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Non-Narcotic Treatment for Postherpetic Neuralgia

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Abstract

Postherpetic neuralgia (PHN) is a complication of herpes zoster that contributes to significant suffering for many patients. Analgesics, anticonvulsants, antidepressants, topical formulations and some interventional treatments have all been utilized in treating the neuropathic pain associated with PHN. Due to the current opioid epidemic, it is more important than ever for providers to find alternative methods of pain control for patients experiencing chronic pain. Medications in a variety of classes have shown varying levels of efficacy in providing relief for PHN patients, and providers should be aware of the evidence supporting the prescription of these treatments. Evidence supporting the use of gabapentin, pregabalin, amitriptyline, topical capsaicin, botulinum toxin injection, vitamin B12 supplementation, and interventional treatments has been reviewed to determine efficacy and assist providers in determining best practice when prescribing these medications. Safety considerations related to the previously mentioned medications have also been reviewed as available. Recommendations for use considering the quality of available evidence have been provided.

Keywords: postherpetic neuralgia, neuropathic pain, anticonvulsants, antidepressants, topical formulations, interventional therapies, emerging treatments

Non-Narcotic Treatment for Postherpetic Neuralgia

Herpes zoster (shingles) is an infectious disease that results from reactivation of the varicella zoster virus (chickenpox) that remains present in the dorsal root ganglion after infection (Shrestha & Chen, 2018). The reactivated virus travels along a sensory dermatome, resulting in a maculopapular rash with fluid filled vesicles that lasts for about ten days (Saguil et al., 2017). There are about one million new occurrences of herpes zoster every year in the United States, and it is estimated that about 3 in 10 adults will develop herpes zoster in their lifetime (Saguil et al., 2017). Pain, itching and burning are often experienced along the path of the dermatome prior to the rash eruption, with some patients experiencing neuropathic pain long after the rash has resolved (Shrestha & Chen, 2018). Long term neuropathic pain from herpes zoster, better known as postherpetic neuralgia (PHN), is the most common complication of shingles with higher incidence occurring in patients over age 50 (Saguil et al., 2017). In this paper, a case report about a 70 year old woman who developed shingles will be reviewed. Due to the diagnosis of this patient, as well as her age, she is at high risk of developing PHN, and long term treatment may need to be considered for neuropathic pain relief.

Current treatments for PHN are wide ranging, include analgesics, anticonvulsants, antidepressants, topical formulations, interventional treatments and combination treatments, with new treatments in development as well (Shrestha & Chen, 2018). As with all treatments, there are risks and benefits to consider when selecting the right plan for any given patient. While opioid analgesics may be effective in providing pain relief, the number of negative side effects and long term dependence issues should make them a last resort when considering the need for chronic pain control. With the availability of so many other options, it is up to providers to be up to date on the latest evidence that supports the use of these treatments to treat PHN without

having to resort to the use of opioid analgesics. The purpose of this report is to review currently recommended or developing treatments for PHN and determine the quality of evidence supporting their use.

Case Report

History

Patient is a 70 year old Caucasian female that presented complaining of back pain that began two days ago. She reports the pain is located in her lower back, on the right side. She has been experiencing the pain off and on over the past two days, but it has been more present than not. She describes the pain as a burning, itching sensation. It is worse when there is pressure on it, like when her clothes rub against it or she lays down on that side. She has tried taking over the counter Tylenol and applying ice to the area which have helped a bit, but the pain continues to return after treatment. She reports that the pain is worse in the evening after she has been moving around throughout the day. She describes the severity of the pain as being a six out of ten on a numeric rating scale of 0-10 for pain.

Past medical history includes hypertension (for which she takes Lisinopril 20 mg PO daily) and rheumatoid arthritis (Prednisone 5 mg PO PRN). Past surgical history includes a hysterectomy two years ago, as well as an appendectomy at that time. Patient has no known allergies, and reports she is up to date on all immunizations except for the shingles vaccine. Patient's family history includes heart disease in her mother, she is unaware of any health conditions her father may have had. Patient is a retired secretary that lives at home with her husband. She has two children that live in town and a couple of grandsons. She spends her time gardening and working in her yard when the weather is nice, and sewing during the winter months. Patient denies any smoking history or tobacco use in any form. She reports drinking

the occasional glass of wine with dinner, about 2-3 drinks/month. Patient denies the use of any illegal substances or inappropriate drug use.

