Original Article

Long-term Safety and Tolerability of Fentanyl Buccal Tablet for the Treatment of Breakthrough Pain in Opioid-Tolerant Patients With Chronic Pain: An 18-Month Study

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Abstract

Context. Breakthrough pain (BTP) is highly prevalent in patients with chronic cancer and noncancer pain, commonly requiring treatment with short-acting or rapid-onset opioids. This is the first report of an analysis of long-term safety from combined clinical trials of a rapid-onset transmucosal formulation of fentanyl, the fentanyl buccal tablet (FBT).

Objectives. This long-term (18-month), open-label study assessed the safety and tolerability of FBT for the treatment of BTP in a large cohort ($n = 646$) of opioid-tolerant patients receiving around-the-clock (ATC) opioids for persistant noncancer pain.

Methods. This was a long-term, multicenter, open-label safety study that accepted patients naive to FBT (new patients) as well as rollover patients from one of two previous short-term, randomized, placebo-controlled studies involving opioid-tolerant adults with chronic noncancer pain. All patients gave written informed consent, and the study was conducted according to Good Clinical Practice and with Independent Ethics Committee or Institutional Review Board approval.

Results. During maintenance treatment, 70 of 646 patients (11%) discontinued because of adverse events (AEs), 69 of 646 (11%) because of withdrawn consent, and 57 of 646 (9%) because of noncompliance. A total of 571 of 646 patients (88%) had one or more AEs; most were mild to moderate in intensity and typical of AEs associated with opioid use in a noncancer chronic pain population. Serious AEs

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were seen in 118 of 646 patients (18%); most were considered by the investigators to be unrelated or unlikely to be related to FBT. There were six deaths (three myocardial infarction, two cardiac arrest, and one pneumonia) that were considered by investigators to be unrelated or unlikely to be related to FBT. There were two reports of accidental overdose contained within nine reports of nonfatal overdose (FBT and/or ATC and/or other medications). Four patients had AEs of abuse or drug dependence, two in association with FBT. Drug withdrawal syndrome occurred in 23 patients after discontinuation of FBT alone or in combination with other opioids. Secondary assessments showed that average pain ratings, as assessed by the Brief Pain Inventory, remained relatively stable throughout the study and that consistent improvements were noted in functional measures.

Conclusion. FBT was generally safe and well tolerated, with self-reported functional improvement observed in most of the opioid-tolerant patients with BTP in association with chronic noncancer pain. J Pain Symptom Manage 2010;■:■–■.

Key Words
Fentanyl buccal tablet, opioid, long-term safety

Introduction

There has been a steady increase in the use of opioids for the management of chronic noncancer pain over the past two decades.[1–3] In part because of this more widespread acceptance, practice guidelines have been published to provide evidence- and consensus-based recommendations for the optimal use of opioids in the management of chronic pain.[4–7] A key limitation identified during the creation of these guidance documents is a lack of data assessing the long-term benefits and harms of opioid therapy for chronic pain.[8]

With the increasing adoption of opioid treatment for chronic noncancer pain, a significant proportion of patients receiving around-the-clock (ATC) opioids to control their underlying persistent pain still experience breakthrough pain (BTP). Typically, BTP in this population occurs frequently, is unpredictable, and is characterized by a transitory exacerbation or flare of pain that rapidly reaches an intensity that is severe to excruciating.[9,10] In one survey of 228 patients with controlled chronic, persistent, noncancer pain, 74% reported BTP with a median frequency of two episodes per day, a median of 10 minutes from onset to maximum intensity, and a median duration of 60 minutes.[11]

Fentanyl buccal tablet (FBT; FENTORA®, Cephalon, Inc., Frazer, PA, USA) is a novel formulation of fentanyl, which has been developed to provide rapid-onset analgesia by enhancing fentanyl absorption across the buccal mucosa by means of an effervescent reaction.[12,13] The efficacy, tolerability, and safety of FBT for the management of BTP have been studied in short-term, placebo-controlled clinical studies of opioid-tolerant patients with cancer-[9,14] and noncancer-related[15,16] chronic pain. These investigations showed that FBT provided rapid and clinically relevant relief of BTP and that FBT therapy was associated with treatment-related adverse events (AEs) generally typical of opioids.

Against this background, few published studies have evaluated the long-term safety and efficacy of opioids for the management of chronic pain, let alone when a BTP medication is added to chronic opioid therapy.[8,17] With increasing prescriptions of opioids for the management of chronic noncancer-related pain, there is a need to better understand the long-term effects of opioids, including FBT, as well as any patient characteristics associated with positive and negative outcomes. This endeavor entails determining the overall risk vs. benefit profile by monitoring outcomes, such as incidence of AEs, aberrant behaviors, ability to comply with and achieve pain relief from therapy, reasons for discontinuation and the need for dose changes over time, and patient benefit in the form of improved function.

The aim of this open-label study was to assess the long-term safety and tolerability of FBT in a large cohort of opioid-tolerant patients with BTP in association with chronic noncancer-related pain. It is the longest and largest study of its kind to date.

Methods

Patients

The study included adult men and women (aged 18–80 years) who were taking ATC opioid medication for persistent noncancer pain, had controlled pain according to the investigator, and reported an average pain intensity (PI) score over the previous 24 hours of less than 7 on a 11-point visual scale (where 0 = no pain and 10 = worst pain). Patients were opioid tolerant, that is, they were taking a 60 mg or higher dose of oral morphine daily, 25 μg or higher dose of transdermal fentanyl per hour, 30 mg or higher dose of oxycodone daily, 8 mg or higher dose of hydromorphone daily, or an equivalent dose of another opioid daily for one week or longer before study entry. All patients were experiencing an average of one to four episodes of BTP per day, which were relieved (at least partially) by supplemental opioid therapy.

