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ORIGINAL ARTICLE

Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study*

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ABSTRACT

Background: Short-acting opioids are commonly used to treat breakthrough pain (BTP) and rapid-onset formulations are being developed to improve the effectiveness of this approach. Fentanyl buccal tablet (FBT) is a new formulation of fentanyl that enhances transbuccal drug delivery via an effervescent reaction and may provide relatively rapid-onset analgesia. FBT was evaluated for BTP in opioid-treated patients with chronic low back pain – the first such study in a population with chronic non-cancer pain.

Design: Randomized, double-blind, placebo-controlled.

Patients and setting: Patients with chronic low back pain receiving long-term opioid therapy at 16 pain treatment centers in the United States.

Procedures: Following open-label titration to identify an effective FBT dose, patients were randomly assigned to one of three double-blind dose sequences (six doses of FBT, three placebo) to treat nine BTP episodes. Pain intensity (PI), measured on an 11-point scale (0 = no pain; 10 = worst pain), and other outcomes were assessed for 2 h after dosing.

Data analysis: The primary efficacy measure was the sum of pain intensity differences (PIDs) for the first 60 min ($SPID_{60}$); secondary efficacy measures included PIDs at other time points, pain relief (PR), meaningful PR, time to meaningful PR, use of supplementary BTP medication, and self/investigator-reported adverse events.

Results: Of the 124 patients screened, 105 patients were enrolled, 84 identified an effective FBT dose, and 77 entered the double-blind phase. $SPID_{60}$ significantly favored FBT ($p < 0.0001$). All secondary measures also favored FBT, with PIDs and PR showing significant differences versus placebo as early as 10 and 15 min, respectively. An improvement in PI score of ≥ 33% occurred in a significantly larger proportion of FBT-treated episodes versus placebo from 15 min (20% vs. 11%, $p < 0.01$) through 2 h (65% vs. 28%, $p < 0.0001$). Patients were approximately four times more likely to require supplemental opioids for BTP episodes following administration of placebo compared with episodes treated with FBT. AEs were typical for opioids, and were mostly reported during dose titration. Limitations of this study may be related to its open-label dose-titration phase (which has the potential to compromise blinding) and the recruitment of patients from pain clinics, which could potentially yield a study population that is not representative of the general population with BTP.

Conclusions: FBT was efficacious and well tolerated in the treatment of BTP in opioid-treated patients with chronic low back pain.

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Introduction

There is an emerging consensus that long-term opioid therapy may be effective in carefully selected patients with chronic non-cancer pain[1]. Although data from controlled trials are limited, the potential for a prolonged benefit in populations with disorders such as chronic low back pain is supported by both empirical observations[2] and growing experience. Treatment strategies generally are extrapolated from the extensive and favorable experience with opioid treatment of cancer pain.

Among these strategies are approaches to the management of breakthrough pain (BTP), which may be defined as transitory, severe flares of pain that occur on a background of otherwise controlled, baseline, persistent chronic pain[2-5]. Studies in the chronic cancer pain population have demonstrated that BTP is highly prevalent and is associated with a range of adverse consequences[3,5-10]. Although relatively little is known about the occurrence of BTP in patients with chronic non-cancer pain, a recent survey of 228 patients undergoing treatment in US pain management centers observed that BTP occurred in 74% of patients and had characteristics comparable to those reported in cancer populations[4].

The standard of care for the treatment of cancer-related BTP relies on the oral administration of an immediate-release, short-acting opioid formulation, taken 'as needed' to supplement a fixed-schedule opioid regimen[11]. This approach has been empirically extrapolated to the treatment of BTP in selected patients with chronic non–cancer-related pain. Although widely used, oral administration is characterized by an onset of effect that lags behind the time course of most BTP episodes[3,4,8]. This observation has driven the development of rapid-onset opioid formulations that may improve the overall effectiveness of therapy. The first formulation of this type, oral transmucosal fentanyl citrate (OTFC), is commercially available in the United States and other countries.

Fentanyl buccal tablet (FBT; Fentora, Cephalon, Inc., Frazer, PA, USA) is among the new rapid-onset formulations developed for the treatment of BTP and has recently been approved in the United States for the management of BTP in opioid-treated patients with cancer. Compared to OTFC, FBT provides a larger proportion of the dose transmucosally (48% vs. 22%) and has an earlier T_{max} (47 min vs. 91 min)[12]. In a placebo-controlled study of patients with cancer-related BTP, FBT was efficacious, well tolerated, and had an onset of effect more rapid than would be expected from oral therapy[13].

The present study was undertaken to evaluate the efficacy and tolerability of FBT in a population of opioid-treated patients with chronic low back pain.

Methods

This was a randomized, double-blind, placebo-controlled study conducted at 16 centers in the United States between September 2005 and March 2006. The study was conducted in accordance with good clinical practice[14] and the protocol was approved by the Institutional Review Boards at all centers. All patients gave written informed consent prior to undergoing any procedures or assessments.

