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ORIGINAL RESEARCH ARTICLE

# Efficacy and Safety of Sublingual Fentanyl Orally Disintegrating Tablets in Patients with Breakthrough Pain: Multicentre Prospective Study

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**Abstract**

*Background and Objectives* The aim of this study was to evaluate the effectiveness and safety of sublingual fentanyl oral disintegrating tablets (sublingual fentanyl ODT) for the treatment of breakthrough pain (BTP), cancer or non-cancer related, in terms of relief of pain intensity, adverse events (AEs) and patient satisfaction, and to further examine the clinical and epidemiological profile of patients with BTP in a clinical setting.

*Methods* A multicentre, prospective, open-label study was conducted in 19 pain units from Catalonia hospitals (Spain) over a 1-month period. Opioid-tolerant adult patients experiencing episodes of BTP intensity >5 on a visual analogue scale (VAS) during the 12–24 h before screening or AEs related to their previous rescue medication for BTP received sublingual fentanyl ODT in the course of routine clinical practice and completed a 30-day study period consisting of five assessment points: days 0 (baseline), 3, 7, 15 and 30. The efficacy was assessed by

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collecting pain intensity and pain relief data at baseline and at each assessment. AEs were recorded by investigators throughout the study during clinic visits and telephone follow-ups. For all patients, titration was begun with an initial dose of 100 μg. No more than two doses were allowed to treat an episode and patients might wait at least 4 h before treating another BTP episode with sublingual fentanyl ODT. The dose was increased by 100 μg multiples up to 400 μg as needed; and by 200 μg multiples up from 400 to 800 μg, the maximum titration step.

*Results* A total of 182 patients were enrolled and 177 (97.2 %) completed the study: 37 had breakthrough cancer pain (BTcP) and 145 had breakthrough non-cancer pain (BTncP). The mean pain intensity showed a statistically significant improvement at the first assessment point and at all assessments thereafter ($p < 0.0001$). At the end of the study, the time lag between administration and first effect of sublingual fentanyl ODT was ≤10 min in 69.0 % (60 % BTcP and 71.2 % BTncP). The number of daily BTP episodes decreased in both groups, but it was statistically significant in BTcP. 114 patients (62.64 %) experienced AEs during the study. AEs recorded included nausea, vomiting, somnolence and constipation, and seven (4.49 %) were considered severe. No death or discontinuation was considered related to AEs.

*Conclusion* Sublingual fentanyl ODT provided rapid and consistent relief from BTP, both in cancer and non-cancer patients. It was well-tolerated and well-accepted by patients in routine clinical practice.

## 1 Introduction

Breakthrough pain (BTP) is a transitory severe acute pain that occurs in a background of chronic pain that is adequately controlled by an opioid regimen [1].

The effective treatment of BTP over time is an important component of improving patients' well-being. Epidemiological studies of BTP have focused on patients with cancer, particularly those with advanced disease. In these studies, BTP has been identified as a highly prevalent phenomenon, associated with worse quality of life, decreased functional status, higher levels of depression and anxiety [2, 3], and less favourable medical outcomes [4, 5].

Although epidemiological data in populations with chronic non-cancer BTP are limited, they suggest that the prevalence and characteristics of BTP are comparable with the cancer population [6]. However, the distinction between cancer-related and non-cancer-related BTP remains controversial, with some authors in the pain community questioning the evidence supporting the existence of BTP in non-cancer patients with chronic pain, and others asserting that there is no relevant difference between both groups [7–9].

According to most estimates, episodes of BTP-both cancer- and non-cancer-related-have a prevalence >50 % [6, 10] and are associated with pain levels reaching peak intensity within 3–10 min. Given its high prevalence and negative clinical consequences, a treatment approach known as "rescue" dosing has become a widely accepted approach. The ideal rescue medication should be efficacious and patient friendly, with a rapid onset of action, a relatively short duration of action, and minimal adverse effects [11, 12]. As a result, rapid-onset opioids delivered by non-invasive routes have been developed to match the timing of BTP episodes more closely.

The transmucosal route of administration offers a promising alternative for delivering effective analgesic treatment of BPT. The sublingual mucosa, due to its high vascularity and good permeability, offers a direct entry of the drug into systemic circulation, bypassing gastrointestinal and hepatic metabolism. Fentanyl is a synthetic opioid agonist with high lipophilicity, making it well suited to favour the passage through the mucosa and then across the blood–brain barrier to provide fast analgesia [13–15].