Patients were excluded from the study if they had a recent history (i.e. within five years) of alcohol or other substance abuse or if there was a positive urine drug screen for an illicit substance or a medication not currently prescribed for chronic pain by a physician. Other exclusion criteria were the presence of unstable, uncontrolled, or rapidly escalating pain that was not BTP; cardiopulmonary disease that could increase the risk of treatment with opioids; or psychiatric or medical disease that might compromise data collection. In addition, any women who were pregnant or lactating were excluded.

Study Design

This was a long-term, multicenter, open-label safety study that accepted patients naive to FBT (new patients) and rollover patients from one of two previous short-term, randomized, placebo-controlled studies involving opioid-tolerant adults with chronic noncancer pain[15,16] (Fig. 1). All patients gave written informed consent, and the study was conducted according to Good Clinical Practice and with Independent Ethics Committee or Institutional Review Board approval from the 69 centers around the United States conducting the study.

For new patients, the study comprised an initial screening phase, an open-label FBT dose-titration phase, and an 18-month maintenance treatment phase. Rollover patients continued to take their previously identified successful dose of FBT and entered directly into the 18-month maintenance treatment phase.

New patients who satisfied the study entry criteria at the initial screening phase returned to the study center within seven days of the initial visit to begin the dose-titration phase. According to the method previously described,[15,16] patients identified a successful dose of FBT (100, 200, 400, 600, or 800 μg) and then entered the maintenance treatment phase. A successful dose was defined as the single dose between 100 and 800 μg that relieved pain sufficiently within 30 minutes for at least two of three BTP episodes without producing unacceptable AEs.

During the study, patients could take a maximum of eight tablets for treating a maximum of six episodes of BTP per day. Patients could change their ATC opioid and/or FBT dose at the direction of their physician, except if they required a dose higher than 800 μg FBT, in which case they were discontinued from the study.

Assessments

Safety and tolerability were assessed by recording AEs (monthly) and vital signs (monthly) and by performing clinical laboratory tests (study start [new patients], Weeks 24, 52, and 76), and neurological, physical, and oral examinations (study start [new patients], Weeks 52 and 76).

Concomitant medications, including ATC and supplemental medications, together with FBT dosage, were recorded monthly. The following secondary efficacy assessments were also conducted during the study.

Brief Pain Inventory-Short Form. The Brief Pain Inventory-Short Form (BPI-SF)[18] was administered monthly during the first 12 months and every three months thereafter (or at early

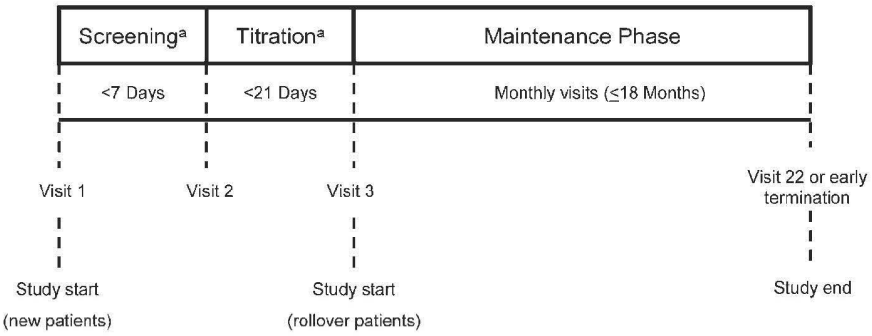

Fig. 1. Study design. [a]For new patients only.

termination) to assess pain history, location, intensity, and effect on daily functioning. PI was measured on a numerical scale of 0 (no pain) to 10 (pain as bad as you can imagine), and was assessed 1) at its worst, 2) at its least, 3) on average, and 4) at the time of the assessment. Interference of pain with activities of daily living and mood (seven domains) was assessed on a scale of 0 (does not interfere) to 10 (completely interferes).

Goal Attainment Scale. The Goal Attainment Scale (GAS), an exploratory assessment, was administered monthly during the first 12 months and every three months thereafter (or at early termination) to evaluate patient-rated change in functioning. Patients selected the three most important functional factors from a list of seven (originating from the BPI-SF) and then rated each factor and assessed the effect of the pain on that item. An additional assessment was added to the GAS during the conduct of the study, after protocol amendment, to indicate the patient's assessment of the degree of improvement or worsening (very much worsened, much worsened, slightly worsened, unchanged, slightly improved, much improved, or very much improved) of the three most important functional factors identified on the BPI-SF. Because the additional assessment was added after study start, not all patients were able to contribute data to the assessment.

Patient Assessment of Function and Clinician Assessment of Patient Function. The Patient Assessment of Function (PAF) and Clinician Assessment of Patient Function (CAPF) were exploratory assessments based on items of the BPI Interference Scale, administered every three months or at early termination. The PAF and CAPF were added during the conduct of the study, after protocol amendment, to allow for additional assessments of change in patient functioning in daily activities; as such, not all patients contributed data to these assessments. They evaluated patient functioning when performing normal activities (e.g., going to work, walking, exercising) from the patient's (PAF) or physician's (CAPF) perspective. Answers were rated on a scale of very much worsened to very much improved.

Modified Oswestry Disability Index. The Oswestry Disability Index,[19] modified by removing the first question about PI, was administered monthly during the first 12 months and every three months thereafter (or at early termination) to assess pain and functioning in 10 areas (e.g., walking, sleeping, traveling) that were allocated a score on a scale of 0 (highest level of functioning) to 5 (lowest level of functioning). Scores were totaled (range: 0–50) to provide the total disability index; this index was used to calculate the percentage disability as follows: percentage disability = (total score ÷ 50) × 100.

Profile of Mood States. The Profile of Mood States (POMS)[20] was used to assess patient mood every three months (or at early termination). POMS scale variables included scores for total mood disturbance and subscales of tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.

Short-Form Health Survey-36. The Short-Form Health Survey-36 (SF-36)[21,22] was administered every three months (or at early termination) to evaluate patient quality of life using 36 questions grouped into eight domains and two composite scores (mental and physical).

