REVIEW ARTICLE

Treatment of Breakthrough Pain with Fentanyl Buccal Tablet in Opioid-Tolerant Patients with Chronic Pain: Appropriate Patient Selection and Management

Perry G. Fine, MD,* Arvind Narayana, MD,† and Steven D. Passik, PhD‡

*Department of Anesthesiology, University of Utah, Salt Lake City, Utah, USA;
†Cephalon, Inc., Frazer, Pennsylvania, USA;
‡Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Reprint requests to: Perry G. Fine, MD, Department of Anesthesiology, Pain Research Center, Ste 200, 615 Arapeen Drive, University of Utah, Salt Lake City, UT 84109, USA. Tel: 801-585-7690; Fax: 801-585-7694; E-mail: perry.fine@hsc.utah.edu.

Abstract

Background. Opioids can be a safe and effective option for carefully selected patients with a structured treatment program that includes consistent monitoring. However, the benefits and risks of opioid therapy for patients with chronic pain, and society as a whole, have been sharply debated. A key component of this debate has involved the administration of rapid-onset opioids for the management of breakthrough pain.

Objective. Review key aspects of breakthrough pain management with fentanyl buccal tablet, with a focus on minimizing risk to optimize therapeutic outcomes. Recommendations that apply broadly to all rapid-onset opioids are also discussed.

Design. Available fentanyl buccal tablet clinical and post-marketing data were reviewed.

Results. Like other schedule II controlled substances, and because fentanyl buccal tablet is a highly potent opioid, its use is associated with risk of overdose, misuse, and diversion. As with all rapid-onset opioids, particular attention to patient selection and risk assessment is warranted. The inclusion and exclusion criteria in fentanyl buccal tablet clinical studies represent patient selection standards that should be translated to clinical practice, most importantly, that patients are opioid-tolerant before fentanyl buccal tablet initiation. Titration of fentanyl buccal tablet from a low starting dose to a successful dose allows the safe identification of a dose that provides the greatest pain relief without unacceptable adverse events. After initiating fentanyl buccal tablet therapy, all patients should continue to be regularly monitored for response, including analgesia, functioning, tolerability, and aberrant behavior.

Conclusions. Fentanyl buccal tablet can be an effective and generally safe treatment for breakthrough pain when appropriate patient selection, administration, dosing, and monitoring are applied.

Key Words. Appropriate Patient Selection; Breakthrough Pain; Chronic Pain; Fentanyl; Opioid Analgesics; Pain

Introduction

Opioid prescribing for patients with chronic pain has increased significantly over the last decade [1,2]. However, concurrent with this trend, there has been an increase in prescription opioid misuse. In the United States alone, the number of individuals abusing controlled prescription drugs increased 94% between 1992 and 2003 [3]. Diversions of prescription opioids is also a major concern; in 2007, more than half of those taking pain relievers for nonmedical purposes obtained the drugs from a friend or relative [4]. Growing concern over misuse, abuse, and diversion has triggered efforts by professional societies and the U.S. government to minimize the incidence of these events.

Clinical guidelines for the administration of opioids for chronic noncancer pain were published recently by
the American Pain Society and the American Academy of Pain Medicine, with the goal of promoting adequate pain management for patients and minimizing the risks associated with opioids [1]. In addition, the Food and Drug Administration is mandating the development of coordinated Risk Evaluation and Mitigation Strategies (REMS) by the manufacturers of certain opioid medications (including extended-release opioids, methadone [5,6], and rapid-onset opioids) to reduce the misuse and abuse of, and unintentional overdose on, these drugs.

Given this environment, the management of breakthrough pain (BTP) with opioids requires careful attention to patient selection and risk assessment. BTP is a transitory exacerbation, or flare, of pain that occurs in patients with otherwise stable, persistent pain controlled with around-the-clock (ATC) opioid therapy [7–9]. Episodes of BTP have been characterized in patients with chronic cancer pain and patients with chronic noncancer pain [7,10–13]. While there are fewer epidemiological data for noncancer-related BTP than cancer-related BTP, the characteristics of both are similar, based on the published evidence. According to most estimates, both cancer-related and noncancer-related BTP have a prevalence greater than 50% and are associated with rapidly escalating pain levels reaching peak intensity in 3–10 minutes [12–14]. However, the distinction between cancer-related and noncancer-related BTP remains controversial, with some in the pain community questioning the evidence supporting the existence of BTP in noncancer patients with chronic pain, and others asserting that there is no relevant difference between BTP in cancer patients and in noncancer patients with regards to pain management [15,16].

