REVIEW ARTICLE

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A Comprehensive Review of Rapid-Onset Opioids for Breakthrough Pain

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Abstract

Breakthrough pain (BTP) is a transitory pain (reaching maximum severity in ~15 minutes and lasting ~60 minutes in patients with cancer) that occurs despite the management of chronic pain with long-term around-the-clock analgesia. BTP occurs in 33–65% of patients with chronic cancer pain and in ~70% of patients with chronic noncancer pain. BTP has historically been managed with short-acting opioids; however, these medications have a pharmacokinetic profile that does not correlate with the sudden onset and short time to maximum severity of BTP. Interest in rapid-onset opioids to relieve BTP has therefore been growing. This comprehensive review aims to summarize the currently available clinical data for the approved rapid-onset opioids, which comprise different formulations of fentanyl, a μ-opioid receptor agonist with anaesthetic and analgesic properties. Administration routes for fentanyl in the management of BTP currently include the transmucosal and intranasal routes; an intrapulmonary formulation is also in development. The findings of this review suggest that the efficacy and safety of the approved rapid-onset opioids are comparable.

1. Introduction

Breakthrough pain (BTP) is a transitory pain that occurs despite the use of long-term, around-the-clock analgesia to control chronic pain.[1] Three types of BTP have been classified: spontaneous/idiopathic, incident and end-of-dose failure BTP (figure 1). BTP may be nociceptive (localized pain due to injury outside the nervous system), neuropathic (pain caused by damage to the central or peripheral nervous system) or a mixture of the two pain types.[2]

BTP is highly prevalent in certain patient populations, occurring in 33–65% of patients with chronic cancer pain[3,4] and ~70% of patients with chronic noncancer pain.[5] In patients with cancer, the median time from BTP onset to maximum intensity is 15 minutes and the median duration of BTP in these patients is ~60 minutes.[6] In patients with noncancer pain, peak pain intensity reportedly occurs within 10 minutes of onset and episodes can last for up to 1 hour.[5] BTP is frequently detrimental to quality of life. In a study of 43 patients with chronic noncancer pain and BTP, 93% of patients reported that BTP had a substantial effect on their general activity level and ability to work, and 86% of patients stated that it affected their enjoyment of life.[7] Despite the impact of BTP, this condition is currently under-recognized and under-treated.[8,9] Only 55% of patients take medication every time they experience BTP even though 60% of all patients with BTP describe it as a severe pain.[6]

Oral morphine and other traditional short-acting opioids have traditionally been the backbone of both chronic pain and pharmacological BTP management; however, the pharmacokinetic profile of these agents – slow onset of analgesia (time to achieve maximal plasma concentration [t_{max}] for normal-release morphine is 1.1 hours and onset of analgesia ~30 minutes), long half-life ($t_{½}$; 2 hours for oral morphine), extensive first-pass metabolism and poor bioavailability (20–40%) – does not correlate with the sudden onset and short time to maximum severity of BTP.[10-13] The need for more rapid pain relief in BTP has led to growing interest in the use of rapid-onset opioids (ROOs) for use in this setting. The first ROO

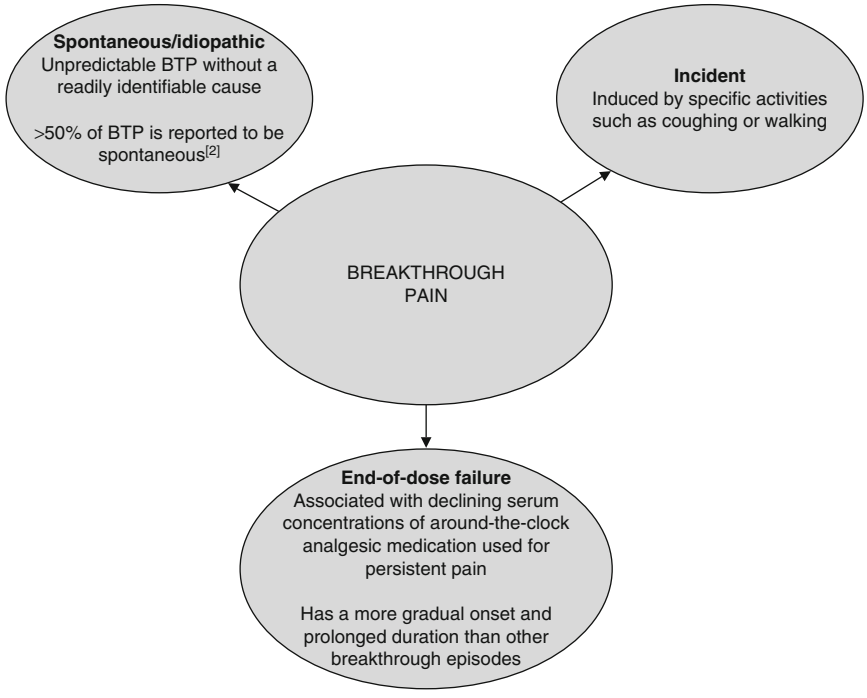

Fig. 1. Categorization of breakthrough pain (BTP).

indicated for BTP in opioid-tolerant patients with cancer was oral transmucosal fentanyl citrate (OTFC), a lozenge containing fentanyl citrate incorporated into a dissolvable sugar-based matrix. Since the approval of OTFC, several other formulations and delivery routes have been developed for this indication (figure 2).

Clinical studies evaluating pain often focus on statistically significant improvements, but greater emphasis is increasingly being placed on clinically meaningful changes in efficacy assessments. A study of 130 patients with cancer-related BTP who were undergoing titration to an efficacious dose of OTFC revealed that a clinically important improvement in pain intensity difference (PID) could be defined as a decrease of >33% from baseline within 30 minutes of administration.[14] Other measures of clinically important improvements in pain were a ≥2-point reduction in absolute pain intensity (on an 11-point numeric scale where 0 = no pain and 10 = worst pain imaginable), pain relief scores of ≥2 (on a 5-point categorical scale where 0 = no pain relief and 4 = complete pain relief) and a global medication performance score of ≥2 (on a 5-point categorical scale where 0 = poor and 4 = excellent).[14] In addition, 33% and 50% improvements in pain intensity scores have been judged to be of moderate and substantial clinical importance, respectively, in a recent consensus statement on meaningful outcomes in clinical studies of medications for chronic pain.[15]

This review evaluates current and future pharmacological methods of alleviating BTP. The pharmacokinetics of available formulations will be explored as well as their efficacy and safety profiles compared with placebo and with other opioids, with inclusion of data on clinically meaningful responses in patients with chronic cancer or non-cancer pain and BTP where available.

1.1 Search Strategy and Selection Criteria

A MEDLINE search was conducted on September 20, 2011 using the following search terms: 'rapid onset opioids' OR 'rapid acting opioids' OR 'ultra rapid acting opioids'; 'Fentanyl'[Mesh]

AND ('Administration, Buccal'[Mesh] OR 'Administration, Sublingual'[Mesh] OR 'Administration, Oral'[Mesh] OR 'Administration, Intranasal'[Mesh] OR 'Administration, Intrapulmonary'[Mesh]); 'Fentanyl'[Mesh] AND 'Pharmacokinetics'[Mesh]; 'Fentanyl'[Mesh] AND ('Patient Satisfaction'[Mesh] OR 'Patient Preference'[Mesh]).

Papers were limited to those written in English that were concerned with human subjects. Date limits were January 1, 2000 to September 20, 2011. Additional articles were identified by searching the reference lists of included papers.