Sleep Questionnaire. The Sleep Questionnaire was an exploratory assessment administered monthly during the first 12 months and every three months thereafter (or early termination). It was used to evaluate the effect of pain on sleep onset (cannot sleep within 30 minutes: not during the past month, less than once a week, once or twice a week, three or more times a week); sleep duration (time asleep, hours); awakenings (waking up during the night or early morning: not during the past month, less than once a week, once or twice a week, or three or more times a week); and sleep quality (very good, fairly good, fairly bad, very bad).

Global Medication Performance Assessment. The Global Medication Performance Assessment (GMPA), an exploratory measure, was a questionnaire administered monthly during the first 12 months and every three months thereafter (or at early termination) to assess how well FBT controlled BTP on a five-point scale of 0 (poor) to 4 (excellent).

Medication Preference Questionnaire. The Medication Preference Questionnaire, an exploratory measure, was completed by patients after 1, 12, and 18 months (or at early termination) to assess their preference for BTP medication (either FBT or the supplemental opioid they were taking before study entry) and the reasons for their preference.

Statistical Analyses

All data were processed and summarized using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). The safety or tolerability analysis was performed on three populations:

1. *The safety analysis set*, comprising all patients who received at least one dose of FBT, either during the titration phase (new patients) or the maintenance treatment phase (all patients).
2. *The titration safety analysis set*, comprising patients (new patients only) who received at least one dose of FBT during the titration phase of the study.
3. *The maintenance safety analysis set*, comprising patients who received at least one dose of FBT during the long-term maintenance treatment phase of the study.

Secondary efficacy (functional) analyses were performed using the maintenance safety analysis set. As this was an open-label study, descriptive statistics were used to summarize observational data.

Results

Baseline Characteristics

The 728 patients who entered the study and were included in the overall safety analysis had a mean age of 48 years and a mean body weight of 89.3 kg; 56% were women and 93% were white (Table 1).

All patients in the safety analysis set had at least one coexisting medical condition on entry to the study, with the most frequently reported comorbidities being musculoskeletal (99%), neurological (76%), gastrointestinal or digestive (74%), and psychiatric (74%) disorders (Table 2). Fifty-seven percent of patients had a history of depressive disorder, and 36% had a history of anxiety disorder. All patients were taking at least one concomitant medication (consistent with the protocol requirement for ATCs and opioid tolerance), and virtually all patients (99%) were taking at least one medication other than an analgesic.

Table 1
Patient Demographics[a]

Parameter	Total
Age (years), mean ± SD	48.1 ± 9.82
Gender, *n* (%)	
Men	320 (44)
Women	408 (56)
Race, *n* (%)	
White	674 (93)
Black	36 (5)
Asian	1 (<1)
American Indian or Alaskan Native	3 (<1)
Other	14 (2)
Weight (kg), mean ± SD	89.3 ± 25.42
Height (kg), mean ± SD	171.0 ± 10.24
Body mass index (kg/m^2), mean ± SD	30.5 ± 7.95

SD = standard deviation.
[a]Overall safety analysis set; $n = 728$.

Table 2
Comorbid Conditions[a]

Category	Total, *n* (%)
Musculoskeletal	719 (99)
Neurological	553 (76)
Gastrointestinal/digestive	540 (74)
Psychiatric	537 (74)
Allergy/drug sensitivity	463 (64)
Genitourinary	423 (58)
Cardiovascular	414 (57)
Head, eyes, ears, nose, and throat	372 (51)
General	291 (40)
Respiratory	288 (40)
Endocrinological	253 (35)
Dermatological	210 (29)
Metabolic/nutritional	158 (22)
Hematologic/lymphatic	145 (20)

[a]Overall safety analysis set; $n = 728$.

The pathophysiology of BTP varied, with about one-third of patients each having pain that was predominantly neuropathic, predominantly nociceptive, or of mixed etiology (Table 3). The nature of the primary painful condition also varied widely, with the most frequently reported condition being back pain (57% of patients) (Table 3).

ATC and supplemental opioids taken before study entry are detailed in Table 4. The mean (median) dose of baseline ATC medication was 209 (120) mg/day of oral morphine equivalents. The mean (median) dosage of supplemental medication (in oral morphine equivalents) was 28 (20) mg/BTP episode.

Table 3
Pathophysiology of BTP and Primary Painful Conditions[a]

Parameter	Total, *n* (%)
Pathophysiology of BTP[b]	
Predominantly neuropathic	205 (28)
Predominantly nociceptive	237 (33)
Mixed (50:50)	216 (30)
Primary painful condition	
Chronic low-back pain	416 (57)
Traumatic injury	71 (10)
Osteoarthritis	46 (6)
Complex regional pain syndrome	38 (5)
Chronic headache	34 (5)
Diabetic peripheral neuropathy	29 (4)
Postherpetic neuralgia	3 (<1)
Other[c]	91 (13)

[a]Safety analysis set; $n = 728$.
[b]Pathophysiology data were not collected for 69 (9%) patients, and data are missing for one (<1%) patient.
[c]Conditions most commonly recorded as "other" include neck pain, back pain, degenerative disc disease, peripheral neuropathy/neuropathic pain, fibromyalgia and myofascial pain, limb and joint pain, reflex sympathetic dystrophy, and abdominal/pelvic pain.

