Transdermal fentanyl as a front-line approach to moderate-severe pain: a meta-analysis of randomized clinical trials

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CRD summary
The authors concluded that transdermal fentanyl and slow release oral morphine seemed to have different side-effect profiles; transdermal fentanyl seemed to be preferred by patients. Given the lack of reporting on certain review processes and the small number of included trials (some of which were of poor quality) the reliability of the authors’ conclusion is unclear.

Authors' objectives
To compare the safety of and patients' compliance to transdermal fentanyl and slow-release oral morphine in cancer and non-cancer pain patients.

Searching
MEDLINE and EMBASE were searched from January 1966 to June 2007. Search terms were reported. Reference lists of retrieved randomised controlled trials (RCTs) and systematic reviews were searched.

Study selection
Eligible studies were phase III RCTs that compared transdermal fentanyl with slow-release oral morphine in cancer or non-cancer patients with stable opiate requirements and reported safety and/or patient compliance.

Outcomes of interest included: overall safety; gastrointestinal effects (constipation, diarrhoea, anorexia, nausea and vomiting); neurological effects (insomnia, somnolence, depression and dizziness); hypoventilation, skin rash, itching, dry mouth, fatigue, sweating, urinary retention; efficacy (uncontrolled pain that required dosage adjustment, abdominal pain); and patient compliance (patient preference, trial withdrawal).

All included studies were funded by a pharmaceutical company.

The authors did not report how many reviewers performed study selection.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad scale of randomisation, double blinding, withdrawals and dropouts (maximum possible score was 5). There was an error in one of the tables so that data provided in the Jadad scores column were the studies’ sample sizes. Any disagreements were resolved by discussion.

Data extraction
Data was extracted in order to calculate odds ratios (OR) and 95% confidence intervals (CI). The authors did not state how this process was performed.

Methods of synthesis
Odd ratios were combined in a random-effects model. Heterogeneity was assessed with the Mantel-Haenszel test. Analysis was performed for trials of cancer and non-cancer pain together and separately.

Results of the review
Five studies were included in the analysis (n=1,272 patients). Two of these studies were randomised crossover trials (n=414 patients). Three studies were in cancer patients (n=380) and two were in non-cancer patients (n=892). The number of patients reported here were calculated from tables in the review as there were discrepancies between the tables and text. Three trials scored 3 on the Jadad scale. Two trials that scored 2 were classed as low quality.

Compared to slow release oral morphine, transdermal fentanyl was associated with reduced constipation (OR 0.56,
p<0.001), urinary retention (OR 0.56, p=0.015) and laxative use (OR 0.56, p<0.01) and increased nausea (OR 1.26, p=0.048), diarrhoea (OR 1.87, p=0.001) and sweating (OR 1.91, p<0.001) in both cancer and non-cancer patients. Statistically significant heterogeneity was reported for diarrhoea (value not reported).

Fewer patients (both cancer and non-cancer) preferred slow release oral morphine compared to transdermal fentanyl (OR 0.23, p<0.001).

There was no statistically significant difference between transdermal fentanyl and slow release oral morphine for all other outcomes. Statistically significant heterogeneity was reported for trial withdrawal rate (value not reported).

Subgroup analyses were reported.

**Authors' conclusions**

Transdermal fentanyl and slow release oral morphine seemed to have different side-effect profiles; transdermal fentanyl seemed to be preferred by patients.

**CRD commentary**

The review addressed a clear research question. Inclusion criteria were poorly specified, especially in relation to participant and pain type. The search strategy was adequate, although there were no apparent attempts to locate unpublished material and so relevant studies may have been missed. Study quality was assessed using an appropriate tool, although this tool did not consider allocation concealment. Two reviewers assessed study quality, which reduced risks of reviewer error and bias. It was unclear how many reviewers performed study selection and data extraction and consequently it was unclear whether these processes were subject to reviewer error and bias. There were minimum data on patient characteristics; therefore, generalisability of the authors findings' was unclear. Synthesis methods were appropriate, although ideally 95% CI should have been reported instead of p values for the pooled odds ratios.

The authors' conclusion reflected the evidence presented but given the lack of reporting on certain review processes and the small number of included trials (some of which were of poor quality) the reliability of the authors' conclusion is unclear.

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

**Practice:** The authors stated that the hierarchical approach traditionally recommended by the main scientific societies (oral morphine and then transdermal fentanyl) could be replaced by a front-line approach based on patients' characteristics and needs.

**Research:** The authors stated that greater methodological care was needed in further trials that investigated possible alternatives to oral morphine in clinical practice.

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