Treatment of postherpetic neuralgia: a systematic review of the literature

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Authors' objectives
To determine whether any treatment has been shown to reduce pain or disability from postherpetic neuralgia (PHN).

Searching
MEDLINE (from 1966 to October 2000) and the Cochrane Controlled Trials Register (Issue 3, 2000), were searched using combinations of the following terms: 'post-herpetic' or 'postherpetic'; and 'neuralgia' or 'neuropathy' or 'pain'. Current Contents was searched for more recent references. Additional trials were identified through article reference lists, contact with authors and content experts, and the Food and Drug Administration website. Studies were restricted to those reported in full in the English language.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible. Both parallel-group and crossover trials were included. Trials scoring one point on the validity scale were generally excluded. The exceptions were two RCTs that could not be adequately blinded.

Specific interventions included in the review
The inclusion criteria for the interventions were not specified and any treatments were eligible. The following treatments were included:

- topical therapies compared with placebo (lidocaine patch, capsaicin 0.075% cream and benzydamine cream);
- comparisons of amitriptyline, lorazepam, fluphenazine, amitriptyline- fluphenazine combination, nortriptyline, maprotiline or desipramine with placebo or each other;
- tramadol compared with clomipramine with and without levomepromazine;
- comparisons of gabapentin, oxycodone controlled-release, dextromethorphan, memantine or acyclovir with placebo;
- vincristine iontophoresis compared with saline iontophoresis;
- acupuncture compared with mock and actual transcutaneous electrical nerve stimulation;
- intrathecal lidocaine with and without methylprednisolone compared with no treatment;
- intrathecal compared with epidural methylprednisolone;
- a mixture of gangliosides (Cronassial) compared with placebo; and
- bupivacaine sympathetic blocks compared with intravenous lidocaine.

The duration of the treatments ranged from 2 days to 12 weeks.

Participants included in the review
PHN. Patients with PHN, i.e. those with a history of zoster, pain in the dermatomal distribution of the zoster rash, and pain persisting or occurring after cutaneous healing of zoster, were eligible. Most of the included patients had suffered from PHN for more than 1 year.

Outcomes assessed in the review
Studies with evaluation periods lasting longer than 24 hours, which addressed pain resolution, pain severity or quality of life, were eligible. Pain was assessed on the basis of visual analogue scores, a 50% reduction in pain scores, 50% pain relief, and categorical ratings. Adverse effects were also evaluated. The duration of the follow-up ranged from 2 days to 2 years.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection. [A:Both authors independently evaluated studies for inclusion based on pre-determined inclusion criteria. Any disagreements were resolved by discussion]

Assessment of study quality
Study validity was assessed and scored using the 5-point scale described by Jadad et al. (see Other Publications of Related Interest). The criteria assessed were the method of randomisation, allocation concealment, blinding, and accounting of drop-outs. Two reviewers independently evaluated study quality, and any disagreements were resolved by discussion.

Data extraction
Two reviewers independently extracted data on the treatment and control interventions, the duration of treatment and follow-up, and efficacy and safety.

Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
Differences between the studies were discussed, with studies grouped according to topical therapies, oral therapies and other therapies.

Results of the review
Twenty-seven RCTs were included. The number of participants was not reported.

The studies suffered from a variety of methodological flaws. These included a lack of intention to treat analysis in parallel trials; a lack of washout periods in crossover trials; potentially significant baseline differences between the groups; small sample sizes; and short study durations.

Topical therapies.
Lidocaine patch versus placebo (2 RCTs ranging in duration from 2 days to 4 weeks): the results were inconsistent. One RCT reported no statistically-significant difference in the pain scores between lidocaine and placebo. The other RCT enrolled patients who had obtained at least moderate relief after using a lidocaine patch for at least a month, and had reported significant benefit from lidocaine.

Capsaicin 0.075% versus placebo (2 RCTs of 6 weeks' duration): both RCTs reported reduced pain scores for capsaicin compared with placebo. Skin reactions and drop-outs (1 RCT) were significantly more common in the capsaicin-treated groups. Blinding was a problem due to the stinging effect of the capsaicin. Benzydamine cream versus placebo (2 RCTs of 2 weeks' duration): neither of the RCTs reported a statistically-significant difference between the treatments in terms of pain measures.