Table 4
ATC and Supplemental Opioids Taken Before Study Entry[a]

	Total
ATC opioid medication,[b] *mg/day of oral morphine equivalents*	
Patients taking oral opioids ($n = 544$)	
Mean + SD	209.4 + 209.34
Median (range)	120.0 (15.0–2,160.0)
Patients taking transdermal fentanyl ($n = 166$)	
Mean ± SD	215.3 ± 149.50
Median (range)	180.0 (60.0–1,440.0)
ATC opioids taken most commonly,[c] *n* (%)	
Fentanyl	166 (23)
Oxycodone	229 (31)
Morphine	154 (21)
Methadone	119 (16)
Supplemental medication,[b] *mg of oral morphine equivalents per BTP episode*	
Patients taking oral opioids ($n = 540$)	
Mean ± SD	28.1 ± 28.97
Median (range)	20.0 (1.3–240.0)
Patients taking transdermal fentanyl ($n = 163$)	
Mean ± SD	27.2 ± 24.78
Median (range)	20.0 (0.5–150.0)
Supplemental opioids taken most commonly,[c] *n* (%)	
Oxycodone	287 (39)
Hydrocodone	244 (34)
Fentanyl	86 (12)
Morphine	48 (7)
Hydromorphone	47 (6)

[a]Safety analysis set; $n = 728$.
[b]Excludes 18 patients who received intrathecal opioid medication because their ATC dosage was not converted to oral morphine equivalents.
[c]Patients may have reported more than one drug for ATC and supplemental medications.

Patient Disposition

Of the 731 patients enrolled, 140 patients were rolled over from the two previous short-term, controlled studies, and 591 patients were enrolled de novo and entered the dose-titration phase (Fig. 2). In this dose-titration cohort, three patients did not receive FBT. Therefore, 728 patients were included in the overall safety analysis, and 588 patients were included in the titration safety analysis.

By the end of dose titration, 513 of 588 patients (87%) had achieved a successful dose and, 82 of 588 patients (14%) had discontinued treatment, mainly because of AEs ($n = 38$) or lack of efficacy ($n = 23$) (Fig. 2). A total of 506 patients from the titration phase joined the 140 rollover patients to enter the maintenance phase

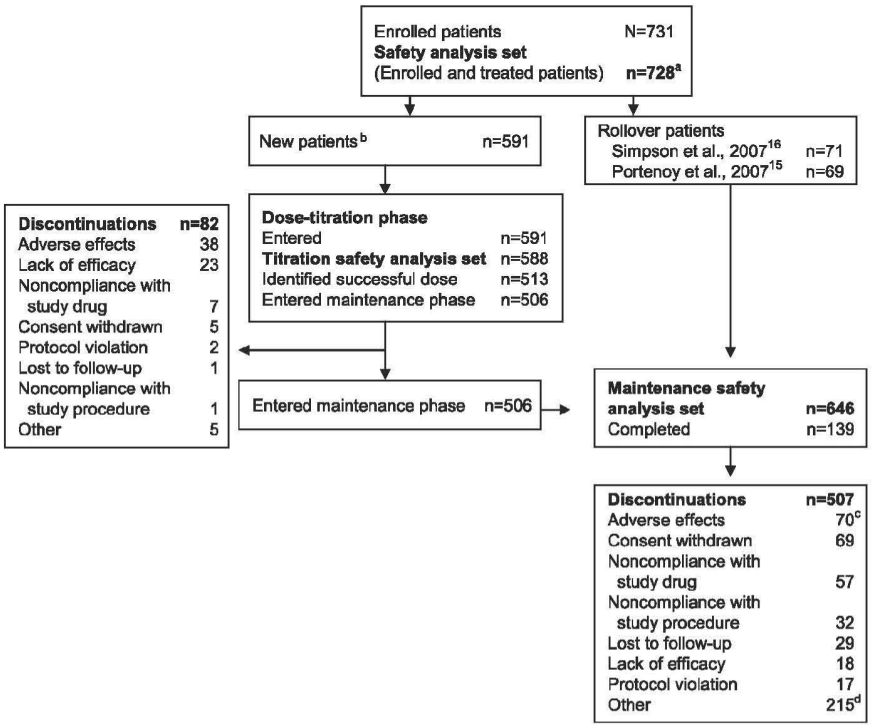

Fig. 2. Patient disposition. [a]Three patients enrolled but did not receive FBT. [b]New patients were FBT treatment-naive patients at study start. [c]Two patients reported AEs that began before the maintenance phase. These events are not included in the maintenance safety analysis set. [d]One hundred fifty-six patients discontinued the study because the sites were closed by Cephalon, Inc. Other reasons (in ≥2 patients) included patient or study center opting not to continue participation (17 patients); investigator discretion (9 patients); testing positive for substances of abuse (9 patients); moving out of country/state/town (5 patients); recent/planned surgery to relieve pain (4 patients); medication theft (4 patients); pain uncontrolled by ATC medication (2 patients); and no longer needing study drug (2 patients). Safety analysis set = enrolled patients who received one or more doses of FBT during the titration or maintenance treatment phase. Titration safety analysis set = newly enrolled patients who received one or more doses of FBT during the dose-titration phase. Maintenance safety analysis set = enrolled patients who received one or more doses of FBT during the long-term maintenance treatment phase.

($n = 646$) and were included in the maintenance phase safety analysis.

In total, 139 of 646 patients (22%) completed the 18-month maintenance phase of the study (Fig. 2). A total of 507 patients discontinued treatment, the principal reasons being site closure (at the point the study met the regulatory objective; $n = 156$), AEs ($n = 70$), consent withdrawal ($n = 69$), and noncompliance with study medication ($n = 57$). Only 18 of 646 patients (3%) discontinued because of lack of efficacy.

Exposure to Fentanyl Buccal Tablet

During the combined dose-titration and maintenance phases of the study, patients were exposed to FBT for a median of 329 (range: 1–638) days to treat a median of 1,110 (range: 1–5,226) episodes of BTP. During the 18-month maintenance phase, median exposure to FBT was 365 (range: 1–624) days to treat a median of 1,342 (range: 2–5,213) episodes of BTP.