Papers were included in this review if they reported on BTP in patients with chronic cancer or noncancer pain and included information on pharmacokinetics, efficacy or safety. Papers were excluded if they concerned transdermal fentanyl (indicated for the treatment of chronic pain), treatment of chronic pain, case studies, postoperative or labour pain, oral forms of opioids (i.e. opioids that are not rapid onset) or were reviews of BTP in general. For papers detailing efficacy, priority was given to reporting the findings from randomized controlled trials.

A summary of the randomized clinical studies is given in table I; this table includes both study design and Jadad scale scores in order that the reader may draw conclusions as to the methodological quality of the studies. Jadad scale scores range from 0 (very poor methodological quality) to 5 (rigorous methodological quality).[33]

2. Administration Routes for Breakthrough Pain (BTP)

Route of administration is an important consideration in the treatment of a fast-onset condition such as BTP, as it can affect the rate of dissolution and absorption and consequently can affect the bioavailability of a drug. Table II summarizes the different routes used to administer opioid medications for treating BTP. The choice of administration route for ROOs is heavily dependent on individual patient characteristics, including their clinical stability in terms of their underlying disease, likely adherence to medication regimens, the characteristics of their BTP (onset, predictability, severity and duration) and formulation preferences. For example, some patients may find it difficult or uncomfortable to use a medication that requires inhalation, while individuals with severe dysphagia may prefer not to use oral formulations.

Patients may express preference for certain administration routes for BTP medications. In a questionnaire study of 100 patients with cancer pain, 97%, 50%, 63% and 44% of patients reported that they would find it acceptable to take oral, nasal, sublingual and buccal medications for

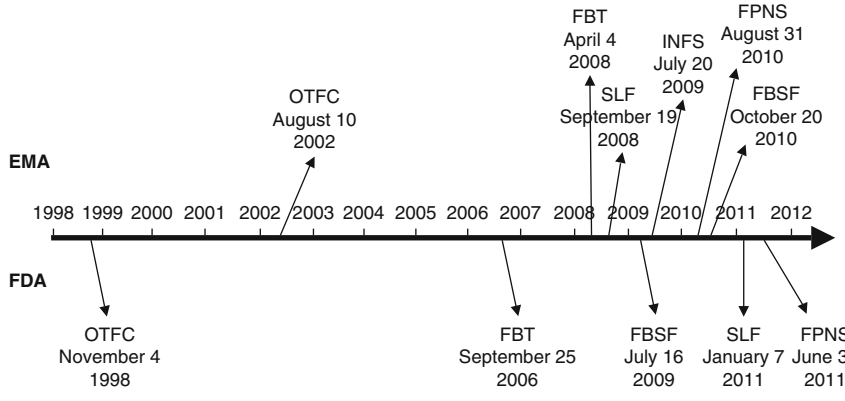

Fig. 2. Timeline of rapid-onset opioid approval in the US and EU. **EMA** = European Medicines Agency; **FBSF** = fentanyl buccal soluble film; **FBT** = fentanyl buccal tablet; **FPNS** = fentanyl pectin nasal spray; **INFS** = intranasal fentanyl spray; **OTFC** = oral transmucosal fentanyl citrate; **SLF** = sublingual fentanyl.

Table I. Studies included in this review

Study	Setting and patients	Study design and comparator	Jadad score	Open-label titration phase?	No. of patients who identified an effective dose (%)	No. of patients who completed the treatment phase (%)
OTFC						
Farrar et al.[16]	23 sites in the US Opioid-tolerant patients with chronic cancer pain, BTP and oral mucositis	Randomized, double-blind, crossover study vs placebo	5	Yes	93/130 (72)	72/92 (78)
Coluzzi et al.[17]	19 sites in the US Opioid-tolerant patients with chronic cancer pain and BTP	Randomized, double-blind, double-dummy, multiple crossover study vs oral immediate-release morphine sulphate	5	Yes	OTFC: 93/141 (66) Immediate-release morphine was taken at the dose usually used by the patient to control their BTP	84/93 (90)
Mercadante et al.[18]	Single site in Italy Opioid-tolerant patients with chronic cancer pain and BTP	Randomized, crossover study vs intravenous morphine sulphate	3	No	NA	25 (NA)
FBT						
Portenoy et al.[19]	32 sites in the US Opioid-tolerant patients with chronic cancer pain and BTP	Randomized, double-blind, crossover study vs placebo	5	Yes	80/123 (65)	68/77 (88)
Portenoy et al.[20]	16 sites in the US Opioid-tolerant patients with noncancer chronic pain and BTP	Randomized, double-blind, crossover study vs placebo	5	Yes	77/104 (74)	75/77 (97)
Simpson et al.[21]	17 sites in the US Opioid-tolerant patients with noncancer chronic pain and BTP	Randomized, double-blind, crossover study vs placebo	5	Yes	80/102 (78)	77/79 (97)
Slatkin et al.[22]	30 sites in the US Opioid-tolerant patients with chronic cancer pain and BTP	Randomized, double-blind crossover study vs placebo	5	Yes	87/125	75/86
Farrar et al.[23]	21 sites in the US Opioid-tolerant patients with noncancer chronic pain and BTP	Randomized, double-blind, multiple crossover study vs placebo	5	Yes	105/148 (71)	81/91 (89)
Ashburn et al.[24]	46 sites in the US Opioid-tolerant patients with cancer or noncancer chronic pain and BTP	Randomized, double-blind, crossover study vs oral immediate-release oxycodone	5	Yes	203/323 (63) achieved a successful dose with both drugs	180/190 (95) completed both double-blind phases

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Table I. Contd

Study	Setting and patients	Study design and comparator	Jadad score	Open-label titration phase?	No. of patients who identified an effective dose (%)	No. of patients who completed the treatment phase (%)
FBSF						
Rauck et al.[25]	30 sites in the US Opioid-tolerant patients with chronic cancer pain and BTP	Randomized, double-blind, crossover study vs placebo	5	Yes	82/151 (54)	70/82 (85)
SLF						
Rauck et al.[26]	36 sites in the US Opioid-tolerant patients with chronic cancer pain and BTP	Randomized, double-blind, crossover study vs placebo with a 12-month safety extension phase	5	Yes	78/131 (60)	60/66 (91) completed the double-blind phase; 25/75 (33) completed the 12-month extension phase
Lennernas et al.[27]	5 sites in Sweden Opioid-tolerant patients with chronic cancer pain and BTP	Randomized, double-blind, four-period crossover study vs placebo	5	No	NA	23/38 (61)
INFS						
Kress et al.[28]	Multiple sites across Austria, Denmark, France, Germany and Poland Opioid-tolerant patients with chronic cancer pain and BTP	Randomized, double-blind, crossover study vs placebo with a 10-month, open-label extension phase	5	Yes	112/119 (94)	110/111 (99) completed the double-blind phase; 15/108 (14) completed the 10-month extension phase
Mercadante et al.[29]	44 sites across Austria, France, Germany, Italy, Poland, Spain and the UK Opioid-tolerant patients with chronic cancer pain and BTP	Open-label, randomized crossover study vs OTFC	3	Yes	INFS: (85) OTFC: (88)	INFS: (93) OTFC: (92) 86/139 (62) completed both treatments
FPNS						
Portenoy et al.[30] and Taylor et al.[31]	Multiple sites in the US, Costa Rica and Argentina Opioid-tolerant patients with chronic cancer pain and BTP	Multicentre, randomized, double-blind crossover study vs placebo	5	Yes	83/113 (73)	76/83 (92)
Davies et al.[32]	35 sites in Europe and India Opioid-tolerant patients with chronic cancer pain and BTP	Multicentre, randomized, double-blind, double-dummy, crossover study vs immediate-release oral morphine sulphate	4	Yes	FPNS: 84/106 (79) Immediate-release morphine was given at a dose 1/6th of each patient's usual background morphine dose	79/84 (94)