The current study aimed to evaluate the effectiveness and safety of sublingual fentanyl oral disintegrating tablets (sublingual fentanyl ODT) for the treatment of BTP, both cancer-related and non-cancer-related, in terms of relief of pain intensity, adverse events (AEs) and patient satisfaction, and to further examine the clinical and epidemiological profile of patients with BTP in routine clinical practice.

## 2 Methods

A multicentre, prospective, open-label study was conducted in 19 pain units from Catalonia hospitals (Spain) over a 1-month period. Written informed consent was obtained from all patients before study enrolment. The study procedures were performed in accordance with Good Clinical Practice and the Declaration of Helsinki and Instrucción 1/2003, Generalitat de Catalunya, Dirección General de Recursos Sanitarios, which legislates on post-approval prospective studies.

### 2.1 Study Population

Study participants were opioid-tolerant adults, over 18 years of age, with chronic pain receiving ≥60 mg/day of oral morphine or an equivalent, stable daily dose of another opioid for 1 week or longer. In addition, participants had to report experiencing episodes of BTP during the 12–24 h before screening or AEs related to their previous rescue medication for BTP. The BTP that patients had to experience was defined as temporary flares of severe or excruciating pain [visual analogue scale (VAS) >5],

each lasting 20–30 min, and that were at least partially relieved (VAS ≤4) by their current supplemental opioid.

Exclusion criteria included a history of alcohol or other substance abuse, or generalized muscle pain.

## 2.2 Study Design

The 30-day period included five assessment points: day 0 (baseline, enrolment at clinic), days 3 and 7 (telephone assessments), day 15 (clinical visit or telephone assessment) and day 30 (clinical visit) (Fig. 1).

Data collected included patient age, sex, underlying pain aetiology (cancer, non-cancer), type of BTP (incidental, idiopathic), baseline opioid regimen (drug and dose/day), number of BTP episodes per day and the successful dose of sublingual fentanyl ODT both per episode and per day.

Efficacy was assessed by collecting pain intensity and pain relief data at baseline and at each assessment. Pain intensity was measured using a 0–10 numerical rating scale, where 0 is no pain and 10 is worst pain conceivable. Pain relief was recorded using a list of time intervals (<5, 6–10, 11–16, >15 min) at which "first effect" was achieved.

AEs were recorded by investigators throughout the study during clinic visits and telephone follow-ups. AEs were defined as any unfavourable or unintended changes in signs, symptoms or laboratory results, or worsening of pre-existing condition. All AEs were rated in terms of intensity as mild, moderate or severe by clinicians.

Finally, patients and investigators were asked to evaluate the treatment as "excellent", "good", "fair" or "bad".

## 2.3 Dosing

For each BTP episode, patients self-administered sublingual fentanyl ODT (Abstral®, ProStrakan Ltd, Galashiels, UK) by placing the tablet on the floor of the mouth, under the tongue, and allowing it to dissolve, without sucking, chewing or swallowing.

For all patients, titration was begun with an initial dose of 100 μg. If adequate analgesia was not obtained within 30 min of administration, patients might use a second 100 μg dose. No more than two doses were allowed to treat an episode and patients were required to wait at least 4 h before treating another BTP episode with sublingual fentanyl ODT.

If adequate analgesia was not achieved dose escalation was continued in a stepwise manner over consecutive BTP episodes until adequate analgesia with tolerable side effects was obtained. The dose was increased by 100 μg multiples up to 400 μg as needed; and by 200 μg multiples up from 400 to 800 μg, the maximum titration step.

