful skin areas, using up to 4 patches. Furthermore, the patches should be applied for 60 minutes and repeat every 3 months or as warranted by the return of pain (not more frequently than every 3 months).

In a pilot study, Nabarawy et al (2011) evaluated the effect of narrow-band ultra-violet light B (nbUVB) in the treatment PHN. The study included 17 patients with distressing PHN. Patients were evaluated using the Verbal Rating Scale (VRS). They received nbUVB
sessions, 3 times a week, for a total of 15 sessions or until the pain disappeared. Patients were followed-up for a period of 3 months after the end of therapy. Using intention-to-treat analysis, more than 50% improvement was achieved in 6 (35.29%) and 8 (47.06%) patients, at the end of therapy and after 3 months follow-up, respectively. An improvement of less than 50% was achieved in 11 (64.71%) and 9 (52.94%) patients, at the end of therapy and after 3 months follow-up, respectively. The pain severity assessed by the VRS significantly improved both at the end of sessions \( p = 0.005 \) and after 3 months follow-up \( p = 0.005 \). The authors concluded that nbUVB may be of beneficial use in the treatment of PHN. The drawbacks of this pilot study were small number of patients and limited follow-up period. These preliminary findings need to be validated by well-designed studies.

Barros et al (2012) stated that herpes zoster infection may cause PHN. This phenomenon may be reversed by (S)-ketamine (SKET), but its use results in intolerable side effects, while its topical administration seems to be safe. In a cross-over study, these researchers examined the effectiveness of topical (S)-ketamine for pain management of PHN. A total of 12 patients were randomly divided into 2 groups. There was a significant effect of time on pain intensity, but no statistical difference in pain scores for SKET or placebo use in this sample in this treatment regimen. Only few mild cutaneous reactions were observed with topical SKET use.

In a Cochrane review, Han and colleagues (2013) examined the effectiveness of corticosteroids in preventing PHN. These researchers updated the searches for randomized controlled trials (RCTs) of corticosteroids for preventing PHN in the Cochrane Neuromuscular Disease Group Specialized Register (April 16, 2012), CENTRAL (2012, Issue 3), MEDLINE (January 1966 to April 2012), EMBASE (January 1980 to April 2012), LILACS (January 1982 to April 2012), and the Chinese Biomedical Retrieval System (1978 to 2012). They also reviewed the bibliographies of identified trials, contacted authors and approached pharmaceutical companies to identify additional published or unpublished data. These investigators included all RCTs involving corticosteroids given by oral, intramuscular, or intravenous routes for people of all ages with HZ of all degrees of severity within 7 days after onset, compared with no treatment or placebo but not with other treatments. They did not include quasi-RCTs (trials in which a systematic method of randomization such as alternation or hospital number was used). Two authors identified potential articles, extracted data, and independently assessed the risk of bias of each trial. Disagreement was resolved by discussion among the co-authors. A total of 5 trials were included with 787 participants in total. All were randomized, double-blind, placebo-controlled, parallel-group studies. They conducted a meta-analysis of 2 trials (114 participants) and the results gave moderate quality evidence that oral corticosteroids did not prevent PHN 6 months after the onset of herpes (RR 0.95, 95% CI: 0.45 to 1.99). One of these trials was at high-risk of bias because of incomplete outcome data, the other was at low-risk of bias overall. The 3 other trials that fulfilled inclusion criteria were not included in the meta-analysis because the outcomes were reported at less than 1 month or not in sufficient detail to add to the meta-analysis. These 3 trials were generally at low-risk of bias. Adverse events during or within 2 weeks after stopping treatment were reported in 5 included trials. There were no significant differences in serious or non-serious adverse events between the corticosteroid and placebo groups. There was also no significant difference between the treatment groups and placebo groups in other secondary outcome analyses and subgroup analyses. The review was first published in 2008 and no new RCTs were identified for inclusion in subsequent updates in 2010 and 2012. The authors concluded that there is moderate quality evidence that corticosteroids...
given acutely during zoster infection are ineffective in preventing PHN. In people with acute HZ the risks of administration of corticosteroids do not appear to be greater than with placebo, based on moderate quality evidence. Corticosteroids have been recommended to relieve the zoster-associated pain in the acute phase of disease. These investigators stated that if further research is designed to evaluate the effectiveness of corticosteroids for HZ, long-term follow-up should be included to observe their effect on the transition from acute pain to PHN; and future trials should include measurements of function and quality of life.