For the management of BTP, a short-acting opioid (e.g., immediate-release morphine or oxycodone) is often added as supplemental medication to an ATC opioid regimen [1,8,17]. However, the delay in the onset of analgesia associated with traditional short-acting opioids (approximately 30–60 minutes to therapeutic analgesic levels; 60–120 minutes to peak effect) may limit their effectiveness in relieving BTP [8,18,19].

As a result, rapid-onset opioids have been developed to match the timing of a typical BTP episode more closely. The first rapid-onset opioid, oral transmucosal fentanyl citrate (OTFC®), was approved in 1998 for BTP in patients who are already receiving and are tolerant to opioid therapy for their underlying persistent cancer pain [20]. OTFC is contraindicated in the management of acute or post-operative pain, including headache/migraines. The majority of BTP clinical studies were conducted in patients with cancer-related BTP [21–27]. In these studies, analgesia was generally reported with OTFC beginning at 15 minutes and continuing through 60 minutes; tolerability was generally similar to other opioids.

Fentanyl buccal tablet (FBT) was subsequently approved in 2006 in the United States and in 2008 in Europe with the same indication and contraindications [28,29]. FBT employs OraVescent® technology, which enhances the rate and extent of fentanyl absorption through the buccal mucosa [30]. In a pharmacokinetic study, using intravenous fentanyl as the reference, absolute bioavailability was 65% with FBT and 47% with OTFC [31]. This difference in absolute bioavailability is mainly due to greater early systemic fentanyl exposure with FBT than OTFC [31]. The most recent addition in 2009 to this group of approved rapid-onset opioids for this same indication in the United States is a rapidly dissolving fentanyl buccal soluble film (FBSF). Additional novel formulations of fentanyl are in various stages of development as rapid-onset opioids for the treatment of BTP [32].

A component of the U.S. approval of FBT was a risk minimization action plan designed to mitigate FBT administration to opioid nontolerant patients and to minimize misuse, abuse, diversion, and accidental exposure. As required for all rapid-onset opioids, a REMS is being developed for FBT to further minimize potential risks [33]. FBSF has been approved with a REMS that requires prescriber, pharmacy, and patient enrollment and utilizes specialty pharmacies to restrict distribution [34].

Like other schedule II opioids, FBT is associated with a risk of overdose, misuse, and diversion. Because of its potency, FBT is intended only for opioid-tolerant patients, and particular attention to patient selection and risk assessment is warranted. This article reviews the key aspects of BTP management with FBT, with a focus on minimizing risk in order to optimize therapeutic outcomes. Most of the patient selection criteria, monitoring, and risk minimization strategies presented here could be applied to all rapid-onset opioids for the treatment of BTP. However, key differences among the rapid-onset opioids have led to important differences in initial dosing and titration.

General Considerations for Treatment of Chronic Pain with Opioids

In addition to treating the underlying source of the pain, the American Pain Society–American Academy of Pain Medicine’s guidelines recommend selecting patients and stratifying risks properly before implementing therapy with any opioid for chronic pain [1]. Clinicians should conduct a thorough medical history, including assessment of risk of substance abuse, misuse, or addiction, and a physical examination [1,35]. Screening tools that can assist in risk stratification include the Screener and Opioid Assessment for Patients in Pain (SOAPP) [36], the SOAPP-Revised [37], the Opioid Risk Tool [38], and the Diagnosis, Intracatability, Risk, and Efficacy score [39]. Additional assessment methods, such as urine drug testing (UDT), pill counts, family member or caregiver interviews, and review of prescription monitoring program data can be included in the treatment plan [1]. The existence of a strong family or caregiver support system can be an important factor in the estimation of risk [40].

The assessment of risk for abuse and misuse involves many factors. Some data indicate that the onset of a drug’s
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effect, as measured by the rate of increase in blood levels, may contribute to a drug’s abuse liability [41]. However, no controlled studies in chronic pain exist to prove this theory, and it is believed that speed of onset is not the only factor that contributes to the occurrence of abuse or misuse. Other factors such as genetic predisposition (specific opioid receptor binding/interaction features and other neurobiological factors that influence behavior), dose, patient history, and environment are also influential.

