

## Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain

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### Abstract

**Objectives** To compare patients' preference for transdermal fentanyl or sustained release oral morphine, their level of pain control, and their quality of life after treatment.

**Design** Randomised, multicentre, international, open label, crossover trial.

**Setting** 35 centres in Belgium, Canada, Denmark, Finland, the United Kingdom, the Netherlands, and South Africa.

**Participants** 256 patients (aged 26-82 years) with chronic non-cancer pain who had been treated with opioids.

**Main outcome measures** Patients' preference for transdermal fentanyl or sustained release oral morphine, pain control, quality of life, and safety assessments.

**Results** Of 212 patients, 138 (65%) preferred transdermal fentanyl, whereas 59 (28%) preferred sustained release oral morphine and 15 (7%) expressed no preference. Better pain relief was the main reason for preference for fentanyl given by 35% of patients. More patients considered pain control as being "good" or "very good" with fentanyl than with morphine (35% *v* 23%,  $P = 0.002$ ). These results were reflected in both patients' and investigators' opinions on the global efficacy of transdermal fentanyl. Patients receiving fentanyl had on average higher quality of life scores than those receiving morphine. The incidence of adverse events was similar in both treatment groups; however, more patients experienced constipation with morphine than with fentanyl (48% *v* 29%,  $P < 0.001$ ). Overall, 41% of patients experienced mild or moderate cutaneous problems associated with wearing the transdermal fentanyl patch, and more patients withdrew because of adverse events during treatment with fentanyl than with morphine (10% *v* 5%). However, within the subgroup of patients naïve to both fentanyl and morphine, similar numbers of patients withdrew owing to adverse effects (11% *v* 10%, respectively).

**Conclusion** Transdermal fentanyl was preferred to sustained release oral morphine by patients with chronic non-cancer pain previously treated with

opioids. The main reason for preference was better pain relief, achieved with less constipation and an enhanced quality of life.

### Introduction

In 1998 the World Health Organization survey of nearly 26 000 patients in primary care in five continents reported that 22% had had persistent pain sometime over the previous year.<sup>1</sup> Pain is one of the commonest reasons for visiting a doctor and is often undertreated or mistreated, with patients going from doctor to doctor for relief and finally moving outside mainstream medicine in increasing numbers.<sup>2</sup>

Opioids are the mainstay of cancer pain management, providing effective pain relief.<sup>3-4</sup> They are the most powerful analgesics, but politics, prejudice, and continuing ignorance still impede optimum prescribing.<sup>5</sup> A review of retrospective and survey data confirms the efficacy of opioids in the treatment of chronic non-cancer pain and found that fears of addiction were not justified.<sup>6</sup> Randomised controlled trials of intravenous opioids in chronic non-cancer pain show benefit over placebo for morphine and fentanyl, whereas oral placebo controlled trials show efficacy for codeine, morphine, and oxycodone.<sup>7-11</sup> Worldwide, the value of opioids in this role has led to the development of management guidelines, with recommendations from national organisations.<sup>12-15</sup>

Morphine is the standard opioid against which others are judged and is usually prescribed in a sustained release oral formulation for the treatment of chronic pain.<sup>5,10</sup> Severe constipation, however, may affect some patients' quality of life more than their pain.<sup>16</sup>

Fentanyl, a lipid soluble synthetic opioid, can be delivered in a transdermal controlled release formulation, providing continuous, controlled systemic delivery of fentanyl for up to 72 hours.<sup>17</sup> Studies with transdermal fentanyl have shown analgesic efficacy in cancer pain.<sup>18-22</sup> Most patients preferred fentanyl, which was associated with less constipation than morphine.<sup>21,22</sup> Also, fentanyl has been shown to relieve neuropathic pain that is relatively insensitive to opioids.<sup>8,23</sup>

Opioids are individually titrated to an effective dose. Therefore little difference would be expected between opioids in efficacy or improvements in quality of life.<sup>5 6 24 25</sup> Recognising the increasing importance of patient preference and choice, we investigated in a large, multicentre, two way crossover trial whether patients with chronic non-cancer pain accustomed to opioids would prefer transdermal fentanyl over sustained release oral morphine, as has been found in patients with cancer pain.<sup>21</sup> We also assessed pain control, quality of life, and adverse events.