Patient population

Eligible patients were between 18 and 80 years old; had been diagnosed with chronic low back pain associated with osteoarthritis, degenerative disc disease, or spondylolisthesis (and other conditions permitted with prior approval from the sponsor) that resulted in functional disability for at least 3 months; and were receiving oral morphine ≥ 60 mg/day, oxycodone ≥ 30 mg/day, hydromorphone ≥ 8 mg/day, transdermal fentanyl ≥ 25 µg/h, or an equivalent dose of another opioid for at least 7 days. Also required were an average pain intensity (PI) during the 24 h prior to consent of ≤ 6 on an 11-point numeric scale (0 = no pain; 10 = worst pain); a report of one to four episodes of BTP per day; a duration of BTP of generally less than 4 h; and use of an opioid to treat BTP that was described as at least somewhat effective.

Patients were excluded from the study if they had uncontrolled or rapidly escalating pain; allergies or contraindications to any ingredient in the study drug; cardiopulmonary disease that in the investigator's opinion would affect the study drug's safety; psychiatric or medical disease that in the investigator's opinion would compromise data collection; or a history of alcohol or substance abuse during the past 5 years. Patients were also excluded if they were female and lactating, participated in an earlier FBT trial, or were expected to have surgery during the study period.

Study procedures

The study consisted of a screening visit, an open-label dose-titration phase, and a randomized, double-blind phase. At the screening visit, information was obtained about demographics, medical conditions, and pain characteristics, and the patient completed the Brief Pain Inventory[15] and the Oswestry Disability Index[16]. During the open-label dose-titration phase, FBT was taken for episodes of BTP in gradually escalating doses for the purpose of identifying a dose that was effective for the patient's BTP. This effective dose was then tested in the subsequent double-blind phase, in which

treatments were randomized and placebo-controlled. Patients continued their fixed-schedule opioid regimen during both study phases.

Dose-titration phase

Patients were provided with a titration kit consisting of 100, 200, 400, 600, and 800 µg doses of FBT and were instructed to self-administer the drug by placing a single tablet between the upper gum and cheek, above a rear molar tooth. After 30 min, any remaining drug could be swallowed with a glass of water. The initial dose was 100 µg. If the patient did not experience adequate pain relief within 30 min, a second tablet of the same strength could be taken. If the patient still did not experience adequate pain relief 30 min after the second tablet, the supplemental ('rescue') opioid used prior to study entry could be taken if needed.

At least 2 h had to elapse before the next FBT dose, and between subsequent doses. If two of three episodes of BTP were not adequately controlled by the single 100 µg dose (i.e., two FBT tablets were needed, or the two tablets taken 30 min apart were together ineffective), and the drug was well tolerated, the patient could progress to the next higher dose. Treatment of this episode was again initiated with a single tablet, which could be repeated after 30 min if pain relief was not judged by the patient to be adequate. If this dose again failed to provide adequate relief with one tablet during two of three episodes of BTP, and the treatment was well tolerated, the patient could proceed to the next higher dose. This process continued through the available doses of FBT.

If two of three episodes of BTP were adequately relieved within 30 min using a single FBT dose, and no unacceptable adverse events (AEs) occurred, the patient was considered to have identified an effective FBT dose and could begin the double-blind phase of the study. Patients discontinued the study during the titration phase if they did not obtain satisfactory relief at a dose of or below 800 µg (the highest dose) of FBT or if they experienced unacceptable AEs.

Double-blind phase

Patients were allowed as long as 3 weeks to complete the double-blind phase. During this phase, patients were randomly assigned to one of three prespecified sequences of treatment with nine tablets: six tablets of the previously identified effective dose of FBT and three matching placebo tablets. The prespecified sequences ensured that two-thirds of BTP episodes were treated with FBT and that placebo was not used for consecutive BTP episodes. Random assignment of these treatment sequences to study patients was computer-generated by a statistician not directly involved in the conduct of the study.

Both patients and investigators were blinded to the order in which FBT and placebo were to be taken over the course of the nine BTP episodes. Patients continued their fixed-schedule opioid regimen and continued to have access to their usual supplemental opioid if satisfactory relief was not achieved within 30 min following study drug administration, or if episodes of BTP occurred that were not treated with the study drug.

Efficacy measures

Using an electronic diary program (DiaryPRO; invivodata, inc., Pittsburgh, PA, USA) on a personal digital assistant (models M500 and M515; Palm, China), patients rated their PI just before study drug administration and at 5, 10, 15, 30, 45, 60, 90, and 120 min after treatment. PI was measured using an 11-point numeric scale (0 = no pain; 10 = worst pain). Pain relief (PR) was measured at post-treatment time points using a 5-point Likert scale (0 = none; 4 = complete). Patients also noted whether the relief of BTP at each time point was 'meaningful' and, using the stopwatch function on the personal digital assistant, indicated the onset time of meaningful relief. Use of supplemental opioid doses other than the study drugs also was recorded.