Physical Examination

The patient's blood pressure upon exam was 154/90, pulse was 78 bpm, temperature was 99.1 orally, and oxygen saturation was 96% on room air. Patient reported she was in pain, and rated her pain a six out of ten. The patient was in no apparent distress, a systolic grade 2 murmur was noted upon cardiac auscultation and lung sounds were clear to anterior and posterior auscultation. Examination of the patient's back revealed a one inch by five inch cluster of reddened skin with raised, yellow, fluid filled vesicles along the right L3 dermatome. The rash began midline to the lower spine and extended along the right side of the patient's back towards the hip, it did not extend across midline or towards the left at all.

Diagnosis, Treatment and Follow Up

The diagnosis in this case was herpes zoster along the right L3 dermatome. The symptoms had been present for approximately 48 hours without any complications, making this patient a good candidate for antiviral treatment. The recommended treatment in this case was oral Valacyclovir 1000 mg three times daily for one week. The goals of this therapy are to decrease the length of illness and severity of symptoms associated with herpes zoster (Albrecht, 2018). Antiviral therapy can prevent the development of new herpetic lesions as well as improve the rate of healing for current lesions (Albrecht, 2018). Transmission of the herpes zoster virus is possible during infection, and antiviral therapy can help decrease viral shedding to lower the risk of spreading the disease (Albrecht, 2018). In addition to the above goals, completing this treatment is meant to prevent the development of postherpetic neuralgia in patients with herpes zoster (Albrecht, 2018).

For acute pain and discomfort associated with an uncomplicated herpes zoster infection, the treatment plan should also include NSAIDS or Tylenol while the patient recovers with the disease (Albrecht, 2018). In some instances, like with severe or sleep disturbing pain, opioid pain relief has been considered useful for a short amount of time (Albrecht, 2018). Close patient monitoring is recommended while patients are treated and as clinical symptoms resolve. It is recommended that this patient return to clinic at the completion of antiviral therapy, about one week later, to assess for healing and pain control (Albrecht, 2018). The goal is to be able to discontinue analgesic treatment of any acute pain associated with shingles. It is also important to provide patient education on the possible long term complication of PHN to this patient due to her age.

Literature Review

To begin the literature review on this topic, the PubMed database was first searched for relevant research due to the inclusion of biomedical and health literature. The PubMed search was performed using the medical subject headings (MeSH) terms: (a) "postherpetic neuralgia"; and (b) "treatment." The medical subject headings were combined with the Boolean connector "AND" to make sure all topics were included in relevant articles. Additional limits on the search included articles written within the last 5 years, articles written in English, studies limited to human subjects, and systematic reviews or meta-analysis articles only in order to obtain the most current and relevant articles of the highest quality. The search resulted in 33 articles that met the established criteria. After reviewing the literature, nine articles were found to contain relevant information for non-opioid treatment of PHN.

Next, the Cochrane Database of Systematic Reviews was searched to find relevant articles. The previous MeSH terms used in the PubMed search ("postherpetic neuralgia" and

"treatment") were also utilized with the Boolean connector "AND" in an advanced search of the Cochrane library. A limit of articles written after 2015 was also placed on the search. The results of this literature search yielded fifteen articles. Many of these reviews had been located in the PubMed database search, the results of this search only identified one additional article to add to the literature review.

The PubMed and Cochrane database searches resulted in a total of ten relevant articles for the literature review. Articles with at least moderate-quality evidence were selected for this review if the researchers in the studies presented this information. Bias within the articles was also taken in to account to prevent inclusion of too many articles with a high risk of bias. The selected articles include four meta-analyses (Song et al, 2018; Wang et al., 2018; Wang et al., 2017; Zhang et al, 2018), five systematic reviews (Derry et al, 2019; Derry et al., 2017; Lin et al., 2019; Moore et al., 2015; Wiffen et al., 2017), and one systematic review with meta-analysis (Shackleton et al., 2016). These ten articles review current and emerging non-opioid treatments for PHN.