## Participants and methods

### Protocol

The study was approved by local ethics committees, and patients were recruited from 35 specialist pain clinics in Belgium, Canada, Denmark, Finland, the United Kingdom, the Netherlands, and South Africa.

Patients were invited to participate if they had chronic non-cancer pain requiring continuous treatment with potent opioids. Baseline assessment included recording the patients' characteristics, medical history, physical abnormalities, and vital signs. Patients' pain was classified as nociceptive, neuropathic, or combined nociceptive and neuropathic.

The requirement for opioid was determined individually immediately before the trial, and analgesic doses of fentanyl equivalent to the patients' previous opioid dose were calculated from the manufacturer's recommendations.<sup>26</sup> Patients were treated with fentanyl patches (Durogesic, Janssen-Cilag) releasing 25, 50, 75, or 100 µg fentanyl/hr and sustained release oral morphine as 10, 30, 60, 100, or 200 mg tablets (MS Contin, Napp Laboratories).

**Subject preferences**—The primary efficacy variable was the patient's preference for transdermal fentanyl or sustained release oral morphine and their main reason for preference. This evaluation was completed either at the end of the trial or at the end of treatment in patients who withdrew before completion.

**Pain control and treatment assessment**—At each visit patients were assessed for pain control compared with the previous visit. Both investigator and patient completed a global treatment assessment at the end of each treatment period.

**Quality of life assessment**—Quality of life (SF-36) and pain intensity (0 being low and 100 high) were assessed at baseline and at the end of each treatment period.<sup>27</sup>

**Statistical analyses**—The primary efficacy variable was analysed with a binomial test determining whether the proportion of patients who either "preferred" or "very much preferred" a treatment was larger than 0.5. Differences in personal variables at baseline between treatment groups were analysed with the Van Elteren test for continuous variables and the Cochran-Mantel Haenszel test for categorical variables. The mean daily dose of rescue drug, assessment of global treatment, assessment of pain control, and quality of life scores were compared with the Koch non-parametric paired analysis for crossover designs.<sup>28</sup>

**Assignment**—Patients were assigned to treatment groups by using the central randomisation minimisation technique.<sup>29</sup> One group was randomised to four weeks of treatment with sustained release oral morphine followed by transdermal fentanyl for four

weeks. The second group received the same treatments but in reverse order.

## Results

### Participant flow

The figure shows the progress of patients through the study. Baseline characteristics did not differ between the two groups (table 1).

### Analysis

#### Patient preference

Preference could not be assessed in 39 of 251 patients, leaving a total of 212 patients for analysis. A higher proportion of patients preferred or very much preferred transdermal fentanyl to oral sustained release morphine (138 (65%) *v* 59 (28%);  $P < 0.001$ ) (table 2). Fifteen patients (7%) did not express a preference. After exclusion of 24 patients with a "bad" or "very bad" score while taking morphine before the study, 69% of patients expressed a "strong" or "very strong" preference for fentanyl.

Patient preference for fentanyl was not significantly different in patients with nociceptive pain (75 of 108, 69%), neuropathic pain (31 of 53, 58%), or mixed neuropathic and nociceptive pain (32 of 51, 63%). The predominant reason given for preferring fentanyl was better pain relief, followed by greater convenience and fewer adverse events (table 2). In a subgroup of 66 patients who were neither accustomed to fentanyl nor morphine, 62% preferred fentanyl.