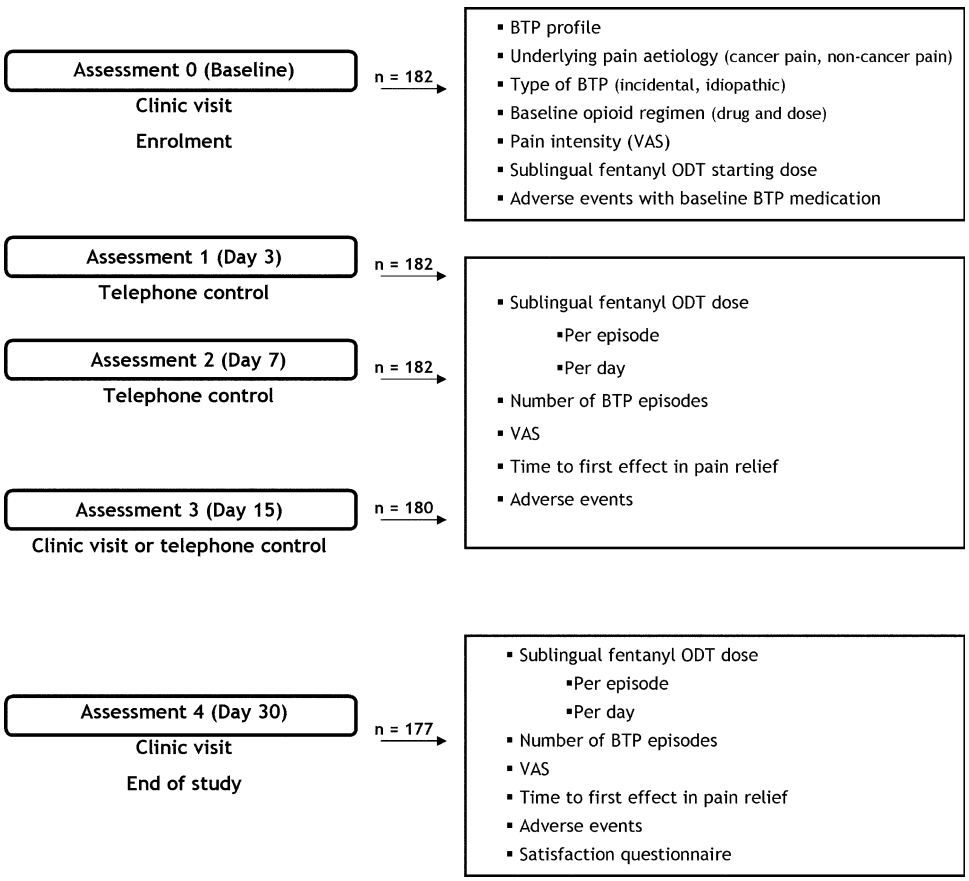


**Fig. 1** Study design. *BTP* breakthrough pain, *ODT* oral disintegrating tablets, *VAS* visual analogue scale

All patients continued taking their baseline opioid regimen in accordance with the treatment centre's standards and clinical procedures. Patient's previously prescribed BTP medication was permitted as rescue medication if required, and its use was recorded throughout. Laxatives and anti-emetics were prescribed at the time of commencement of treatment with sublingual fentanyl ODT.

### 2.4 Statistical Considerations

The maximum planned enrolment was 285 and no formal sample size calculation was performed prior to study.

Descriptive statistics were used to characterise the demographics and disease-related features of the total sample with BTP: mean, standard deviation (SD), 95 % confidence interval, standard error and range. Categorical variables were described by absolute and relative frequencies and percentage.

Intragroup data were analysed with paired Student's test for numeric variables and Bowker test for ordinal variables. Intergroup comparison was analysed with parametric Student's test, and non-parametric Wilcoxon rank-sum for quantitative variables and the Cochran–Mantel–Haenszel test for qualitative ones. We also performed ANCOVA and repeated-measures analysis for multiple comparisons. Data from all patients who enrolled in the study were included in the analyses.

SAS version 9.0 (SAS Institute Inc., Cary, NC, USA) statistical software was used to perform all statistical analyses.

## 3 Results

A total of 182 patients were enrolled in the study. Of these, 177 (97.2 %) completed the study. The five who did not provide data included those who were lost to follow-up ($n = 2$), one who withdrew after agreeing, one lack of efficacy (reported by a patient who wished to return to the previous BTP medication) and one death due to cancer progression.

The baseline demographic characteristics of participants are presented in Table 1. Overall, of the 182 patients, 37 had cancer-related pain and 145 had non-cancer-related pain. The mean ± SD age was approximately equal in both groups (69 ± 14.6; range 27–91 years). There were approximately equal numbers of women and men in the cancer group (45.9 vs. 54.1 %, respectively), but more women than men in the non-cancer group (67.1 vs. 32.9 %). The presence of BTP was reported by 37 (100 %) of the patients with cancer-related pain and by 124 (90.4 %) of the patients with non-cancer pain ($p = 0.03$). BTP was incidental in 144 patients (79.1 %).