Gabapentin

Two studies directly evaluated the use of gabapentin, an anticonvulsant, for the treatment of PHN. In a meta-analysis of gabapentin efficacy, eleven randomized control trials were evaluated comparing the use of gabapentin with placebo in reducing pain intensity (Zhang et al., 2018). All clinical trials were randomized and double-blinded, with parallel and placebo design, providing high quality evidence to be used for the meta-analysis. All eleven studies showed positive results for gabapentin over placebo in reducing patient pain intensity by at least 50% [RR=-1.79, 95% CI= 1.43, 2.25, P<0.00001] (Zhang et al., 2018). The analysis also revealed that gabapentin led to improved sleep rating scores for patients suffering from PHN (Zhang et

al., 2018). All studies recognized the downfall of adverse events related to the use of gabapentin, which included peripheral edema, dizziness and somnolence reported by subjects (Zhang et al., 2018). Despite these adverse events, subjects found that the significant pain relief outweighed the adverse effects of gabapentin usage during the study. Three different formulations of gabapentin were included: an immediate release form, an extended release form, and an extended release form including enacarbil, a prodrug to gabapentin. Of the three formulations, the gabapentin with enacarbil provided the best pain relief and improved sleep scores to subjects, with no notable difference in adverse effects in comparison to the other formulations (Zhang et al., 2018). Researchers believe that further studies need be done on the long-term safety and efficacy of gabapentin usage for PHN relief (Zhang et al, 2018). Notable limitations to this analysis include a lack of diversity in study subjects and a lack of long-term usage results (Zhang et al., 2018).

A Cochrane systematic review on the use of gabapentin for treatment of neuropathic pain yielded similar results regarding the relief of pain in patients with PHN (Wiffen et al., 2017). The review included eight studies focused on subjects with PHN, with an average of 32% of subjects in these studies reporting at least a 50% reduction of pain severity score [RR=1.69, 95% CI= 1.43-2.0, P= 0.020] (Wiffen et al., 2017). This review also included evidence of at least moderate quality, yielding higher reliability in study findings. The Cochrane review endorsed higher occurrences of adverse effects with gabapentin including gait disturbance in addition to the previously mentioned adverse effects, but did note that no serious adverse events occurred with gabapentin use over placebo (Wiffen et al., 2017). An important limitation noted in this study was the inclusion of some smaller study sizes that may introduce higher levels of bias into the review (Wiffen et al., 2017).

Pregabalin

In the evaluation of pregabalin as treatment for postherpetic pain, the other highly utilized anticonvulsant for this purpose, a meta-analysis and systematic review were used. The meta-analysis of pregabalin use directly analyzed it's efficacy in providing pain control for patients with PHN. This analysis reviewed seven studies, and that found more subjects reported at least 50% pain relief with pregabalin than with a placebo treatment [RR=1.15, 95% CI, 1.03, 1.29, P=0.010] (Wang et al., 2017). Patients in the analyzed studies reported less sleep interference when taking pregabalin leading to increase sleep quality for PHN patients (Wang et al., 2017). One negative of pregabalin noted in the study was cost, but current evaluation of the market recognizes a generic is now available which may make this a more realistic option for some patients. While two studies in the analysis did not describe their randomization process, the five remaining studies were performed with low risk of bias, improving the reliability of the results compared in this analysis (Wang et al., 2017). Adverse effects of pregabalin were not evaluated in this study, which may be a future area to consider in evaluating the safety of this medication for treating PHN.