BTP = breakthrough pain; **FBSF** = fentanyl buccal soluble film; **FBT** = fentanyl buccal tablet; **FPNS** = fentanyl pectin nasal spray; **INFS** = intranasal fentanyl spray; **NA** = not applicable; **OTFC** = oral transmucosal fentanyl citrate; **SLF** = sublingual fentanyl.

mild/moderate BTP, respectively; for severe BTP the rates were 88%, 68%, 75% and 63%, respectively.[35] All of the patients were familiar with using oral medications and the small proportion of respondents who stated that such medication would be unacceptable for BTP gave ''slow onset of analgesia'' as their reason. By contrast, only 2% of respondents had previous experience of using buccal medications (the OTFC lozenge on a stick) and perhaps unsurprisingly gave unfamiliarity as a major motive for finding this treatment modality unacceptable. In addition, respondents reported concerns regarding the potential for an unpleasant taste/nausea and the childish appearance of buccal medications. Worries regarding the fear of an unpleasant taste/nausea were also given as reasons for the unacceptability of nasal and inhaled medications for BTP. Previous bad experiences with sublingual and inhaled medications were further motives for rejection.[35] Patients with pain/disease in the area where a drug would be administered, e.g. due to cancer of the head and neck, responded that they would find nasal or inhaled drug administration unacceptable due to the nature of their illness. The acceptability rates and reasons given by respondents highlight the necessity for individualization of treatment for patients with chronic pain and BTP.

3. Current Treatments for BTP

At present the only rapid-onset analgesic that is suitable for the treatment of BTP is fentanyl, a μ-opioid receptor agonist with anaesthetic and analgesic properties. It is highly lipophilic, so it diffuses quickly across the blood-brain barrier.[37] The pharmacokinetics of fentanyl makes it particularly suitable for the treatment of BTP. For example, fentanyl has an equilibration $t_{½}$ of 6 minutes compared with 2–3 hours for morphine.[11] This means that fentanyl produces rapid analgesia that appears to closely match the time course of many episodes of BTP.[13] Fentanyl is primarily metabolized by cytochrome P450 (CYP) 3A4 and concomitant use with inhibitors of this enzyme can lead to increased fentanyl levels and an increased risk of respiratory depression. Patients taking fentanyl with CYP3A4 inhibitors should be monitored closely and dosage increases should be carried out conservatively. Moreover, fentanyl should not be administered to patients who have taken monoamine oxidase inhibitors within the previous 14 days[38,39] or patients who are opioid non-tolerant.[40] As with all opioid analgesics, fentanyl overdose may result in respiratory failure due to severe hypoventilation.[41,42]

Only limited data are available on the relationship between the total daily dose of a fixed-schedule opioid regimen and the dose of opioid required to manage BTP. In a preliminary study in 12 patients with cancer-related BTP, fentanyl buccal tablet (FBT) in doses proportional to the high doses of opioids used for background analgesia was efficacious.[43] However, it should be noted that doses of fentanyl that prove efficacious with one formulation may not demonstrate the same efficacy and tolerability when administered by another route.[29] Thus, different fentanyl formulations require individually titrated regimens based on patient response.[44] Studies of fentanyl usually include a dose-titration phase so that individual patients can identify the dose of the formulation that provides them with the best balance of efficacy and tolerability.

Of note, fentanyl formulations are currently only indicated for the management of BTP in opioid-tolerant patients with cancer, and are not recommended for the management of BTP in patients with pain of non-cancer origin. Use of these agents in patients with non-cancer pain is currently off label and is not supported by current literature. Key concerns with the use of fentanyl in patients with conditions other than cancer are those of abuse and addiction,[45] and potential fatalities in patients who are not opioid tolerant. Despite these concerns, the off-label use of fentanyl preparations is widespread. In 2007, a study observed that nearly 90% of OTFC prescriptions were off label, or not prescribed according to the FDA guidelines.[46] Off-label use may contribute to the fatalities that are observed with these products. For example, during the period January 2004 to June 2011, 55 deaths occurred in which OTFC was considered to be the primary suspect.[47] In recognition of concerns about misuse, abuse, addiction, overdose and serious

Table II. Characteristics of the various administration routes used for opioid medications with a particular focus on breakthrough pain[2,34]

Administration route	Fentanyl formulations available/ in development for BTP	Description	Advantages	Disadvantages
Transmucosal	Fentanyl buccal lozenge (OTFC) Fentanyl buccal tablet Fentanyl buccal soluble film Fentanyl sublingual tablet	Medication absorbed by the buccal (cheek) and sublingual (under the tongue) mucosa Some transmucosal formulations require active participation by the patient (e.g. continual movement of the fentanyl buccal lozenge), while others require no patient participation (soluble film)	• Can be used by patients who are unable to swallow or find medications difficult to swallow due to nausea/vomiting • A smaller proportion of the drug is swallowed and lost to first-pass metabolism compared with oral administration • Fast absorption and onset of action with lipophilic drugs such as fentanyl • Noninvasive route of administration • Drug administration can be interrupted quickly if toxicity is suspected during treatment	• To be efficiently absorbed by the buccal mucosa, drugs must be both hydrophilic and lipophilic to improve dissolution and absorption, respectively • Patients with dry mouth/oral mucositis/sores in the mouth due to cancer or cancer treatments may find transmucosal drugs uncomfortable to use or find it difficult to produce enough saliva for dissolution, although some studies have reported successful use in patients with mucositis • Application-site reactions may be experienced by patients using transmucosal formulations • Patients may require training regarding the correct use of the OTFC lozenge • Some tablets and lozenges can take 15–25 min to fully dissolve • Some patients report that the buccal OTFC lozenge appears childish due to the presence of the stick to assist with administration[35]
Intranasal	Intranasal fentanyl spray Fentanyl pectin nasal spray	Medication inhaled through the nose; usually one nostril is used for a single administration	• Noninvasive route of administration • Can be used by patients who are unable to swallow or find medications difficult to swallow due to nausea/vomiting • Cells of the nasal cavity are highly permeable, allowing fast absorption • Almost all of the drug is absorbed from the nasal cavity and therefore very little is lost to first-pass metabolism	• Patients may require training on the correct administration technique for intranasal sprays • Unsuitable route of administration for patients with cancer localized to the nose • Dose of drug absorbed may be variable • May also be unsuitable for patients experiencing blocked nasal passages due to cold/influenza/allergies • Nasal irritation may be experienced by patients taking intranasal sprays • Effective intranasal administration can accommodate only small volumes of liquid (150 μL per nostril[36]) and therefore route is only suitable for highly soluble drugs • Objections to intranasal administration include worries about an unpleasant taste in the back of the throat and patients finding nasal dosing difficult
Intrapulmonary	Intrapulmonary fentanyl dry powder	Aerosolized medication is inhaled directly into the lungs	• Lungs have a large area for absorption as well as highly permeable epithelial cells with high levels of blood perfusion offering the potential for rapid drug absorption • Avoids hepatic first-pass metabolism • Rapid onset of action	• Requires the use of aerosol inhaler/nebulizer devices • Patients may require training on the correct administration technique for intrapulmonary aerosol sprays • Worries regarding the medication tasting bad, medication catching the back of the throat and difficulties with using inhalers/nebulizers have been given as potential barriers to patient satisfaction with intrapulmonary drugs
Oral	Large number of opioids are available for use as medication in patients with BTP	Oral formulations include liquids, capsules and tablets that are not designed to allow transmucosal absorption of medication The drug is absorbed from the gastrointestinal tract	• Convenient for self-administration of medication by patient • If BTP is incident (has an identifiable and predictable cause) then traditional short-acting opioids can be taken before the trigger in order to accommodate the slow time to onset	• Slow time to onset of action (30 min) • Long duration of action • A large proportion of the drug will be lost during first-pass metabolism resulting in poor bioavailability • Not suitable in patients with dysphagia/nausea/vomiting