**Table 1** Baseline and demographic characteristics of study patients

| | Total | BTcP | BTncP |
|---|---|---|---|
| Underlying pain aetiology | $n = 182$ | $n = 37$ | $n = 145$ |
| Sex | | | |
| Female | 113 (62.8) | 17 (45.9) | 96 (67.1) |
| Male | 67 (37.2) | 20 (54.1) | 47 (32.9) |
| Age (years) | | | |
| Mean (SD) | 69.0 (14.6) | 66.8 (13.4) | 65.2 (14.9) |
| Range | 27–91 | 40–85 | 27–91 |
| BTP profile | | | |
| BTP ≥5 (last 12–24 h) | 161 (90.4) | 37 (100) | 124 (87.9) |
| AEs on previous BTP medication | 17 (9.6) | 0 | 17 (12.1) |
| VAS | | | |
| Mean (SD) | 6.5 (1.6) | 6.4 (1.4) | 6.5 (1.7) |
| Baseline opioid regimen (drug) | | | |
| Buprenorphine | 4 (2.2) | 1 (2.7) | 3 (2.1) |
| Fentanyl | 97 (53.3) | 28 (75.7) | 69 (47.6) |
| Hydromorphone | 51 (28.0) | 2 (5.4) | 49 (33.8) |
| Morphine | 6 (3.3) | 3 (8.1) | 3 (2.1) |
| Oxycodone | 17 (9.4) | 3 (8.1) | 14 (9.7) |
| Tramadol | 3 (1.7) | – | 3 (2.1) |
| Type of BTP | | | |
| Idiopathic | 25 | | |
| Incidental | 144 | | |
| Unknown | 10 | | |
| Mixed | 3 | | |

Data are *n* (%) unless stated otherwise

*AE* adverse effects, *BTP* breakthrough pain, *BTcP* breakthrough cancer pain, *BTncP* breakthrough non-cancer pain, *SD* standard deviation, *VAS* visual analogue scale

At baseline, the majority of patients were receiving fentanyl, hydromorphone or oxycodone for their background pain (53.3, 28.0 and 9.4 % of patients, respectively).

### 3.1 Efficacy

The mean pain intensity showed a statistically significant improvement since the first assessment point and at all assessments thereafter ($p < 0.0001$ for each assessment). By pain aetiology, patients with breakthrough cancer pain (BTcP) achieved a significantly greater improvement than patients with breakthrough non-cancer pain (BTncP) at assessment 3 (mean ± SD, $-2.3 \pm 1.4$ vs. $-1.9 \pm 1.5$; $p = 0.02$) and assessment 4 (mean ± SD, $-3.1 \pm 1.2$ vs. $-2.1 \pm 1.7$; $p < 0.0001$). A mean of 35.4 % improvement in pain relief was reported at the end of the study (48.4 % in BTcP, 33.9 % in BTncP) (Fig. 2).

At assessment 4 (end-of-study), patients reported that the time to first effect following administration of