During opioid therapy, periodic monitoring of analgesia, functioning, adverse drug effects, and aberrant behaviors is necessary to maintain an ongoing assessment of the benefit-risk profile. In addition to soliciting patients’ reports of aberrant behaviors and noting observable behaviors, tools exist to facilitate monitoring for aberrant behaviors and opioid misuse during opioid therapy, such as UDT, the Pain Assessment and Documentation Tool (PADT), the Current Opioid Misuse Measure, and the Addiction Behaviors Checklist [42–45]. Considerations in selecting an appropriate assessment tool include the diagnostic accuracy of each tool, the patient population, and the specific screening needs [35,46].

Diagnosis of Breakthrough Pain

By consensus definition, the diagnosis of BTP can only be made in patients with chronic, persistent pain that is controlled by ATC opioid therapy. BTP should be assessed separately from baseline pain [1,9,47]. The origin of BTP can be idiopathic, incident (predictable or unpredictable), or related to end-of-dose failure [7,48]. Although the diagnosis is made primarily based on a patient’s own descriptions of the pattern of pain, patients are often unfamiliar with the concept of BTP. When discussing pain with patients, it is often necessary to be alert for terms that can indicate BTP, such as “pain flares,” “pain spikes,” or “worst pain.” As memory is often unreliable and office visit time limited, pain diaries can be the most effective and efficient means of characterizing, as well as quickly and reliably communicating, the nature, duration, severity, and predictability of BTP episodes [47]. The full evaluation of BTP may require additional diagnostic testing, follow-up visits, or consultation in order to identify the etiology of the BTP or the precipitating factors [1].

Patient Selection for FBT Therapy

As with all rapid-onset opioids, rigorous patient selection criteria are necessary when considering initiation of therapy with FBT. Most importantly, patients must be opioid-tolerant before initiating treatment with a rapid-onset opioid such as FBT. In addition, physicians should have a thorough understanding of the patient’s history and potential risk factors before therapy with FBT is added to the ATC opioid regimen.

Characteristics of BTP

It is important to evaluate the characteristics of the BTP episodes when considering treatment options. If the episodes slowly increase in intensity and are predictable, then a traditional short-acting opioid—taken in anticipation of the predictable event—would probably be sufficient. However, if the BTP episodes rapidly increase in intensity and/or are unpredictable, then a rapid-onset opioid such as FBT should be more effective. If patients are experiencing BTP close to the end of the ATC opioid dosing interval, presumably because of waning concentration of opioid blood levels (i.e., end-of-dose failure), the dose and/or frequency of the ATC opioid should be adjusted before considering the addition of a supplemental medication [12,49].

Underlying Pain Etiology

The efficacy of FBT for the treatment of BTP has been shown in multiple chronic pain populations. In five double-blind, placebo-controlled, crossover studies, FBT was efficacious in opioid-tolerant patients with BTP associated with various pain etiologies (i.e., cancer pain, noncancer-related low back pain, and noncancer-related neuropathic pain; see Table 1), as shown by the reduction in the intensity of pain over 60 minutes [summed pain intensity difference [SPID] between FBT and placebo at 60 minutes [SPID<sub>60</sub>: P < 0.01 in each study; Table 1] [50–54]. SPID allows the evaluation of pain intensity improvement over a clinically relevant time period and is a common measure of efficacy of episodic and acute pain therapies in clinical studies [23,55,56]. The additional measures of pain intensity differences and pain relief also favored FBT across studies, showing significant differences (P < 0.05) vs placebo as early as 5–15 minutes [50–54]. The consistent efficacy response shown in these studies is notable because the patients had numerous co-morbid conditions, a situation similar to that of patients in clinical practice.

Patient Characteristics

The inclusion and exclusion criteria in the FBT clinical studies exemplify patient selection standards that can be used in clinical practice [50–53,57]. Study participants were opioid-tolerant adults with persistent pain who were taking ATC opioids. In addition, patients had to have an overall average pain intensity score of ≤6 (scale: 0–10) for chronic pain during the previous 24 hours to confirm that their persistent pain was controlled and that they were achieving at least partial relief of their BTP with a traditional short-acting opioid. Patients were excluded if they had a recent history (within 5 years) of alcohol or substance abuse or positive UDT for illicit substances or medications without legitimate medical explanation. Patients were also excluded if they had any co-morbid condition that could jeopardize their safety during long-term opioid therapy (e.g., severe psychiatric disorders or cardiopulmonary disease).