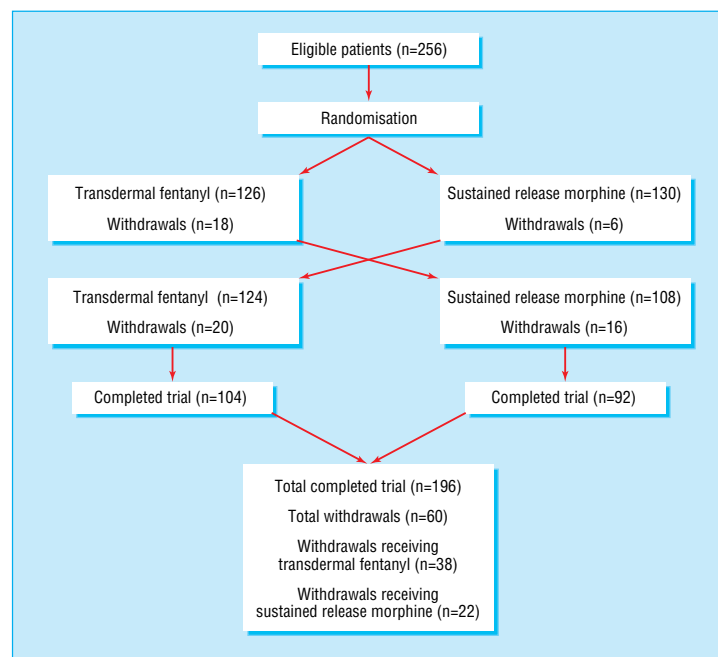
#### Pain control, treatment assessments, and rescue drug

Patients treated with fentanyl had on average lower pain intensity scores than those treated with morphine (mean 57.8, range 33.1-82.5 *v* mean 62.9, range 41.2-84.6;  $P < 0.001$ ). More patients receiving fentanyl considered their pain control to be good or very good than those receiving morphine (35% *v* 23%,  $P = 0.002$ ).

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Flow of patients through trial

**Table 1** Characteristics at baseline of patients receiving transdermal fentanyl or sustained release oral morphine. Values are numbers (percentages) unless stated otherwise

Characteristic	Randomised to fentanyl first (n=126)	Randomised to morphine first (n=130)
Female:male	60:66	60:70
Mean age (range) in years	50.9 (28-82)	51.9 (26-82)
Mean weight (range) in kg	74.3 (38-138)	77.9 (45-130)
Mean height (range) in cm	170 (144-200)	170.5 (151-196)
White	125 (99)	126 (97)
Other	1 (1)	4 (3)
Mean (SE) duration of chronic pain (range) in years	9.5 (0.74) (0.2-50)	9.1 (0.73) (0.3-46)
Pain type:		
Neuropathic	31 (25)	35 (27)
Nociceptive	64 (51)	64 (49)
Combined neuropathic and nociceptive	31 (25)	31 (24)
Classification of (most common) pain*:		
Axis I: region		
Lower back	52 (41)	50 (39)
Lower limbs	27 (21)	32 (25)
Axis II: system		
Musculoskeletal or connective tissue	51 (41)	64 (50)
Nervous system	61 (48)	47 (36)
Axis III: temporal characteristics		
Continuous, fluctuating severity	52 (41)	62 (48)
Continuous, non-fluctuating severity	38 (30)	32 (25)
Axis IV: intensity; time since onset		
Medium (>6 months)	27 (21)	34 (26)
Mild (>6 months)	4 (3)	2 (2)
Axis V: aetiology		
Degenerative or mechanical	40 (32)	46 (36)
Trauma, operation, or burns	37 (29)	33 (26)
Opioid use before trial:		
Morphine or morphine sulphate	91 (72)	103 (79)
Efficacy evaluation "bad" or "very bad"	9 (10)	15 (15)

\*According to the International Association for the Study of Pain.

Analysis of the consumption of rescue drug during the last three weeks of each treatment period showed that the mean (standard deviation) consumption was significantly higher with fentanyl (29.4 (33.0) mg) than with morphine (23.6 (32.0) mg;  $P < 0.001$ ).

**Quality of life**—Patients receiving fentanyl had higher overall quality of life scores than patients receiving morphine in each SF-36 category, and these were significant in the categories for bodily pain, vitality, social functioning, and mental health.

**Adverse effects**—The overall incidence of treatment related adverse events was similar in both groups, as was the proportion of patients with adverse events (74% v 70%). Fentanyl was associated with a higher

incidence of nausea (26% v 18%) than was morphine, whereas constipation was less common with fentanyl than with morphine (16% v 22%). Reduced constipation was confirmed by the bowel function questionnaire (29% fentanyl v 48% morphine;  $P < 0.001$ ). Few patients had serious adverse events (2.8% v 3.8% for fentanyl and morphine, respectively), and only one patient, in the morphine group, hypoventilated. No deaths occurred, and no clinically important changes of vital signs were observed.