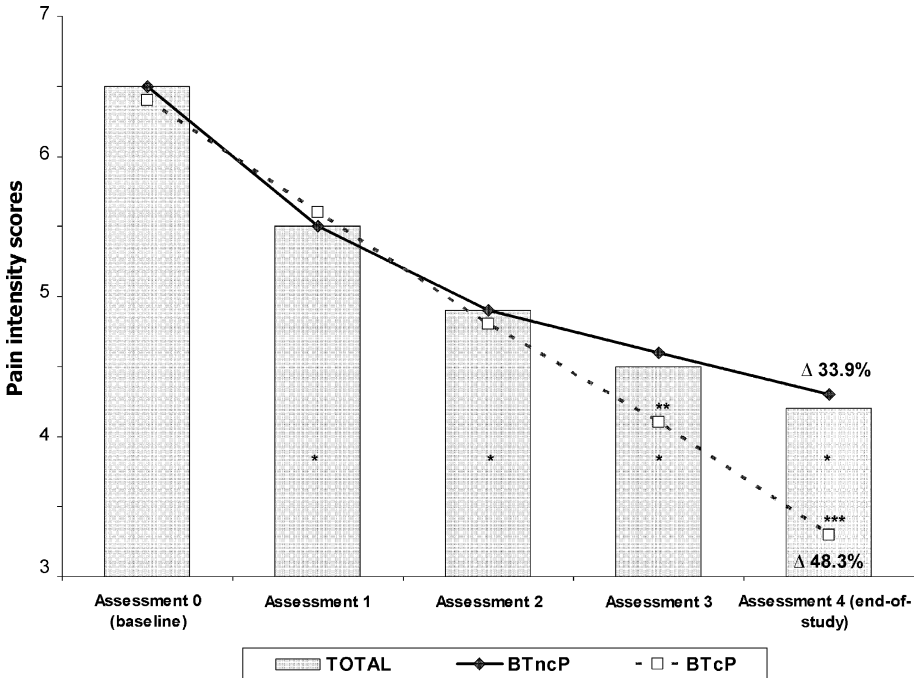


**Fig. 2** Mean pain intensity scores. *BTcP* breakthrough cancer pain, *BTncP* breakthrough non-cancer pain, Δ percentage improvement in pain relief versus baseline, * $p < 0.0001$ versus assessment 0 (baseline), ** $p = 0.02$ versus BTncP at assessment 3, *** $p < 0.0001$ versus BTncP at assessment 4

sublingual fentanyl ODT was ≤10 min in 69.0 % episodes (60 % BTcP and 71.2 % BTncP). Indeed, first effect was reported within 5 min in 21.3 % of episodes (23.3 % BTcP vs. 20.8 % BTncP) and between 6 and 10 min in 47.7 % of episodes (36.7 % BTcP vs. 50.4 % BTncP). Additionally, first effect was reported between 11 and 15 min in 18.7 % of episodes (36.7 % BTcP vs. 14.4 % BTncP; $p = 0.02$) (Fig. 3).

### 3.2 Safety and Tolerability

The average number of episodes per day in BTncP patients decreased slightly over the analysis period from 2.8 ± 2.1 episodes (mean ± SD) at assessment 1 (range 1–6) to 2.4 ± 1.5 at the end of study (range <1–5). In contrast, BTcP patients reported a statistically significant reduction of number of episodes (mean ± SD) in all assessments from 4.0 ± 3.0 (range 1–9) at assessment 1 to 2.9 ± 1.7 (range <1–6) at assessment 4 ($p = 0.04$) (Fig. 4).

When the dose per episode was examined, the BTncP group showed a slightly greater percentage of increasing dose adjustment from assessment point 1 to assessment 4: 106.9 ± 28 μg (mean ± SD), range 100–300, median 100 vs. 127.1 ± 50.7 μg, range 100–300; median 100. The BTcP patients reported a statistically significant increase in assessment 1 and assessment 3 compared with BTncP patients: 124.3 ± 43.5 μg (mean ± SD), range 100–200, median 100, $p = 0.03$ vs. 154.1 ± 80.3 μg, range 100–400, median 100, $p = 0.04$, respectively (Fig. 4).

The average daily dose of sublingual fentanyl ODT increased over the 30-day analysis period from 283.5 μg/day [283.5 ± 215 (mean ± SD), range 100–300, median 100] to 396.5 μg/day [396.5 ± 340 (mean ± SD), range 100–1,200, median 300]. By underlying disease, BTcP patients showed a statistically significant increase in all assessments compared with BTncP ($p = 0.02$).

Of the 182 enrolled patients, 114 (62.6 %) experienced at least one AE during the study. The AEs recorded included nausea, vomiting, somnolence and constipation. The majority of AEs were considered mild or moderate in intensity (146/156, 93.6 %) and seven (7/156, 4.5 %) were considered severe. No death or discontinuation was considered related to AEs. There was no statistically significant difference between groups (Table 2).

On the satisfaction questionnaire assessment, 58 % of patients reported "good" and 27.3 % "excellent" ratings for sublingual fentanyl ODT; similarly, 61 % of investigators reported "good" and 28.3 % "excellent" ratings (Fig. 5).

## 4 Discussion

Rapid-onset opioids have been increasingly prescribed over recent years for the management of BTP due to the fast onset of action and easy and convenient route of administration. The scientific literature regarding BTP has largely focused on oncological patients and very few studies have evaluated BTP in populations with chronic non-cancer pain.

