Economic evaluation of the fentanyl transdermal system for the treatment of chronic moderate to severe pain
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The health intervention examined in the study was fentanyl transdermal system, an opioid analgesic used for the management of chronic moderate to severe pain. The transdermal system provides a continuous dosing of fentanyl for up to 72 hours.

Type of intervention
Analgesic treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients suffering from moderate to severe pain and requiring stable long-term opium treatment.

Setting
The setting was outpatient. The economic study was carried out in the USA.

Dates to which data relate
Effectiveness evidence and data on resource use were derived from studies published in 1997 and 1998. No price year was reported.

Source of effectiveness data
A review of the literature was used to derive the effectiveness evidence. Several experts' opinions were also used to support the data derived from the literature.

Modelling
A decision tree model was constructed to assess one-year costs and benefits of the three opioids. Three phases of pain control were considered: titration (lasting for a few days), stabilisation (lasting 30 days), and long-term use (lasting until the first year of therapy was completed). Steps of the model were reported in detail. Basically, patients who experienced a failure were re-assessed and then switched not to one of the two competing opioids, but to an alternative method not detailed within the model. The average daily cost of this treatment was assumed to be the same, regardless of the initial therapy, and applied to the remaining number of days necessary to complete the model year.

Outcomes assessed in the review
The outcomes assessed from the literature and used as model inputs were disutility values of uncontrolled and controlled pain; drug-specific stabilisation probabilities for nausea/vomiting, mental cloudiness/somnolence, constipation, and switching due to unacceptable toxicity; and drug-specific long-term use switching due to unacceptable long-term use events.

**Study designs and other criteria for inclusion in the review**
The primary studies were mainly randomised, blind, controlled trials when possible. Case-control studies as well as case-reports and editorials were included to obtain all possible information on the three opioids.

**Sources searched to identify primary studies**
The literature search was performed on the National Library of Medicine's MEDLINE database and the HealthSTAR database.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Six primary studies were used as main the source of effectiveness evidence. However, several other studies were used to support the data required in the decision model.

**Methods of combining primary studies**
Primary studies were combined using narrative methods. When multiple clinical trials were found for the same parameter estimate, primary studies were ranked according to the quality of the study and larger trial were preferred over smaller ones.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The results of the review were as follows:

The disutility values of uncontrolled and controlled pain were 0.47 and 0.27, respectively.

The drug-specific stabilisation probabilities for:

- nausea/vomiting: fentanyl transdermal system 32%, controlled-release morphine 23%, and controlled-release oxycodone 16%;
- mental cloudiness/somnolence: fentanyl transdermal system 17%, controlled-release morphine 19%, and controlled-release oxycodone 25%;
- constipation: fentanyl transdermal system 6%, controlled-release morphine 15%, and controlled-release oxycodone 67%; and
- switching due to unacceptable toxicity: fentanyl transdermal system 17%, controlled-release morphine 2%, and
controlled-release oxycodone 18%.

The probability of drug-specific long-term use switching due to unacceptable long-term use events was 23% with fentanyl transdermal system, 3.7% with controlled-release morphine, and 27% with controlled-release oxycodone.

**Methods used to derive estimates of effectiveness**

Expert's opinions were widely used to provide data, which were then used to populate the decision tree model.

**Estimates of effectiveness and key assumptions**

The numerous experts' assumptions referred to duration of events (such as respiratory depression, nausea/vomiting, constipation, etc.), disutility values, and drug-specific probabilities during the three phases of the decision model.

**Measure of benefits used in the economic analysis**

The benefit measure used in the economic analysis was the number of quality-adjusted life-days (QALDs), then translated into quality-adjusted life-years (QALYs). QALYs were not discounted since the time frame of the study was one year. Data on quality weights were derived from experts' opinions and published studies.

**Direct costs**

Discounting was not relevant since the time horizon of the study was one year. Unit costs were reported. The cost/resource boundary was not clearly stated. The cost items included in the analysis referred to titration, toxicity during stabilisation, long-term use, pain and rescue medications, one-time pain assessment prior to switching, and alternative therapy. A detailed list of costs incurred was provided. The estimation of costs was based on publicly available data, and both primary studies and official reports. No price year was reported.