The primary efficacy measure was the sum of PI differences (PIDs) from 5 through 60 min ($SPID_{60}$). PIDs were calculated as the difference between the pre-treatment PI and a specific post-treatment PI score. $SPID_{60}$ was derived as follows: $SPID_{60} = (⅓ \times PID_5) + (⅓ \times PID_{10}) + (⅓ \times PID_{15}) + PID_{30} + PID_{45} + PID_{60}$, where $PID_i = PI_0 - PI_i$ and i = 5, 10, 15, 30, 45, and 60. The first three time points were multiplied by one-third to provide four equally weighted 15-min periods over 60 min.

Secondary efficacy measures included the individual PIDs; the proportions of BTP episodes with an improvement in PI scores of ≥ 33% and ≥ 50% following FBT and placebo; PR at each post-treatment time point; the proportion of BTP episodes in which meaningful PR was obtained; time to meaningful PR; and proportion of BTP episodes that required the use of supplemental medication.

Safety and tolerability were assessed based on patient and investigator reports of any AEs that occurred from study entry until the end of the study (or early withdrawal), including both the dose-titration and double-blind phases. In addition, serious AEs, withdrawals because of AEs, and results of clinical laboratory tests, vital signs, physical examinations, and oral mucosa examinations were also evaluated.

Statistical analysis

The estimate of sample size was based on data from two double-blind, placebo-controlled studies in patients with BTP associated with cancer[13,17]. A difference in the $SPID_{60}$ of 3.00 was considered clinically relevant. A sample size of 70 evaluable patients yielded a power of 90–94% using a 1-sample *t*-test with alpha = 0.05, 2-sided, standard deviation (SD) = 7.58. Considering the titration success rate, a total of approximately 140 patients were to be enrolled in the dose-titration phase.

All efficacy analyses were performed on the full analysis set, which was defined as those patients who treated at least one BTP episode with FBT and one episode with placebo, and had a PI score immediately prior to study drug administration for each of these episodes. Differences between FBT and placebo for $SPID_{60}$ were evaluated using an analysis of variance (ANOVA), with treatment, episode and carryover as fixed factors and patients as a random factor.

Statistical analyses of all secondary variables were 2-tailed, using alpha = 0.05. The 1-sample Wilcoxon signed rank test was used for analysis of PR scores. Differences between FBT and placebo for meaningful PR were evaluated using a Pearson's chi-square test, and time to meaningful PR was determined using a Ridit analysis. No adjustment for multiple testing was implemented for the secondary variables. PID responder outcomes were determined by comparing the proportions of BTP episodes with an improvement in PI scores of ≥ 33% and ≥ 50% achieved with FBT treatment and placebo.

To clarify the impact of baseline patient characteristics on the response to FBT, an exploratory analysis of covariance was performed using $SPID_{60}$ as the outcome. The covariates selected for evaluation included age and gender, baseline worst pain (as recorded on the Brief Pain Inventory), baseline score on the Oswestry Disability Index, and the number of titration episodes required to reach the effective FBT dose. A univariate model evaluated the impact of each of these characteristics on the change in $SPID_{60}$ between the FBT-treated episodes and the episodes for which placebo was administered, and a repeated-measures model was constructed to assess the treatment × covariate interaction on this outcome.

Results

Demographics and baseline characteristics

Of the 124 patients screened for the study, 105 were enrolled in the dose-titration phase, and 104 received at least one dose of FBT and were evaluated for safety (Figure 1). A total of 27 (26%) patients withdrew during the dose-titration phase. The most common reasons for withdrawal were the occurrence of an AE (n = 11; 10%) and withdrawal of consent (n = 9; 9%). Of the 77 patients entering the double-blind phase, 75 (97%) completed the study and 73 (95%) were evaluable for efficacy.

The baseline demographics and pain characteristics of the 77 patients who entered the double-blind phase