In initiating a course of therapy with FBT, it is critical to confirm that patients are opioid-tolerant because serious adverse events, including deaths, have occurred in opioid
nontolerant patients [58]. In the context of prescribing FBT, patients are considered to be opioid-tolerant if they have been receiving a total ATC dose of at least 60 mg of oral morphine daily, at least 25 mg of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equivalent dose of another opioid daily for 1 week or longer (Table 2). UDT can be used to confirm the presence of prescribed ATC opioids but not the dose.

An understanding of the contextual meaning of “opioid tolerance” in the prescribing of rapid-onset opioids is essential. In this context, tolerance means that patients have had the requisite exposure to ATC opioids for persistent pain such that they are at reduced risk for serious, opioid-related adverse events (e.g., respiratory depression). This pragmatic determination of tolerance should not be confused with the more common understanding of tolerance, namely, that which refers to the need for increasing doses of opioids to maintain analgesia, in the absence of disease progression or other external factors [59]. More precisely, tolerance is the state of adaptation in which exposure to a drug induces changes that result in a reduction of one or more of the drug’s effects over time [60]—a definition that encompasses both analgesic tolerance as well as tolerance to side effects. Because of the potential for confusion about tolerance, health care providers must understand the use of the term in the context of safe prescribing of rapid-onset opioids, including FBT, and communicate this clearly to all those involved in the care of patients for whom BTP medications are prescribed.

Only a relatively small fraction of the population of patients with chronic pain fulfill the criteria for opioid tolerance and thus would be eligible to be considered for treatment with a rapid-onset opioid such as FBT. According to an analysis of data at a state subsidiary of a managed care organization, 0.9% of the population analyzed took opioids regularly (i.e., received >180 days of supply per year) in 2004 [61]. Similarly, a recent analysis of a large U.S. health care claims database provided an estimate of 2.2–2.6 million opioid-tolerant adult patients (approximately 1% of the total U.S. adult population) [62]. By comparison, it is estimated that 19% of American adults have chronic pain [63,64].

Clinicians should also confirm that their patients understand and are able to complete the steps involved in administering and titrating FBT. Asking the patients to explain proper administration and titration is a simple method to identify any confusion. The risk in prescribing FBT to patients who do not understand the titration process is that they could become confused and consume too many tablets.

Table 1  Summed pain intensity difference at 60 minutes (SPID60) in FBT clinical studies*

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>FBT</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Cancer pain [50]</td>
<td>Malignant solid tumor or a hematological malignancy</td>
<td>10.2</td>
<td>5.8</td>
<td>4.4</td>
</tr>
<tr>
<td>2: Cancer pain [51]</td>
<td>Malignant solid tumor or a hematological malignancy</td>
<td>9.7</td>
<td>4.9</td>
<td>4.8</td>
</tr>
<tr>
<td>3: Noncancer neuropathic pain [52]</td>
<td>Chronic neuropathic pain associated with DPN, PHN, traumatic injury, or CRPS</td>
<td>9.6</td>
<td>5.7</td>
<td>3.9</td>
</tr>
<tr>
<td>4: Noncancer low back pain [53]</td>
<td>Chronic low back pain associated with OA, degenerative disk disease, or spondylolisthesis</td>
<td>8.3</td>
<td>3.6</td>
<td>4.7</td>
</tr>
<tr>
<td>5: Noncancer pain (double-blind period 3) [54]</td>
<td>Chronic pain associated with DPN, PHN, traumatic injury, CRPS, back pain, neck pain, fibromyalgia, chronic pancreatitis, or OA</td>
<td>7.7</td>
<td>4.6</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* All P < 0.01, FBT vs placebo.

FBT = fentanyl buccal tablet; OA = osteoarthritis; DPN = diabetic peripheral neuropathy; PHN = post-herpetic neuralgia; CRPS = complex regional pain syndrome.

