

Primary care

Systematic review of topical capsaicin for the treatment of chronic pain

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Abstract

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

Data sources Cochrane Library, Medline, Embase, PubMed, an in-house database, and contact with manufacturers of topical capsaicin.

Study selection Randomised controlled trials comparing topically applied capsaicin with placebo or another treatment in adults with chronic pain.

Data extraction Primary outcome was dichotomous information for the number of patients with around at least 50% pain reduction. Outcomes were extracted at four weeks for musculoskeletal conditions and eight weeks for neuropathic conditions. Secondary outcomes were adverse events and withdrawals due to adverse events.

Data synthesis Six double blind placebo controlled trials (656 patients) were pooled for analysis of neuropathic conditions. The relative benefit from topical capsaicin 0.075% compared with placebo was 1.4 (95% confidence interval 1.2 to 1.7) and the number needed to treat was 5.7 (4.0 to 10.0). Three double blind placebo controlled trials (368 patients) were pooled for analysis of musculoskeletal conditions. The relative benefit from topical capsaicin 0.025% or plaster compared with placebo was 1.5 (1.1 to 2.0) and the number needed to treat was 8.1 (4.6 to 34). Around one third of patients experienced local adverse events with capsaicin, which would not have been the case with placebo.

Conclusions Although topically applied capsaicin has moderate to poor efficacy in the treatment of chronic musculoskeletal or neuropathic pain, it may be useful as an adjunct or sole therapy for a small number of patients who are unresponsive to, or intolerant of, other treatments.

Introduction

Capsaicin, from chilli peppers, binds to nociceptors in the skin, causing excitation of the neurones and a period of enhanced sensitivity perceived as itching, pricking, or burning, with cutaneous vasodilation. This is followed by a refractory period with reduced sensitivity and, after repeated applications, persistent desensitisation.¹

Topical creams with capsaicin are used to treat pain from postherpetic neuralgia and diabetic neuropathy, osteoarthritis, and rheumatoid arthritis.^{2,3} Capsaicin is available in the United Kingdom on prescription only, but may be present in small quantities in topical rubefacients sold through pharmacies.

Adverse events from capsaicin are mainly burning, stinging, and erythema at the application site; systemic events are rare.² Respiratory irritation has also been reported from inhalation of dried cream.⁴

We performed a meta-analysis of randomised controlled trials to determine the efficacy of topical capsaicin in the treatment of chronic pain from neuropathic and musculoskeletal disorders and adverse events and withdrawals.

Methods

Relevant studies were sought through the Cochrane Library, Medline, PreMedline, Embase, and PubMed up to April 2003. We also searched an in-house database of 13 000 randomised clinical trials in pain research from 1950 identified through a refined Medline search strategy together with handsearching of 40 biomedical journals.⁵ Reference lists of retrieved articles and reviews were also examined.

We identified randomised, active or placebo controlled trials in which treatments were in adults with chronic pain from either neuropathic conditions or musculoskeletal disorders. Treatment had to be applied 3-4 times daily, with at least 10 patients in each group. Outcomes closest to four weeks (minimum three weeks) were extracted in musculoskeletal conditions and outcomes closest to eight weeks (minimum six weeks) were extracted in neuropathic conditions.

Quality and validity assessment and data abstraction

Each trial was assessed for quality using a validated scale with a maximum score of five.⁶ Studies had to score at least two points (randomised, double blind) to

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Details of search terms and studies are on bmj.com



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be included for efficacy analysis. Trial validity was assessed on a 16 point scale.⁷

Outcomes were extracted by one reviewer and verified by another. Assessments of quality and validity were made independently by at least two reviewers. Disputes were settled by consensus.

Outcomes

We defined clinical success as about a 50% reduction in pain.⁷ This was the number of patients with either a “good” or “excellent” global assessment of treatment or “none” or “slight” pain on rest or movement. We also included patients showing undefined “improvement.” We performed a separate sensitivity analysis on these trials. Secondary outcomes were the numbers of patients reporting one or more local adverse event, cough, and withdrawal due to adverse events.

Quantitative data synthesis

Analysis was based on an intention to treat. We calculated the numbers needed to treat and relative benefits along with 95% confidence intervals.^{8, 9} Numbers needed to harm and relative risks were similarly calculated for adverse effects and withdrawals.