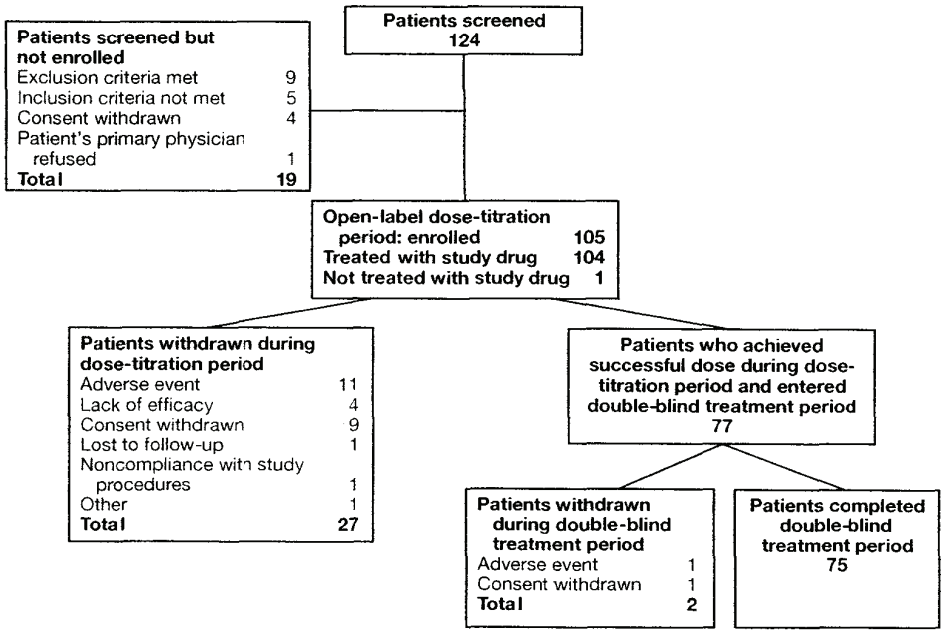


Figure 1. Patient disposition

were similar to those of the overall population, with a mean baseline PI of 5.1 in both groups (Table 1). Of the 104 patients in the overall population, 71 patients reported concurrent painful conditions, including osteoarthritis (n = 26) and chronic headache (n = 17). At the start of the study, all 104 patients were taking a fixed-schedule ('around-the-clock'; ATC) opioid regimen. There were 76 patients taking an oral formulation for the fixed-schedule regimen (mean ± SD daily dose, 494.0 ± 2032.3 morphine equivalent mg) and 28 patients taking transdermal fentanyl (mean ± SD daily dose, 175.7 ± 90.8 morphine equivalent mg). Among patients who were taking non-transdermal opioids ATC, the mean ± SD dose of supplemental medication for BTP was 24.7 ± 17.6 morphine equivalent mg. In patients who were taking transdermal fentanyl ATC, the mean ± SD dose of supplemental medication for BTP was 27.1 ± 25.2 morphine equivalent mg (Table 2).

Dose-titration phase

During the dose-titration phase, 81% (84/104) of treated patients identified an effective dose of FBT. The dose at which a single tablet provided reproducible benefit was 800 µg in 56% of patients, 600 µg in 24%, 400 µg in 15%, and 200 µg in 5%. There was no clinically meaningful correlation between the effective dose of FBT and the dose of fixed-schedule opioid regimen or the dose of supplemental medication used prior to the study.

Efficacy measures

Primary efficacy measure

During the double-blind phase, 413 episodes of BTP were treated with FBT and placebo was administered for 207 episodes. $SPID_{60}$ was greater for episodes treated with FBT (mean ± standard error [SE], 8.3 ± 0.66 vs. 3.6 ± 0.57; $p < 0.0001$).

Secondary efficacy measures

As assessed by PID, there was a greater reduction in BTP intensity following FBT than placebo at 10 min ($p < 0.02$) and at all subsequent time points through 2 h ($p < 0.0001$ for each time point; Figure 2, Panel A). PR was significantly better with FBT than with placebo as early as 15 min ($p = 0.0002$) and at all subsequent time points through 2 h ($p < 0.0001$ for each time point; Figure 2, Panel B). Patients reported meaningful PR for more BTP episodes treated with FBT (70%, 289/413) than episodes for which placebo was administered (30%, 63/207, $p < 0.0001$). Time

Table 1. *Baseline demographics and pain characteristics*

Parameter	Overall* (N = 104)	Double-blind (n = 77)
Age, years (mean ± SD)	47.5 ± 10.0	46.6 ± 10.21
Sex, n (%)		
Men	48 (46)	35 (45)
Women	56 (54)	42 (55)
Race, n (%)		
White	93 (89)	68 (88)
Black	8 (8)	6 (8)
Other	3 (3)	3 (4)
Weight, kg (mean ± SD)	90.7 ± 25.12	90.9 ± 24.57
Height, cm (mean ± SD)	171.9 ± 11.17	172.1 ± 10.94
BMI, kg/m^2 (mean ± SD)	30.6 ± 8.17	30.8 ± 8.54
Primary etiology of low back pain, n (%)		
Degenerative disc disease	73 (70)	52 (68)
Osteoarthritis	7 (7)	6 (8)
Spondylolisthesis	5 (5)	5 (6)
Other	19 (18)†	14 (18)
Pain intensity (mean ± SD)	5.1 ± 1.18	5.1 ± 1.21

