Systematic review of topical capsaicin for the treatment of chronic pain

CRD summary
This review evaluated topically applied capsaicin for the treatment of chronic neuropathic and musculoskeletal pain. The authors concluded that capsaicin had a poor to moderate efficacy, but may be useful in people unresponsive to, or intolerant of other treatments. Apparent differences across the included studies and the lack of an analysis of data for this subgroup suggest that the conclusions may not be reliable.

Authors' objectives
To determine the efficacy and safety of topically applied capsaicin for chronic pain from neuropathic or musculoskeletal disorders.

Searching
MEDLINE, PREMEDLINE, EMBASE, PubMed and the Cochrane Library were searched up to April 2003; the search strategy was provided. No language restrictions were applied. An in-house database of RCTs was also searched and the reference lists of retrieved articles and reviews were checked. Seventeen manufacturers were also contacted.

Study selection
Study designs of evaluations included in the review
Double-blinded, randomised controlled trials (RCTs) with either placebo or an active control, and at least 10 participants in each arm of the trial, were eligible for inclusion.

Specific interventions included in the review
Studies of topical capsaicin applied 3 to 4 times daily, compared with either placebo or an active control, were eligible for inclusion. The included studies evaluated either 0.025% or 0.075% topical capsaicin, or 11 mg capsinoid capsicum plaster, with or without concomitant oral analgesics. The comparators for studies of neuropathic pain were placebo or amitriptyline; the comparators for studies of musculoskeletal pain were placebo or 0.25% capsaicin.

Participants included in the review
Studies of adults with chronic neuropathic or musculoskeletal pain were eligible for inclusion. Studies of neuropathic pain included people with diabetic neuropathy, postherpetic neuralgia, neuropatic pain, polyneuropathy, postmastectomy pain and human immunodeficiency virus-associated neuropatic pain. Studies of musculoskeletal conditions included people with osteo and rheumatoid arthritis, back pain and jaw pain. The age of the participants ranged from 20 to 95 years. Some of the included studies were restricted to participants who were unresponsive or intolerant to conventional therapies.

Outcomes assessed in the review
The primary outcome was improvement in pain. The hierarchy of outcomes in order of preference was: number of patients with a 50% or more reduction in pain, patient-reported global assessment of treatment, pain on movement, pain on rest or spontaneous pain, physician or investigator global assessment of treatment. The secondary outcomes were adverse events, coughing and withdrawal due to adverse events. The studies had to report outcomes after at least 3 weeks for musculoskeletal conditions and after at least 6 weeks for neuropathic conditions.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The criteria used to assess the quality of the included studies were randomisation, blinding and withdrawals; the
maximum quality score attainable was 5. The authors also assessed validity using a 16-point scale. At least two reviewers independently assessed study quality, with any disagreements resolved by consensus.

**Data extraction**
One reviewer extracted the outcomes, which were verified by a second reviewer. Data were extracted on the number of patients responding to treatment, using an intention-to-treat format.

**Methods of synthesis**
How were the studies combined?
The studies were combined using a fixed-effect meta-analysis. Pooled relative risks (RRs) and the number-needed-to-treat (NNT) or harm (NNH), along with 95% confidence intervals (CIs), were calculated separately for efficacy, adverse event data and adverse event-related withdrawals.

How were differences between studies investigated?
The authors investigated heterogeneity visually using L’Abbé plots, and statistically using chi-squared and I² tests. Sensitivity analyses were conducted to investigate the effect of trial size and outcome measured.

**Results of the review**
Sixteen studies (n=1,556) were included in the review.

Four studies scored 4 out of 5 on the quality assessment, ten scored 3, and two scored 2. On the 16-point validity assessment, the scores ranged from 9 to 14.

**Efficacy.**
Based on 313 patients in 4 studies, capsaicin resulted in a statistically significant improvement in neuropathic pain at 4 weeks (RR 1.4, 95% CI: 1.1, 1.7); the corresponding NNT was 6.4 (95% CI: 3.8, 21). No results for the assessment of heterogeneity were presented. Capsaicin also resulted in a statistically significant improvement in neuropathic pain at 8 weeks (RR 1.4, 95% CI: 1.2, 1.7) and a corresponding NNT of 5.7 (95% CI: 4.0, 10), based on 656 patients in 6 studies. There was evidence of statistical heterogeneity for the comparison at 8 weeks (P=0.02; I²=62.5%).

Based on 368 patients in 3 studies, capsaicin resulted in a statistically significant improvement in musculoskeletal pain at 4 weeks (RR 1.5, 95% CI: 1.1, 2.07) and a corresponding NNT of 8.1 (95% CI: 4.6, 34, P=0.01). There was no evidence of statistical heterogeneity (P=0.36; I²=2.5%). Subgroup analyses showed no significant effect of trial size or outcome measured.

**Adverse events.**
Based on 300 patients in 4 studies, capsaicin caused a statistically significant higher rate of local adverse events at 8 weeks than placebo when used for neuropathic pain (RR 3.2, 95% CI: 2.2, 4.6; NNH 2.5, 95% CI: 2.0, 3.3).

Based on 190 patients in 3 studies, capsaicin caused a statistically significant higher rate of local adverse events at 4 weeks than placebo when used for musculoskeletal pain (RR 5.0, 95% CI: 2.6, 9.6; NNH 2.6, 95% CI: 2.06, 3.6).

**Withdrawals due to adverse events** were significantly higher with capsaicin than placebo when used for neuropathic pain (5 studies with 503 patients; RR 5.5, 95% CI: 2.6, 12; NNH 7.5, 95% CI: 5.5, 12) and for musculoskeletal pain (4 studies with 398 patients; RR 2.5, 95% CI: 1.1, 5.6; NNH 16, 95% CI: 9.1, 63).

**Authors’ conclusions**
Capsaicin has poor to moderate efficacy in the treatment of chronic neuropathic and musculoskeletal pain. However, it may be useful in people who are unresponsive to, or intolerant of other treatments.
CRD commentary
The authors carried out an extensive search with no language restrictions, thus minimising the possibility of publication and language bias. It was not reported whether any methods were used to minimise bias in the study selection process. However, methods were used to minimise reviewer bias and error in the data abstraction and quality assessment. Adequate details of each included study were given.

A visual assessment of the L’Abbe plot indicates some degree of heterogeneity in the neuropathic pain studies, and there was evidence of statistical heterogeneity. This suggests that the method used to combine these studies might not have been appropriate. In addition, there was no subgroup analysis of those studies restricted to people unresponsive or intolerant of conventional treatments. Therefore, the conclusion that capsaicin may be useful in these people may not be reliable.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

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