The successful dose of FBT at the beginning of the maintenance phase was 100 μg for 24 of 646 patients (4%), 200 μg for 72 of 646 patients (11%), 400 μg for 126 of 646 patients (20%), 600 μg for 155 of 646 patients (24%), and 800 μg for 269 of 646 patients (42%). Although there were dose changes over time, the final dose was the same as the initial successful dose for many patients (64%; 413 of 646; Table 5). Dose increases were mainly driven by need for greater efficacy. For patients

Table 5
Shifts From Successful Dose to Final Dose During the Maintenance Phase of the Study

	Successful Dose,[a] *n* (%)					
Final dose (μg)	100 μg: 24 (4)	200 μg: 72 (11)	400 μg: 126 (20)	600 μg: 155 (24)	800 μg: 269 (42)	Total: 646 (100)
100	**8 (33)**	1 (1)	1 (<1)	0	0	10 (2)
200	8 (33)	**25 (35)**	5 (4)	0	0	38 (6)
400	5 (21)	25 (35)	**40 (32)**	3 (2)	1 (<1)	74 (11)
600	2 (8)	11 (15)	46 (37)	**78 (50)**	6 (2)	143 (22)
800	1 (4)	10 (14)	34 (27)	74 (48)	**262 (97)**	381 (59)

Bold value indicates patients for whom the final dose was the same as the initial successful dose (413 of 646 = 64%).
[a]Successful doses were identified either during the titration phases (new patients) or during the previous studies (rollover patients).

who had a successful dose of 800 μg (and, therefore, were not allowed a further dose increase), 10 discontinued because of lack of efficacy.

Safety and Tolerability

The frequency and type of AEs occurring during the titration phase were similar to what has been reported previously.[15,16] AEs were experienced by 237 of 588 (40%) patients; the most commonly reported AEs (≥5%) during titration were nausea (12%), dizziness (7%), and somnolence (5%).

A total of 571 of 646 patients (88%) in the maintenance phase experienced at least one AE, and in 43% of these patients, AEs were considered to be causally related to treatment. With the exception of back pain and urinary tract infection, the most common AEs were those generally associated with opioids. The incidence of AEs decreased over time (Table 6). Most AEs were mild to moderate in intensity.

Application-site AEs, typically pain, ulcer, or erythema, were recorded for 94 of 728 patients (13%) in the overall population. Most application-site AEs (97%) were transient and classified as mild to moderate in severity; 11 instances (2%) led to discontinuation.

AEs were the reason for the discontinuation of 68 of 646 patients (11%) during the maintenance phase. Nausea ($n = 6$ patients), vomiting ($n = 6$), dizziness ($n = 4$), and depressive illness ($n = 4$) were the most common causes for discontinuation, and each occurred in less than or equal to 1% of patients. Dose reductions because of AEs were recorded for 38 of 646 patients (6%), although some dose reductions were short term.

Serious AEs occurred in 118 of 646 patients (18%), the most common being chest pain, pneumonia, and vomiting (five patients each). Six patient deaths occurred during the study, recorded as being the result of myocardial infarction ($n = 3$), cardiac arrest ($n = 2$), or pneumonia ($n = 1$); all were considered by investigators to be unrelated ($n = 3$) or unlikely to be related ($n = 3$) to FBT. There were two reports of accidental overdose contained within nine reports of AEs associated with overdose of opioid medication (ATC and/or FBT and/or other medications). Circumstances leading to overdose included attempted suicide, altered mental state, and aberrant drug-related behaviors. None of these AEs was fatal. However, one case of fatal drug diversion occurred when the husband of a patient, a 54-year-old man with a history of drug abuse, died after a suspected overdose of FBT.

Four patients (<1%) had an AE of drug dependence for FBT ($n = 1$), FBT in combination with an ATC and supplemental medication ($n = 1$), oxycodone ($n = 1$), or alcohol and barbiturates ($n = 1$). Dependence was reported by each investigator and may or may not have met formal criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, for this disorder. Four additional patients had an AE of drug abuse. Drug withdrawal syndrome occurred in 23 of 646 patients (4%) after discontinuation of FBT alone or in combination with other opioid medications. Thirteen patients had urine drug screens that were positive for an illicit substance or a medication for which there was no legitimate medical explanation, and 38 patients reported theft of their medication. No meaningful differences were noted in the demographic and other baseline pain characteristics between patients with occurrences of abuse, addiction, and/or overdose, and those without. However, the small number of patients with abuse, addiction, and/or overdose events limits the strength of this analysis.

Table 6
Adverse Events Occurring in 5% or More of Patients by 3-Month Intervals During the Maintenance Treatment Phase

