Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain

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CRD summary
This network meta-analysis found that buprenorphine patches had similar efficacy and fewer side effects than fentanyl patches in the treatment of moderate to severe chronic pain. The short duration and low quality of the included studies mean that the reliability of the results is uncertain.

Authors’ objectives
To assess the efficacy and safety of buprenorphine patches versus fentanyl patches in the treatment of moderate to severe chronic pain.

Searching
Nine databases (including MEDLINE and EMBASE) were searched to November 2010. The MEDLINE search strategy was reported. Three trial registries, two guideline databases and four relevant websites were searched. Reference lists of related reviews and identified studies were handsearched. No language or publication status restrictions were applied.

Study selection
Parallel randomised controlled trials (RCTs) of buprenorphine patches in the treatment of moderate to severe chronic pain due to any cause in adults aged over 18 years were eligible for inclusion. Cross-over trials were eligible if they presented results for the first phase separately. Abstracts were included where full papers were not available. The primary comparator of interest was fentanyl patch, but no relevant studies were found. Other comparators were morphine controlled-release pills or capsules, oxymorphone, oxycodone, hydromorphone or methadone compared to buprenorphine or fentanyl patch. Placebo-controlled studies were eligible. Dosages for all drugs were appropriate for stage III of the World Health Organisation pain ladder. Studies that reported clinical, patient-reported and safety outcomes were eligible for inclusion; specific outcomes were listed in the review.

The included studies involved comparisons of fentanyl patch versus sustained-release oral morphine; buprenorphine patch versus placebo; fentanyl patch versus placebo; and buprenorphine patch versus morphine. Dosages for each study are given in the review. Studies included cancer and non-cancer related pain. Where reported, the mean age of participants ranged from 50.9 to 66 years. The proportion of women ranged from 27.5% to 67%. Few studies reported the proportion of patients in severe pain; some studies were solely based on severe pain. Study duration ranged from seven days to 24 months; few were longer than one month. Included outcomes were pain intensity, quality of life, patient global impression of change, quality of sleep, adverse events, serious adverse events and treatment discontinuation.

Two reviewers independently selected studies.

Assessment of study quality
Quality was assessed using the Cochrane Risk of Bias tool for method of allocation sequence generation, allocation concealment, blinding, handling of incomplete outcome data, selective outcome reporting and other sources of bias. For each item, studies were scored as high, unclear or low risk of bias. It was not clear how many reviewers performed the quality assessment.

Data extraction
Data were extracted as odds ratios (OR) for dichotomous data and mean differences for continuous data, with 95% confidence intervals (CI). Where standard deviations were missing they were imputed. In trials that used several doses of the same drug, all doses were included as one intervention. Different pain scales were standardised to a single scale.

Data were extracted onto a standardised form by one reviewer and checked by another reviewer. Disagreements were
resolved by discussion and checked by a third reviewer.

Methods of synthesis
Pooled odds ratios (DerSimonian and Laird's method) and mean differences (MDs), with 95% confidence intervals (CI), were calculated using random-effects models. Enriched and non-enriched network meta-analyses were used to estimate a comparison between buprenorphine patch, fentanyl patch, morphine and placebo. An overall meta-analysis included all studies.

Results of the review
Fourteen trials reported in 17 publications (more than 2,617 participants) were included in the review. At most, three of the six quality criteria were met by individual studies.

Fentanyl patches versus buprenorphine patches: Fentanyl patches were associated with more nausea (OR 4.86, 95% CI 2.14 to 11.07) and vomiting (OR 17.32, 95% CI 4.43 to 67.71) and a higher risk of treatment discontinuations due to adverse events (OR 4.37, 95% CI 1.81 to 10.50).

Buprenorphine patches versus morphine: Buprenorphine patches were associated with better control of pain intensity (MD -16.20, 95% CI -28.92 to -3.77); morphine was associated with a greater risk of constipation (OR 5.63, 95% CI 1.73 to 18.29), nausea (OR 4.23, 95% CI 1.83 to 9.79), vomiting (OR 15.85, 95% CI 3.92 to 64.13) and a higher risk of treatment discontinuations due to adverse events (OR 4.26, 95% CI 1.68 to 10.81).

Placebo versus buprenorphine patches: Placebo was associated with a higher risk of treatment discontinuations due to lack of effect (OR 3.31, 95% CI 1.60 to 6.88) or any cause (OR 1.93, 95% CI 1.36 to 2.72).

Differences in other outcomes for each drug comparison, where they could be estimated, were not statistically significant between treatment arms.

Results from the enriched and non-enriched subgroup analyses supported the full analyses.

Authors’ conclusions
Buprenorphine patches had similar efficacy and fewer side effects than fentanyl patches.

CRD commentary
The review question was clearly stated. Inclusion criteria were defined for participants, interventions and study design. Outcome inclusion criteria were broad and those included were specified. The search included several databases of published and unpublished sources and included no language restrictions, thus minimising the chance of bias. No assessments of publication bias were reported. Efforts were made to minimise errors and bias in the review process. Details of the participants were given and allowed some assessment of the generalisability of the results.

A wide variety of outcome measures were used in the meta-analysis and the authors acknowledged that this made some comparisons impossible. The included studies were all short-term, which precluded assessment of the longer term effect of pain relief or addiction. Study quality was assessed using an appropriate tool; most of the studies were of low quality. Although no attempt was made to investigate the effect of study quality on the results of the review, the low quality of the included studies was acknowledged by the authors.

Network meta-analysis was appropriate in the absence of any relevant head-to-head trials. The authors acknowledged that this provided less robust evidence than direct comparisons. The reasons for the decision to combine arms within trials of the same drug at different dosages was unclear. A large number of treatment comparisons and outcomes were considered, but the authors did not address the issue of multiple testing.

The short duration and low quality of the included studies mean that the reliability of the results is uncertain.

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

Research: The authors stated a need for further large RCTs to compare buprenorphine to fentanyl patches directly or to...
the major step three opioids and report sufficient data for inclusion in meta-analyses. These studies should assess relevant outcomes with longer term (at least one year) follow-up and use standardised outcome measures.

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