Pregabalin use for neuropathic pain also received a Cochrane systematic review, with eight studies focused on its use specifically for PHN (Derry et al., 2019). The eight studies were all randomized control trials comparing pregabalin with placebo, all with parallel designs. While some studies in the entire systematic review were recognized to have a high risk of bias due to sample size, the studies included for the use of pregabalin to treat PHN had larger sized studies, eliminating a higher risk for bias. This review did have studies that evaluated the different efficacy between 300 mg and 600 mg doses, and found that for patients reporting at least a 50% reduction in their pain rating, the 600 mg dose was slightly more effective than to 300 mg dose

[RB=2.7, 95% CI 2.0-3.5 for 600 mg, vs. RB=2.5, 95% CI 1.9-3.4 for 300 mg] (Derry et al., 2019). The evidence in this review received a moderate quality rating, which indicates the improvement in pain relief is most likely due to the pregabalin, at whichever dose the patient is receiving. This review did find that the adverse effects of dizziness and sleepiness were more common in patients receiving pregabalin instead of placebo, but did not find any significant difference in severe adverse events between treatment and placebo groups (Derry et al., 2019).

Amitriptyline

There was one Cochrane systematic review that evaluated the efficacy of amitriptyline for neuropathic pain, the most popular antidepressant utilized in treating PHN. This review included five studies that compared efficacy of amitriptyline with various other psychoactive drugs (fluphenazine, lorazepam, desipramine, maprotiline, nortriptyline and fluoxetine) in addition to placebo (Moore et al., 2015). Some studies included a cross-over design, but all were actively controlled. Study comparisons between amitriptyline and the other drugs varied in efficacy, and there was no convincing evidence that supported the efficacy of amitriptyline as being superior to any other treatment (Moore et al., 2015). Study sizes within this review were notably small, resulting in increased bias which further limited the low quality evidence supporting the use of amitriptyline. One notable recommendation about this treatment is that many guidelines still recognize amitriptyline as the first line of treatment for neuropathic pain, often at lower doses than recommended for use as an antidepressant (Moore et al., 2015). While this does contradict the lack of quality evidence provided by this review, the researchers did acknowledge that providers should continue to use this as a treatment option due to the length of time patients have reported good outcomes with use, and the fact that there was also no evidence supporting that amitriptyline had no effect on neuropathic pain (Moore et al., 2015).

Topical Capsaicin

Topical application of high concentration capsaicin in treating neuropathic pain also received a Cochrane systematic review, with four studies in the review focused on its use specifically for PHN. One difficulty noted in this review was for studies to truly be blinded, due to side effects like redness and burning produced at the application site by any product containing capsaicin, which were also the most notable adverse events reported in the study for both treatment groups (Derry et al., 2017). A subject receiving a true placebo would not experience these side effects, therefore the participants were given a very low dose capsaicin in some trials to compare with a high concentration dose to allow for more reliability in results. The results did show that more participants receiving the high concentration capsaicin did report at least a 50% reduction in pain severity when compared to the low dose capsaicin or placebo[RR=1.44, 95% CI 1.12, 1.86, P= 0.005] (Derry et al., 2017). One downfall of the findings in this review was the low percentage of participants that did report pain reduction, which signifies that while it may be highly effective, it may also only be effective for a small amount (Derry et al., 2017). While the review did judge the evidence to be of moderate quality, due to some small sample sizes and lack of true blinding in some studies, the evidence was downgraded by the reviewers to low quality despite the positive results reported by patients (Derry et al., 2017).

Botulinum Toxin

The article supporting the use of botulinum toxin in treating PHN was a systematic review with meta-analysis that looked at efficacy for PHN, but also trigeminal neuralgia. These two types of neuropathic pain were not differentiated within the review or analysis. Six studies were reviewed, with only one study found to have a high risk of bias due to having an unclear

description of their randomization process (Shackleton et al., 2016). All studies found that the use of botulinum toxin resulted in more pain reduction for participants. Three of the studies measured pain reduction of at least 50% in participants receiving the botulinum toxin [RR=2.892, 95% CI 1.726, 4.848, $P<0.001$], which was 2.9 times more likely to occur with treatment than with placebo (Shackleton et al., 2016). Since the analysis contained a smaller amount of articles, reviewers were only able to recommend botulinum toxin treatment be viewed as moderate evidence for PHN. One positive point mentioned in this review was the lack of systemic side effects or any adverse events reported by participants, with the only notable side effect mentioned being injection site pain (Shackleton et al., 2016). However, since there were a limited amount of studies to review, further studies would have to be performed to truly evaluate for all possible side effects.