BMI = body mass index
*Safety analysis set
†The most frequent etiologies of low back pain in the 'other' category were myofascial pain (n = 4, 4%); herniated disk (n = 2, 2%); and spondyloarthropathy (n = 2, 2%)

*Table 2. ATC and supplemental medications prior to study entry (N = 104)**

ATC medication, mg/day of oral morphine equivalents	
Patients taking non-transdermal fentanyl (n = 76)	
Mean ± SD	494.0 ± 2032.3
Median (min, max)	160.0 (45.0, 17 500.0)†
Patients taking transdermal fentanyl (n = 28)‡	
Mean ± SD	175.7 ± 90.8
Median (min, max)	150.0 (60.0, 360.0)
Distribution of ATC opioid usage, n (%)	
Oxycodone	37 (36)
Fentanyl (transdermal)	27 (26)
Morphine	18 (17)
Methadone	12 (12)
Hydrocodone–acetaminophen	12 (12)
Hydromorphone	2 (2)
Supplemental medication, mg/day of oral morphine equivalents	
Patients taking non-transdermal fentanyl (n = 76)	
Mean ± SD	24.7 ± 17.6
Median (min, max)	20.0 (5.0, 120.0)
Patients taking transdermal fentanyl (n = 28)†	
Mean ± SD	27.1 ± 25.2
Median (min, max)	20.0 (5.0, 120.0)
Distribution of supplemental opioid usage, n (%)	
Hydrocodone/hydrocodone–acetaminophen	39 (38)
Oxycodone	23 (22)
Oxycodone/acetaminophen	18 (17)
Fentanyl/fentanyl citrate	14 (14)
Morphine	7 (7)
Tramadol	5 (5)
Codeine/acetaminophen	2 (2)
Hydromorphone	2 (2)
Propoxyphene–acetaminophen	2 (2)
Dextropropoxyphene	1 (< 1)
Methadone	1 (< 1)

ATC = around-the-clock

*Safety analysis set: patients may have reported more than one drug for ATC and supplemental medications

†Two patients were taking large doses of ATC medication; specifically, 4000 and 17 500 of morphine equivalent mg/day.

‡For transdermal fentanyl, the following conversion was applied: 25 μg/h = 60mg oral morphine

to meaningful PR was shorter for BTP episodes treated with FBT than for episodes for which placebo was administered: by 30 min, meaningful PR had occurred in 38% of episodes treated with FBT and 16% of episodes treated with placebo ($p < 0.0001$; Figure 3). Supplemental medication was used in 65 of 413 (16%) BTP episodes treated with FBT compared with 96 of 207 (46%) episodes for which placebo was administered (odds ratio, 0.22; 95% CI, 0.13, 0.35).

An improvement in PI scores of ≥ 33% occurred in a larger proportion of BTP episodes treated with FBT compared with placebo from 15 min (20% vs. 11%, $p < 0.01$) through 2 h (65% vs. 28%, $p < 0.0001$; Table 3). The difference in the proportion of BTP episodes with an improvement in PI scores of ≥ 50% following FBT or placebo administration was significant at 30 min (30% vs. 13%, $p < 0.0001$), and continued for all subsequent time points ($p < 0.0001$, Table 3).

Covariate analyses

In the exploratory univariate analyses, only gender was found to be significant ($p < 0.05$). The change