Reviews on “Evidence-based guidance for the management of postherpetic neuralgia in primary care” (Harden et al, 2013), “Management of herpes zoster and post-herpetic neuralgia” (Gan et al, 2013) and “Herpes zoster: Diagnostic, therapeutic, preventive approaches” (Bader, 2013), and “Options for treating postherpetic neuralgia in the medically complicated patient” (Bruckenthal and Barkin, 2013) mentioned the use of topical lidocaine, but not intravenous lidocaine, as a therapeutic option.

Furthermore, an UpToDate review on “Postherpetic neuralgia” (Bajwa et al, 2014) states that “The effectiveness of therapies such as TENS and acupuncture has not been proven. Intravenous lidocaine may provide benefit in patients who do not respond to other therapies; however, small controlled trials have not convincingly demonstrated that this therapy is superior to placebo”.

In a Cochrane review, Wiffen et al (2104) evaluated the analgesic effectiveness and adverse events of levetiracetam in chronic neuropathic pain conditions in adults. These investigators searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 6) (via the Cochrane Library), MEDLINE, EMBASE, and two clinical trials databases (ClinicalTrials.gov and the World Health Organization Clinical Trials Registry Platform) to July 3, 2014, together with reference lists of retrieved papers and reviews. They included randomized, double-blind studies of 2 weeks duration or longer, comparing levetiracetam with placebo or another active treatment in adults with chronic neuropathic pain conditions. Studies had to have a minimum of 10 participants per treatments arm. Two review authors independently extracted effectiveness and adverse event data, and examined issues of study quality. They performed analysis using 3 tiers of evidence. First tier evidence derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction; intention-to-treat analysis without imputation for drop-outs; at least 200 participants in the comparison; 8 to 12 weeks duration; parallel design); 2nd tier evidence from data that failed to meet 1 or more of these criteria and that these researchers considered at some risk of bias but with at least 200 participants in the comparison; and 3d tier evidence from data involving fewer than 200 participants that was considered very likely to be biased or used outcomes of limited clinical utility, or both. These investigators included 6 studies: 5 small, cross-over studies with 174 participants, and 1 parallel group study with 170 participants. Subjects were treated with levetiracetam (2,000 mg to 3,000 mg daily) or placebo for between four and 14 weeks. Each study included participants with a different type of neuropathic pain; central pain due to multiple sclerosis, pain following spinal cord injury, painful polyneuropathy, central post-stroke pain, PHN, and post-mastectomy pain. None of the included studies provided 1st or 2nd tier evidence. The evidence was very low quality, down-graded because of the small size of the treatment arms, and because studies reported results using last observation carried forward (LOCF) imputation for withdrawals or using only participants who completed the study according to the protocol, where there were greater than 10% withdrawals. There were insufficient data for a
pooled efficacy analysis in particular neuropathic pain conditions, but individual studies did not show any analgesic effect of levetiracetam compared with placebo. These researchers did pool results for any outcome considered substantial pain relief (greater than or equal to 50 % pain intensity reduction or “complete” or “good” responses on the verbal rating scale) for 4 studies with dichotomous data; response rates across different types of neuropathic pain was similar with levetiracetam (10 %) and placebo (12 %), with no statistical difference (RR 0.9; 95 % CI: 0.4 to 1.7). They pooled data across different conditions for adverse events and withdrawals. Based on very limited data, significantly more participants experienced an adverse event with levetiracetam than with placebo (number needed to treat for an additional harmful event (NNH) 8.0 (95 % CI: 4.6 to 32)). There were significantly more adverse event withdrawals with levetiracetam (NNH 9.7 (6.7 to 18)). The authors concluded that the amount of evidence for levetiracetam in neuropathic pain conditions was very small and potentially biased because of the methods of analysis used in the studies. There was no indication that levetiracetam was effective in reducing neuropathic pain, but it was associated with an increase in participants who experienced adverse events and who withdrew due to adverse events.