Initially, sublingual fentanyl ODT was studied in opioid-tolerant patients with chronic persistent cancer BTP [16–18]. The evidence for the efficacy and tolerability of

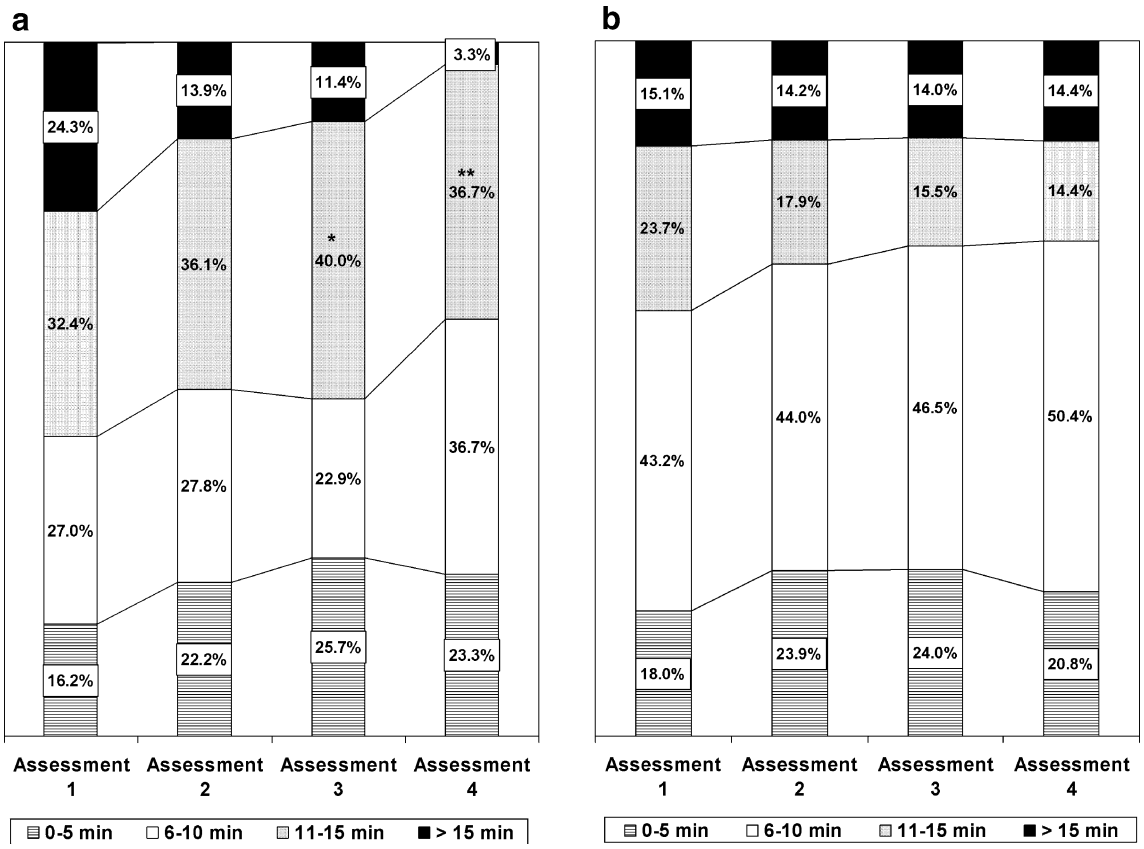


**Fig. 3** Time to first effect following administration of sublingual fentanyl oral disintegrating tablets for episodes of **a** cancer BTP and **b** non-cancer BTP. *BTP* breakthrough pain, * $p = 0.008$ versus non-cancer BTP at assessment 3, ** $p = 0.02$ versus non-cancer BTP at assessment 4