Oral therapies.
Tricyclic antidepressants (6 RCTs). Amitriptyline was significantly more effective in relieving pain than either lorazepam or placebo in one RCT, and was more effective than placebo in improving a sleep score in another.
RCT showed there was no significant difference between amitriptyline and nortriptyline. In one RCT, amitriptyline was associated with significantly less pain than maprotiline when measured on a visual analogue score scale. However, there was no difference in pain relief, sleep or disability in this RCT. Desipramine was associated with significantly greater pain relief than benztrapine in one RCT.

One RCT of 8 weeks' duration showed gabapentin was more effective than placebo in terms of pain, quality of life and sleep. The number-needed-to-treat ranged from 3.2 to 13.9 for the different outcomes. Controlled-release oxycodone was more effective than placebo in a crossover RCT of 4 weeks' duration. Tramadol was not compared against placebo.

Acyclovir, lorazepam, fluphenazine, and dextromethorphan were no more effective than placebo (1 RCT for each).

Other therapies.

There was no difference between vincristine and saline iontophoresis in one RCT. Acupuncture was no more effective than mock transcutaneous electrical nerve stimulation in one RCT with a high drop-out rate (43%) in the active treatment group. In addition, auricular acupuncture was reported as being a painful and unpleasant experience. A smaller trial suggested a short-term benefit during treatment, but all but one acupuncture patient dropped out because of inadequate pain relief. Intrathecal methylprednisolone plus lidocaine was more effective at relieving pain after 2 years than lidocaine alone or no treatment. The side-effects were not formally reported.

Gangliosides were more effective than placebo in one RCT, but poor tolerability and the use of bovine brain tissue limit their acceptability.

Sympathetic blocks using bupivacaine were more effective than intravenous lidocaine infusions in one RCT but the results were not reported in full.

Safety.

The rates of adverse reactions were high in all effective oral and topical therapies. No clinical complications were reported in the trials of intrathecal steroids. Specific side-effects relating to the intrathecal steroid trials were not reported.

Cost information
The costs of selected drug therapies were reported.

Authors' conclusions
The best single treatment for PHN remains unknown. Tricyclic antidepressants, topical capsaicin, gabapentin and oxycodone were effective for alleviating PHN; however, the long-term, clinically meaningful benefits are uncertain and side-effects are common. Patients refractory to these methods may benefit from intrathecal methylprednisolone. Little evidence is available regarding treatment of PHN of less than 6 months' duration.

CRD commentary
The aims of the review were stated, and the inclusion criteria were defined in terms of the study design, participants and outcome. Several relevant sources of literature were searched and attempts were made to locate unpublished material. However, the methods used to select the studies for inclusion were not described. Eligible studies were restricted to those published in the English language and this may, as the authors acknowledged, have resulted in the omission of other studies. The included studies were restricted to RCTs. The validity of the studies was assessed and scored using predefined criteria, and the methods used to assess validity were described. A narrative review was appropriate given the diversity of the interventions, but the results were not considered in relation to the methodological flaws.

In view of the deficiencies highlighted and the lack of a formal report of the side-effects, the evidence presented is limited and any conclusions must be interpreted with caution.
Implications of the review for practice and research

Practice: The authors state that there is evidence that for post-herpetic neuralgia that has lasted longer than 6 months, tricyclic antidepressants, topical capsaicin 0.075%, gabapentine, controlled-release oxycodone and intrathecal prednisolone are more effective than placebo. None of the tricyclic antidepressant therapies lasted beyond 8 weeks, thus the long-term efficacy is unknown. The treatments all have adverse effects or costs and should be considered on an individual basis.

Research: The authors did not state any implications for further research.

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11978209

Other publications of related interest

This additional published commentary may also be of interest. McQuay H. Review: tricyclic antidepressants, capsaicin, gabapentin, and oxycodone are effective for postherpetic neuralgia. Evid Based Med 2002;7:147.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.