Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature

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CRD summary
This review found that transdermal opiates and slow-release oral morphine had similar overall adverse effect rates, for patients with moderate-to-severe cancer pain, but transdermal opiates had lower rates of some effects, such as constipation. Due to limitations including questionable trial quality, low sample numbers, and inconsistency in some analyses, these conclusions require cautious interpretation.

Authors' objectives
To evaluate the adverse effects of transdermal opiates compared with slow-release oral morphine for treating moderate-to-severe cancer pain.

Searching
MEDLINE and EMBASE were searched for articles from 1966 to June 2007 (also reported as 2006). Search terms were reported. The references of retrieved studies and systematic reviews were checked.

Study selection
Eligible studies were phase three randomised controlled trials (RCTs) of transdermal opiates (fentanyl or buprenorphine) compared with slow-release oral morphine for treating moderate-to-severe cancer pain in patients with a defined opiate requirement on trial entry. The primary review endpoint was the overall adverse effects. Secondary endpoints were the overall neurological and gastrointestinal adverse events, constipation, nausea, somnolence, patient preferences, and trial withdrawal. Trials were excluded if they did not report adequate randomisation, did not report safety data, or included patients treated with other analgesics.

The transdermal opiate used by most participants in the included trials was fentanyl. Doses varied across trials, but the authors assumed that the groups within each trial received equally analgesic doses. The outcomes reported were constipation, diarrhoea, anorexia, somnolence, confusion, uncontrolled pain, nausea, vomiting, itching, hypoventilation, insomnia, headache, vertigo, skin rash, sweating and urinary retention. Where reported, these were assessed in the first two to four weeks of treatment or weekly.

Two authors independently selected trials for inclusion.

Assessment of study quality
Trial quality was evaluated using the Jadad scale, which assessed the adequacy of reported randomisation, blinding, and withdrawals or dropouts. The maximum possible score was five points. Two authors conducted the assessment independently, with disagreements resolved by consensus.

Data extraction
Odds ratios and their 95% confidence intervals were extracted or calculated from the number of events in each group of each trial. Data from crossover trials were extracted before the crossover. The authors did not state how many reviewers extracted the data.

Methods of synthesis
The data were combined in a random-effects meta-analysis to calculate pooled odds ratios and 95% confidence intervals. Heterogeneity was assessed with the Mantel-Haenszel test.

Results of the review
Four RCTs were included in the review (425 participants; range 40 to 202). One was a crossover trial. Two trials scored three out of five points on the Jadad scale; the other two scored two points and were rated as low quality.
There was no significant difference between the two groups in the rates of all side-effects (OR 0.789, 95% CI 0.625 to 3.728; four RCTs), gastrointestinal side-effects (OR 0.695, 95% CI 0.323 to 1.495; four RCTs), neurological side-effects (OR 0.614, 95% CI 0.319 to 1.184; four RCTs), nausea (OR 0.860, 95% CI 0.424 to 1.742; four RCTs), somnolence (OR 0.634, 95% CI 0.326 to 1.23; four RCTs), hypoventilation (OR 2.2, 95% CI 0.769 to 6.298; two RCTs), trial withdrawal (OR 0.623, 95% CI 0.109 to 3.569; two RCTs), and change in opiate treatment (OR 0.575, 95% CI 0.07 to 4.733; two RCTs).

The transdermal group had significantly lower rates of constipation (OR 0.38, 95% CI 0.228 to 0.635; four RCTs) and higher rates of patient preference (OR 0.43, 95% CI 0.22 to 0.841; three RCTs). There was no significant statistical heterogeneity for any outcomes except trial withdrawal (p<0.001) and change in opiate treatment (p=0.008).

**Authors’ conclusions**
Among patients taking opiates for moderate-to-severe cancer pain there was no difference between transdermal opiates and slow-release morphine in the overall rate of adverse effects, but transdermal opiates had lower rates of some adverse effects, such as constipation, and were more often preferred by patients.

**CRD commentary**
The objectives and inclusion criteria were clear, but only two databases were searched and it was unclear whether the search was limited by language or publication status. No specific attempts were made to locate unpublished trials, and language and publication bias are possible. One of the included trials stated in its title that it focused on patients with mild-to-moderate pain. It was unclear whether adequate steps were taken to minimise the risk of reviewer bias and error in the process of data extraction. None of the trials scored more than three points on the Jadad scale and the details of the quality characteristics of each trial were not reported. The Jadad scale does not assess some important aspects of trial quality, such as allocation concealment and specific dropout rates.

It was unclear how patient preference was assessed in trials where all participants did not receive both treatments. There were few trials, with samples and wide confidence intervals for some outcomes. There was inconsistent reporting of the final search date and one trial sample size. It was also unclear why some of the rates for individual adverse effects were higher than overall rates. These factors make it difficult to have confidence in the review findings. The authors concluded that overall there was no difference between adverse event rates for the two groups, but there might not have been sufficient data to reach this conclusion.

Due to limitations including low or unknown trial quality, low sample numbers, and inconsistency in some analyses, the authors' conclusions require cautious interpretation.

**Implications of the review for practice and research**

**Practice:** The authors stated that patient preference and less constipation supported the increasing use of transdermal opiates in clinical practice. They suggested that different analgesics may be justified in different settings, such as for patients with impaired bowel function.

**Research:** The authors stated that high quality trials were needed to investigate alternatives to oral morphine.

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