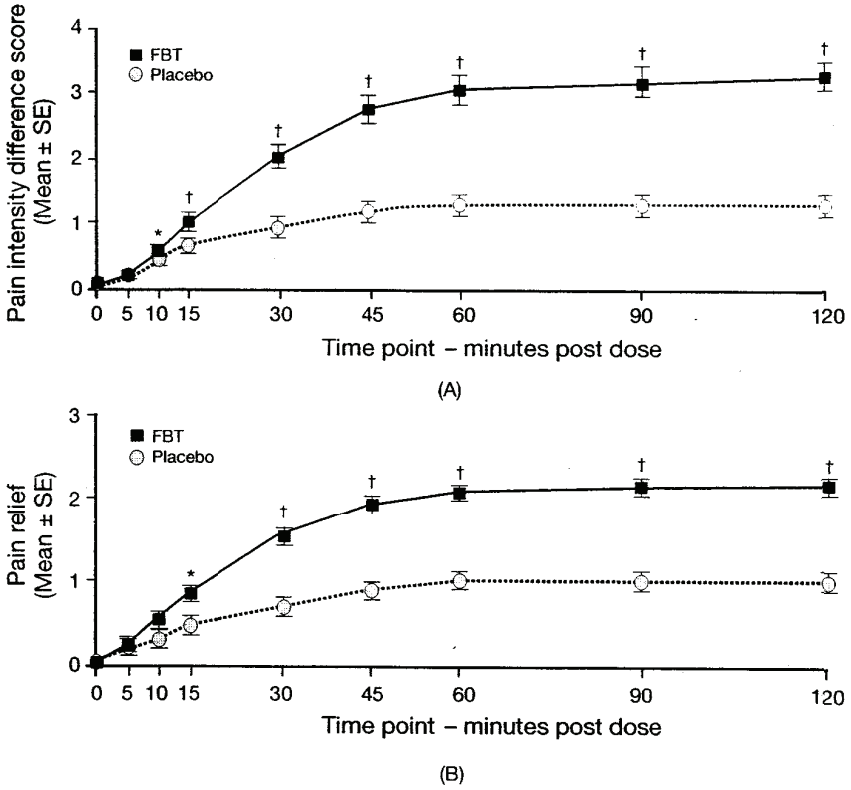
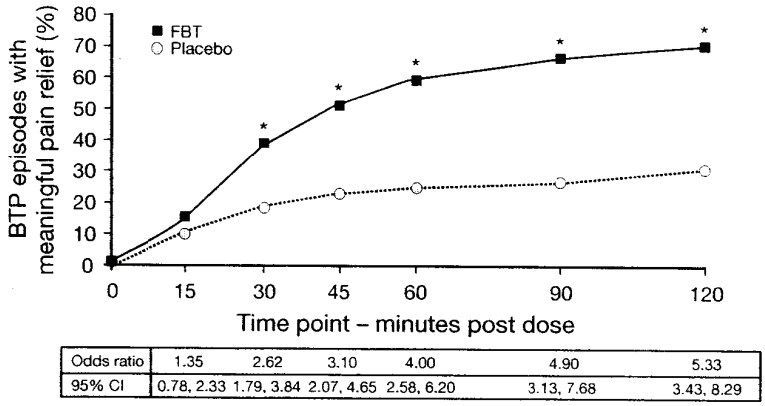


Figure 2. *(A) Effect of FBT and placebo on PID score in patients with BTP associated with chronic low back pain.* n = 73. *p < 0.02; †p < 0.0001, *ANOVA model for crossover design. (B) Effect of FBT and placebo on PR in patients with BTP associated with chronic low back pain.* n = 73. *p = 0.0002; †p < 0.0001, *1-sample Wilcoxon signed rank test. AE = adverse event; FBT = fentanyl buccal tablet; PID = pain intensity difference; PR = pain relief; SE = standard error*



Odds ratio	1.35	2.62	3.10	4.00	4.90	5.33
95% CI	0.78, 2.33	1.79, 3.84	2.07, 4.65	2.58, 6.20	3.13, 7.68	3.43, 8.29

Figure 3. *Effect of FBT and placebo on time to meaningful PR in patients with BTP associated with chronic low back pain.* n = 413 *BTP episodes, FBT;* n = 207 *BTP episodes, placebo.* *p < 0.0001, *percentage of BTP episodes treated with FBT versus placebo for which patients experienced meaningful PR; cumulative comparison, Ridit analysis. BTP = breakthrough pain; FBT = fentanyl buccal tablet; PR = pain relief*

in $SPID_{60}$ for FBT-treated episodes versus episodes for which placebo was administered was greater for females than for males. In the multivariate model, significant treatment interactions were observed with gender, age, and the Oswestry total score (Table 4). Patients ≤ 39 years of age responded better to FBT than placebo, but the differential effect was modest (65%). By comparison, patients between 40 and 46 years of age, and those 55 years and older, had four- to five-fold increases in $SPID_{60}$ with FBT versus placebo. The largest differential effect (3-fold difference) in $SPID_{60}$ between FBT and placebo occurred in patients with an Oswestry total of 33–36. Although less disabled patients, specifically those with Oswestry totals of

Table 3. Number (%) of responder episodes with ≥ 33% and ≥ 50% improvement of PI scores

	Percent reduction of PI scores			
	≥ 33%		≥ 50%	
Time point	FBT (n = 413)	Placebo (n = 207)	FBT (n = 413)	Placebo (n = 207)
5 min	7 (2)	5 (2)	3 (< 1)	3 (1)
10 min	43 (10)	12 (6)	16 (4)	7 (3)
15 min	83 (20)*	22 (11)	45 (11)	11 (5)
30 min	172 (42)†	38 (18)	122 (30)†	27 (13)
45 min	225 (54)†	47 (23)	161 (39)†	34 (16)
60 min	241 (58)†	53 (26)	182 (44)†	32 (15)
90 min	263 (64)†	54 (26)	193 (47)†	37 (18)
120 min	269 (65)†	57 (28)	198 (48)†	33 (16)

FBT = fentanyl buccal tablet
PI = pain intensity
*$p < 0.01$; †$p \leq 0.0001$ versus placebo

Table 4. Predictors of differences between FBT and placebo: exploratory multivariate analysis