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Table II. Contd

Administration route	Fentanyl formulations available/ in development for BTP	Description	Advantages	Disadvantages
Transdermal	None to date	Transdermal patches allow passive diffusion of medication through the skin	• Can be used by patients who are unable to swallow or find medications difficult to swallow due to nausea/vomiting • Avoids hepatic first-pass metabolism • Convenient for self-administration of medication by patient	• Passive diffusion of medication via a transdermal patch is too slow for the treatment of BTP; patches are more commonly used for the treatment of chronic pain
Subcutaneous	None to date	Administration of medication as a bolus into the skin via an injection	• The subcutaneous route confers predictable bioavailability with fast onset of action • Higher doses of opioids can be administered	• Many patients dislike injections, which may limit self-administration of medication by this route • Requires equipment such as a pain pen to facilitate self-administration by patients
Intravenous	None to date	Administration of medication directly into a vein	• Medications given intravenously bypass the requirement for absorption – it is therefore the fastest route of drug delivery	• Cannot be used for regular self-administration of analgesia by patients with BTP

BTP = breakthrough pain; **OTFC** = oral transmucosal fentanyl citrate.

complications due to medication errors, a risk evaluation and mitigation strategy for all transmucosal immediate-release fentanyl formulations was introduced in December 2011.[48]

3.1 Oral Transmucosal Fentanyl Citrate

OTFC (Actiq®) is a sweetened lozenge containing fentanyl citrate that is attached to a stick to help the patient sweep the medication across the buccal mucosa (lining of the cheek). Administration of the lozenge takes ~15 minutes.[49] OTFC was developed by Anesta Corp. (later acquired by Cephalon, Inc.) and was approved in the US in 1998 for BTP in adults with cancer who are receiving, and are tolerant of, opioid analgesics for underlying chronic cancer pain. OTFC was approved in Europe for the same indication in 2002. OTFC is available in six dose strengths: 200, 400, 600, 800, 1200 and 1600 μg.

The sugar content of the OTFC lozenge improves its palatability for patients but some concerns have been raised regarding dental problems with prolonged and repeated use.[50] Furthermore, self-administration of medication for BTP may be seen as a burden for chronically ill patients; consequently, formulations developed after OTFC tended to focus on ease of administration/lack of active participation on the part of the patient.[50]

3.1.1 Pharmacokinetics

When the OTFC lozenge is administered as directed, 25% of the total dose of fentanyl is absorbed by the buccal mucosa and becomes systemically available. Approximately 75% of the OTFC dose is swallowed and is then absorbed from the gastrointestinal tract where two-thirds is eliminated via first-pass metabolism.[51] The bioavailability of OTFC is therefore ~50% of the total dose, split evenly between transmucosal and (slower) gastrointestinal absorption.[51] This relatively lower bioavailability among ROOs does not appear to significantly affect the clinical efficacy and safety profiles of OTFC as these are comparable to those of other available agents. In a multiple-dose pharmacokinetic study in healthy volunteers (800 μg for three consecutive doses), the bioavailability of OTFC was reported to be

40% with central and peripheral distributions of 17 L and 26 L, respectively.[52] Multiple doses of OTFC did not result in a pharmacokinetic profile that was substantially different to that observed after single-dose administration.[52] Summary pharmacokinetic data for OTFC are detailed in table III.

OTFC has demonstrated dose proportionality at 200, 400, 800 and 1600 μg, as increasing doses result in increasing serum levels of fentanyl. The median t_{max} for these four doses ranged from 40 minutes to 20 minutes, the mean maximal plasma concentration (C_{max}) ranged from 0.4 ng/mL to 2.5 ng/mL and the mean $t_{½}$ ranged from 3.2 hours to 6.4 hours (for the 200 μg and 800 μg doses, respectively).[53]

3.1.2 Clinical Efficacy versus Placebo

The efficacy of OTFC has been compared with placebo in a multicentre, double-blind, random-

Table III. Summary pharmacokinetic data[a] for fentanyl formulations

Formulation and dose (μg)	t_{max} mean (median), min	C_{max} mean, ng/mL	$t_{½}$ mean (median), h	Bioavailability, %	References
OTFC					
200	(40)	0.4	3.2		
400	(25)	0.8	6.4	40–50	51,53
800	(25)	1.6	6.4		
1600	(20)	2.5	6.0		
FBT					
100	(45)	0.3	(2.6)		
200	(40)	0.4	(4.4)		
400	(35)	1.0	(11.1)		
600	(78)	1.4	16.0	65	54,55
800	(40)	1.6	(11.7)		
1000	(84)	2.0	18.1		
1200	(96)	2.3	18.8		
1300	(60)	2.8	20.1		
FBSF					
600	60–120	1.0–1.1	9.8–12.7	71	56
800	90	1.3	19.0		
SLF					
100	40	0.2	6.1		
200	49	0.4	6.3	NA	57
400	57	0.9	5.4		
INFS					
50	23 (15)	0.4	3.2		
100	24 (12)	0.6	4.3	89	58,59
200	13 (15)	1.2	3.5		
FPNS					
100	20	0.4	21.9		
200	15	0.8	24.9	NA	60
400	21	1.6	15.0		
800	20	2.8	24.9		

a Results are from different studies in healthy volunteers and patients with chronic pain and therefore are not directly comparable.

C_{max} = maximal plasma concentration; **FBSF** = fentanyl buccal soluble film; **FBT** = fentanyl buccal soluble tablet; **FPNS** = fentanyl pectin nasal spray; **INFS** = intranasal fentanyl spray; **NA** = not available; **OTFC** = oral transmucosal fentanyl citrate; **SLF** = sublingual fentanyl; **$t_{½}$** = half-life; **t_{max}** = time taken to achieve maximal plasma concentration.

ized study of opioid-tolerant patients with cancer and BTP (table I).[16] Compared with BTP episodes in patients administered placebo, PID scores for episodes in those treated with OTFC were significantly greater from 15 minutes to 1 hour after administration ($p < 0.0001$).[16] Significant differences between OTFC and placebo were also evident in terms of global performance (mean scores 1.98 and 1.19 for OTFC and placebo, respectively; $p < 0.0001$) and use of rescue medications (supplementary medication taken in addition to the initial dose of opioid for BTP; 15% vs 34% of episodes; $p < 0.0001$).

3.1.3 Clinical Efficacy versus Other Opioids

OTFC has been compared with morphine administered by a variety of routes. The efficacy of OTFC was compared with that of intravenous morphine in a study of 25 opioid-tolerant patients with cancer and BTP.[18] Pain intensity decreased by 41.4% and 51.7% in the first 15 minutes after dosing with OTFC and intravenous morphine, respectively ($p = 0.026$ for treatment comparison). At 30 minutes, the reduction in pain intensity was 65.9% and 73.8%, respectively ($p = 0.136$ for treatment comparison).[18] Although the intravenous route provided rapid and effective pain relief, OTFC conferred the advantage of ease of use; self-administration of parenteral morphine is unlikely to be practical for the day-to-day management of BTP.[18]

In a randomized, double-blind, crossover study of opioid-tolerant patients with cancer that compared OTFC with immediate-release oral morphine sulphate (table I), the buccal lozenge was significantly more effective across all time points when assessed by reductions in pain intensity ($p \leq 0.033$), mean PID ($p < 0.008$), pain relief ($p \leq 0.009$) and global performance rating ($p \leq 0.001$). Furthermore, a significantly greater proportion of BTP episodes treated with OTFC demonstrated a clinically significant ≥33% change in pain intensity at 15 minutes compared with immediate-release morphine sulphate (table IV).[17] Rescue medication due to perceived treatment failure was required in a similar proportion of BTP episodes treated with OTFC or oral morphine (2% and 1%, respectively; $p = 0.5385$).[17]

3.1.4 Safety and Tolerability

Across the clinical studies of OTFC, reported adverse effects were typical of opioids and included somnolence, nausea and dizziness.[16,44,61] Hallucinations and confusion relating to the use of OTFC have also been reported in clinical studies of this formulation.[17]

Both the OTFC lozenge and a compressed powder formulation of OTFC were easily tolerated by patients with radiation-induced oral mucositis (ulceration of the oral mucous membranes). OTFC has therefore been suggested as a useful treatment for pain in patients with severe oral mucositis,[62] although it is possible that some patients may find it difficult to produce enough saliva for dissolution.