Provided there was sufficient information, we aimed to perform sensitivity analyses on pooled outcomes using the z test (P < 0.01 for a significant difference) in neuropathic compared with musculoskeletal pain and in any given pain condition.¹⁰ Homogeneity of trials was assessed visually.¹¹

Results

Overall, 38 potential papers were identified and 22 excluded (see table A on bmj.com). A large review included 14 trials and 991 patients.¹² We excluded nine of those trials for various reasons. In addition to the five remaining papers from the review,¹³⁻¹⁷ we found

seven with information on efficacy and four with information only for adverse events or withdrawals.¹⁸⁻²⁸ We included 16 papers in this review, totalling 1556 patients aged 20 to 95 years.

Only two trials scored fewer than three points for quality (see tables B and C on bmj.com).^{24, 25} One, the only single blind trial, was an active controlled trial comparing different doses of capsaicin.²⁴ Validity scores ranged from nine to 14. In 11 trials baseline pain was moderate to severe, and in five trials patients were only included if they were unresponsive or intolerant to conventional therapies. In neuropathic pain, seven trials^{15, 16, 17, 20, 22, 23, 28} allowed concomitant oral drugs for pain without change in dose or frequency, and three trials made no mention of concomitant therapy.^{14, 21, 27} In musculoskeletal pain, two trials allowed concomitant oral drugs for pain without change in dose or frequency,^{15, 25} three trials prohibited concomitant therapy,^{18, 19, 24} and one trial made no statement.²⁶

Efficacy and sensitivity analyses

Capsaicin was significantly better than placebo for the treatment of both neuropathic and musculoskeletal pain (table and figure; also see bmj.com). In neuropathic conditions, the mean treatment response rate (percentage of patients with at least 50% pain relief) at four weeks for capsaicin 0.075% was 57% (range 53% to 75% in individual trials), and the mean placebo response rate was 42% (range 31% to 55%). The number needed to treat was 6.4 (95% confidence interval 3.8 to 21). The mean treatment response rate at eight weeks for capsaicin 0.075% was 60% (range 20% to 75%), and the mean placebo response rate was 42% (range 10% to 65%; figure). The number needed to treat was 5.7 (4.0 to 10).

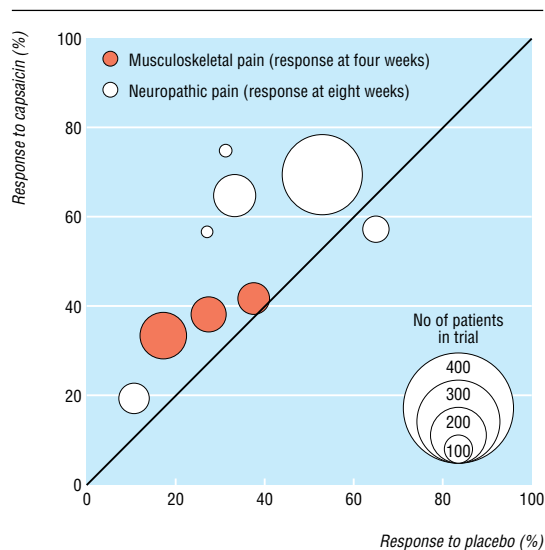
Estimates of efficacy and harm from meta-analysis of randomised controlled trials of capsaicin for treatment of chronic pain associated with neuropathic or musculoskeletal conditions