Covariate	N	FBT*	Placebo*
Age group			
≤ 39	21	7.70 (5.82, 9.57)	4.66 (2.52, 6.79)
40 to ≤ 47	17	7.85 (5.75, 9.93)	1.33 (–1.03, 3.68)
48 to ≤ 54	18	11.03 (9.02, 13.03)	6.59 (4.33, 8.84)
> 54	17	7.32 (5.21, 9.44)	1.51 (–0.91, 3.92)
Gender			
Female	40	9.04 (7.61, 10.47)	2.52 (0.91, 4.12)
Male	33	7.76 (6.17, 9.35)	5.02 (3.24, 6.79)
Oswestry total			
≤ 26	21	11.96 (10.14, 13.78)	5.52 (3.41, 7.61)
26 to ≤ 32	15	7.60 (5.48, 9.73)	3.57 (1.13, 6.01)
33 to ≤ 36	15	8.38 (6.25, 10.52)	2.05 (–0.41, 4.50)
> 36	13	6.91 (4.63, 9.18)	3.82 (1.20, 6.44)

FBT = fentanyl buccal tablet
*Least squares means and 95% CI of $SPID_{60}$ by subgroup

≤ 26, had higher $SPID_{60}$ values than other subgroups, the approximately two-fold difference between FBT and placebo was comparable to the other groups.

Safety and tolerability

Adverse events were reported by 65% of patients and occurred more frequently during the dose-titration phase (57%) than during the double-blind phase (34%). The most commonly reported AEs included: nausea (19%), dizziness (13%), somnolence (9%), dysgeusia (8%), vomiting (6%), and dry mouth (5%) (Table 5). Reports of dysgeusia were elicited by the taste of the FBT tablet. Of the 12 patients who discontinued the study because of AEs, 11 withdrew during the dose-titration phase. AEs that led to withdrawal in more than one patient were nausea (five patients), vomiting (three patients), and somnolence (two patients). Mild treatment-related AEs involving the application site of FBT were reported in five (5%) patients during the dose-titration phase, including irritation in two patients and discoloration, erythema, and ulcer in one patient each. One patient reported an application-site reaction during the double-blind phase and one patient withdrew before entering the double-blind study. Two patients experienced serious AEs during the study: diabetic gastroparesis and accidental overdose resulting in a loss of consciousness. The latter patient took four of the 600 µg tablets without explanation; he was revived with oxygen and was admitted to the hospital where he fully recovered. In patients treated with FBT, there were no clinically meaningful changes

Table 5. AEs occurring in ≥ 5% of patients

	Number (%) patients*		
	Dose-titration period (N = 104)	Double-blind treatment period (n = 77)	Overall (N = 104)
AEs	59 (57)	26 (34)	68 (65)
Nausea	20 (19)	1 (1)	20 (19)
Dizziness	12 (12)	3 (4)	14 (13)
Somnolence	9 (9)	0	9 (9)
Dysgeusia	8 (8)	6 (8)	8 (8)
Vomiting	6 (6)	0	6 (6)
Dry mouth	4 (4)	3 (4)	5 (5)

AEs = adverse events
*Patients may have reported more than one AE type

in laboratory values (serum chemistry, hematology, and urinalysis), vital signs measurements (heart rate and blood pressure), and physical examination findings.

Discussion

Studies of populations with chronic cancer pain have confirmed the high prevalence and adverse consequences of poorly controlled BTP[3,5–10]. The specific treatment of BTP is considered a standard of care during cancer pain management, and the most widely accepted therapeutic approach involves the use of a short-acting opioid dose offered as needed during treatment with a fixed-schedule opioid regimen[3,11].

BTP also occurs in populations with chronic non–cancer-related pain, but epidemiologic data are sparse. In the only prospective survey to date, the prevalence of BTP in a sample of 228 patients undergoing treatment in pain management programs was 74% and the characteristics of BTP were comparable to those observed in the cancer population[4]. The prevalence of BTP in other populations is not known and the extent to which BTP is associated with various adverse consequences remains to be determined.

There have been no previous studies assessing the efficacy of a treatment for non–cancer-related BTP. Given this lack of information, the role of supplemental doses during opioid therapy for chronic non-cancer pain has been ill-defined and clinical practice among pain specialists varies. Further research to clarify the epidemiology of BTP, and both the efficacy and tolerability of treatment strategies, is needed. The present study is the first to evaluate a treatment for BTP in a population with chronic non-cancer pain.

When BTP is managed with an oral short-acting opioid, the objective is to relieve pain as quickly as possible, without risking untoward opioid-related effects. For some patients, an optimal outcome may be difficult because of a 'mismatch' between the time course of the BTP episode and the onset of effect of the orally administered opioid. In studies of cancer-related BTP, patients noted that maximum PI was usually reached in approximately 3 min and that the average BTP episode persisted for 30 min[3,8]; in the survey of patients with non-cancer pain[3,4], peak PI was reported to occur in less than 10 min and pain duration was less than 1 h. These observations suggest that the effectiveness of supplemental doses for BTP is likely to be improved with drugs that have a more rapid onset of effect.