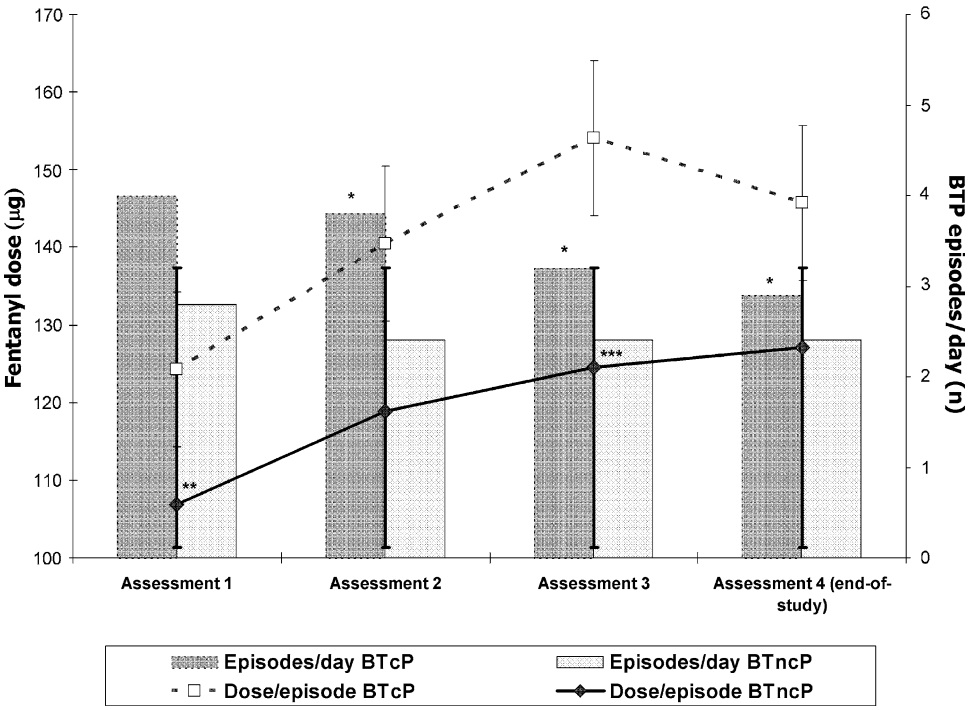


**Fig. 4** Mean number of daily breakthrough pain episodes and mean sublingual fentanyl oral disintegrating tablet dose changes per episode over time. *Error bars* represent standard deviation. *BTP* breakthrough pain, *BTcP* breakthrough cancer pain, *BTncP* breakthrough non-cancer pain, * $p = 0.04$ versus BTcP episodes/day at assessment 1, ** $p = 0.03$ versus dose/episode BTcP at assessment 1, *** $p = 0.04$ versus dose/episode BTcP at assessment 3

**Table 2** Treatment-related adverse effects

| | Nausea | Vomiting | Constipation | Somnolence |
|---|---|---|---|---|
| BTcP | 8 (21.6) | 1 (2.9) | 14 (37.8) | 17 (45.9) |
| | | | 1 (2.9)[a] | 1 (2.8)[a] |
| BTncP | 23 (16.1) | 4 (2.8) | 44 (30.8) | 43 (29.9) |
| | | | 4 (2.8)[a] | 1 (0.7)[a] |
| Total | 31 (17.2) | 5 (2.8) | 58 (32.2) | 60 (33.1) |
| | | | 5 (2.8)[a] | 2 (3.3)[a] |

Data are *n* (%)

*BTcP* breakthrough cancer pain, *BTncP* breakthrough non-cancer pain

[a] Severe adverse effects

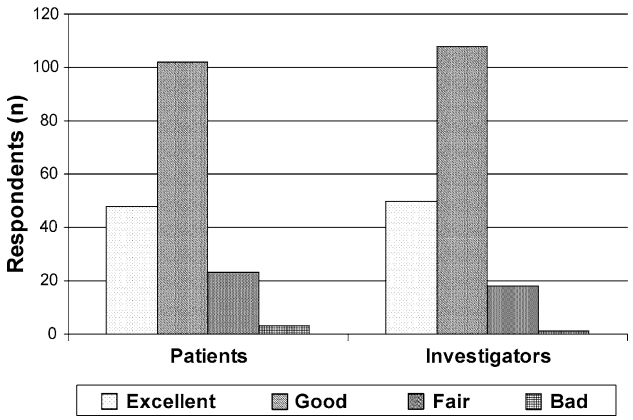


**Fig. 5** Patient and investigator treatment satisfaction ratings

sublingual fentanyl ODT as single fixed [17] or titrated doses [16] was based primarily on two randomised, double-blind, placebo-controlled, multicentre trials. Later, in a similar non-randomized study [18], sublingual fentanyl ODT was found to be effective and tolerated, with an increase in satisfaction during the 12 months of the study.