| Characteristic | No of trials | No of patients | No (%) responding to intervention | | Relative benefit (95% CI)* | Number needed to treat (95% CI)† |
|-------------------------------------|--------------|----------------|-----------------------------------|---------|----------------------------|----------------------------------|
| | | | Treatment | Placebo | | |
| Efficacy | | | | | | |
| Musculoskeletal pain: | | | | | | |
| At four weeks | 3 | 368 | 70/186 | 46/182 | 1.5 (1.1 to 2.0) | 8.1 (4.6 to 34) |
| Neuropathic pain: | | | | | | |
| At four weeks | 4 | 313 | 91/159 | 64/154 | 1.4 (1.1 to 1.7) | 6.4 (3.8 to 21) |
| At eight weeks | 6 | 656 | 197/331 | 136/325 | 1.4 (1.2 to 1.7) | 5.7 (4.0 to 10) |
| By outcome type: | | | | | | |
| Undefined improvement | 4 | 532 | 179/268 | 128/264 | 1.4 (1.2 to 1.6) | 5.5 (3.8 to 10) |
| Global or percentage pain reduction | 2 | 124 | 18/63 | 8/61 | 2.1 (0.99 to 4.3) | 6.5 (3.4 to 69) |
| By trial size: | | | | | | |
| <40 patients | 2 | 57 | 20/30 | 8/27 | 2.3 (1.2 to 4.3) | 2.7 (1.6 to 7.7) |
| ≥40 patients | 4 | 599 | 177/301 | 128/298 | 1.4 (1.2 to 1.6) | 6.3 (4.2 to 13) |
| Harm | | | | | | |
| Musculoskeletal pain: | | | | | | |
| Local adverse events at four weeks | 3 | 190 | 48/98 | 9/92 | 5.0 (2.6 to 9.6) | 2.6 (2.0 to 3.6) |
| Withdrawals at four weeks‡ | 4 | 398 | 19/203 | 6/195 | 2.5 (1.1 to 5.6) | 16.0 (9.1 to 63) |
| Neuropathic pain | | | | | | |
| Local adverse events at eight weeks | 4 | 300 | 89/154 | 26/146 | 3.2 (2.2 to 4.6) | 2.5 (2.0 to 3.3) |
| Withdrawals at eight weeks‡ | 5 | 503 | 40/253 | 6/250 | 5.5 (2.6 to 12) | 7.5 (5.5 to 12) |
| Combined | | | | | | |
| Local adverse events | 7 | 490 | 137/252 | 35/238 | 3.6 (2.6 to 5.0) | 2.5 (2.1 to 3.1) |
| Withdrawals‡ | 9 | 901 | 59/456 | 12/445 | 4.0 (2.3 to 6.8) | 9.8 (7.3 to 15) |

*Relative risks (95% confidence intervals) for harm.

†Numbers needed to harm (95% confidence intervals) for harm.

‡Related to adverse events.



L'Abbé plot showing response to capsaicin and placebo in individual randomised controlled trials

In musculoskeletal conditions, the mean treatment response rate at four weeks for capsaicin 0.025% or plaster was 38% (range 34% to 42%; figure), and the mean placebo response rate was 25% (range 17% to 37%). The number needed to treat was 8.1 (4.6 to 34). Only one of the three trials with efficacy data allowed concomitant oral therapy.

Data were insufficient from which to draw any conclusions concerning relative efficacy for alternative drugs or doses. Sensitivity analyses of pooled information showed no significant difference between numbers needed to treat for trial size, type of pain, or outcome (table). Insufficient information prevented other sensitivity analyses.

Adverse events and withdrawals

Significantly more patients had local adverse events and adverse event related withdrawals with capsaicin than with placebo.

The number needed to harm for one patient to have a local adverse event with capsaicin who would not have done so with placebo was 2.5 (2.1 to 3.1). Adverse event related withdrawals occurred in 13% of capsaicin treated patients and 3% of patients receiving placebo. The number needed to harm was 9.8 (7.3 to 15.0).

Discussion

Topical capsaicin is better than placebo in the treatment of chronic pain from neuropathic and musculoskeletal disorders. This finding agrees with the results of a review published in 1994, but there are also major differences.¹² Firstly, we have given numbers needed to treat rather than odds ratios, because they are easier to understand and interpret and give an absolute rather than relative measure of treatment effect.^{29, 30}

Secondly, more trials have become available since the 1994 review, and our findings are based on more studies and more patients. We excluded nine of 14 studies in the previous review because they were duplicate publications, concerned dermatological condi-

tions, used outcomes that were not direct measurements of pain, or provided insufficient information on relevant outcomes. We used intention to treat analysis and a more structured hierarchy of outcomes from which to extract information. The net effect of these differences should be a more accurate, but more conservative, estimate of efficacy.