FBT is a new formulation that uses OraVescent drug delivery technology to provide rapid penetration of fentanyl through the buccal mucosa[18]. In pharmacokinetic studies, FBT delivered a larger proportion of the dose transmucosally (48% vs. 22%) and produced a greater early systemic exposure of fentanyl than OTFC, as demonstrated by median T_{max} (range, 35–72 min), mean AUC_{0-Tmax} (range, 0.09–1.6 ng · h/mL) and mean C_{max} (range, 0.25–2.8 ng/mL)[19–21]. A randomized, placebo-controlled trial of FBT for cancer-related BTP demonstrated that the formulation was efficacious and well tolerated[13]; 65% of the 123 patients identified an effective dose during open-label titration, and significantly better efficacy compared with placebo was confirmed at every assessment, including early time points.

In the present study, 81% of patients with BTP associated with chronic non-cancer pain identified an effective dose during the open-label dose-titration phase; in the double-blind phase, FBT was found to be efficacious compared with placebo, producing effects as early as 10 min that were sustained throughout the 2-h period of observation. Evidence of early treatment effect was observed in all secondary efficacy measures.

No correlations were found between the effective doses of FBT and either the baseline fixed-schedule opioid regimen or quantity of supplemental opioids used prior to the study. This observation, which is consistent with a study of FBT in cancer-related BTP and several studies of OTFC[13,17,22,23], indicates that selection of a supplemental dose based on the dose of the fixed-schedule regimen, which is conventional practice, is not appropriate for either FBT or OTFC. FBT should be initiated at a low starting dose (100 µg) and then titrated to an effective dose. The reasons for the lack of correlation between supplemental FBT or OTFC doses and fixed-schedule doses (as well as doses of prior supplemental medications) have not been determined and warrant further investigation.

The exploratory covariate analyses suggest that age, gender, and functional status are associated with the response of patients to FBT. The reasons that women, patients in some age groups, and patients with relatively high (but not the highest) disability may be more likely to respond to FBT than to placebo are not apparent from the data. Additional studies are needed to elucidate further whether patient characteristics or pain syndromes influence the response to FBT or other supplemental medications. If confirmed, these data may help guide patient selection or dosing decisions, and further refine study design.

FBT was generally well tolerated at doses of 100–800 µg. AEs were typical for opioids, such as nausea and dizziness, and were observed more frequently during the dose-titration phase. Tolerability of FBT in this population of patients with chronic low back pain and BTP was similar to that seen in patients with BTP and cancer-related chronic pain[13]. One patient experienced serious AEs during the study that were considered by the investigator to be possibly related to the study drug (accidental overdose resulting in a loss of consciousness). As with any opioid medication, careful patient counseling on proper medication use and the potential dangers of inappropriate use is essential. The AEs that occurred at the mucosal application site were mild and transient.

Several limitations of this study are notable. First, the use of an open-label dose-titration phase may increase the likelihood of unblinding by sensitizing patients to the effect of FBT. Although this was not noted by the investigators, and although a placebo response was evident during the double-blind phase of the study, the occurrence of inadequate blinding was not assessed dose-to-dose and cannot be excluded. Second, the double-blind phase was conducted in a subgroup that demonstrated a favorable response to open-label administration; this 'enriched enrollment' approach can be used to determine efficacy among those patients who can tolerate the drug (and are, therefore, most likely to use it), but cannot provide accurate data concerning the overall responsiveness of the population with BTP. Third, this placebo-controlled trial was intended to assess the efficacy and tolerability of FBT, and conclusions concerning comparative efficacy against other drugs, or the effectiveness of the rapid-onset opioid strategy for BTP treatment, are not possible. Although the findings suggest that clinically meaningful analgesic effects are likely to occur more quickly with FBT than is possible with oral opioid administration[24–27], additional studies are needed to assess the comparative benefits and risks of FBT and other treatments for BTP. Finally, the study population of chronic low back pain patients was drawn from pain clinics and may not be representative of the larger population of opioid-treated patients with chronic low back pain in terms of demographics or other factors.

Conclusion

The results of this controlled study show that FBT was efficacious and well tolerated in the management of opioid-treated patients with BTP associated with chronic low back pain. It is the first such study in non–cancer-related BTP and provides evidence that a rapid-onset opioid can provide meaningful pain relief in patients with chronic pain not associated with cancer. The decision to use supplemental opioid medication as part of the treatment of chronic pain, as with opioid therapy in general, should be guided by careful assessment of potential benefits and risks. Future studies of FBT and other BTP therapies in this population, as well as other populations of patients with non–cancer-related BTP, will help guide an individualized and effective approach to treatment.

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