Vitamin B12

One meta-analysis evaluated the efficacy of Vitamin B12 supplementations in reducing pain associated with PHN. This analysis included four randomized control trials with rather high reliability due to lack of bias (Wang et al., 2018). The reduction of pain measurement in this analysis was different than the other articles in this review, with decrease in score using the numerical rating scale being evaluated. Overall, results for patients receiving the B12 supplementation were positive, show significantly decreased score after supplementation [MD= -4.01, 95% CI -4.7, -3.33, $P<0.01$] (Wang et al., 2018). With these promising results and low risk of bias, reviewers deemed Vitamin B12 supplementation to be moderate quality evidence for PHN treatment (Wang et al., 2018). Of note, there were smaller sample sizes and less studies in this analysis than others, which may limit how significant of an effect this may result in for all patients. Also, the study noted that more participants were recruited during the acute herpetic

neuralgia stage than the postherpetic stages, which may mean that results might not apply as well to all patients with postherpetic neuralgia (Wang et al., 2018).

Interventional Treatments

One systematic review looked at a number of interventional treatments to treat PHN, which may be useful after patients have failed to receive relief with typical oral medications or topical treatments. The interventional treatments reviewed included various nerve injections, different types of nerve stimulation, spinal cord stimulation, and dorsal root ganglion destruction (Lin et al., 2019). Due to a variety of different treatments with different measures being evaluated in this review, the reviewers did not make any specific comparisons between the treatments. It was noted that a lack of studies for all interventions and high or unclear risk of bias in most studies may severely limit the applicability of this review (Lin et al., 2019). The reviewers recommended that procedure invasiveness, cost of treatment and patient safety all be considered when determining an interventional treatment, as no single treatment was found to be more effective than another (Lin et al., 2019). Nerve injections with botulinum toxin or triamcinolone, stellate ganglion nerve block, transcutaneous electrical nerve stimulation, or peripheral nerve stimulation should be considered as the first interventional treatments to utilize for PHN (Lin et al., 2019). Paravertebral block or pulsed radiofrequency would be the next line of treatments to attempt, and spinal cord stimulation may be used for persistent pain. Two interventional treatments, dorsal root ganglion destruction and intrathecal methylprednisolone injections, had the highest amount of adverse events and were only recommended as a last resort treatment to be performed by an expert in these procedures (Lin et al., 2019). The reviewers did grade their evidence to be of moderate quality with value to be considered in treating PHN, but should not be used as standard treatments (Lin et al., 2019).

Treatment Comparisons

Limited studies were available that compared all of the previously mentioned treatments for PHN with each other, but one meta-analysis did attempt to compare a number of different treatments. Reviewers conducted an analysis comparing topical therapies, antiepileptics, analgesics, antipsychotics, antidepressants, anti-dementia drugs, antivirals and magnesium sulfate, and provided rankings on how each treatment performed on providing pain relief for PHN (Song et al., 2018). Of the treatments analyzed that were not analgesics, magnesium sulfate received the highest rank for PHN treatment (Song et al., 2018). It is noted that only one study in the meta-analysis included this treatment for comparison, and the sample size in the study was quite small, making this result considerably biased and significantly limited (Song et al., 2018). The next three highest ranking treatments, in order of efficacy, were antidepressants (amitriptyline, nortriptyline, TCAs), antiepileptics (gabapentin, pregabalin, divalproex sodium, carisbamate) and topical therapies (capsaicin, lidocaine), all with sufficient evidence to support their practical use in treating PHN (Song et al., 2018). This analysis did recognize that not all treatments within a certain class were equal in their ability to treat PHN, i.e. gabapentin outperformed carisbamate in the antiepileptic class (Song et al., 2018). Of the topical therapies mentioned in this analysis, both capsaicin and lidocaine were noted to perform well, but limited recent evidence supporting the use of lidocaine was found in the entire body literature. Further review of lidocaine efficacy within the topical treatment class would be recommended to determine its use as a treatment for PHN. Anti-dementia drugs and antipsychotics were ranked next, and antivirals (which are typically used as prevention) actually ranked below placebo in pain reduction for PHN (Song et al., 2018). The last three treatments mentioned do not have a

lot of evidence in current literature, which does not support their use at this time due to the number of other treatments available with proven efficacy.

