Analgesic therapy in postherpetic neuralgia: a quantitative systematic review
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CRD summary
The authors concluded that there was support for the use of tricyclic antidepressants, certain opioids, gabapentinoids and topical lidocaine and capsaicin. Overall, the review was well-conducted and the authors’ conclusion reflects the evidence presented.

Authors' objectives
To evaluate the efficacy and adverse effects of analgesic treatments for patients with postherpetic neuralgia (PHN).

Searching
MEDLINE, PubMed, EMBASE and CINAHL were searched from inception to 2004 without any language restrictions; the search terms were reported. In addition, the Cochrane Controlled Trials Register and the Cochrane Library (2004) were searched, and reference lists in identified studies and reviews were checked. Unpublished studies and studies reported as abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Blinded randomised controlled trials (RCTs) that scored 3 or more on the Jadad validity scale and involved more than 10 enrolled patients were eligible for inclusion. Both crossover and parallel-group RCTs were included in the review.

Specific interventions included in the review
Inclusion criteria were not explicitly reported in terms of the interventions, but it was clear that studies evaluating analgesic treatments were eligible for inclusion. Studies on the prevention of PHN were excluded. The included studies evaluated:
oral tricyclic antidepressants (amitryptiline, desipramine and nortriptyline),
gabapentinoids (gabapentin, pregabalin),
opioids (levorphanol, oxycodone, morphine, methadone, tramadol),
N-methyl-D-aspartate (NMDA) receptor antagonists (dextromethorphan, memantine, lorazepam, GV196771),
topically administered treatments (capsaicin cream, aspirin, indomethacin, diclofenac, benzydamine, lidocaine),
intravenous lidocaine,
intrathecal and epidural administered therapies (lidocaine and lidocaine plus methylprednisolone),
other oral therapies (lorazepam acyclovir, ibuprofen, codeine, clonidine, buspirone and M-chloropiperazine),
other therapies (acupuncture and vincristine iontophoresis), and
the injection of bovine gangliosides.

Participants included in the review
Studies of adults with PHN (defined in the review as zoster-associated pain for more than 3 months) were eligible for inclusion. Studies that included some patients with PHN were excluded unless they reported the results for PHN.
Outcomes assessed in the review
Studies that reported at least one clinically relevant measure of pain were eligible for inclusion. The review assessed
pain-relief outcomes, major adverse effects (all withdrawals), minor adverse effects (where treatment continued and the
patient completed the study) and withdrawals. The reviewers extracted pain outcomes according to a hierarchy (details
were reported). The included studies used a variety of methods to assess outcomes. Most of the included studies
assessed outcomes at the end of treatment; 3 studies reported longer follow-up of up to 2 years.

How were decisions on the relevance of primary studies made?
At least two reviewers independently selected the studies.

Assessment of study quality
At least two reviewers independently assessed validity using the Jadad scale. Any disagreements were resolved through
recourse to a third reviewer. Studies were also assessed for the use of intention-to-treat analysis. Crossover studies were
also assessed for the use of washout periods and any verification of the adequacy of the washout period.

Data extraction
Two reviewers independently extracted data on the outcomes of interest. For crossover studies, a patient who completed
both active and placebo arms was counted as two patient episodes. Where possible, dichotomous pain outcome data
were extracted for a 50% decrease in baseline pain (the methods used to transform reported measures into a
dichotomous measure were reported). Authors were contacted for dichotomous data where required. For each study
that provided dichotomous efficacy data, the relative benefit (RB) and number-needed-to-treat (NNT) were calculated,
along with the respective 95% confidence intervals (CIs); for safety data, the relative risk (RR) and number-needed-to-
harm (NNH) were calculated, along with 95% CIs, for placebo-controlled studies. Data were extracted for the longest
follow-up periods reported in the trials. When calculating odds ratios (ORs), 0.5 was added to each cell in the 2x2 table
to account for cells containing values of zero.

Methods of synthesis
How were the studies combined?
The studies were grouped by treatment. The pooled RB or RR and NNT or NNH were calculated using data from
statistically homogeneous studies. Studies with no dichotomous data were combined in a narrative.

How were differences between studies investigated?
Statistical heterogeneity was assessed (p<0.05 indicated significant heterogeneity). Outliers were identified using
methods described by Galbraith.

Results of the review
Thirty-five studies (n=2,446) were included in the review: 18 crossover RCTs and 17 parallel-group RCTs. Thirty-one
studies were placebo-controlled and were considered suitable for meta-analysis. Of these, 25 studies provided
dichotomous data and were included in the meta-analysis.

Fourteen studies did not report intention-to-treat analysis; in these studies non-completer rates ranged from 1 to 24%.
Seven studies reported 100% completion rates and 3 studies reported intention-to-treat analysis. Fourteen of the 18
crossover RCTs reported a washout period and 10 of these studies verified the adequacy of the washout period.
Tricyclic antidepressants were associated with significantly improved analgesia compared with placebo; the pooled RB
was 4.07 (95% CI: 2.25, 7.34, p<0.001) and the NNT 2.64 (95% CI: 2.1, 3.54, p<0.001), based on 4 RCTs with 248
patient episodes. Of the studies not included in the meta-analysis, one reported no significant difference between
amitriptyline and maprotiline, one reported no significant difference between amitriptyline and nortriptyline, and one
reported that amitriptyline was of greater benefit than fluphenazine and placebo and there was no benefit in adding
fluphenazine to amitriptyline.
Gabapentinoids (gabapentin and pregabalin) were associated with significant benefits. For gabapentin, the RR was 2.65 (95% CI: 1.9, 3.6, p<0.001) and the NNT 4.39 (95% CI: 3.34, 6.07, p<0.001), based on 2 studies with 559 patient episodes. For pregabalin, the RR was 2.56 (95% CI: 1.8, 3.64, p<0.001) and the NNT 4.93 (95% CI: 3.66, 7.58, p<0.001), based on 2 studies with 411 patient episodes.