**Statistical analysis of costs**

No statistical analysis of costs was carried out.

**Indirect Costs**

Indirect costs were not included.

**Currency**

US dollars ($).

**Sensitivity analysis**

One-way sensitivity analyses were carried out to take into account uncertainty around the following model parameters: cost of alternative therapy, cost of pain medication, cost of nausea and vomiting; probability of chronic constipation and utility of achieving pain control with the fentanyl transdermal system.

**Estimated benefits used in the economic analysis**

The number of QALDs per year was 243.62 with fentanyl transdermal system, 235.63 with controlled-release morphine, and 230.94 with controlled-release oxycodone. The difference in QALDs lost due to chronic constipation was the crucial factor in the analysis.

**Cost results**

Total costs of the one-year treatment were $2,490.73 for fentanyl transdermal system, $2,037.28 for controlled-release...
morphine, and $2,307.46 for controlled-release oxycodone.

When fentanyl transdermal system was compared with controlled-release morphine, the difference in costs was mainly due to the high cost of the alternative therapy with fentanyl transdermal system, while when comparing fentanyl transdermal system with controlled-release oxycodone, the difference in costs was due to the high cost of the fentanyl transdermal system itself.

Synthesis of costs and benefits
An incremental cost-utility analysis was carried out to combine costs and benefits. The expected incremental cost per QALY gained with fentanyl transdermal system was $20,709 over controlled-release morphine and $5,273 over controlled-release oxycodone. The cost-utility of fentanyl transdermal system was quite robust. However, rate of constipation and cost of fentanyl were the model parameters with the greatest impact on the results.

Authors' conclusions
The authors concluded that fentanyl transdermal system proved to be a cost-effective pain control method in comparison with both controlled-release morphine and oxycodone. The incremental cost per QALY gained was close to that of a "Grade B technology" (less than $20,000/QALY), whose utilisation is considered appropriate in the health care system.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of the comparators. The two oral opioids were selected because of their widespread used as analgesics. In particular, oral morphine was considered the gold standard. You, as a user of this database, should assess whether they represent widely used analgesics in your own setting.

Validity of estimate of measure of effectiveness
The analysis of the effectiveness was carried out on the basis of a formal review of the literature. The authors reported search methods, design of the primary studies, and methods of combination of data used in the model. However, due to the lack of published data, numerous assumptions based on expert opinions were used to populate the decision model. This could have limited the internal validity of the analysis.

Validity of estimate of measure of benefit
QALYs were selected as benefit measures used in the economic analysis. They appear to have been the most appropriate measure, since the interventions under study were likely to affect the quality of life of patients rather than merely the length of life. Unfortunately, the quality weights were assumed rather than reflecting actual individual preferences.

Validity of estimate of costs
The authors carried out a detailed analysis of costs: unit costs were reported and although treated deterministically, sensitivity analyses were performed on the crucial variables. Costs were mainly estimated from published sources. However, the perspective of the study was not clearly stated, no indirect costs or price year were given, and no statistical analyses of quantities were reported. Although the comparison between fentanyl and morphine to give the incremental cost-effectiveness ration was appropriate, that between fentanyl and oxycodone, at least in the base case, was not. This is because oxycodone, in the base case, was dominated by (i.e., was more costly and less effective than) morphine and would therefore not be considered. Of course this could have varied in any sensitivity analysis.

Other issues
The authors made some comparisons of their findings with those from other studies. The issue of the generalisability of the study results was not explicitly addressed but several sensitivity analyses were carried out and unit costs were
reported, thereby enhancing the external validity of the study. The authors appear to have presented their findings selectively. Patients suffering from moderate to severe pain were included in the decision model and this was reflected in the authors' conclusions. The authors reported a specific limitation of their analysis, related to the numerous assumptions made due to the lack of published data.

**Implications of the study**
The authors recommend that the findings of this study should be used by decision makers to inform the choice of the optimal pain control method for the management of patients suffering from moderate to severe pain. They note that the conclusions of the analysis should be evaluated empirically in a prospective comparative study.

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