Treatments for postherpetic neuralgia—a systematic review of randomized controlled trials

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Background. A number of different therapies have been used for postherpetic neuralgia. We decided to conduct a systematic review of existing randomized controlled trials.

Objective. To determine the efficacy of available therapies for relieving the pain of established postherpetic neuralgia.

Methods. We performed a systematic review, including meta-analysis, of existing randomized controlled trials. Eleven published trials and one unpublished trial were identified which met the inclusion criteria and were included in the current review.

Results. Pooled analysis of the effect of tricyclic antidepressants demonstrate statistically significant pain relief (OR 0.15, CI 0.08-0.27). Pooling of the results of the three trials comparing the effects of capsaicin and placebo could not be done due to heterogeneity. This heterogeneity was mainly attributable to an unpublished trial which differed in terms of the dose and duration of treatment. When this study was omitted, no heterogeneity was found and the pooled analysis revealed a statistically significant benefit (OR 0.29, 95% CI 0.16-0.54). However, problems with blinding in patients using capsaicin may have accounted for the positive effect. One small study of vincristine iontophoresis compared to placebo also yielded a favourable result (OR 0.05, 95% 0.01-0.26). Other treatment evaluated include lorazepam, acyclovir, topical benzydamine, and acupuncture. We found no evidence that these are effective in relieving pain associated with postherpetic neuralgia.

Conclusion. Based on evidence from randomized trials, tricyclic anti-depressants appear to be the only agents of proven benefit for established postherpetic neuralgia.

Keywords. Postherpetic neuralgia, treatment, systematic review, meta-analysis, randomized controlled trials.

Introduction

Postherpetic neuralgia (PHN) has been defined as pain persisting in the dermatomes affected by herpes zoster (shingles) after the disappearance of the characteristic rash caused by the infection.¹

Estimates of the overall incidence of PHN from population-based studies vary from 9-14%.²,³ However, the frequency of the condition is strongly related to age and incidence in patients over the age 60 years has been reported to exceed 50%.⁴ In those who are affected by this condition, pain persists three months after the infection in half the cases and up to one third continue to experience pain one year after onset.³,⁵ The nature of the pain may be steady and boring or paroxysmal and lancinating. Itching and allodynia (pain from a non-painful stimulus) are also frequently encountered. While most cases of PHN appear to resolve spontaneously, the condition can be prolonged, severe and debilitating, especially in the elderly.

To date an effective treatment for established PHN has been elusive. The wide variety of medical and surgical strategies attempted over the years testifies to the need for agreement on which treatments are of proven therapeutic value.⁶

In view of the lack of consensus prevailing in this area we decided to conduct a systematic review (including meta-analysis) of existing randomized controlled trials that have examined the effectiveness of treatments
for PHN. Our *a priori* hypothesis was that clinically worthwhile pain relief can be achieved by treating established PHN. We were particularly interested in therapies that could be used in ambulatory patients. This study follows a recent review of evidence for the prevention of PHN by means of treatment during the acute phase of herpes zoster.7

**Methods**

**Inclusion criteria**
Studies were included in the analysis if at least two treatment groups could be identified and treatment allocation had been by formal randomization. The review was restricted to trials which evaluated the effect of treatment on patients suffering from PHN (defined as pain persisting one month or more after the onset of herpes zoster) and in which only patients with this condition were studied. All randomized trials identified up until December 1993 were included.

**Identification of studies**
In order to identify published trials the Medline and Embase databases were searched using the Datastar software system and the search terms ‘herpes zoster’ and ‘postherpetic neuralgia’ in combination with ‘randomized controlled trials’ or ‘prospective’ or ‘random allocation’ or ‘double-blind method’. Publications obtained by means of this strategy were examined for relevant references. In addition, previous reviews, conference abstracts and major medical textbooks were handsearched for references. Where unpublished trials were identified, authors were contacted for details.

**Outcome measures**
In this review the outcome measure of interest was the number of subjects in each group who reported pain relief at the end of the treatment period. The usual methods for quantifying pain relief involved asking patients to mark a visual analogue scale or reporting response with the aid of a verbal rating scale. A favourable outcome was one in which the investigators of the study considered pain relief to have been clinically significant.

**Data extraction**
Information on the following items was obtained for each study: 1) study design; 2) study population; 3) interventions used; 4) pain relief; and 5) adverse effects. Data were extracted from published reports by two authors (JV and SG) and disagreements were resolved by discussion with a third (TL).