Opioids (oxycodone and morphine controlled-release or methadone) were associated with significant benefits; the RR was 3.89 (95% CI: 2.23, 6.77, p<0.001) and the NNT 2.67 (95% CI: 2.07, 3.77, p<0.001), based on 2 studies with 211 patient episodes. Studies not included in the meta-analysis reported a greater reduction in pain associated with 0.75 mg compared with 0.15 mg levorphanol (1 study), a significant improvement associated with intravenous morphine compared with placebo (1 study), and significant benefits associated with tramadol (based on 1 study with 108 patient episodes).

There was no significant difference between NMDA receptor antagonists and placebo; the RR was 1.48 (95% CI: 0.66, 3.3, p=0.7), based on 3 studies with 131 patient episodes. Studies not included in the meta-analysis reported no difference between either GV 196771 and placebo (1 study), or memantine and placebo (1 study).

Topically administered capsaicin was associated with significant benefits; the RR was 1.98 (95% CI: 1.33, 2.95, p<0.008) and the NNT 3.26 (95% CI: 2.26, 5.85, p<0.0001), based on 2 studies with 175 patient episodes. Studies not included in the meta-analysis reported no difference between benzodiazine cream and placebo (1 study), a significant benefit for topical lidocaine patches compared with placebo patches (1 study; RR 2.23, 95% CI: 1.45, 3.44; NNT 2, 95% CI: 1.43, 3.31), greater pain relief with lidocaine patches compared with placebo patch and no patch (1 study), and comparable analgesic efficacy for local lidocaine gel and placebo (1 study).

Intrathecal lidocaine plus methylprednisolone was associated with significant benefits; the RR was 27.64 and the NNT 1.13 (95% CIs were not reported), based on 1 study with 179 patient episodes.

No significant heterogeneity was found for any of the above meta-analyses.

Other treatments reviewed were not associated with efficacy, but the authors stated that this might be due to small patient numbers or single-dose studies. Results were also reported for studies that were not included in the meta-analyses.

Adverse events.

Triyclic antidepressants: the NNH was 5.67 (95% CI: 3.34, 18.58) for minor adverse events and 16.9 (95% CI: 8.85, 178) for major adverse events. Gabapentin: the NNH was 4.07 (95% CI: 3.15, 5.74) for minor adverse events and 12.25 (95% CI: 7.69, 30.2) for major adverse events.

Opioids: the NNH was 6.29 (95% CI: 4.16, 12.8) for major adverse events.

Capsaicin: the NNH was 3.94 (95% CI: 2.5, 8.6) for minor adverse events and 4.67 (95% CI: 3.13, 9.19) for major adverse events.

Lidocaine patches: there was no significant difference between lidocaine and placebo in minor adverse events. Intrathecal lidocaine plus methylprednisolone: no minor adverse events were reported. One patient had a major adverse event that was thought not to be treatment-related.

Authors' conclusions

There was support for the use of tricyclic antidepressants, certain opioids, gabapentinoids, topical lidocaine patches and topical capsaicin in the treatment of PHN. Intrathecal methylprednisolone appeared effective, but more safety data are required.

CRD commentary

The review question was clear with respect to the participants, intervention, outcomes and study design. Several relevant
sources were searched and the absence of language restrictions minimises language bias. The exclusion of unpublished studies raises the potential for publication bias. Only blinded RCTs that met minimum defined quality criteria were included; this ensured that only higher quality studies were included. No information about the participants was provided, which made it difficult to determine which patient groups the results might apply to. Methods were used to minimise reviewer error and bias in the study selection, data extraction and validity assessment processes.

Only statistically homogeneous studies were pooled using meta-analysis (although the threshold for determining the presence of significant heterogeneity was p<0.05 rather than the more usual level of p<0.10). Overall, the review was well-conducted and the authors' conclusion reflects the evidence presented.

Implications of the review for practice and research
Practice: The authors stated that pharmacologically-based managements of PHN should be used in combination with the management of psychological and social aspects. Research: The authors suggested that future RCTs should report responder rates for both 30% and 50% pain reduction and be adequately powered to examine the effect of treatment on subgroups of patients categorised using quantitative sensory evaluation. They also stated the need for a further high-quality RCT evaluating intrathecal steroids.

Bibliographic details

PubMedID
16013891

DOI
10.1371/journal.pmed.0020164

Original Paper URL
http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pmed.0020164

Indexing Status
Subject indexing assigned by NLM

MeSH
Analgesics /pharmacology; Antidepressive Agents /therapeutic use; Antidepressive Agents, Tricyclic /therapeutic use; Clinical Trials as Topic; Herpes Zoster /drug therapy; Humans; Lidocaine /therapeutic use; Methylprednisolone /administration & dosage; Narcotics /therapeutic use; Neuralgia /drug therapy; Receptors, N-Methyl-D-Aspartate /metabolism; Time Factors

AccessionNumber
12006003601

Date bibliographic record published
30/11/2007

Date abstract record published
30/11/2007

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.