Table 2  Criteria for opioid tolerance: around-the-clock (ATC) dosages

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>ATC Dosages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine†</td>
<td>20 (IV), 60 (oral) mg/day</td>
</tr>
<tr>
<td>Transdermal fentanyl†</td>
<td>25 µg/hour (transdermal delivery system)</td>
</tr>
<tr>
<td>Oxycodone†</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>Hydromorphone†</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4 mg/day</td>
</tr>
<tr>
<td>Methadone</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>20 mg/day</td>
</tr>
</tbody>
</table>

† Dosages included in the oral transmucosal fentanyl citrate, fentanyl buccal tablet, and fentanyl buccal soluble film prescribing information [20,29,34]. Equivalent doses for other commonly used opioids are based on the published literature. All dosages are oral unless stated otherwise.
Risk Assessment and Stratification

Any signals of potential risk should be appropriately addressed before a rapid-onset opioid such as FBT is prescribed. Patient characteristics that appear to be most strongly associated with risk of abuse, misuse, or other aberrant drug-related behaviors are personal or family history of alcohol or drug abuse, younger age, and presence of severe psychiatric conditions [65–69]. In most cases, FBT would not be appropriate for patients with a history of chemical coping (reliance on a drug for psychological stability), abuse, or addiction.

The decision to initiate FBT therapy should be based on an overall analysis of risks and benefits for each patient (Figure 1). As with any opioid, counseling about therapy with FBT is important. The discussion with each patient should include a review of the goals, expectations, potential risks, and alternatives to FBT. In addition, the existing opioid agreement plan may be updated to include the physician’s and the patient’s responsibilities and expectations with regard to FBT. For example, the patient should acknowledge that he or she will continue to take his/her ATC opioid medication(s) while taking FBT and that he/she understands and will follow the dosing directions.

It is important to remember that concerns about abuse, misuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of misuse, abuse, and addiction, as the use of opioids carries the risk of addiction even when medically required and under appropriate medical care. Often, physicians are faced with the challenge of managing patients with some characteristic suggesting increased risk (e.g., family history of substance abuse), but who are likely to benefit from FBT therapy. In these cases, physicians must conduct a frank assessment of their own experience and their practice’s capacity to appropriately manage this type of patient (who often require more frequent visits, UDT, pill counts, etc.) to determine whether they can safely prescribe FBT. For these patients, a multidisciplinary approach to treatment implemented by a clinician with experience managing patients at increased risk for misuse, abuse, or diversion can be an option to ensure adequate pain management while minimizing risk [70]. Alternatively, these patients can be referred to a practice adequately equipped to provide care.

Proper FBT Administration

As previously noted, most of the patient selection criteria, monitoring, and risk minimization strategies can be applied to all rapid-onset opioids for BTP. However, because of important differences in the formulation of various rapid-onset opioids, the initial dosing and titration recommendations are not the same for all rapid-onset opioids. The information below provides an example of the level of understanding that a physician should have before prescribing a rapid-onset opioid.

After removing FBT from the blister package, patients should be instructed to immediately place it in the buccal cavity above a rear molar. The tablet dissolves in approximately 14–25 minutes without any further action required by patients, but the tablet should remain in place to optimize buccal contact [29]. Systemic absorption of fen-
tanyl from FBT was shown to be the same when FBT was placed buccally or sublingually, providing an alternative tablet placement option for patients with buccal mucosa limitations (e.g., radiation-damaged mucosa, cancer-related mucositis, post-surgical alterations) and for caregivers who must administer the tablet [71]. Swallowing the tablet prematurely may result in prolonged absorption from the gastrointestinal tract, decreased bioavailability, and a delayed time to analgesia. In order to prevent diversion and keep it out of the reach of children, patients and their caregivers must be instructed not to share FBT, or any opioid, with others and to keep all tablets safely stored. Children who have accidentally ingested OTFC have died.

**General Dosing Guidelines**

As stipulated in the prescribing information for FBT, to prevent confusion and possible overdose, only one FBT dosage strength should be provided to patients [29]. Patients should not take more than two doses of FBT per BTP episode and these doses must be separated by at least 30 minutes. After an episode of BTP has been treated, patients must wait at least 4 hours before treating another episode with FBT. This, in a single day, patients may treat no more than six episodes with FBT. These recommendations are supported by post-marketing findings of serious adverse events, including death, related to the frequency of FBT administration [33]. The effect of concomitant medications (e.g., monoamine oxidase inhibitors, cytochrome P450 3A4 inhibitors, and other drugs that act on the central nervous system) and co-morbid conditions (e.g., chronic pulmonary disease and renal or hepatic impairment) should also be considered before initiation of therapy with a rapid-onset opioid such as FBT.