	Months							
	0 to ≤3 ($n=646$)	>3 to ≤6 ($n=539$)	>6 to ≤9 ($n=462$)	>9 to ≤12 ($n=398$)	>12 to ≤15 ($n=330$)	>15 to ≤18 ($n=230$)	>18 ($n=141$)	Overall ($n=646$)
Patients with at least one adverse event	451 (70)	331 (61)	263 (57)	230 (58)	183 (55)	115 (50)	43 (30)	571 (88)
Nausea	50 (8)	30 (6)	18 (4)	12 (3)	11 (3)	8 (3)	1 (<1)	110 (17)
Back pain	36 (6)	24 (4)	23 (5)	20 (5)	14 (4)	8 (3)	5 (4)	98 (15)
Vomiting	32 (5)	21 (4)	14 (3)	11 (3)	14 (4)	6 (3)	2 (1)	78 (12)
Headache	26 (4)	17 (3)	20 (4)	11 (3)	10 (3)	3 (1)	1 (<1)	70 (11)
Constipation	27 (4)	13 (2)	4 (<1)	11 (3)	4 (1)	2 (<1)	1 (<1)	59 (9)
Urinary tract infection	14 (2)	15 (3)	13 (3)	10 (3)	10 (3)	3 (1)	2 (1)	58 (9)
Arthralgia	19 (3)	15 (3)	7 (2)	12 (3)	8 (2)	6 (3)	1 (<1)	56 (9)
Pain in extremity	18 (3)	11 (2)	12 (3)	16 (4)	8 (2)	5 (2)	1 (<1)	56 (9)
Diarrhea	16 (2)	8 (1)	9 (2)	10 (3)	6 (2)	2 (<1)	1 (<1)	46 (7)
Edema peripheral	14 (2)	11 (2)	5 (1)	13 (3)	5 (2)	3 (1)	1 (<1)	46 (7)
Depression	11 (2)	10 (2)	6 (1)	8 (2)	8 (2)	5 (2)	0 (0)	45 (7)
Upper respiratory tract infection	12 (2)	12 (2)	14 (3)	10 (3)	7 (2)	5 (2)	1 (<1)	45 (7)
Sinusitis	13 (2)	16 (3)	8 (2)	6 (2)	8 (2)	6 (3)	0 (0)	44 (7)
Nasopharyngitis	15 (2)	11 (2)	8 (2)	5 (1)	5 (2)	2 (<1)	2 (1)	43 (7)
Insomnia	15 (2)	12 (2)	9 (2)	6 (2)	1 (<1)	1 (<1)	1 (<1)	43 (7)
Somnolence	26 (4)	4 (<1)	4 (<1)	4 (1)	4 (1)	1 (<1)	0 (0)	41 (6)
Bronchitis	11 (2)	11 (2)	9 (2)	8 (2)	3 (<1)	6 (3)	1 (<1)	40 (6)
Anxiety	17 (3)	7 (1)	5 (1)	7 (2)	6 (2)	1 (<1)	1 (<1)	39 (6)
Dizziness	21 (3)	8 (1)	3 (<1)	1 (<1)	2 (<1)	1 (<1)	0 (0)	35 (5)
Contusion	3 (<1)	8 (1)	10 (2)	6 (2)	5 (2)	2 (<1)	1 (<1)	32 (5)
Influenza	12 (2)	10 (2)	5 (1)	3 (<1)	4 (1)	2 (<1)	1 (<1)	31 (5)
Muscle spasms	12 (2)	5 (<1)	5 (1)	6 (2)	2 (<1)	3 (1)	0 (0)	30 (5)
Pyrexia	14 (2)	4 (<1)	2 (<1)	7 (2)	5 (2)	0 (0)	0 (0)	30 (5)

Secondary Efficacy Assessments

Analysis of the BPI showed that pain levels remained relatively stable throughout the maintenance phase of the study, with improvements of less than an average of 1 point seen in the assessments of pain factors, functional factors, and pain interference. Indeed, for the BPI pain factors, there was very little change from baseline in mean scores at final visit for the categories of "pain at its worst in the past 24 hours" (7.3 at baseline vs. 7.1 at final visit), "pain at its least in the past 24 hours" (4.2 vs. 4.1), "mean average pain" (5.5 vs. 5.4), and "pain right now" (5.6 vs. 5.5). There was, however, improvement in the "percentage of relief from pain medications in the past 24 hours" for 62.7% of patients compared with 45.5% at baseline. BPI functional factors showed only slight improvements from baseline to final visit in general activity (6.7 vs. 6.3), mood (6.1 vs. 5.8), walking ability (6.0 vs. 5.9), normal work (7.0 vs. 6.5), relations with people (5.4 vs. 5.3), sleep (6.7 vs. 6.4), and enjoyment of life (7.0 vs. 6.3). There was also a slight improvement in mean pain interference score (6.4 at baseline vs. 6.1 at final visit), although the mean pain severity score increased marginally (7.1 vs. 7.3). In concert with these findings, the Modified Oswestry Scale showed no meaningful change in either the total disability index (30.2 at baseline vs. 30.4 at final evaluation) or the corresponding percentage disability rating (60% at both assessment points).

The overall mood of patients, assessed using the POMS, showed a slight overall improvement during the study. The mean total mood disturbance score declined from 34.7 at baseline to 31.4 at final visit. Minor improvements were also noted across all quality-of-life domains of the SF-36. No meaningful changes were observed on the Sleep Questionnaire.

On the GAS, each patient identified the three areas from the BPI-SF functional factors deemed the most important areas in which improvement was desired. The three areas identified by the greatest number of patients were enjoyment of life (469 [73%] patients), general activity (391 [61%] patients), and sleep (309 [48%]) patients). Outcomes showed improvements across all functional domains for