**Patient withdrawals**—Within the total patient population the number of withdrawals in the fentanyl group was almost double (16%) that in the morphine group (9%). More patients withdrew because of adverse events during treatment with fentanyl (11%) than with morphine (4%). However, 66 patients who had taken neither fentanyl nor morphine before the study showed a similar rate of withdrawal (11% v 9.8%) owing to adverse events.

## Discussion

Patients with chronic non-cancer pain generally preferred treatment with transdermal fentanyl (65%) than with sustained release oral morphine (28%). A similar result was observed in patients with cancer pain.<sup>21 22</sup> Furthermore, our findings confirm that potent opioids can provide satisfactory pain relief for the difficult clinical problem of chronic non-cancer pain. Although recruitment bias cannot be excluded, it cannot entirely explain the observed difference in treatment outcome.

Despite preference and better pain relief, more patients withdrew because of adverse events in the first fentanyl period than in the first morphine period. The phenomenon of preference for an opioid despite higher reporting of adverse events is well recognised in blinded controlled trials.<sup>7 9-11</sup> Most patients (76%) had taken morphine for six weeks before the study and would be accustomed to its side effects, making it unlikely that they would report additional adverse events when randomised to morphine. This may represent "incomplete cross tolerance" leading to a greater than anticipated potency,<sup>3 30</sup> supported by similar withdrawal rates for both opioids within a subgroup of patients who had taken neither morphine nor fentanyl before the study.

Comparisons of opioid action must be made at equianalgesic doses, as improvements in pain control and constipation with fentanyl could be explained by an incorrect initial dose ratio. The dosage of fentanyl increased consistently, and these patients consumed more rescue drug than those receiving morphine. These findings confirm that a higher ratio of starting dose may be required compared with the conservative table for equianalgesic dose table used in this study.<sup>19</sup> However, individual dose titration is vital and allows for the variability in patients' response to different opioids<sup>3 21</sup> and the reported need to reduce the dose during "opioid rotation" in patients showing toxicity.<sup>31</sup>

Our patients were conditioned to opioids, mainly morphine, and switching to fentanyl may partly explain the improved pain control. The switch may have raised expectation of increased pain relief, partly attributable to a placebo analgesic effect.<sup>32</sup> Most

**Table 2** Patients' preferences for transdermal fentanyl or sustained release oral morphine. Values are numbers (percentages) unless stated otherwise

Preference	Randomised to fentanyl first (n=124)	Randomised to morphine first (n=127)	Overall (n=212)	Reasons for preference (%)
Strong preference for fentanyl	41 (41)	43 (38)	138* (65)	Better pain relief (35), fewer adverse events (14), more convenient (15), other (1)
Preference for fentanyl	13 (13)	41 (36)		
No preference	12 (12)	3 (3)	15 (7)	
Preference for morphine	20 (20)	18 (16)	59 (28)	Better pain relief (17), fewer adverse events (5), more convenient (5), other (0.9)
Strong preference for morphine	13 (13)	8 (7)		
No preference assessed	25	14	—	

\* $P < 0.001$  different from preference for morphine.

patients, however, preferred fentanyl regardless of the order of treatment. Exclusion of patients dissatisfied with morphine did not affect the percentage of patients preferring fentanyl.

The higher consumption of rescue drug during treatment with fentanyl was small (5.8 mg/24 hr overall), and probably not clinically important, but may reflect a less flexible dose titration with fentanyl. Differences in pain relief may also be explained by selectivity of opioid receptors. Indeed, recent research indicates a genetic basis for differences in pain sensitivity and response to analgesics.<sup>33</sup> A significantly lower incidence of constipation was detected in the formal assessment of bowel function by patients receiving fentanyl, confirming previous reports, supported by the more favourable dose-analgesia to dose-constipation ratio for fentanyl than for morphine observed in rats.<sup>18-22 34</sup>

The fentanyl patch formulation affords a convenient system of delivery over 72 hours. It may prevent "clock watching" and breakthrough pain associated with shorter acting formulations, thus improving compliance.<sup>4</sup> In a "double dummy" design, preference for one delivery system would have been difficult to assess if patients were receiving both drugs together, particularly considering the difficulties and risks associated with simultaneously titrating morphine and fentanyl. Placebo effects can explain analgesia but not poor analgesia.<sup>35</sup> Therefore, although a placebo effect is a possible explanation for our findings, given an overtly different administration, it is a less plausible explanation for those receiving fentanyl or morphine who had poor pain control. These findings are consistent with other reports that opioids do not provide adequate pain control to all patients with chronic non-cancer pain.<sup>5 9 10</sup>