3.1.5 Patient Satisfaction/Preference and Quality of Life

In an open-label, long-term safety study, OTFC (200–1600 μg) was used to treat 38 595 episodes of BTP in 155 opioid-tolerant patients with cancer. These patients consistently gave global satisfaction ratings above 3 (where 0 = poor and 4 = excellent), indicating that the pain relief provided by OTFC was very good or excellent.[63] In a small study ($n = 14$) of OTFC formulated as either a sweetened matrix or a compressed powder in patients with radiation-induced oral mucositis, 50% of patients preferred the sweetened matrix compared with 21% for the powder ($p = 0.343$). This numeric difference in preference ratings may be due to the occurrence of a burning sensation in the mouth reported by more patients during administration of the powder than the sweetened matrix (10 patients vs 4 patients).[62]

OTFC has been reported to improve quality of life in patients with noncancer pain and BTP. In a study of 43 patients (mostly with chronic back pain), 65% reported that OTFC improved their enjoyment of life by "quite a bit" or "very much", and 61% and 58% reported that OTFC improved their mood and their general activity level by "quite a bit" or "very much", respectively.[7] In the same study, patients reported a statistically significantly greater preference for OTFC versus their previous BTP medication (hydrocodone, acetaminophen [paracetamol], oxycodone or a combination) in terms of satisfaction ($p < 0.001$),

Table IV. Clinically meaningful improvements with fentanyl vs comparators (placebo or other opioids)

Reference	Study design and fentanyl formulation	Moderate (≥33%) clinically relevant improvement in pain intensity (% episodes)	Substantial (≥50%) clinically relevant improvement in pain intensity (% episodes)
Active control			
Coluzzi et al.[17]	OTFC vs MSIR in 93 opioid-tolerant patients with chronic cancer pain and BTP; randomized, double-blind, double-dummy, crossover study	At 15 min: OTFC = 42.3%, MSIR = 31.8% ($p < 0.001$)	Not available
Mercadante et al.[29]	INFS vs OTFC in 139 opioid-tolerant patients with chronic cancer pain and BTP; open-label, randomized study	At 5 min: INFS = 25%, OTFC = 7% ($p < 0.001$) At 10 min: INFS = 51%, OTFC = 24% ($p < 0.001$)	At 5 min: INFS = 13%, OTFC = 2% ($p < 0.001$) At 10 min: INFS = 37%, OTFC = 10% ($p < 0.001$)
Ashburn et al.[24]	FBT vs OxyIR in 190 opioid-tolerant patients with chronic cancer/noncancer pain and BTP; randomized, double-blind, active-controlled, crossover study	At 15 min: FBT = 13%, OxyIR = 9% ($p < 0.05$) At 30 min: FBT = 41%, OxyIR = 32% ($p < 0.05$)	At 15 min: FBT = 6%, OxyIR = 4% (p = NS) At 30 min: FBT = 21%, OxyIR = 16% ($p < 0.05$)
Placebo control			
Portenoy et al.[19]	FBT vs placebo in 77 opioid-tolerant patients with chronic cancer pain and BTP; randomized, double-blind study	At 15 min: FBT = 13%, placebo = 9% ($p = 0.045$) At 30 min: FBT = 48%, placebo = 29% ($p < 0.0001$) At 45 min: FBT = 71%, placebo = 44% ($p < 0.0001$) At 60 min: FBT = 75%, placebo = 48% ($p < 0.0001$)	At 15 min: FBT = 8%, placebo = 6% (p = NS) At 30 min: FBT = 24%, placebo = 16% ($p < 0.05$) At 45 min: FBT = 51%, placebo = 25% ($p < 0.0001$) At 60 min: FBT = 64%, placebo = 35% ($p < 0.0001$)
Portenoy et al.[20]	FBT vs placebo in 77 opioid-tolerant patients with chronic low back pain and BTP; randomized, double-blind study	At 15 min: FBT = 20%, placebo = 11% ($p < 0.01$) At 30 min: FBT = 42%, placebo = 18% ($p \leq 0.0001$) At 60 min: FBT = 58%, placebo = 26% ($p \leq 0.0001$) At 2 h: FBT = 65%, placebo = 28% ($p \leq 0.0001$)	At 15 min: FBT = 11%, placebo = 5% (p = NS) At 30 min: FBT = 30%, placebo = 13% ($p \leq 0.0001$) At 60 min: FBT = 44%, placebo = 15% ($p \leq 0.0001$) At 2 h: FBT = 48%, placebo = 16% ($p \leq 0.0001$)
Simpson et al.[21]	FBT vs placebo in 79 opioid-tolerant patients with chronic noncancer pain with BTP; randomized, double-blind study	At 10 min: FBT = 9%, placebo = 3% ($p = 0.008$) At 15 min: FBT = 23%, placebo = 13% ($p = 0.006$)	At 15 min: FBT = 12%, placebo = 5% ($p = 0.001$)
Kress et al.[28] [a]	INFS vs placebo in 111 opioid-tolerant patients with chronic cancer pain and BTP; double-blind, randomized study	At 10 min: INFS = 58%, placebo = 28% ($p < 0.001$) At 20 min: INFS = 80%, placebo = 44% ($p < 0.001$) At 40 min: INFS = 86%, placebo = 48% ($p < 0.001$) At 60 min: INFS = 87%, placebo = 49% ($p < 0.001$)	At 10 min: INFS = 37%, placebo = 14% ($p < 0.001$) At 20 min: INFS = 60%, placebo = 28% ($p < 0.001$) At 40 min: INFS = 69%, placebo = 33% ($p < 0.001$) At 60 min: INFS = 73%, placebo = 38% ($p < 0.001$)
Slatkin et al.[22]	FBT vs placebo in 86 opioid-tolerant patients with chronic cancer pain and BTP; double-blind, randomized study	At 10 min: FBT = 16%, placebo = 10% ($p = 0.007$) At 15 min: FBT = 29%, placebo = 14% ($p < 0.0001$) At 30 min: FBT = 51%, placebo = 26% ($p < 0.0001$)	At 10 min: FBT = 7%, placebo = 4% ($p = 0.033$) At 15 min: FBT = 18%, placebp = 8% ($p < 0.0001$) At 30 min: FBT = 38%, placebo = 15% ($p < 0.0001$)

Continued next page

Table IV. Contd

Reference	Study design and fentanyl formulation	Moderate (≥33%) clinically relevant improvement in pain intensity (% episodes)	Substantial (≥50%) clinically relevant improvement in pain intensity (% episodes)
Farrar et al.[23] a	FBT vs placebo in 91 opioid-tolerant patients with chronic noncancer pain and BTP; multiple crossover study with 3 randomized, double-blind phases over 12 wk	At 5 min: FBT = 7%, placebo = 3% (p = 0.0150) At 15 min: FBT = 26%, placebo = 15% (p < 0.05) At 30 min: FBT = 40%, placebo = 26% (p ≤ 0.0001) At 90 min: FBT = 54%, placebo = 31% (p ≤ 0.0001)	At 5 min: FBT = 4%, placebo = 2% (p = NS) At 15 min: FBT = 17%, placebo = 10% (p = 0.0216) At 30 min: FBT = 29%, placebo = 15% (p = 0.0005) At 90 min: FBT = 41%, placebo = 23% (p ≤ 0.0001)
Rauck et al.[25]	FBSF vs placebo in 82 opioid-tolerant patients with chronic cancer pain and BTP; randomized, multiple crossover study	At 30 min: FBSF = 47%, placebo = 38% (p = 0.009)	At 30 min: FBSF = 33%, placebo = 24% (p = 0.002)

a Values were read from graphs and are therefore approximate.