To date, there have been no clinical trials focusing on the efficacy and safety of sublingual fentanyl ODT in the management of BTP in patients with chronic non-cancer pain. However, based on individual studies, bioequivalence was shown for sublingual and buccal tablet placement [19], and the clinical study programme for fentanyl buccal tablet (FBT) provided data about efficacy, safety and tolerability in opioid-tolerant patients with BTP in association with chronic non-cancer pain through three double-blind placebo-controlled and two open-label studies [20–24]. These studies showed that FBT was effective in providing rapid and meaningful relief of BTP and had a tolerability profile typical of opioids [25].

The current study aimed to complement the earlier findings by assessing treatment outcomes in a diverse patient population, with chronic cancer pain or chronic non-cancer pain, receiving sublingual fentanyl ODT in routine practice for their BTP.

This study shows that sublingual fentanyl ODT is effective in the relief of pain intensity in BTP. There are many similarities and some differences in the outcomes in BTP treatment reported by patients with chronic cancer pain and chronic non-cancer pain [6, 26]. Overall, the efficacy of relief of pain was significant in both groups compared with baseline, but improvement was significantly higher in BTcP patients from assessment 3. Moreover, a clinically meaningful response has been defined as a $\geq$33 % improvement in pain intensity [27], and in our study patients reported 48.4 % in BTcP and 33.9 % in BTncP patients.

The patient perception of the onset of relief provided by sublingual fentanyl ODT occurred by 10 min in approximately 71.2 % of episodes in BTncP patients and 60 % of episodes in BTcP patients. These findings suggest that sublingual fentanyl ODT provided an onset of analgesia that matches the time course of a BTP episode.

The number of daily BTP episodes recorded during the study decreased in both groups, but it was statistically significant in BTcP. The dose adjustment in BTcP patients indicated that the mean dosage per episode increased in each consecutive assessment, capturing the upward titration of sublingual fentanyl ODT. In contrast, BTncP patients reported an increase that was not significant. Although the differences between the groups were statistically significant, in most cases they were numerically small.

Overall, sublingual fentanyl ODT was well-tolerated in both oncological and non-oncological patients. The most common AEs related to the study medication included nausea, vomiting, somnolence and constipation, all of which are commonly observed with opioid analgesics and were consistent with those observed in previously published studies [16, 25]. The patient-perceived benefit of the fast onset of relief provided by sublingual fentanyl ODT was highlighted by the results of the satisfaction questionnaire.

The findings of the current study are similar to those reported in two prospective, multicentre surveys that assessed the efficacy and safety of sublingual fentanyl ODT in clinical practice [28, 29], which reported that the study medication was effective, well-tolerated and associated with significant improvements in quality-of-life scores in BTcP patients [29] and found no significant differences between BTcP and BTncP patients [28].

A potential limitation of this study was the small size of the sample and the short follow-up period. The subgroups of BTcP and BTncP were relatively small and the possible differences would have been better defined with a larger number of patients. Nevertheless, the study was not designed to follow patients for a longer treatment period nor for the most advanced stages of their illness in BTcP patients. The evaluations conducted in this study might also

be limited by the fact that the measures of time lag to first effect used in the current study have not been validated, and further investigation would be required to evaluate its reliability to objectivise clinical outcomes.

In clinical practice, several key parameters are expected to differ from the clinical trial. In particular, factors such as patient demographics and concomitant drug use may influence both effectiveness and safety, and the consequences of these differences should be assessed. In our study, patients were older, on average, than those in the clinical trials: 69.0 versus 56.0 years, respectively [16–18]. Moreover, it is difficult to determine whether patients are taking their medications as reported and this may complicate efforts to interpret data.

As previously reported in the few surveys that compared BTP in those with cancer pain and non-cancer pain [6, 26, 30, 31], some characteristics, such as the significantly higher prevalence of unpredictable episodes in BTcP patients, distinguished the subgroups. Nevertheless, studies of larger samples would be needed to perform subgroup analyses relevant to different types of BTP.

## 5 Conclusion

We conclude that sublingual fentanyl ODT provides rapid and consistent relief from BTP, both in cancer and non-cancer patients. It is well-tolerated and well-accepted by patients undergoing treatment in routine clinical practice.

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