Our review gives lower estimates of efficacy for capsaicin. In neuropathic conditions the number needed to treat at eight weeks was 5.7. This means that for around every six patients using topical capsaicin 0.075%, one would achieve at least a 50% reduction in pain who would not have done so if given placebo. At four weeks, the number needed to treat was slightly worse (6.4). In musculoskeletal conditions, the number needed to treat at four weeks was 8.1 for at least 50% pain relief with topical capsaicin 0.025% or plaster compared with placebo.

Even this may be an overestimate, due to the difficulty in creating double blind conditions; some patients will recognise a stinging or burning sensation with treatment. Both active and placebo treatments were rubbed on, precluding any effect of rubbing. Average placebo responses in topical capsaicin trials of 42% for neuropathic pain and 25% for musculoskeletal conditions are comparable with placebo responses for oral analgesics or topical NSAIDs (12%-40%) for a variety of conditions and end points.³¹

Although capsaicin has lower efficacy in musculoskeletal conditions, the difference was not statistically significant. Too few trials were available to be certain if the difference in efficacy resulted from the lower dose of capsaicin. Patients with neuropathic pain received three times the dose used in musculoskeletal pain. In addition, efficacy estimates for musculoskeletal pain were based on information from fewer trials and fewer patients than for neuropathic pain and are therefore less robust.

We only had sufficient information to pool results from placebo controlled trials, making it impossible to judge relative efficacy with other analgesics. Indirect comparisons between treatments are still valid, however.³² A substantial meta-analysis of topical NSAIDs and a review of rubefacients from limited data have been performed.^{7, 33} In chronic musculoskeletal conditions, capsaicin 0.025% or plaster was not as effective as topical NSAIDs (number needed to treat 3.1, 95% confidence interval 2.7 to 3.8) or rubefacients (5.3, 3.6 to 10.2), giving a rank order of efficacy of topical NSAIDs (most effective), followed by rubefacients then capsaicin. The efficacy of topical NSAIDs and rubefacients in neuropathic pain is unknown.

Local adverse events were common when reported. The number needed to harm for local adverse events for capsaicin in musculoskeletal and neuropathic pain were similar, despite dose. Around one in three patients treated with capsaicin will experience a local adverse event who would not have done so if given placebo. Combined outcomes in neuropathic and musculoskeletal pain give a number needed to harm for adverse event related withdrawals of 9.8; for every 10 patients treated with capsaicin, one will withdraw due to an adverse event who would not have done so if given placebo.

A study in healthy volunteers showed that epidermal nerve fibres significantly degenerate within

What is already known on this topic

A large review found that capsaicin was effective in reducing pain associated with diabetic neuropathy, osteoarthritis and psoriasis, but was less effective for postherpetic neuralgia

What this study adds

Compared with placebo, treatment of neuropathic pain with 0.075% capsaicin for eight weeks would benefit one additional patient for every six treated

Compared with placebo, treatment of musculoskeletal pain with 0.025% capsaicin for four weeks would benefit one additional patient for every eight treated

One in three patients experienced local adverse events with capsaicin, and one in 10 withdraw from treatment, who would not have done so with placebo

a few days of capsaicin 0.075% treatment.¹ Once capsaicin is discontinued, reinnervation occurs, with almost full return of sensation (over six weeks after three weeks of treatment).

Most of the trials stated that patients had moderate or severe chronic pain, and some recruited patients only if they were unresponsive to other treatments. For patients with chronic moderate or severe pain, even a small reduction in pain can be beneficial.

Contributors: See bmj.com

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Competing interests: RAM and HJM have consulted for various pharmaceutical companies, but no company manufacturing capsaicin. RAM, HJM, and JE have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. All authors have received research support from charities, government, and industry sources at various times, but no such support was received for this work. No author has any direct stock holding in any pharmaceutical company.

Ethical approval: Not required.

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Endpiece

The brutalised poor of our manufacturing districts

It has been too common to accuse the poor of our manufacturing districts of stupidity and barbarism; but when they have been suffered to remain in this state of supine stolidity, it is the fault of their superiors. Nothing can file off those moral asperities which deform and brutalise the character, but a better education; a blessing let us hope, not too distant from the meanest.

Walker JK. A sketch of the medical and general topography of Huddersfield and its adjacent district. *Lond Med Repository* 1818;10:1-16

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