BTP = breakthrough pain; **FBSF** = fentanyl buccal soluble film; **FBT** = fentanyl buccal tablet; **INFS** = intranasal fentanyl spray; **MSIR** = morphine sulphate immediate release; **NS** = not significant; **OTFC** = oral transmucosal fentanyl citrate; **OxyIR** = oxycodone immediate release.

pain relief that allows a return to sleep ($p < 0.001$), ease of use ($p < 0.05$), rapid onset of effect ($p < 0.001$), adequate pain relief ($p < 0.001$), ease of understanding ($p < 0.001$) and perception of safety ($p < 0.001$). The only domain that did not reach statistical significance was that of comfort with taking in public.[7]

3.2 Fentanyl Buccal Tablet

The FBT Fentora® was developed by Cephalon Inc. It was approved in the US in 2006 for BTP in adults with cancer pain who are receiving and are tolerant of opioid analgesics for underlying chronic cancer pain. FBT was approved for the same indication in the EU in 2008 under the brand name Effentora®. FBT is available in doses of 100, 200, 400, 600 and 800 μg. FBT uses OraVescent® delivery technology to alter the pH of the oral environment in order to assist with dissolution and maximize absorption of fentanyl. Dissolution takes 14–25 minutes with FBT and does not require active participation from the patient.[64] The OraVescent® system produces an effervescence reaction that releases carbon dioxide to produce carbonic acid in the buccal cavity. The resultant decrease in pH optimizes tablet dissolution. FBT then releases sodium carbonate to raise the pH in order to increase permeation of fentanyl through the buccal mucosa.[65,66] The buccal pH changes orchestrated by this effervescence reaction result in a greater proportion of fentanyl being absorbed transmucosally instead of being swallowed and absorbed by the slower gastrointestinal route. Because 50% of the fentanyl in FBT is absorbed transmucosally,[54] CYP metabolism is bypassed to a greater extent than with traditional short-acting opioids and OTFC, so a greater proportion of fentanyl enters the systemic circulation.[67] The time taken for FBT to dissolve in the mouth (''dwell time'') does not affect the rate and extent of fentanyl absorption through the buccal mucosa.[68]

3.2.1 Pharmacokinetics

Summary pharmacokinetic data for FBT are detailed in table III. In a study of 39 healthy volunteers that evaluated the single-dose pharmacokinetics of FBT (270–1300 μg), mean $t_{½}$ values ranged from 6.6 hours to 13.2 hours.[67] The t_{max} values were comparable for doses ranging from 270 μg to 1080 μg (median 54–72 minutes), although t_{max} was longer after administration of FBT 1300 μg (90 minutes). C_{max} increased in a less than dose proportional manner at doses higher than 810 μg; however, this was offset by a sustained peak serum fentanyl concentration with higher FBT doses so that total systemic exposure was dose proportional across the full range of doses assessed. Dose proportionality has also been

demonstrated for FBT over the 600–1300 μg range in terms of mean C_{max} and area under the plasma concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$) [overall systemic exposure].[69] The t_{max} values in this study ranged from 1.0 hours for the 1300 μg dose to 1.6 hours for the 1200 μg dose.[69] Dose proportionality in terms of systemic exposure is important as it indicates that stepped increases in FBT dose will result in a proportionally increased circulating fentanyl concentration. A predictable and linear increase in systemic exposure can therefore be expected with FBT titrated up to 1300 μg.[67,69]

Use of four 100 μg doses of FBT was reported not to be bioequivalent to one 400 μg dose of FBT, although differences in C_{max} and $AUC_{0-\infty}$ were small (~10%).[70] The difference was attributed to the buccal mucosa coming in contact with a larger surface area of tablet when four smaller doses were used, thereby increasing absorption.[70] Because fentanyl exposure with one 400 μg dose of FBT was less than that with four doses of FBT 100 μg, patients can use the four single tablets to titrate up to the 400 μg dose.

The bioavailability of FBT has been directly compared with that of OTFC.[67] A lower dose of FBT (1080 μg) provided comparable systemic exposure to that of a higher dose of OTFC (1600 μg) [$AUC_{0-\infty}$ mean (SD): 18.0 (5.4) vs 18.0 (7.1) ng • h/mL for FBT 1080 μg and 1600 μg, respectively]. FBT had a t_{max} of 1.0 hours compared with 2.0 hours for OTFC ($p < 0.001$) and the AUC_{0-tmax} was 1.5 ng • h/mL versus 0.8 ng • h/mL ($p < 0.001$). These results indicate that compared with the fentanyl lozenge, FBT provided higher early systemic exposure, which could result in the earlier onset of pain relief,[67] although studies that directly compare the efficacy of OTFC with that of FBT have not been performed.

In an additional study that directly compared the pharmacokinetics of FBT 400 μg with those of OTFC 800 μg, the median t_{max} was 47 minutes and 91 minutes, respectively.[54] Furthermore, FBT had greater absolute bioavailability compared with OTFC (65% vs 47%). Approximately 48% of the total fentanyl dose in FBT was absorbed buccally compared with 22% for OTFC.[54] In addition, dose normalization of OTFC to 400 μg revealed greater earlier systemic exposure with FBT compared with OTFC to the extent that a 30% lower dose of FBT would result in comparable systemic exposure to that of the fentanyl lozenge.[54]

Xerostomia (dry mouth due to a lack of saliva) and oral mucositis are common issues in patients with cancer. The absorption of FBT was compared between patients with and without mild oral mucositis (eight patients in each group).[71] In this study, FBT dissolved within 30 minutes in 14 of 16 patients with or without oral mucositis and t_{max} and C_{max} were comparable in both groups. Patients with oral mucositis did not experience exacerbations of their oral symptoms during the study.

The sublingual area has greater salivary flow than the buccal cavity and therefore sublingual placement may be more comfortable for patients and allow more rapid absorption of transmucosal preparations.[72] Bioequivalence has been demonstrated between sublingual and buccal placement of FBT in healthy volunteers meaning that patients taking FBT have the option of using either administration site without compromising absorption.[73] These findings indicate that FBT is a useful treatment option for patients with cancer and BTP who have low levels of saliva or oral problems.[71,73] FBT provides equivalent absorption in such patients as well as an alternative site of administration so that particularly sore or dry areas of the mouth can be avoided.