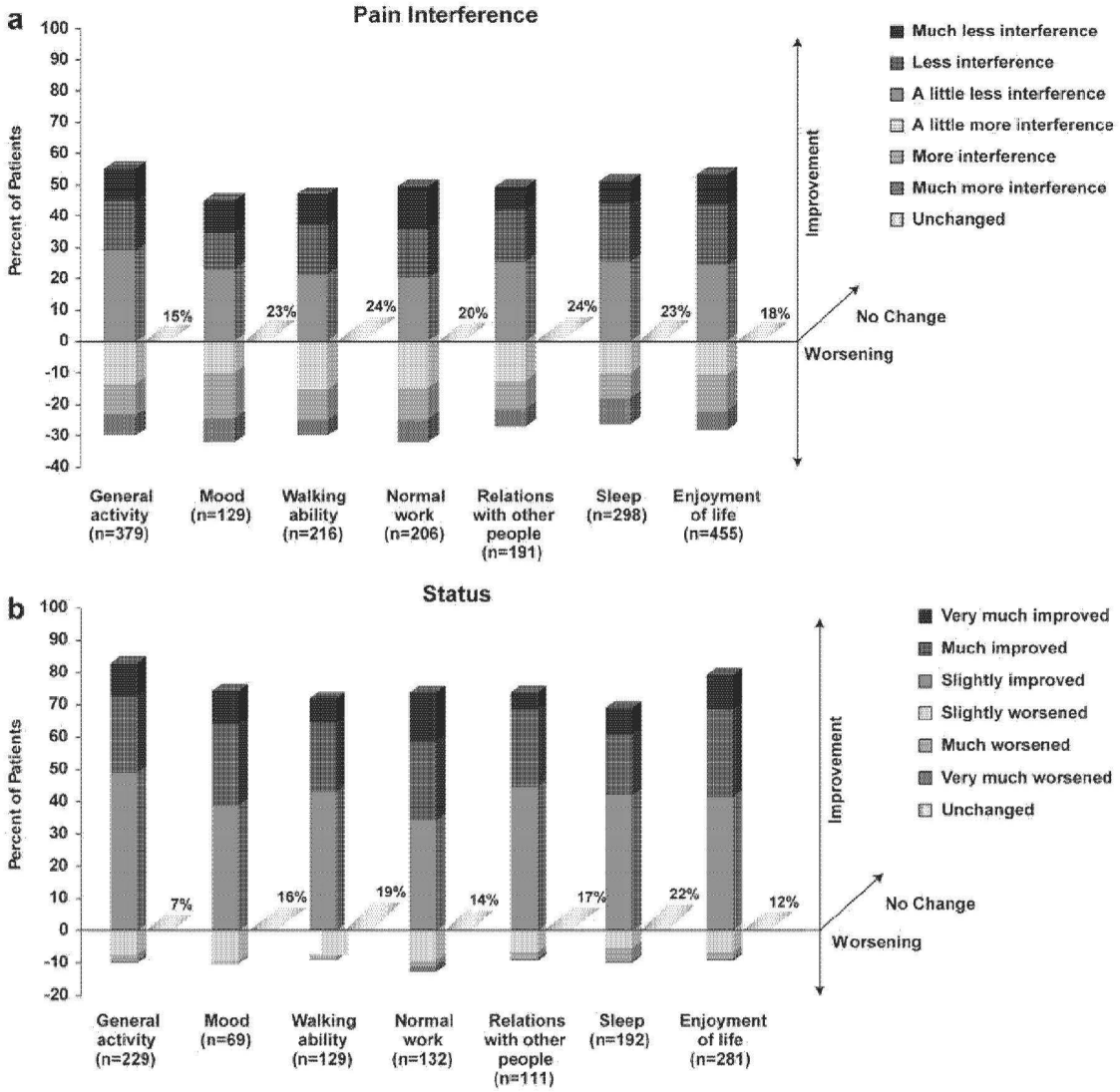

Fig. 3. Patient-rated changes in (a) pain interference and (b) status, as measured by GAS at final evaluation.

pain interference and status, the effects being greater for status (Fig. 3). Approximately half of patients reported lessening of interference of pain with their enjoyment of life, general activity, and sleep. More than 65% of patients reported that the status of these three functional factors was slightly improved, much improved, or very much improved at the end of the maintenance phase.

Analysis of PAF responses (Fig. 4) showed improvements in functioning across all domains, with more than half of patients reporting improvements in six of the seven areas of functioning. Notably, 73% of patients reported improvements in their ability to work (both within and outside of the home), 77% of patients reported improvements in their ability to participate in social events, and 83% reported improvements in their ability to enjoy life. These patient-reported outcomes were further supported by clinician assessments using the CAPF (Fig. 5). Indeed, clinicians reported improvements for more than two-thirds of patients in each area of functioning assessed. These findings included improvements for 80% or more of patients in their

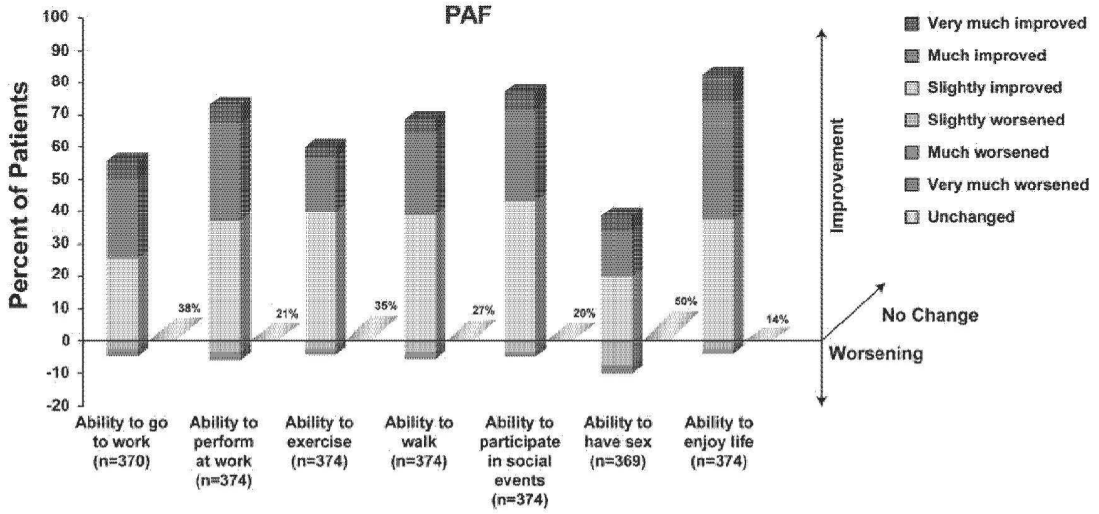

Fig. 4. Patient assessment of function at final evaluation.

ability to work or perform activities of daily living, the ability to enjoy life, and the ability to perform general activities.

Responses on the GMPA showed that a consistently high proportion of patients (≥90%) rated FBT as being good, very good, or excellent in controlling their BTP throughout the maintenance phase of the study. In terms of the Medical Preference Questionnaire, more patients at all visits preferred FBT to their pre-study medication for control of their BTP. The principal distinguishing attributes of FBT were considered to be a faster onset of pain relief and an easier, more convenient means of administration. Throughout the study, FBT was consistently rated as being good or excellent in terms of its onset of action (94%–97% of patients), ease of administration (81%–94% of patients), and convenience (80%–91%).