**Initiation**

FBT is initiated at a low dose and titrated to a successful dose, that is, one that provides adequate analgesia with tolerable adverse events. The initial dose in patients not switching from OTFC is 100 µg. When switching from OTFC, patients must begin with conservative starting doses because FBT provides approximately 30–50% greater fentanyl exposure than OTFC [29,31]. Patients receiving ≤400 µg OTFC should initiate titration with FBT 100 µg tablets, while patients receiving ≥600 µg OTFC should initiate titration with FBT 200 µg tablets (Table 3).

**Table 3 Starting dose of FBT for initiation of titration**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Current OTFC Dose</th>
<th>Starting Dose of FBT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients not switching from OTFC</td>
<td>—</td>
<td>1 x 100 µg</td>
</tr>
<tr>
<td>Patients switching from OTFC</td>
<td>200 µg</td>
<td>1 x 100 µg</td>
</tr>
<tr>
<td></td>
<td>400 µg</td>
<td>1 x 100 µg</td>
</tr>
<tr>
<td></td>
<td>600 µg</td>
<td>1 x 200 µg</td>
</tr>
<tr>
<td></td>
<td>800 µg</td>
<td>1 x 200 µg</td>
</tr>
<tr>
<td></td>
<td>1,200 µg</td>
<td>2 x 200 µg</td>
</tr>
<tr>
<td></td>
<td>1,600 µg</td>
<td>2 x 200 µg</td>
</tr>
</tbody>
</table>

† These starting doses are not intended to represent equivalent doses of OTFC and FBT.

OTFC = oral transmucosal fentanyl citrate; FBT = fentanyl buccal tablet.

These starting doses are not intended to represent equivalent doses of OTFC and FBT. In addition to the pharmacokinetic differences between OTFC and FBT, inconsistent active administration of OTFC (i.e., amount of vigorous rubbing against the buccal mucosa) could lead to variable exposure to fentanyl with OTFC. Therefore, an equivalent dose switch from OTFC to FBT could expose patients to a higher level of fentanyl and pose a safety risk. Evidence of this variability has been observed in FBT clinical studies, which show that the previous OTFC dose is poorly correlated with the successful FBT dose (data on file, Cephalon, Inc., Frazer, PA).

**Titration**

Patients should be instructed to administer one dose of FBT for an episode of BTP. If the BTP episode is not relieved within 30 minutes, patients can be instructed to take one additional dose of the same strength for that BTP episode. As always, patients should be instructed to wait at least 4 hours before treating another BTP episode with FBT. Using multiple 100-µg tablets, the dosage strength can be titrated up to 400 µg to find a successful dose (Figure 2). If adequate analgesia is not achieved with ≤400 µg, patients can be instructed to titrate FBT to higher doses with multiple 200-µg tablets (Figure 2). It is

![Figure 2 Fentanyl buccal tablet dose-titration steps.](https://academic.oup.com/painmedicine/article-abstract/11/7/1024/1822289/Treatment-of-Breakthrough-Pain-with-Fentanyl/1029)
recommended that patients not possess multiple dosage strengths at one time to minimize the risk of mistakenly taking the wrong dosage strength during titration. Once the successful dose is identified, patients may continue on this dosage strength.

In the clinical efficacy studies of FBT, 65–81% of patients were able to identify a successful dose of FBT (the dose that provides adequate analgesia with tolerable adverse events). These patients titrated FBT to various doses; the majority found a successful dose between 400 and 800 \( \mu g \) (Figure 3) [50–53]. In these studies, there was no simple linear relationship between the successful dose of FBT and the dose of the ATC opioid regimen or the previous supplemental opioid, indicating that doses of FBT should be individually titrated to effectiveness [50–53]. This lack of correlation was also observed in OTFC and FBSF studies [23–25,34,50] and runs counter to older recommendations, which suggested that the short-acting opioid supplemental doses should always be estimated based on the ATC dose [72].