3.2.2 Clinical Efficacy versus Placebo

FBT has been shown to confer statistically and clinically significant improvements in the treatment of BTP in patients with cancer and non-cancer pain in five placebo-controlled studies.[19-23] The clinically relevant improvements in pain intensity observed in these studies are summarized in table IV. In brief, compared with placebo, FBT demonstrated significant reductions in summed PIDs over 60 minutes ($SPID_{60}$) and PID from 10 minutes, significant increases in pain relief from 10 minutes and moderate and substantial clinically relevant improvements in pain intensity from 5 and 15 minutes, respectively.[19-23] In addition, lower rates of rescue medication use and

significantly greater medication performance assessment scores were reported with FBT.[19-23]

3.2.3 Clinical Efficacy versus Other Opioids

The efficacy of FBT has been compared with that of immediate-release oral oxycodone in a recently reported randomized, double-blind crossover study of 190 opioid-tolerant patients with chronic cancer or noncancer pain and BTP.[24] As mentioned previously, compared with traditional short-acting opioids, ROOs have a pharmacokinetic profile that more closely matches the dynamics of BTP. The findings of this study support this supposition as FBT treatment resulted in statistically significantly greater PID scores than immediate-release oxycodone within 5 minutes ($p = 0.0081$) and this significant difference was maintained through 60 minutes ($p < 0.0001$). Pain relief was significantly better with FBT versus immediate-release oxycodone at 10 minutes ($p = 0.0275$) through 60 minutes ($p < 0.05$). The primary efficacy assessment of this study was the mean PID at 15 minutes (PID_{15}) measured on an 11-point numeric scale. The study results demonstrated that the mean PID_{15} was significantly greater with FBT compared with oxycodone (0.82 vs 0.60; $p < 0.0001$). $SPID_{60}$ and total pain relief at 60 minutes were also significantly greater with FBT ($p < 0.0001$ for both), indicating that FBT not only had a rapid onset of effect but also maintained its analgesic effects when compared with a traditional short-acting opioid.[24] Patients stated that the 30-minute post-dose medication performance of FBT was ''good'' to ''excellent'' in 41% of BTP episodes compared with 26% of episodes treated with oxycodone ($p < 0.0001$).[24]

3.2.4 Safety and Tolerability

No unexpected safety or tolerability concerns have been noted with FBT. The most common adverse events experienced with FBT are typical of opioids, for example, nausea, dizziness and vomiting, and decrease in incidence over time.[74] Application-site abnormalities were reported by 5–15% of patients in clinical studies of FBT but were predominantly transient and mild to moderate in severity.[20-24,74,75]

3.2.5 Patient Satisfaction/Preference and Quality of Life

Patients reported FBT to be preferable to traditional short-acting opioids in three studies. When patients with noncancer pain and BTP were queried about their medication preferences in an open-label tolerability study of FBT, more patients at all study visits (over an 18-month period) reported that they preferred FBT to their previous BTP medication (for example, oral morphine, oxycodone or hydrocodone). Patients ascribed this preference to the faster onset of action (94–97% of patients), convenience (80–90% of patients) and ease of administration (81–94% of patients) of FBT compared with traditional short-acting opioids.[75]

In a long-term, open-label study, patients with chronic cancer pain stated a greater overall preference for FBT compared with their previous BTP medication (88% vs 12%).[74] Greater patient satisfaction with FBT versus previous medications was also reported for time to onset of pain relief (95% vs 5%), ease of administration (66% vs 34%) and convenience of use (68% vs 32%). Moreover, 93%, 82% and 80% of patients stated that FBT was excellent/good for onset of action, convenience of use and ease of administration, respectively.[74]

In a study comparing FBT with immediate-release oxycodone for BTP in patients with cancer or noncancer pain, 52% of patients stated a preference for FBT compared with 33% for oxycodone; the remaining patients expressed no preference or did not complete the questionnaire.[24] Patients were blinded to treatment in this analysis, so the results of this assessment were more rigorous than reported when querying patients about preferences in open-label studies.

In a 12-week, randomized, double-blind study of FBT, improvements in all subscales of the Medical Outcomes Study Short-Form (36-item) Health Survey were reported at the final study visit with particular improvements in role limitations and social functioning. Moreover, total scores and anxiety also improved on the Profile of Mood States.[23]

In a long-term, open-label safety study, opioid-tolerant patients with chronic noncancer pain

and BTP (n = 646) reported that FBT improved their quality of life across a number of generalized scales. Of note, >65% of patients reported that FBT lessened the interference of pain in their enjoyment of daily life and it also improved their general activity and sleep. In addition, 70–80% of patients reported improvements in their ability to work, socialize and enjoy life.[75]

3.3 Fentanyl Buccal Soluble Film

The fentanyl buccal soluble film (FBSF) Onsolis™ was developed by Meda Pharmaceuticals Inc. and utilizes BioErodible MucoAdhesive (BEMA™) technology (BioDelivery Sciences International). It was approved in the US in 2009 for BTP in adults with cancer who are receiving and who are tolerant of opioid analgesics for chronic cancer pain. FBSF was approved in the EU in 2010, where it is marketed as Breakyl® for the same indication. FBSF is available in doses of 200, 400, 600, 800 and 1200 μg per film.

FBSF presents fentanyl in a layer that adheres to the inside of the patient's cheek; an outer layer isolates the fentanyl-containing layer from saliva. In this way, the FBSF minimizes the quantity of fentanyl that is swallowed in the saliva and that is consequently lost during first-pass metabolism.[56] The size of each FBSF is directly proportional to the strength of the administered fentanyl dose. FBSF does not require continuous patient participation for effective administration (compared with OTFC, which must be swept across the buccal mucosa) and disintegrates completely in the mouth.

3.3.1 Pharmacokinetics

Summary pharmacokinetic data for FBSF are presented in table III. The pharmacokinetics of FBSF 800 μg preparations at pH 6, 7.25 and 8.5 were compared with those of OTFC 800 μg in an open-label, single-dose, crossover study in 12 healthy subjects in order to determine the pH that allowed the most rapid dissolution with effective absorption.[76] Compared with OTFC, all three FBSF formulations had higher C_{max} values (1.0 ng/mL vs 1.4–1.7 ng/mL; p = 0.03) and greater overall systemic exposures ($AUC_{0-\infty}$ 10.3 ng • h/mL vs 13.1–14.5 ng • h/mL). t_{max} was 2.0 hours for the pH 6 and pH 8.5 FBSF preparations and for OTFC. t_{max} for the pH 7.25 FBSF was half that of the other formulations assessed and this preparation led to the greatest overall systemic exposure (41% higher than OTFC) and C_{max} (65% higher than OTFC; $p < 0.05$). The pH 7.25 FBSF was therefore selected for further evaluation in the FBSF development programme.[76]

Overall mean plasma concentration was reproducible after single doses of FBSF 600 μg and the median t_{max} of this formulation was 1.0–2.0 hours in a study where healthy volunteers received two doses of FBSF with a 3-day dosing interval.[77]

A pharmacokinetics study that evaluated a single 800 μg dose of FBSF compared with four 200 μg films taken simultaneously reported that these two treatments were bioequivalent.[56] C_{max}, overall exposure (as measured by $AUC_{0-\infty}$) and absolute bioavailability were the same for the two dosing methods.[56] t_{max} occurred slightly later when fentanyl was administered as four separate films (2.5 vs 1.5 hours for the 800 μg single FBSF dose), although this difference did not reach statistical significance (p = 0.078).[56] The study authors stated that bioequivalence of the two FBSF regimens occurred because the absorption of fentanyl was proportional to the surface area of the film – the surface area of four 200 μg films being identical to that of a single 800 μg film.[56] The absolute bioavailability of fentanyl from FBSF was reported to be 71%, with ~51% of the administered dose being absorbed through the buccal mucosa.[56]

FBSF demonstrated low intra-individual pharmacokinetic variability (coefficient of variation 7–10%) in a study of 24 healthy subjects, indicating that it would be expected to have consistent effects within a single individual in clinical practice.[78] By contrast, FBSF demonstrated wide inter-individual pharmacokinetic variability (23–39%), emphasizing the need for careful titration when using rapid-onset fentanyl formulations.[78]

3.3.2 Clinical Efficacy versus Placebo

The efficacy of FBSF has been assessed in a multicentre, randomized, placebo-controlled,

multiple crossover study of 80 opioid-tolerant adult patients with cancer who experienced BTP. Patients were eligible to enter the double-blind crossover period if they were successfully titrated within a 2-week period to an FBSF dose (200–1200 μg) that provided suitable pain relief. Compared with placebo, FBSF significantly reduced pain intensity, as measured by summed PIDs over 30 minutes ($SPID_{30}$; 38.1 vs 47.9; $p = 0.004$).[25] A statistically significant ($p < 0.05$) improvement with FBSF over placebo was reported for the SPID from 15 minutes and persisted to the last time point assessed in this study (60 minutes; $p < 0.001$).[25] PID over time was statistically significantly greater for FBSF versus placebo from 30 minutes until the final assessment ($p < 0.01$). The proportion of BTP episodes with clinically relevant improvements in pain intensity is reported in table IV. With FBSF, 30% of BTP episodes required rescue medication versus 45% with placebo ($p = 0.002$).