Learning Points

- Management of PHN can be achieved for many patients without the long term use of opioid analgesics
- Gabapentin, pregabalin and amitriptyline can provide significant reduction for many patients with PHN, and should be considered as first line treatment options
- Topical use of capsaicin (and possibly lidocaine) can also be useful in treating PHN, and are considerable options for second line treatment
- Botulinum toxin injections and other interventional treatments may be of value in treating refractory pain due to PHN
- Vitamin B12 supplementation in combination with other treatments may provide improved pain control for PHN patients

References

Albrecht, M. A. (2018). Treatment of herpes zoster in the immunocompetent host. *UpToDate.*

Derry, S., Bell, R. F., Straube, S., Wiffen, P. J., Aldington, D., & Moore, R. A. (2019). Pregabalin for neuropathic pain in adults. *Cochrane Database of Systematic Reviews, Jan 2019*(1), CD007076. https://doi-org.ezproxy.library.und.edu/10.1002/14651858.CD007076.pub3.

Derry, S., Rice, A. S., Cole, P., Tan, T., & Moore, R. A. (2017). Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews, Jan 2017*(1), CD007393. https://dx-doi-org.ezproxy.library.und.edu/10.1002/14651858.CD007393.pub4.

Lin, C. S., Lin, Y. C., Lao, H. C., & Chen, C. C. (2019). Interventional treatments for postherpetic neuralgia: A systematic review. *Pain Physician, 22*(3), 209-228.

Moore, R. A., Derry, S., Aldington, D., Cole, P., & Wiffen, P. J. (2015). Amitriptyline for neuropathic pain in adults. *Cochrane Database of Systematic Reviews, July 2015*(7), CD008242. https://doi.org/10.1001/14651858.CD008242.pub3.

Saguil, A., Kane, S., Mercado, M., & Lauters, R. (2017). Herpes Zoster and postherpetic neuralgia: Prevention and management. *American Family Physician, 96*(10), 656-663.

Shackleton, T., Ram, S., Black, M., Ryder, J., Clark, G. T., & Enciso, R. (2016). The efficacy of botulinum toxin for the treatment of trigeminal and postherpetic neuralgia: A systematic review with meta-analyses. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, 122*(1), 61-71. https://doi.org/10.1016/j.oooo.2016.03.003.

Shrestha, M. & Chen, A. (2018). Modalities in managing postherpetic neuralgia. *The Korean Journal of Pain, 31*(4), 235-243. https://doi.org/10.3344/kjp.2018.31.4.235.

Song, D., He, A., Xu, R., Xiu, X., & Wei, Y. (2018). Efficacy of pain relief in different postherpetic neuralgia therapies: A network meta-analysis. *Pain Physician, 21*(1), 19-32.

Wang, J.Y., Wu, Y. H., Liu, S. J., Lin, Y. S., & Lu, P. H. (2018). Vitamin B12 for herpetic neuralgia: A meta-analysis of randomized controlled trials. *Complementary Therapies in Medicine, 41,* 277-282. https://doi.org/10.1016/j.ctim.2018.10.014.

Wang, S. L., Wang, H., Nie, H. Y., Bu, G., Shen, X. D., & Wang, H. (2017). The efficacy of pregabalin for acute pain control in herpetic neuralgia patients: A meta-analysis. *Medicine (Baltimore), 96*(51), e9167. doi: 10.1097/MD.0000000000009167.

Wiffen, P. J., Derry, S., Bell, R. F., Rice, A. S., Tolle, T. R., Phillips, T., & Moore, R. A., (2017). Gabapentin for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews, June 2017*(6), CD007938. https://doi-org.ezproxy.library.und.edu/10.1002/14651858.CD007938.

Zhang, M., Gao, C. X., M., K. T., Li., L., Dai., Z. G., Wang, S., & Si., J. Q. (2018). A meta-analysis of therapeutic efficacy and safety of gabapentin in the treatment of postherpetic neuralgia from randomized controlled trials. *BioMed Research International, 2018,* 7474207. doi: 10.1155/2018/7474207.