Finally, we believe that using a pragmatic, clinical practice based approach, particularly in a large sample size, is justified, especially in the light of recent problems applying quality designs to clinical trials.<sup>36 37</sup> The "explanatory" (evidence based) approach requires a placebo for comparison, whereas the "pragmatic" approach generally compares a new treatment with the best in clinical use for the particular clinical circumstances of patients.<sup>38</sup> The existence of a gold standard treatment allows direct comparison rather than a placebo control, so that fentanyl can be directly compared with morphine.<sup>39</sup>

Strong treatment preferences can present difficulties but may be avoided by the crossover design.<sup>40 41</sup> Patients' preference, although important for all clinical decisions, deserves special emphasis when diseases or treatments affect quality of life, the treatment involves risks or side effects, or the choice between treatments is a "close call."<sup>42</sup> The patient may be the best judge of the delicate balance between analgesic efficacy, side effects, and the overall experience of pain. This reflects our choice of patients' preference as the primary efficacy variable. Furthermore, pragmatic outcome measures such as quality of life and patients' preference may, ultimately, provide a more accurate evaluation of treatment effects than pain measures alone.

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### What is already known on this topic

The clinical use of potent opioids in the treatment of chronic non-cancer pain is supported by retrospective, survey data and small randomised controlled trials showing efficacy and safety

Studies with transdermal fentanyl have shown efficacy and preference over sustained release oral morphine in the treatment of cancer pain

### What this study adds

This is the first study to provide comparative data supporting treatment options with potent opioids for chronic non-cancer pain

Both transdermal fentanyl and sustained release oral morphine provided effective and well tolerated pain relief

During fentanyl treatment patients experienced superior pain relief, higher quality of life, and less constipation; fentanyl was preferred to morphine by 65% of patients

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## General practitioners' reasons for removing patients from their lists: postal survey in England and Wales

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The removal of patients from doctors' lists causes considerable public and political concern, with speculation that patients are removed for inappropriate, including financial, reasons.<sup>1</sup> In 1999 the House of Commons Select Committee on Public Administration noted that little evidence was available on either the frequency of, or the reasons for, removal of patients.<sup>2</sup> National statistics do not distinguish between patients removed after moving out of a practice area and those removed for other reasons. Two postal surveys have reported why general practitioners might, in general, remove patients,<sup>3,4</sup> and one small study has described the reasons doctors give for particular removals.<sup>5</sup> We therefore determined the current scale of, and doctors' reasons for, removal of patients from their lists in England and Wales.

### Participants, methods, and results

In April 2000 we sent a questionnaire to 1000 general practitioners in a random sample of practices, but to no more than one doctor per practice. Up to two reminders were sent to non-respondents at fortnightly intervals.

The questionnaire asked for the number of patients removed from the practice list in the previous six

months (for reasons other than living outside the practice area), the reasons contributing to the most recent removal, and whether that removed patient was given a reason. A list of suggested reasons for removal was included (having been compiled in the light of published opinions<sup>3,5</sup>), and respondents were asked to indicate which of these were "primary" reasons and which others were "contributory."

The questionnaire also asked whether target payment systems (for childhood immunisation and cervical smear testing) and financial arrangements for drug budgets and out of hours care created financial incentives for removing patients.

Of the 1000 doctors surveyed, 14 replied that they were not working in general practice. Of the remaining 986, 748 (76%) responded. In the previous six months 300 out of 745 practices (40% (95% confidence interval 37% to 44%)) had removed one or more patients. When 21 practices whose list size was not stated were excluded, 988 patients had been removed during this period from a registered population of 4.6 million, (removal rate of 4.3 (4.1 to 4.6) per 10 000 patients a year).

The primary and contributory reasons given for the most recent removal by each of these 300 practices are shown in the table. Violent, threatening, or abusive behaviour was given as a primary reason in 176 of