In a Cochrane review, Gaskell et al (2014) evaluated the analgesic effectiveness and adverse events of oxycodone for chronic neuropathic pain and fibromyalgia. On November 6, 2013, these investigators searched CENTRAL, MEDLINE and EMBASE databases. They reviewed the bibliographies of all included studies and of reviews, and also searched 2 clinical trial databases, ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform, to identify additional published or unpublished data. They included RCTs with double-blind assessment of participant outcomes following 2 weeks of treatment or longer (although the emphasis of the review was on studies of 8 weeks or longer) that used a placebo or active comparator. Two review authors independently extracted efficacy and adverse event data, examined issues of study quality, and assessed risk of bias. They performed analysis using 3 tiers of evidence. First tier evidence was derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for dropouts; at least 200 participants in the comparison, 8 to 12 weeks duration, parallel design), 2nd tier from data that failed to meet 1 or more of these criteria and were considered at some risk of bias but with adequate numbers in the comparison, and 3rd tier from data involving small numbers of participants that was considered very likely to be biased or used outcomes of limited clinical utility, or both. These researchers included 3 studies with 254 participants; 204 had painful diabetic neuropathy and 50 PHN. Study size ranged from 45 to 159 participants. Two studies used a cross-over design and 1 a parallel group design; study duration was 4 or six weeks. Controlled release oxycodone (oxycodone CR) was used in all 3 studies, with doses titrated up to a maximum of between 60 and 120 mg daily; mean doses achieved ranged between 37 and 45 mg daily. All studies used a placebo comparator, although in 1 study, an active placebo (benztropine) was used. All studies had 1 or more sources of potential major bias. No study reported the proportion of participants experiencing at least 50 % pain relief or who were very much improved, while 1 reported the proportion with at least 30 % pain relief, 2 reported at least moderate pain relief, and 1 reported the number of participants who considered treatment to be moderately effective. No study provided 1st or 2nd tier evidence for an efficacy outcome. Third tier evidence indicated greater pain intensity reduction and better patient satisfaction with oxycodone than with placebo in all 3 studies, but such evidence was derived mainly from group mean data, with LOCF imputation or
completer analysis, in small studies lasting less than 8 weeks (very low quality evidence). Adverse events were more common with oxycodone CR than with placebo. At least 1 adverse event was experienced by 86% of participants taking oxycodone CR and 63% taking placebo, and the NNH was 4.3. The effect of oxycodone on serious adverse events reported was uncertain in comparison with placebo (oxycodone 3.4% versus placebo: 7.0%); RR 0.48 (95% CI: 0.18 to 1.23; very low quality evidence); 1 death was reported with oxycodone CR, but was not attributed to treatment. Adverse event withdrawals did not differ significantly between groups, occurring in 11% of participants with oxycodone CR and 6.4% with placebo (RR 1.69 (0.83 to 3.43); very low quality evidence). Withdrawals due to lack of efficacy were less frequent with oxycodone CR (1.1%) than placebo (11%), with an NNT to prevent 1 withdrawal of 10 (RR 0.12 (0.03 to 0.45); very low quality evidence). These investigators found no relevant studies in chronic neuropathic pain conditions other than painful diabetic neuropathy or PHN, or in fibromyalgia. The authors concluded that no convincing, unbiased evidence suggests that oxycodone (as oxycodone CR) is of value in treating people with painful diabetic neuropathy or PHN. There is no evidence at all for other neuropathic pain conditions, or for fibromyalgia. Adverse events typical of opioids appear to be common.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria is met:

62310
62311

CPT codes not covered for indications listed in the CPB (not all-inclusive):

0228T
+ 0229T
0230T
+ 0231T
62281
62282
62318
62319
63650
63655
64420
64421
64479
+ 64480
64483
+ 64484
64510
64555
64575
64600 - 64640
64650
64653
64680 - 64681
64802 - 64818
+ 95873
+ 95874
96910
97033
97810 - 97814