Discussion

This is the first long-term (18-month) study of opioid-tolerant patients with chronic non-cancer pain and BTP. Administration of 100–800 μg FBT was associated with a safety

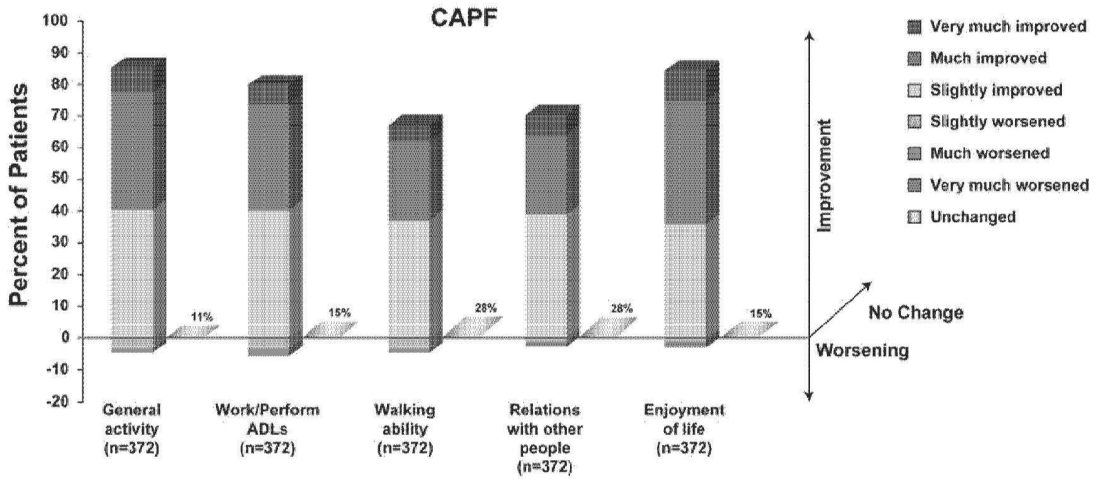

Fig. 5. Clinician assessment of patient function at final evaluation. ADLs = activities of daily living.

and tolerability profile typical of a potent opioid analgesic. AEs recorded during the maintenance phase of this study occurred in 88% of patients, although AEs were judged to be causally related to treatment in only half of these cases. The disparity between these findings illustrates the potential contribution of the underlying conditions and comorbidities to AEs in this population. Furthermore, the most frequent AEs (≥5% of patients), apart from back pain and urinary tract infection, were generally those associated with opioids and were mild to moderate in intensity. Serious AEs occurred in 18% of patients, and 11% of patients discontinued from the study because of AEs. Additional assessments, such as tests for endocrine function and mandatory urine drug screening, could have been beneficial in assessing some of the long-term risks of chronic opioid administration.

There are few similar studies with which we can compare and contrast the safety and tolerability results of our investigation and none that specifically evaluates the long-term safety and tolerability of a potent opioid in the management of BTP in association with chronic noncancer pain. Similar to our data, in one long-term (three-year) observational study of oxycodone for the treatment of persistent noncancer pain (but not specifically BTP), AEs were recorded for 88% of the 227 patients, 18% of patients discontinued because of AEs, 29% of patients experienced serious AEs (including seven deaths) unrelated to treatment, and 3% of patients displayed probable drug abuse or dependence.[3]

With necessary prudence in interpreting efficacy measures involving patient recall in an open-label study, the potential benefits of treatment with FBT were apparent for some patients in terms of improved functional outcomes, including less interference of pain with daily activities and improvements in their ability to work, socialize, and enjoy life. Marked changes in the PAF, CAPF, and GAS over time may indicate the suitability of these measures (rather than BPI-SF) for the assessment of the patient with BTP. The magnitude of observed effects with these measures appears to depend on the way the question was framed. Patients reported a greater benefit when asked about the change in status since the start of the study (i.e., GAS status), rather than the impact of pain (i.e., GAS interference). This finding is not unexpected, as patients treat an episode of BTP as it occurs, rather than use FBT in the control of persistent pain and/or the prevention of pain flares. However, the PAF, CAPF, and GAS scales require validation before these results can be fully appraised.

The proportion of patients achieving a successful dose in this study was greater than that in short-term studies of patients with cancer-related BTP.[9,14] Furthermore, the successful dose was also the final dose for most patients on study completion, suggesting that patients who can find an initially successful dose are often able to continue on the same dose for the long term. This observation is consistent with findings from a 13-month study of patients ($n = 680$) with chronic low-back pain, which suggested that a one-month opioid trial (with transdermal fentanyl or sustained-release oral morphine) is sufficient in most cases to determine response and tolerability.[23]

The overall completion rate for this study was low (139 of 646; 22%). However, 156 (24%) patients were still enrolled when their study site closed because the study had reached the endpoints necessary for regulatory submission. As such, 46% of the patients were either receiving ongoing treatment or had completed 18 months of treatment at the time the study was concluded. This percentage is within the range of completion rates reported in previous long-term analgesic studies of both opioids and nonopioids (13%–84%).[23–28]

Although the applicability of these findings to clinical practice is limited by the controlled nature of the clinical study setting, the study inclusion and exclusion criteria may offer an example of risk assessment and stratification standards that can identify patients for whom a trial of therapy with FBT might be most appropriate. If we make the assumption that the patients enrolled in this study are reflective of those seen in clinical practice with regard to age, weight, and comorbidities, then patients with BTP in association with chronic noncancer pain are typically middle aged or older, are overweight, and have a number of comorbidities that are being treated with analgesic and nonanalgesic medications. Their progress through the study shows us that benefits can be achieved by the addition of a rapid-onset

opioid to long-term opioid therapy while managing the inherent risks in most patients. Translation of these findings to clinical practice will be helped by the application of recent clinical guidelines that support the utility of long-term opioid therapy for chronic noncancer pain,[5] paying particular attention to key elements, such as patient selection and monitoring, treatment plans, and the identification of aberrant drug-related behaviors.[5,29]

In summary, the safety and tolerability profile of FBT in this study was generally typical of a potent opioid. The AEs observed were, in most cases, predictable, manageable, and tolerable. The small number of abuse-related events, even within the confines of a clinical study, speaks of the need for a structured patient treatment plan in clinical practice, so that risks associated with opioid therapy can be both anticipated and managed, and reinforces the need for ongoing, careful monitoring of the goals of therapy, AEs, and treatment plan adherence.

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