**Assessment of study quality**
The methodological quality of the studies included in the review was assessed using a scheme previously described. Accordingly three dimensions of each trial which are potential sources of bias were assessed: 1) the quality of the randomization procedure (control of selection bias at entry); 2) the extent to which the primary analysis included all subjects initially randomized (control of selection bias after entry); 3) the extent to which those assessing outcome were aware of the treatment of those being assessed (control of bias in assessment of outcome). As the measures of pain were self-report, ratings on dimension 3 were based on the degree to which patients were judged to have been aware of their treatment group. The quality rating for each dimension was assessed using a three point scale ranging from 1 if there had been little or no effort to control bias to 3 if the effort to control bias was maximal.

**Statistical methods**
Where appropriate a meta-analysis was performed using the Mantel-Haentzel-Peto method. The method involves calculating for each trial the expected number of events in the experimental group under the assumption that treatment had no effect. This number of expected events (E) is then subtracted from the number of events that were actually observed (O) in the experimental group. Adding these separate differences (O—E) and their variances derived from each trial yields a statistic that can be used to test whether the totalled (O—E) differs more from zero than can be expected from chance. Under the ‘fixed effect’ assumption that all trials are estimating the same underlying effect, an overall average of observed treatment effects is obtained by weighting each treatment effect (O—E/V) inversely according to its variance. As (O—E/V) can be regarded as an approximation to the log odds ratio an average odds ratio can be derived which together with its 95% confidence interval estimates the magnitude of the overall effect. Before pooling the results we conducted formal tests for homogeneity in treatment effects using the chi-square statistic. All estimates reported in this review are based on an ‘intention-to-treat’ analysis.

**Results**
Eleven published trials and one unpublished trial were identified which met the inclusion criteria. Five studies evaluated the effect of tricyclic antidepressants. In three of these, amitriptyline or desipramine was compared with placebo. Amitriptyline was also compared with maprotiline. A further trial compared the efficacy of a combination of clomipramine and the anti-convulsant carbamazepine with that of transcutaneous electrical nerve stimulation. One trial comparing zimelidine with amitriptyline was identified. However, this study was excluded from the present review as treat-
ment allocation had not been randomized. Published placebo-controlled trials were also identified for lorazepam, acyclovir, capsaicin, benzydamine, vincristine iontophoresis and acupuncture.

Examination of conference abstracts revealed one unpublished trial of capsaicin and another of indomethacin stufe. Attempts to contact the authors by letter and by telephone yielded information on only one of these (capsaicin) and this study was subsequently included in the review.

Characteristics of the trials included in this report are summarized in Table 1. We calculated estimates of effectiveness expressed as odds ratios (OR) with 95% confidence intervals (CI) for failure to obtain pain relief. An OR less than 1 indicates that treatment is beneficial; while an OR greater than 1 favours the control intervention. When the 95% CI for the OR overlaps 1 the effect is not statistically significant.

Both amitriptyline and desipramine appear to be effective for relieving pain associated with PHN. Estimates of effect are graphically represented in Figure 1. In one trial of amitriptyline relatively fewer patients receiving the drug responded. This may have been due to the low average dose of 65 mg/day in this study compared with doses of 75 mg/day for amitriptyline and 167 mg/day for desipramine in the two comparable studies. As no heterogeneity was detected among this group of trials (chi-square = 2.57, df = 2, P > 0.2) a pooled estimate was produced which shows a statistically significant greater likelihood of pain relief in those receiving antidepressants compared with patients treated with placebo (OR 0.15, 95% CI 0.03-0.7). Visual analogue scores for physical activity and mental outlook also showed greater improvement in the drug group but the differences between the two treatment groups did not reach statistical significance for these outcomes. Although information on adverse effects was collected in this study, it was not reported.

In one trial of amitriptyline the study design also allowed comparison of the benzodiazapine lorazepam with placebo. This drug was not found to be effective in relieving PHN (OR 1.00, 95% CI 0.24-4.18). Important adverse effects were sedation and worsening of mood. Furthermore, severe depression appeared to have been triggered by treatment in four patients.

Treatment with acyclovir has been tested in one small double-blind, controlled trial. No demonstrable benefit was found over placebo (OR 1.16, 95% CI 0.21-6.47). The small sample size may have precluded demonstration of an effect in this study.

Three placebo-controlled trials of topical capsaicin were identified, two of which reported favourable results. Estimates of effect are graphically depicted in Figure 2. Significant heterogeneity was found in this group of trials (chi-square = 9.93, df = 2, P > 0.01). The unpublished study differed from the other two trials in several ways. First, a weaker preparation of capsaicin was used (0.025% versus 0.075%). Second, the duration of treatment was shorter (4 weeks versus 6 weeks). Lastly, the emollient vehicle used was different (Unguentum Merck versus Zostrix cream, Gentem Illinois). When this trial was omitted no heterogeneity was detected (chi-square = 1.51, df = 2, P > 0.2) and the pooled estimate revealed a statistically significant benefit (OR 0.29, 95% CI 0.16-0.54). In all three studies, skin reactions (burning, stinging and erythema) at the site of application were substantially more frequent in those who applied capsaicin cream than in controls. The unblinded study of clomipramine in combination with carbamazepine compared with transcutaneous electrical nerve stimulation (TCENS) achieved the lowest quality rating of the trials included in this review. Of the 16 patients in the drug therapy group three were lost to follow up and four did not respond and were transferred to TCENS treatment. Also, among the 13 patients initially assigned to TCENS, two were lost to follow up and eight crossed over to drug therapy. In estimating treatment effect we considered pain relief to have resulted from the intervention to which patients had originally been randomized. Combination therapy was found to be more successful in relieving pain than TCENS (OR 0.15, 95% CI 0.03-0.7). Visual analogue scores for physical activity and mental outlook also showed greater improvement in the drug group but the differences between the two treatment groups did not reach statistical significance for these outcomes. Although information on adverse effects was collected in this study, it was not reported.

In the trial of the anti-prostaglandin, benzydamine, no benefit was demonstrated with treatment compared to placebo (OR 1.2, 95% CI 0.37-3.92). Rashies were more common in those using benzydamine cream (four patients) than in controls (one patient).

A small study of transdermal, vincristine iontophoresis produced some interesting results. A substantially greater number of patients reported pain relief in the treatment group (vincristine in saline and dimethyl sulphoxide) compared to those in the control group who received saline only (OR 0.05, 95% CI 0.01-0.26). Unfortunately, skin irritation and painless burns were common in both groups.
TABLE 1  Summary of trials included in the review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design, quality rating</th>
<th>Study population</th>
<th>Treatment</th>
<th>Control</th>
<th>Pain relief treatment control</th>
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<tbody>
<tr>
<td>Tri-cyclic antidepressant</td>
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<tr>
<td>Watson et al., 1982 (13)</td>
<td>Double-blind, crossover 2,3,2</td>
<td>PHN &gt; 3 months, median 45.6 months, Age 49-81 years; median 66 years</td>
<td>Amitriptyline for 3 weeks (12.5–25 mg daily increasing by 12.5–25 mg every 2–5 days as required)</td>
<td>Placebo</td>
<td>16/24 1/24 Rated as “excellent” (no pain) or “good” (mild pain)</td>
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<tr>
<td>Max et al., 1988 (14)</td>
<td>Double-blind, crossover 2,2,2</td>
<td>PHN &gt; 3 months, median 19 months, Age 25–86 years; median 72 years</td>
<td>Amitriptyline for 6 weeks (12.5 mg daily increasing by 12.5–25 mg as required)</td>
<td>Lactose placebo (250–1500 mg daily)</td>
<td>16/58 4/58 Rated as “complete”, “a lot” or “moderate”</td>
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<tr>
<td>Kishore-Kumar et al., 1990 (15)</td>
<td>Double-blind, crossover 2,2,2</td>
<td>PHN &gt; 3 months, median 28.5 months, Age 38–79 years; median 62 years</td>
<td>Desipramine for 6 weeks (12.5 mg daily increasing up to 250 mg daily as required)</td>
<td>“Active” Placebo Benztropine (0.5–1 mg daily)</td>
<td>12/26 2/26 Rated as “complete”, “a lot” or “moderate”</td>
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<tr>
<td>Watson et al., 1992 (16)</td>
<td>Double-blind, crossover 3,2,3</td>
<td>PHN &gt; 3 months, median 14 months, Age 55–85 years; median 71 years</td>
<td>Maprotiline for 5 weeks (12.5–25 mg daily increasing by 12.5 mg every 3–5 days as required)</td>
<td>Amitriptyline (12.5–25 mg daily increasing by 12.5 mg every 3–5 days as required)</td>
<td>12/35 15/35 Rated as “no pain” or “mild pain”</td>
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<tr>
<td>Tri-cyclic anti-depressant and anti-convulsant combined</td>
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<tr>
<td>Gerson et al., 1977 (17)</td>
<td>Non-blind, parallel group 1,1,1</td>
<td>PHN &gt; 3 months, Age not given</td>
<td>Clomipramine (10–75 mg daily) and carbamazapine (150–1000 mg daily) for 8 weeks</td>
<td>Transcutaneous Electrical Nerve Stimulation (applied for 15 minutes on each outpatient visit) for 8 weeks</td>
<td>8/16 1/13 Based on improvement of a visual analogue score</td>
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<td>Benzodiazepine</td>
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<tr>
<td>Max et al., 1988 (14)</td>
<td>Double-blind, crossover 2,2,2</td>
<td>PHN &gt; 3 months, median 19 months, Age 25–86 years; median 72 years</td>
<td>Lorazepam (0.5–6 mg daily) for 6 weeks</td>
<td>Lactose placebo (250–1500 mg daily)</td>
<td>4/58 4/58 Rated as “complete”, “a lot” or “moderate”</td>
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<tr>
<td>Antiviral</td>
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<tr>
<td>Surman et al., 1990 (19)</td>
<td>Double-blind, parallel group 3,2,2</td>
<td>PHN &gt; 2 months, mean treatment group 29 months and placebo group 17 months, age 47–82 years; mean 71.6 years, treatment group and 56–81 years (mean 68.6 years) placebo group</td>
<td>Acyclovir (800 mg every 4 hours, during waking hours) for 12 weeks</td>
<td>Placebo</td>
<td>4/11 4/10 “Meaningful Clinical Improvement” based on improvements in scores on McGill Pain Questionnaire</td>
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</table>

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design, quality rating</th>
<th>Study population</th>
<th>Treatment</th>
<th>Control</th>
<th>Pain relief treatment control</th>
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<tbody>
<tr>
<td>Iontophoresis</td>
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<td>Vincristine 0.01% in 0.9% saline and 5% dimethyl sulphoxide given by transdermal iontophoresis 3 times weekly for 4 weeks</td>
<td>Saline 0.9% given by transdermal iontophoresis 3 times weekly for 4 weeks</td>
<td>9/10</td>
</tr>
<tr>
<td>Layman, 1986</td>
<td>Single-blind, parallel group 2,3,2</td>
<td>PHN &gt; 3 months; median 28.5 months; Age 52–83 years; median 70 years</td>
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<td>Acupuncture</td>
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<td>Acupuncture weekly for 8 weeks. Needles were inserted into the pinna and left in situ for 10 min. If no improvement occurred after 2–3 treatments body acupuncture was used</td>
<td>Mock transcutaneous electrical nerve stimulation</td>
<td>7/30</td>
</tr>
<tr>
<td>Lewith et al., 1983</td>
<td>Single-blind, parallel group 3,2,1</td>
<td>PHN &gt; 3 months, median treatment group males 19.6 months, females 41.1 months; control group males 27 months, females 11.5 months. Mean age treatment group males 69.8 years, females 76.4 years; control group mean males 62.4 years, females 75.6 years</td>
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<td>7/32</td>
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<tr>
<td>Topical creams</td>
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<td>Capsaicin 0.075% in a cream base applied locally to painful areas 3–4 times daily for 6 weeks</td>
<td>Identical vehicle cream</td>
<td>8/16</td>
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<tr>
<td>Bernstein et al., 1989</td>
<td>Double-blind, parallel group 3,2,3</td>
<td>PHN &gt; 12 months; mean treatment group males 30 months, control group 41.8 months. Age 54–90 years; mean treatment group 72.3 years, control group 72.6 years</td>
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<tr>
<td>Watson et al., 1993</td>
<td>Double-blind, parallel group 3,2,3</td>
<td>PHN &gt; 6 months; mean treatment group males 26.2 months, control group 38.2 months. Mean age treatment group 71.1 years, control group 70.4 years</td>
<td>Capsaicin 0.075% in a cream base applied locally to painful areas 4 times daily for 6 weeks</td>
<td>Identical vehicle cream</td>
<td>42/74</td>
</tr>
<tr>
<td>Drake et al., 1993</td>
<td>Double-blind, parallel group 2,2,3</td>
<td>PHN &gt; 3 months; mean treatment group males 38 months, control group 25 months. Age all &gt; 60 years; mean treatment group 76 years, control group 78 years</td>
<td>Capsaicin 0.025% in cream base applied locally to painful areas 5 times daily for a week then 4 times daily for a further three weeks</td>
<td>Vehicle cream (Unguentum Merck)</td>
<td>3/15</td>
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<tr>
<td>McQuay, 1990</td>
<td>Double-blind, crossover 2,3,3</td>
<td>PHN &gt; 5 months; mean 23 months; Age: mean 73 years</td>
<td>Benzydamine hydrochloride cream (3% w/w) applied locally up to 6 times daily for 2 weeks</td>
<td>Identical vehicle cream</td>
<td>14/23</td>
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<td>15/23</td>
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**Legend:**
- **PHN >** refers to postherpetic neuralgia.
- **Median** and **mean** values are provided for age and duration where applicable.
- **Improvement** is measured using a variety of methods, including visual analogue scales and verbal pain scales.
Treatments for postherpetic neuralgia