Other CPT codes related to the CPB:
96365 - 96379
99601 - 99602

HCPCS codes covered if selection criteria are met:

J1020 Injection, methylprednisolone acetate, 20 mg [covered for intrathecal/subarachnoid only - not epidural]
J1030 Injection, methylprednisolone acetate, 40 mg [covered for intrathecal/subarachnoid only - not epidural]
J1040 Injection, methylprednisolone acetate, 80 mg [covered for intrathecal/subarachnoid only - not epidural]
J1094 Injection, dexamethasone acetate, 1 mg [covered for intrathecal/subarachnoid only - not epidural]
J1100 Injection, dexamethasone sodium phosphate, 1 mg [covered for intrathecal/subarachnoid only - not epidural]
J1320 Injection, amitriptyline HCL, up to 20 mg
J1700  Injection, hydrocortisone acetate, up to 25 mg (Hydrocortone Acetate) [covered for intrathecal/subarachnoid only - not epidural]

J1710  Injection, hydrocortisone sodium phosphate, up to 50 mg (Hydrocortone Phosphate) [covered for intrathecal/subarachnoid only - not epidural]

J1720  Injection, hydrocortisone sodium succinate, up to 100 mg (Solu-Cortef) [covered for intrathecal/subarachnoid only - not epidural]

J2650  Injection, prednisolone acetate, up to 1 ml (Key-Pred 25, Key-Pred 50, Predcor-25, Predcor-50, Predoject-50, Predalone-50, Predicort-50) [covered for intrathecal/subarachnoid only - not epidural]

J2920  Injection, methylprednisolone sodium succinate, up to 40 mg (Solu-Medrol) [covered for intrathecal/subarachnoid only - not epidural]

J2930  Injection, methylprednisolone sodium succinate, up to 125 mg (Solu-Medrol) [covered for intrathecal/subarachnoid only - not epidural]

J3300  Injection, triamcinolone acetonide, preservative free, 1 mg [covered for intrathecal/subarachnoid only - not epidural]

J3301  Injection, triamcinolone acetonide, not otherwise specified, 10 mg [covered for intrathecal/subarachnoid only - not epidural]

J3302  Injection, triamcinolone diacetate, per 5 mg (Aristocort) [covered for intrathecal/subarachnoid only - not epidural]

J3303  Injection, triamcinolone hexacetonide, per 5 mg (Aristospan) [covered for intrathecal/subarachnoid only - not epidural]

J7335  Capsaicin 8% patch, per square centimeters

**HCPCS codes not covered for indications listed in the CPB (not all-inclusive):**

A4595  Electrical stimulator supplies, 2 lead, per month, (e.g. TENS, NMES)

E0720  Transcutaneous electrical nerve stimulation (TENS) device, two lead, localized stimulation

E0730  Transcutaneous electrical nerve stimulation (TENS) device, four or more leads, for multiple nerve stimulation

E0731  Form-fitting conductive garment for delivery of TENS or NMES (with conductive fibers separated from the patient's skin by layers of fabric)

J0133  Injection, acyclovir, 5 mg

J0190  Injection, biperiden lactate, per 5 mg

J0585  Botulinum toxin type A, per unit

J0587  Botulinum toxin type B, per 100 units
J2060 Injection, lorazepam, 2 mg
J2270 Injection, morphine sulfate, up to 10 mg
J2271 Injection, morphine sulfate, 100 mg
J2275 Injection, morphine sulfate (preservative-free sterile solution), per 10 mg
J9370 Vincristine sulfate, 1 mg
S0093 Injection, morphine sulfate, 500 mg (loading dose for infusion pump)

**ICD-9 codes covered if selection criteria are met:**

053.10 - 053.19 Herpes zoster with other nervous system complications

The above policy is based on the following references:

34. Food and Drug Administration. FDA approves new drug treatment for long-term pain relief after shingles attacks. November 17, 2009. FDA: Silver Spring, MD. Available at:


