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Practice Parameter: Treatment of postherpetic neuralgia

An evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology*

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Abstract—A systematic review of the literature on postherpetic neuralgia was performed. The authors identified studies using the National Library of Medicine's Medline database and Cochrane Library database. The authors determined absolute reduction rate, number needed to treat (NNT), 95% CI for NNT, and number needed to harm (NNH) for successful therapies of postherpetic neuralgia. Tricyclic antidepressants, gabapentin, pregabalin, opioids, and lidocaine patch were found to be effective in reducing the pain of postherpetic neuralgia.

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Acute herpetic neuralgia is characterized as burning, aching, electric shock like pain, or unbearable itching in association with the outbreak of a herpes zoster rash. The pain is associated with dysesthesias, paresthesias, hyperalgesia, hyperesthesia, and allodynia (production of pain by innocuous stimuli).¹ The pain may precede the onset of the herpetic rash and, rarely, herpetic neuralgia can occur without the development of a rash.² Postherpetic neuralgia, persistence of the pain of herpes zoster more than 3 months after resolution of the rash, is relatively common, affecting 10 to 15% of those with herpes zoster. Zoster-associated pain is used to describe the continuum of pain from acute herpes zoster to the development of postherpetic neuralgia. The time interval used in the clinical case definition of postherpetic neuralgia varies in the literature from 1 to 6 months after resolution of the rash. The incidence of postherpetic neuralgia increases with age.³ The duration of postherpetic neuralgia is highly variable. In a longitudinal study, of those who developed postherpetic neuralgia, only 48% were symptomatic 1 year after onset.^{4,5} A prospective study of postherpetic neuralgia, performed through a network of primary care

providers in Iceland from 1990 to 1995, showed that 14 of the 25 who developed postherpetic neuralgia were symptomatic 12 months after onset.⁶ Thus, the natural history of resolution of postherpetic neuralgia over time is a confounder in the evaluation of treatment efficacy and may limit the ability to generalize the results of controlled clinical trials in this population.

Administration of antiviral agents within 72 hours of the onset of herpes zoster can reduce the intensity and duration of acute illness, and can prevent postherpetic neuralgia,⁷ as may the use of amitriptyline.⁸ Efforts at prevention of herpes zoster and postherpetic neuralgia are important in that 40 to 50% of those with postherpetic neuralgia do not respond to any treatment.⁹ The treatment of acute herpes zoster¹⁰ and the prevention of postherpetic neuralgia are beyond the scope of this parameter.

This practice parameter was developed to answer the following clinical question: In patients with postherpetic neuralgia, which treatments provide benefit in terms of decreased pain and improved quality of life?

Process. We searched the National Library of Medicine's Medline database and the Cochrane database for peer-reviewed articles published between 1960 and August 2003, updating in January 2004,

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the September 28 issue to find the title link for this article.

*Members of the Quality Standards Subcommittee are listed in the Appendix on page 964.

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Table 1 Classification of evidence and formulation of recommendations

Rating of recommendation	Translation of evidence to recommendations	Rating of therapeutic article
A = Established as effective, ineffective, or harmful for the given condition in the specified population	Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies	Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) Primary outcome(s) is/are clearly defined. b) Exclusion/inclusion criteria are clearly defined. c) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias. d) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
B = Probably effective, ineffective, or harmful for the given condition in the specified population	Level B rating requires at least one convincing class II study or at least three consistent class III studies	Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criteria a–d.
C = Possibly effective, ineffective, or harmful for the given condition in the specified population	Level C rating requires at least two convincing and consistent class III studies	Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
U = Data inadequate or conflicting. Given current knowledge, treatment is unproven.		Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

using MeSH terms herpes zoster/*complications and neuralgia/*treatment. We first reviewed titles and abstracts of these articles, searching for interventions that decrease the pain of postherpetic neuralgia. Inclusion criteria were articles 1) that addressed alleviation of pain in postherpetic neuralgia, with duration of at least 8 weeks after healing of the herpetic rash, 2) were prospective, retrospective, or case series studies that provided clinical information on the subjects who received treatment, 3) that provided detailed methodology, and a clear outcome measure, 4) whose primary purpose was to demonstrate a decrease of pain related to postherpetic neuralgia, and 5) where treatment was feasible for an outpatient setting. Based upon this initial review, selected articles were then reviewed in their entirety by two of the authors. We searched for additional articles in the references of review articles on the treatment of postherpetic neuralgia, and by Medline searches using the names of authors who had published several articles on herpes zoster treatment.

From articles meeting our search criteria, we compiled an evidence table by extracting methodologic characteristics: method and setting of cohort assem-

bly, number, sex, and age of patients studied, duration of symptoms, duration of follow-up, and number of subjects lost to follow-up. For class I and class II studies, we calculated, where possible, absolute risk reduction (ARR) (the proportion of the control group with benefit minus the proportion of the treated group with benefit); number needed to treat (NNT) for adequate pain relief (the number of subjects who need to receive treatment for one patient to have substantial benefit, corrected for placebo response, as determined by the authors of the study); 95% CI of the NNT; and number needed to harm (NNH) (the number of subjects that need to receive treatment for one patient to suffer harm), defined as an adverse event sufficient to cause withdrawal from treatment. All were calculated using intent to treat analysis. We scored articles on class of evidence using criteria in table 1. If the reviewers were discordant on the level of evidence, discussion was held until the level of evidence was resolved. Based upon literature on treatment of chronic cancer pain, we defined adequate pain relief of postherpetic neuralgia (in articles using the visual analog score [VAS] or a Likert scale) as reduction of pain to below 4, or reduction of

Table 2 Treatment categories for postherpetic neuralgia

Group 1: Medium to high efficacy, good strength of evidence, and low level of side effects	Group 2: Lower efficacy than those listed in group 1, or limited strength of evidence, or side effect concerns	Group 3: Evidence indicating no efficacy compared to placebo	Group 4: Reports of benefit limited to class IV studies
Gabapentin Lidocaine patch Oxycodone or morphine sulfate, controlled release Pregabalin Tricyclic antidepressants	Aspirin in cream or ointment Capsaicin, topical Methylprednisolone, intrathecal*	Acupuncture Benzydamine cream Dextromethorphan Indomethacin Lorazepam Methylprednisolone, epidural Vincristine iontophoresis Vitamin E Zimelidine	Biperidin Carbamazepine Chlorprothixene Cryocautery Dorsal root entry zone lesion Extract of <i>Ganoderma lucidum</i> He:Ne laser irradiation Ketamine Methylprednisolone, iontophoresis Morphine sulfate, epidural Nicardipine Piroxicam, topical Stellate ganglion block Triamcinolone, intralesional

* While there were no severe adverse effects in the reviewed studies, there is potential for chemical meningitis and arachnoiditis with the use of intrathecal methylprednisolone. Methylprednisolone is not approved by the US FDA for intrathecal use in this indication. The concurrent use of intrathecal lidocaine carries the risk of hypotension and respiratory depression. Therefore, these injections are best given by experienced medical personnel in a hospital setting.

the VAS or Likert scale by 50%.¹¹ When other methods of assessment of pain reduction were used, we adopted the authors' definition of moderate (or greater) improvement. Mechanical allodynia can be as debilitating as the chronic component of postherpetic neuralgia. This type of pain was not always assessed in the peer-reviewed literature. As such, it is not discussed further here.

Internal and external review of the document. The first author drafted the document with input and approval from other work group members. After QSS review and approval, the document was circulated to members of AAN Member Review Network and to heads of sections of the AAN. These reviews were addressed before submission to *Neurology*.

Analysis of the evidence. A total of 206 articles met the original Medline search criteria. A total of 111 articles pertained to the treatment of postherpetic neuralgia and were reviewed in their entirety. Forty-two met the predefined inclusion criteria. Nine additional articles meeting the inclusion criteria were found by the search of the bibliographies of review articles, by searching Medline using names of primary authors in the original search. The evidence table for all studies is available on the *Neurology* Web site at www.neurology.org (table E-1).

Tricyclic antidepressants. Eight of 22 articles on use of tricyclic antidepressants met inclusion criteria. In two class I studies,^{12,13} four class II studies,¹⁴⁻¹⁷ and two class IV studies,^{18,19} tricyclic antidepressants were found to be of benefit in treatment of postherpetic neuralgia (table 2).

In two class II studies amitriptyline was compared

to placebo¹⁶ and lorazepam¹⁵ and was found superior to lorazepam and to placebo. A double-blind, placebo-controlled, crossover study found that VAS was decreased with amitriptyline. ARR was 65% and NNT was 1.6 (95% CI 1.2 to 2.4).¹⁶ In a randomized, placebo-controlled, multi-armed crossover study, amitriptyline was found to be superior to both lorazepam and placebo (NNT = 3.2, 95% CI 2.1 to 6.6).¹⁵

Both amitriptyline and nortriptyline, when studied in a randomized, double-blind, crossover trial, resulted in decrease in the VAS (67% of each group reported at least a good response to treatment) and were designated by subjects to be effective in controlling pain (class II).²⁰ While there was a similar magnitude of benefit for both, fewer side effects were reported with nortriptyline. Desipramine was compared to benztropine as an active placebo, in a randomized placebo-controlled study.¹⁴ ARR was 63% and NNT was 1.6 (95% CI 1.1 to 2.6).

In a randomized, double-blind, crossover study, both amitriptyline and maprotiline reduced the VAS when compared to baseline (class II).¹² Amitriptyline had slightly greater efficacy than maprotiline (NNT = 32 for amitriptyline over maprotiline).

A recent double-blind, placebo-controlled, crossover trial compared efficacy of tricyclic antidepressants and opioids in comparison to placebo.¹³ The study was designed to emulate clinical practice. If a subject failed to have improvement during the titration phase a backup medication from the same class was used (desipramine if nortriptyline was not tolerated and methadone if morphine was not tolerated). Forty-four of the initially randomized 76 subjects completed all three treatment periods. Both opioids

and tricyclic antidepressants had similar proportions of treatment responders ($\geq 50\%$ reduction in VAS) with a trend toward favoring opioids (opioids, NNT = 3.0, 95% CI 2.0 to 5.5; tricyclic antidepressants, NNT = 6.2, 95% CI 3.2 to 294). For primary treatments slow-release morphine was more effective than nortriptyline in reducing the pain of postherpetic neuralgia. While there were more side effects reported with opioids, there was little impairment on cognitive testing and more subjects preferred opioids to tricyclic antidepressants.

Conclusion. Based upon class I and class II evidence, the tricyclic antidepressants amitriptyline, nortriptyline, maprotiline, and desipramine are effective in lessening the pain of postherpetic neuralgia.

Antiepileptic drugs. Six of 37 articles that included antiepileptic drugs met inclusion criteria. Of these, three were class I and are discussed further. In a multicenter, randomized, placebo-controlled, double-blind study with 225 subjects, gabapentin, which blocks the $\alpha_{2\delta}$ subunit of a voltage dependent Ca^{2+} channel,²¹ was found to be of benefit in reducing the pain of postherpetic neuralgia (class I).²² Eighty-three percent received $\geq 2,400$ mg and 65% received 3,600 mg daily. The average decrease in an 11-point Likert scale (labeled graduated pain scale from 0 to 10) was 2.1 on gabapentin and 0.5 on placebo. Based upon the subjects' global perception of benefit 66 out of 94 subjects (who responded) on gabapentin had improvement (NNT = 2.2, 95% CI 1.7 to 3.0 for any improvement, NNT = 2.8 for moderate improvement). Intolerable adverse effects leading to withdrawal from the study from gabapentin were dizziness (5.3%) and somnolence (4.4%) compared to the 1.7% who experienced somnolence on placebo (NNH 10.3). A large multicenter, randomized, double-blind, clinical trial compared gabapentin 1,800 mg/day, 2,400 mg/day, and placebo, with a stable dose maintained for the last 4 of the 7-week study.²³ A 50% or greater decrease in pain, as measured by an 11-point Likert scale, occurred in 74/223 of the subjects on gabapentin (no difference was found between the two doses), but only in 16/111 of those on placebo (ARR = 29.5%, NNT = 5.3 [95% CI 3.6 to 10.2]). More subjects dropped study medications on gabapentin (34/223) than on placebo (7/111, NNH = 11.2). No difference was found in response rate or adverse event rate for the two doses of gabapentin. In a multicenter study pregabalin, an $\alpha_{2\delta}$ ligand, at a dose of 600 mg/day, resulted in half of the subjects having a $\geq 50\%$ reduction in pain compared to 20% on placebo.²⁴ (NNT 3.3, 95% CI 2.3 to 5.9.) Thirty-two percent of subjects discontinued pregabalin due to dizziness, somnolence, or other adverse events compared to 5% on placebo (NNH = 3.7).

There is only class IV evidence of the use of carbamazepine in postherpetic neuralgia.

Conclusion. Based upon two class I studies of gabapentin and a single class I study of pregabalin, these antiepileptic drugs are of benefit in the reduc-

tion of pain from postherpetic neuralgia. Data are insufficient to reach a conclusion on the use of carbamazepine.

Opioids. Five of 12 articles on use of opioids in postherpetic neuralgia met inclusion criteria. Of these, one class I¹³ and two class II^{17,25} are discussed further. A 50% decrease in the VAS was reported for 22 of 38 subjects who completed a double-blind, placebo-controlled, two way crossover study of controlled release oxycodone (class II, ARR = 65%, NNT = 2.5, 95% CI 1.7 to 5.1).¹⁷ Overall dropout rate was 24%. Rate of discontinuation due to treatment failure was similar in both arms (23%). Only one subject stopped treatment because of side effects from the controlled release oxycodone (NNH = 38), while the rest did so because of lack of benefit. In a longitudinal study on use of controlled release oxycodone or morphine, 16 out of 18 subjects had continued benefit after 5 months of treatment (class IV).²⁶ Five of 20 subjects stopped morphine due to intractable nausea and vomiting. Two were successfully switched to controlled release oxycodone and one to methadone.

In the randomized placebo-controlled crossover study described above, opioids were compared to tricyclic antidepressants and to placebo.¹³ Overall, opioids were preferred by the subjects who completed all treatment arms and were well tolerated.

Tramadol, a centrally acting μ opioid agonist and a reuptake blocker of norepinephrine and serotonin, was compared to placebo in a multicenter randomized controlled clinical trial (class II).²⁵ A greater than 50% reduction in pain was reported for 49/63 subjects on tramadol compared to 35/62 on placebo. (NNT = 4.7, 95% CI 2.9 to 19.)

Epidural morphine sulfate was given in an ascending dose after initial placebo injection (class IV). No benefit was found from injection of epidural morphine while one subject experienced a 71% decrease in the VAS after insertion of epidural catheter that lasted for over 6 months and another had a 50% reduction in pain after initial injection of saline placebo.

Conclusion. There is class I evidence that long acting oral opioid preparations and class II evidence that tramadol provides relief in treatment of postherpetic neuralgia.

Topical and intradermal agents. Six of 18 articles on the use of topical anesthetics met inclusion criteria. Based upon an open label (class IV) study of 5% lidocaine gel covered by an occlusive dressing,²⁷ a double-blind, randomized, placebo-controlled, crossover study was performed demonstrating a decrease in the VAS over the 8 hours of application. Benefit persisted for over 4 hours after removal (class I).²⁸ There were three randomized, placebo-controlled, double-blind studies of lidocaine in a woven polyethylene patch. In a crossover design of single treatment session in 35 subjects, the average pain relief was 12.3 mm on the VAS from a baseline severity of 48 mm (class I).²⁹ Benefit was reported in 91% of

subjects, using time to exit as a primary outcome measure in a comparison of lidocaine in polyethylene patch and placebo.³⁰ Only patients with clinical open label improvement with topical lidocaine patch (range of use 0.09 to 8.67 years) were recruited for this randomized, double-blind, placebo-controlled study with enriched enrollment. Subjects exited the arm if they felt that pain relief was inadequate. In this enriched population, time to exit for placebo was 3.8 days and >14 days for lidocaine patch (class II, NNT = 2, 95% CI 1.4 to 3.3). A decrease was found in the Neuropathic Pain Score (NPS-10) for subjects using a 5% lidocaine patch compared to placebo (class II, downgraded from class I).³¹ The primary purpose of this post hoc analysis was to determine the utility of the neuropathic pain scale in postherpetic neuralgia.

Eleven articles on the use of topical anti-inflammatory agents were considered and eight met the criteria. In a randomized, double-blind study, a decrease of 73% in VAS was reported for both topical aspirin in ointment and for 5% lidocaine gel when compared to baseline pain intensity (class III, downgraded from class I because of the comparison of two active agents to baseline condition, inclusion of subjects with postherpetic neuralgia 4 weeks after acute herpes zoster, and a lack of complete baseline information on pain severity).³² Based upon an earlier pilot study,³³ a randomized, double-blind, placebo-controlled crossover study of anti-inflammatory agents was performed on 22 subjects. Aspirin/diethyl ether cream was found to decrease the VAS, with an ARR of 32% (NNT = 3, 95% CI 1.7 to 26.1), but indomethacin/diethyl ether and diclofenac/diethyl ether did not (class II).³⁴ There is class II evidence that benzydamine cream is not of benefit.³⁵ There is only class IV evidence for the use of aspirin in chloroform, piroxicam gel, benzydamine cream, and iontophoresis of methylprednisolone.

Capsaicin causes degeneration of intracutaneous nerve fibers. Nine of 24 articles on use of capsaicin met inclusion criteria. In a 6-week randomized, double-blind, placebo-controlled study of 0.075% capsaicin (class I), there was a reduction in the VAS score in 48 of the 74 subjects who received capsaicin (NNT = 3.2, 95% CI 2.1 to 6.3).³⁶ However, magnitude of benefit was a maximum of a 23% decrease in baseline VAS after 4 weeks. Burning was reported in 60% of subjects on capsaicin vs 30% on placebo. However, no subjects stopped treatment because of adverse effects. Seventy-seven of 83 subjects in the 2-year open label continuation of the study were able to maintain pain relief with capsaicin. In the class II study there was a 30% reduction in VAS (from 71 mm to 49 mm) at the end of 6 weeks.³⁷ Rate and magnitude of benefit varied greatly among class IV studies.³⁸⁻⁴³

In a randomized, placebo-controlled, single-blind study of iontophoresis of vincristine, only minimal benefit was found and all subjects reported burning at electrode sites (class II).⁴⁴ Reports of benefit from

topical application of lidocaine gel,⁴⁵ topical lignocaine/prilocaine cream,⁴⁶ intralesional injections of triamcinolone,⁴⁷⁻⁴⁹ and cryocautery with dry ice⁵⁰ were limited to class IV studies.

Conclusion. Based upon class I evidence, topical lidocaine is effective in reducing the pain of postherpetic neuralgia. Based on class II and class III evidence, aspirin in ointment or cream is probably effective in reducing the pain of postherpetic neuralgia. The magnitude of benefit for topical capsaicin and for aspirin in cream is below the level that is considered clinically important in treatment of chronic pain.

NMDA antagonist. Based on the possibility that NMDA antagonists play a role in the processing of nociceptive inputs, the NMDA antagonists ketamine, dextromethorphan, and memantine have been tried in treatment of postherpetic neuralgia. Three of six articles on use of NMDA antagonists met inclusion criteria. In a randomized, placebo-controlled, double-blind, crossover study of high doses of dextromethorphan, there was no improvement when compared to placebo.⁵¹ Five of 18 subjects could not complete the dextromethorphan arm of the study due to sedation (class II). Long lasting benefit has been reported in one subject using ketamine in several forms (class IV).⁵² In a randomized, controlled clinical trial memantine was not superior to placebo (class II).⁵³

Conclusion. There are single class II studies with evidence for the lack of efficacy of the NMDA antagonists dextromethorphan and memantine in treatment of postherpetic neuralgia.

Other modalities. An independent observer was used in a randomized, controlled, single-blind study of four weekly injections of 60 mg of preservative-free methylprednisolone; given either intrathecally or into the epidural space (class II [methylprednisolone is not approved for intrathecal administration by the US Food and Drug Administration; preservative-free methylprednisolone is not currently available in the United States]).⁵⁴ There was substantial benefit for the intrathecal group at 1 and 24 weeks after completion of the series, with a NNT of 1.4 (95% CI 1.0 to 2.1). No benefit was found with epidural injections. A more extensive study of a different population of 277 patients was performed by the same group using the same 4-week paradigm.⁵⁵ In this double-blind, randomized, controlled clinical trial (class I) of patients who had failed conventional treatments, with symptom duration of 38 ± 19 months, subjects were randomized to receive 60 mg of preservative-free methylprednisolone in 3 mL of 3% lidocaine, 3 mL of 3% lidocaine, or control group which did not undergo lumbar puncture. A physician blinded to treatment assignment performed independent assessment of pain. Ninety percent of the methylprednisolone group had good to excellent relief of pain at end of the treatment, which continued through the 2 years of follow-up (NNT = 1.3, 95% CI 1.2 to 1.5). No adverse events were reported in 2 years of follow-up of their subjects. Case series of

subjects who have received intrathecal methylprednisolone for other conditions report a risk for development of chemical meningitis, transverse myelitis, and chronic arachnoiditis.⁵⁶

In a class II study lorazepam was no different than placebo in the control of postherpetic neuralgia.¹⁵ In a randomized study that compared acupuncture to sham transcutaneous electrical stimulation (TENS), using a blinded independent assessor, neither treatment resulted in improvement over baseline pain severity (class II).⁵⁷ This negates the two case series (class IV) showing benefit for acupuncture.^{58,59} There were only class IV studies of He:Ne laser irradiation, nicardipine, chlorprothixene, biperiden, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, stellate ganglion block, and vitamin E.

Conclusion. Based on single class I and II studies, intrathecal methylprednisolone was effective in reducing the pain of postherpetic neuralgia. Due to the invasive nature of this treatment, potential for arachnoiditis, and difficulty in obtaining preservative-free methylprednisolone, it should be considered only after agents noted above have been tried and failed. The minimal benefit reported for iontophoresis of vincristine is negated by side effects.

Recommendations.

1. Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of postherpetic neuralgia (Level A, class I and II). There is limited evidence to support nortriptyline over amitriptyline (Level B, single class II study) and the data are insufficient to recommend one opioid over another. Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine.
2. Aspirin in cream is possibly effective in the relief of pain in patients with postherpetic neuralgia (Level C, class II and III) but the magnitude of benefit is low, as is seen with capsaicin (Level A, class I and II).
3. In countries where preservative-free intrathecal methylprednisolone is available, it may be considered in the treatment of postherpetic neuralgia (Level A, class I and II).
4. Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimeldine are not of benefit (Level B, class II).
5. The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of

postherpetic neuralgia (Level U, single class II study and class IV studies).

6. There is insufficient evidence at this time to make any recommendations on the long-term effects of these treatments.

Future research. Further areas for research in treatment of postherpetic neuralgia should expand upon variety of treatments, the natural history of postherpetic neuralgia, and response of the various components of the pain of postherpetic neuralgia (dysesthesias, paresthesias, hyperalgesia, hyperesthesia, and allodynia) to treatment. The contribution of evoked pain in the outcomes assessment of treatment of postherpetic neuralgia needs to be further addressed. The case definition of postherpetic neuralgia has changed, with a trend toward a longer duration of symptoms required to distinguish postherpetic neuralgia from acute herpetic neuralgia. This is a major confounder in any attempt to generalize the results of many studies. Direct comparison studies of topical and oral agents are needed. Research into use of combinations of therapies and therapies aimed at disease modification needs to be addressed. Long-term efficacy of treatments of postherpetic neuralgia must be compared to the natural history for resolution of postherpetic neuralgia.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use specific procedures. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all the circumstances involved.

Appendix

Quality Standards Subcommittee members: Gary Franklin, MD, MPH (Co-Chair); Gary Gronseth, MD (Co-Chair); Milton Alter, MD (ex-officio); Charles E. Argoff, MD; Steven A. Ashwal, MD (ex-officio); Christopher Bever, Jr., MD; Jody Corey-Bloom, MD, PhD; John D. England, MD; Jacqueline French, MD (ex-officio); Gary H. Friday, MD, MPH; Michael J. Glantz, MD; Deborah Hirtz, MD; Donald J. Iverson, MD; David J. Thurman, MD; Samuel Wiebe, MD; William J. Weiner, MD; and Catherine Zahn, MD (ex-officio).

References

1. Merskey N, Bogduk N. Classification of Chronic Pain, IASP Task Force on Taxonomy. Seattle: IASP Press, 1994.
2. Gilden DH, Wright RR, Schneck SA, Gwaltney JM, Mahalingam R. Zoster sine herpete, a clinical variant. *Ann Neurol* 1994;35:530–533.
3. de Moragas JM, Kierland RR. The outcome of patients with herpes zoster. *Arch Dermatol* 1957;75:193–196.
4. Watson PN, Evans RJ. Postherpetic neuralgia. A review. *Arch Neurol* 1986;43:836–840.
5. Watson CP, Evans RJ, Watt VR, Birkett N. Post-herpetic neuralgia: 208 cases. *Pain* 1988;35:289–297.
6. Helgason S, Petursson G, Gudmundsson S, Sigurdson JA. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow-up. *BMJ* 2000;321:794–796.
7. Kost RG, Straus SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. *N Engl J Med* 1996;335:32–42.

8. Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double blind, placebo-controlled trial. *J Pain Symptom Manage* 1997;13:327-331.
9. Rowbotham MC, Petersen KL. Zoster-associated pain and neural dysfunction. *Pain* 2001;93:1-5.
10. Gnann JWW, Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med* 2002;347:340-346.
11. The management of chronic pain in older persons: AGS Panel on Chronic Pain in Older Persons. American Geriatrics Society. *J Am Geriatr Soc* 1998;46:635-651.
12. Watson CP, Chipman M, Reed K, Evans RJ, Birkett N. Amitriptyline versus maprotiline in postherpetic neuralgia: a randomized, double-blind, crossover trial. *Pain* 1992;48:29-36.
13. Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2002;59:1015-1021.
14. Kishore-Kumar R, Max MB, Schafer SC, et al. Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990;47:305-312.
15. Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology* 1988;38:1427-1432.
16. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology* 1982;32:671-673.
17. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology* 1998;50:1837-1841.
18. Weis O, Sriwatanakul K, Weintraub M. Treatment of post-herpetic neuralgia and acute herpetic pain with amitriptyline and perphenazine. *S Afr Med J* 1982;62:274-275.
19. Watson CP, Evans RJ. A comparative trial of amitriptyline and zimelidine in post-herpetic neuralgia. *Pain* 1985;23:387-394.
20. Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology* 1998;51:1166-1171.
21. Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. *J Biol Chem* 1996;271:5768-5776.
22. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA* 1998;280:1837-1842.
23. Rice ACS, Maton S. Gabapentin in postherpetic neuralgia: a randomized, double blind, placebo controlled study. *Pain* 2001;94:215-224.
24. Dworkin RH, Corbin AE, Young JP, Jr., et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2003;60:1274-1283.
25. Boureau F, Legallier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain* 2003;104:323-331.
26. Pappagallo M, Campbell JN. Chronic opioid therapy as alternative treatment for post-herpetic neuralgia. *Ann Neurol* 1994;35 Suppl:S54-56.
27. Rowbotham MC, Fields HL. Topical lidocaine reduces pain in post-herpetic neuralgia. *Pain* 1989;38:297-301.
28. Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. *Ann Neurol* 1995;37:246-253.
29. Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996;65:39-44.
30. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain* 1999;80:533-538.
31. Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. *Clin J Pain* 2002;18:297-301.
32. Tajti J, Szok D, Vecsei L. Topical acetylsalicylic acid versus lidocaine for postherpetic neuralgia: results of a double-blind comparative clinical trial. *Neurobiology (Bp)* 1999;7:103-108.
33. De Benedittis G, Besana F, Lorenzetti A. A new topical treatment for acute herpetic neuralgia and post-herpetic neuralgia: the aspirin/diethyl ether mixture. An open-label study plus a double-blind controlled clinical trial. *Pain* 1992;48:383-390.
34. De Benedittis G, Lorenzetti A. Topical aspirin/diethyl ether mixture versus indomethacin and diclofenac/diethyl ether mixtures for acute herpetic neuralgia and postherpetic neuralgia: a double-blind crossover placebo-controlled study. *Pain* 1996;65:45-51.
35. McQuay HJ, Carroll D, Moxon A, Glynn CJ, Moore RA. Benzhydramine cream for the treatment of post-herpetic neuralgia: minimum duration of treatment periods in a cross-over trial. *Pain* 1990;40:131-135.
36. Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Ther* 1993;15:510-526.
37. Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. *J Am Acad Dermatol* 1989;21(2 Pt 1):265-270.
38. Don PC. Topical capsaicin for treatment of neuralgia associated with herpes zoster infection. *J Am Acad Dermatol* 1988;18(5 Pt 1):1135-1136.
39. Frucht-Pery J, Feldman ST, Brown SI. The use of capsaicin in herpes zoster ophthalmicus neuralgia. *Acta Ophthalmol Scand* 1997;75:311-313.
40. Peikert A, Hentrich M, Ochs G. Topical 0.025% capsaicin in chronic post-herpetic neuralgia: efficacy, predictors of response and long-term course. *J Neurol* 1991;238:452-456.
41. Watson CP, Evans RJ, Watt VR. Post-herpetic neuralgia and topical capsaicin. *Pain* 1988;33:333-340.
42. Hawk RJ, Millikan LE. Treatment of oral postherpetic neuralgia with topical capsaicin. *Int J Dermatol* 1988;27:336.
43. Bernstein JE, Bickers DR, Dahl MV, Roshal JY. Treatment of chronic postherpetic neuralgia with topical capsaicin. A preliminary study. *J Am Acad Dermatol* 1987;17:93-96.
44. Layman PR, Argyras E, Glynn CJ. Iontophoresis of vincristine versus saline in post-herpetic neuralgia. A controlled trial. *Pain* 1986;25:165-170.
45. Kissin I, McDanal J, Xavier AV. Topical lidocaine for relief of superficial pain in postherpetic neuralgia. *Neurology* 1989;39:1132-1133.
46. Stow PJ, Glynn CJ, Minor B. EMLA cream in the treatment of post-herpetic neuralgia. Efficacy and pharmacokinetic profile. *Pain* 1989;39:301-305.
47. Epstein E. Intralesional triamcinolone therapy in herpes zoster and postzoster neuralgia. *Eye Ear Nose Throat Mon* 1973;52:416-417.
48. Epstein E. Treatment of zoster and postzoster neuralgia by the intralesional injection of triamcinolone: a computer analysis of 199 cases. *Int J Dermatol* 1976;15:762-769.
49. Epstein E. Treatment of herpes zoster and postzoster neuralgia by subcutaneous injection of triamcinolone. *Int J Dermatol* 1981;20:65-68.
50. Suzuki H, Ogawa S, Nakagawa H, et al. Cryocautery of sensitized skin areas for the relief of pain due to post-herpetic neuralgia. *Pain* 1980;9:355-362.
51. Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997;48:1212-1218.
52. Klepstad P, Borchgrevink PC. Four years' treatment with ketamine and a trial of dextromethorphan in a patient with severe post-herpetic neuralgia. *Acta Anaesthesiol Scand* 1997;41:422-426.
53. Eisenberg E, Kleiser A, Dortort A, Haim T, Yarnitsky D. The NMDA (N-methyl-D-aspartate) receptor antagonist memantine in the treatment of postherpetic neuralgia: a double-blind, placebo-controlled study. *Eur J Pain* 1998;2:321-327.
54. Kikuchi A, Kotani N, Sato T, Takamura K, Sakai I, Matsuki A. Comparative therapeutic evaluation of intrathecal versus epidural methylprednisolone for long-term analgesia in patients with intractable postherpetic neuralgia. *Reg Anesth Pain Med* 1999;24:287-293.
55. Kotani N, Kushikata T, Hashimoto H, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Engl J Med* 2000;343:1514-1519.
56. Nelson D. Intraspinal therapy using methylprednisolone acetate: twenty-three years of clinical controversy. *Spine* 1993;18:278-286.
57. Lewith GT, Field J, Machin D. Acupuncture compared with placebo in post-herpetic pain. *Pain* 1983;17:361-368.
58. Jolly C. Acupuncture and postherpetic neuralgia. *BMJ* 1980;281:871.
59. Lewith GT, Field J. Acupuncture and postherpetic neuralgia. *BMJ* 1980;281:622.

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