Ktehore-Kumar (1990)  
Max (1988)  
Watson (1982)  
Total

\[ \text{ FIGURE 1 } \text{Treatment with antidepressant compared with placebo} \]

Bernstein (1989)  
Drake (unpublished)  
Watson (1983)  

\[ \text{ FIGURE 2 } \text{Treatment with capsaicin compared with placebo} \]

Finally, in the single trial of acupuncture this treatment could not be shown to be better than mock transcutaneous nerve stimulation in alleviating the pain of PHN (OR 0.92, 95% CI 0.28–3.00). Auricular acupuncture is a painful treatment and proved unpopular with patients. Consequently, 13 of 30 subjects failed to complete the course of therapy compared with three of 32 in the control group.

Discussion

Tricyclic antidepressants have long been advocated for the treatment of postherpetic neuralgia.\textsuperscript{27} The current view is that analgesia is mediated by mechanisms involving serotonin and noradrenaline which act on descending pathways between the brainstem and dorsal horn of the spinal cord.\textsuperscript{28} Pain relief does not appear to take place via effect on mood, as analgesia occurs even in the majority of sufferers that are not depressed.\textsuperscript{29,30} The trials reported in this review comparing amitriptyline or desipramine with placebo consistently demonstrate a beneficial effect. At low doses, anticholinergic side effects and sedation do not present a major problem. The antidepressant maprotiline was found to be no more effective than amitriptyline and tended to produce more adverse effects. An interesting observation reported in this study is that some patients who did not respond to amitriptyline showed a favourable response to treatment with maprotiline and vice versa. This may indicate some between individual variation in the mechanisms underlying pain relief.

Although a previous study of clomipramine suggested that this drug was not useful in the treatment of PHN\textsuperscript{31} it seems that in combination with carbamazepine it could possibly have a role. The simultaneous use of these drugs resulted in increased plasma levels of both clomipramine and its primary metabolite and this interaction may have enhanced the effect of the antidepressant. It should, however, be stressed that this study has a number of methodological shortcomings and the authors also did not report on side effects. The results are therefore difficult to interpret.

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is a derivative of certain species of plants of the nightshade family.\textsuperscript{32} The basis of capsaicin's action is thought to be its ability to enhance the release of substance P from small diameter nociceptive afferent nerve fibres and prevent its reaccumulation in these fibres.\textsuperscript{33–35} The evidence for the efficacy of capsaicin is conflicting. In the unpublished study which we identified no benefit was detected, and publication bias\textsuperscript{36} may account for enthusiastic published reports. Differences in the dose and delivery of the drug in the unpublished study may also have accounted for a failure to show an effect. It is difficult to achieve effective blinding in trials of capsaicin\textsuperscript{37} and this may be another bias accounting for favourable results in published studies when clinical enthusiasm for the treatment is low.

Vincroline iontophoresis has been evaluated in one small trial only. Although the results suggest some benefit, further elucidation is required. We have also considered the efficacy of lorazepam, acyclovir, benzodamamine cream and acupuncture. Based on available trials there is currently no evidence that these treatments are of any benefit in relieving the pain associated with postherpetic neuralgia.

Meta-analysis is increasingly proposed as a method for resolving uncertainty about the effectiveness of medical interventions. The advantages of a well-conducted meta-analysis over a traditional review article are the greater effort invested to control bias, for
example by using a defined search strategy for identifying studies, and the reduction of random error by combining data from individual studies. The validity of meta-analysis is supported by the concordant results found, for example, in myocardial infarction, where pooled results from smaller studies suggested a risk reduction for death with the use of thrombolytic therapy were similar to that achieved in a very large clinical trial. However, the recently reported discrepancy between meta-analysis of trials of intravenous magnesium (suggesting benefit) and the results of ISIS-4 has raised issues about the validity of meta-analysis, particularly where there are many small trials. Small negative studies may be more prone to selective non-publication yielding spuriously positive results when small published studies are combined. This raises particular issues for the application of the method in primary care. Post-herpetic neuralgia is typical of many clinical problems in primary care where trials are few and often small.

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References