**Maintenance**

It is critical to reiterate that patients must continue to take their ATC medication when taking a rapid-onset opioid such as FBT because of the significant risk of respiratory depression and death. During maintenance therapy, if the BTP episode is not relieved after 30 minutes, patients may take only one additional dose using the same dose and must wait at least 4 hours before treating another BTP episode with FBT [29]. If patients consistently require a second tablet of FBT for BTP episodes, then the dose of FBT can be increased. If sufficient BTP relief is not achieved with FBT 800 \( \mu g \) (the highest dose), then the discontinuation from therapy with FBT or integration of multimodal therapeutic strategies could be considered. If patients are consistently experiencing more than four BTP episodes per day, then the ATC dose should be reassessed. If the ATC dose is optimized, the dose of FBT may need to be titrated again (upward or downward).

**Safety and Tolerability**

As with any potent opioid, the risk of serious adverse events such as respiratory depression exists [29]. The safety and tolerability of FBT was evaluated in two long-term open-label studies and five double-blind, placebo-controlled, crossover studies [50–54,57,73; data on file, Cephalon, Inc]. The adverse events that were common to both long-term studies and were found in ≥5% of patients were nausea, vomiting, constipation, headache, and dizziness (Table 4), and are generally typical of opioids. The majority of serious adverse events were considered by the investigators not to be or unlikely to be related to study medication [57,73]. In the long-term cancer-related BTP study, there was one incidence of withdrawal syndrome [57]. In the long-term noncancer-related BTP study, there were two reports of nonfatal accidental overdose and one report of a fatal drug diversion, which occurred when the patient was not properly monitored.

**Table 4** Adverse events occurring in ≥5% of patients during the maintenance phase of two long-term, open-label studies with FBT† [57,73]

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cancer Patients</th>
<th>Noncancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 197 )</td>
<td>( n = 646 )</td>
</tr>
<tr>
<td>Nausea</td>
<td>63 (32)</td>
<td>110 (17)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>48 (24)</td>
<td>78 (12)</td>
</tr>
<tr>
<td>Constipation</td>
<td>30 (15)</td>
<td>59 (9)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>29 (15)</td>
<td>46 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>24 (12)</td>
<td>70 (11)</td>
</tr>
<tr>
<td>Depression</td>
<td>22 (12)</td>
<td>45 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (11)</td>
<td>35 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (10)</td>
<td>46 (7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>18 (9)</td>
<td>41 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (9)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>15 (8)</td>
<td>98 (15)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15 (8)</td>
<td>56 (9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>15 (8)</td>
<td>39 (6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (7)</td>
<td>42 (7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11 (6)</td>
<td>58 (9)</td>
</tr>
</tbody>
</table>

† Only the adverse events that were reported by ≥5% of patients and were common to both studies are shown. FBT = fentanyl buccal tablet.
spouse of a patient died following a suspected overdose of FBT [33]. In addition, there have been post-marketing reports of serious adverse events related to improper patient selection (e.g., opioid nontolerant patients) and/or improper dosing [33].

In clinical studies, most discontinuations related to FBT occurred during the titration phase, with fewer discontinuations once a successful dose was identified ([50–53]; data on file, Cephalon, Inc.). Application site reactions or abnormalities were reported in approximately 10% of patients in clinical studies; these incidences tended to occur early in treatment, were transitory, and approximately 1% led to study discontinuation ([33,50–53]; data on file, Cephalon, Inc.). Patients experiencing any irritation can be advised to alternate the placement of the tablet on each side of the mouth. As previously noted, fentanyl exposure with sublingual administration of FBT has been shown to be bioequivalent to buccal administration and could be used as an alternative route of administration should patients prefer or need to administer this way [71].

Monitoring

Once patients have begun taking a rapid-onset opioid such as FBT as part of an opioid regimen, they should be regularly monitored for response, including analgesia, functioning, tolerability, and aberrant behavior.

Analgesic Response to FBT

When discussing treatment goals and expectations, it is important to emphasize to patients that FBT will only treat their BTP (not prevent it) and that therapy with FBT is initiated as a trial, with early and frequent evaluation. As with all pain medications, a realistic goal is to reduce pain to a level that comports with the patient’s specific goals and expectations to the safest extent possible.

A clinically meaningful response has been defined as a ≥33% improvement in pain intensity [74]. In the FBT clinical studies, a ≥33% improvement in pain intensity was reported by 30 minutes for about 40–50% of BTP episodes treated with FBT across studies (Figure 4) [50–54,77]. For this measure, statistically significant differences from placebo were observed with FBT as early as 5–15 minutes (P < 0.05 in each study).

Standard tools that assess the impact of treatment on patient functioning, such as the Brief Pain Inventory (BPI) and the Short-Form Health Survey (SF-36), have been utilized in clinical studies of FBT, but they are not designed to allow differentiation of the impact of persistent pain from that of BTP. In addition, they make assessments over time periods unrelated to the initiation of therapy (patients are asked to recall the last 24 hours for the BPI and the last 4 weeks for the SF-36) [75–77]. As a result, questionnaires were developed and utilized in FBT clinical studies to specifically assess the impact of treatment for BTP on patient functioning. These novel measures evaluated the impact of treatment for BTP since the start of therapy.

One such measure, the Goal Attainment Scale (GAS), evaluates patient-rated change in functioning, whereby patients select the three most important functional factors from a list of seven (originating from the BPI) and then rate each factor and assess the effect of the pain on that item. In the long-term noncancer-related BTP study, the three areas identified by the highest number of patients were enjoyment of life (469 [73%] patients), general activity (391 [61%] patients) and sleep (309 [48%] patients). Outcomes on the GAS showed improvements across all functional domains with FBT therapy (Figure 5) [73]. Similarly, the Clinician Assessment of Patient Function records clinician assessments of change in functional status since treatment initiation. Improvements in these functional parameters were also reported for the majority of patients with FBT therapy (Figure 5) [73]. Responses rated as much or very much improved/worsened can be considered clinically meaningful. Measurement of these functional domains in clinical practice could allow assessment

![Figure 4](https://academic.oup.com/painmedicine/article-abstract/11/7/1024/1822289/Treatment-of-Breakthrough-Pain-with-Fentanyl/1031)
of response to therapy with FBT. Considering the risks associated with chronic opioid therapy, continuation of treatment with FBT is only practical if marked reductions in BTP and improvements in patient functioning and quality of life are observed.

The dose of ATC opioid and FBT can be adjusted over time to provide optimal analgesia to manage persistent pain and BTP. The reasons for changing the FBT dose can result from the need for greater efficacy or because of an emergent adverse event. In long-term (>12 months) open-label FBT studies, the majority (64–69%) of patients did not require FBT dose changes over time [57,73]. The continual evaluation of efficacy and tolerability over time allows assessment of the risks vs the benefits of therapy with FBT for each patient.

Aberrant Behaviors

In an analysis of clinical studies in which patients received long-term opioid therapy (including FBT for BTP), 17% of patients had at least one aberrant behavior [78], which is lower than the 32–51% reported in previous studies of long-term opioid therapy in chronic pain patients [38,67,69]. The analysis also reported that <1% of patients had an abuse-related event, <2% had a positive urine drug screen and <1% had an opioid overdose [78]. These rates are similar to other reports where the rate of abuse-related events ranged from <1–3% [79,80]. Abuse-related events and aberrant behaviors were more frequent in men and younger patients (<42 years old) [78], a finding that is consistent with the results of previous studies [35]. The primary pain diagnosis, including low back pain, was not related to the incidence of aberrant behavior.

The detection of an aberrant behavior does not always mean that patients are abusing or diverting their prescribed medications, nor does it mean that treatment must be discontinued. However, any aberrant behavior must be appropriately addressed with each patient. If necessary, a more restrictive opioid agreement plan (e.g., more frequent visits, more frequent UDT, additional patient counseling) can be developed and implemented, with the understanding that treatment may need to be discontinued if patients fail to meet the terms of the opioid agreement.

Conclusion

FBT can be an effective and generally safe treatment for BTP. However, appropriate patient selection, dosing, administration, monitoring, and other risk minimization techniques must be applied. Concerns about misuse, abuse, addiction, and diversion should not prevent the proper management of pain. However, the potential benefits and risks of a therapeutic option must be evaluated for each patient. Management of chronic pain by a
multidisciplinary team may improve the benefit-risk ratio for certain patients.

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