The placebo response rate was noted to be particularly high in this study. Although placebo response rates are often high in pain studies due to a weight of expectation on the part of the patient, the particularly high rates here were attributed to the innovative appearance of the buccal film used to administer both FBSF and placebo. It is thought that the perception of a novel delivery system may have raised patient expectations and sensitized them to even slight changes in pain intensity.[25] However, it appears that other ROOs with novel delivery systems (sublingual fentanyl [SLF] and intranasal fentanyl spray [INFS]) have lower placebo response rates.

To date no comparative studies have been conducted of FBSF versus other opioids.

3.3.3 Safety and Tolerability

Similar to the other fentanyl formulations described, FBSF has been reported to be well tolerated with an adverse-event profile typical of opioid analgesics.[25]

3.3.4 Patient Satisfaction/Preference

Patient global satisfaction with FBSF was significantly greater than with a placebo film using the same BEMA technology in a double-blind, randomized, crossover study of 80 patients with cancer and BTP.[25] Satisfaction with FBSF and placebo was reported to be excellent/good/very good by 67.1% and 47.1% of patients, respectively (no p-value reported), and overall satisfaction mean scores were 2.0 and 1.5, respectively ($p < 0.001$).[25]

3.4 Sublingual Fentanyl

SLF (Abstral®) was developed by ProStrakan. It was approved in the EU in 2008 for BTP in opioid-tolerant adults with cancer and was approved in the US for the same indication in 2011. The sublingual mucosa is highly vascularized and has good permeability, allowing rapid absorption of fentanyl.[27] SLF is a tablet comprising water-soluble carrier particles that are coated with fentanyl and a mucoadhesive agent to hold the tablet under the tongue. SLF is available in doses of 100–800 μg. The median dose used in a phase III study of 60 patients with cancer and BTP was 600 μg (mean 550.8 μg) and a median of three doses was taken each day.[26]

3.4.1 Pharmacokinetics

Summary pharmacokinetic data for SLF are detailed in table III. Total fentanyl exposure with SLF was proportional to the administered dose (dose range 100–400 μg) in a pharmacokinetics study comprising 11 patients with cancer.[57] Systemic exposure and absorption increased in a linear fashion with the doses assessed, and dose proportionality was also reported for the C_{max} of SLF (100 μg 0.24 ng/mL, 200 μg 0.41 ng/mL and 400 μg 0.91 ng/mL). The t_{max} ranged from 40 to 60 minutes for the 100 μg and 400 μg doses, respectively.[57]

A study of 47 healthy opioid-naive Japanese subjects examined the single- and repeat-dose pharmacokinetics of SLF.[79] Subjects received SLF 100, 200, 400 or 800 μg every 6 hours for a total of 14 doses. Subjects administered repeated doses of SLF 400 μg or 800 μg also received naltrexone to prevent opioid-mediated respiratory depression. The plasma concentration of fentanyl was dose proportional with the SLF dose. After a single dose of SLF, median t_{max} ranged from 0.5 to 1.0 hours and after repeat dosing it ranged from 0.5 to 2.0 hours.

3.4.2 Clinical Efficacy versus Placebo

In a small crossover study of 27 adult patients with locally advanced cancer and BTP, patients received placebo and SLF 100, 200 or 400 μg for one BTP episode in a random order separated by a washout period of 1 day.[27] This study did not use a preliminary titration phase to find the dose with optimum efficacy and minimal adverse events for each patient. SLF 400 μg was associated with the greatest improvements in PID when compared with placebo and the other doses assessed. SLF 400 μg demonstrated an improvement of 8.57 mm (on a 100 mm visual analogue scale) compared with placebo over the treatment period ($p < 0.0001$) and also gave a clinically (>20 mm) and statistically significant improvement in PID at an earlier time point (15 minutes; $p = 0.005$) compared with the other doses.[27] Use of rescue medication was significantly less common with SLF 400 μg compared with placebo (5 vs 15 patients; $p = 0.001$). Despite the absence of a dose-titration phase in this study, 22/23 patients (95%) identified one or more doses of SLF that gave them clinically relevant reductions in PID.[27] Compared with placebo, a significantly greater number of patients stated that SLF 400 μg was "excellent" when prompted to give a global assessment of treatment (three patients vs nine patients; $p = 0.0146$).

A multicentre, randomized, placebo-controlled, phase III study conducted in the US assessed the efficacy of SLF 100–800 μg in 66 patients with cancer and BTP who had successfully completed a dose-titration phase (table I).[26] The mean $SPID_{30}$ was significantly greater after administration of SLF compared with placebo (49.5 vs 36.6; $p = 0.0004$). This difference was maintained up to 1 hour after dosing ($SPID_{60}$ 143.0 vs 104.5; $p = 0.0002$). Improvements in PID and pain relief were also significantly greater with SLF compared with placebo from 10 minutes and remained significant throughout the 60-minute assessment period ($p \leq 0.055$ and $p \leq 0.049$, respectively).

To date no published studies have compared SLF with other opioids.

3.4.3 Safety and Tolerability

As with other fentanyl preparations, the most common adverse events are typical of opioids – constipation, nausea/vomiting and somnolence.[27] Application-site abnormalities, for example, stomatitis (inflammation of the mucosa), have been reported only rarely.[26]

3.4.4 Patient Satisfaction/Preference and Quality of Life

In a phase III study that asked patients with cancer pain and BTP to report their level of satisfaction with treatment using the Patient Global Evaluation of Medication (where 1 = excellent and 5 = poor), patients gave SLF an overall satisfaction rating of 3.1 versus 3.6 for placebo ($p = 0.0006$).[26] Furthermore, 29.7% of patients reported that they were very satisfied with SLF at the end of the study compared with 19.7% for placebo.[26] In a large, open-label study of patients with chronic cancer pain and BTP who were treated with SLF; 77% (71/92) of patients in this 12-month maintenance phase study reported that they were "very satisfied" or "satisfied" with SLF treatment.[80]

Quality of life in patients receiving SLF was assessed using the Brief Pain Inventory and the Depression, Anxiety, and Positive Outlook Scale in a 12-month open-label study of 85 patients with chronic cancer pain and BTP.[80] Current pain was significantly reduced at 6 months compared with baseline ($p = 0.01$), while pain relief ($p < 0.05$) and composite score for the interference of pain ($p < 0.001$) were significantly improved at 6 months and study end. Life enjoyment was also significantly improved at study end ($p = 0.02$) and daily-functioning items did not deteriorate over the study period. Depression scores improved significantly over 6 months ($p = 0.011$) and other mood items remained stable over the course of the study.[80]

Sublingual fentanyl was subsequently examined in a phase IV, open-label study in 217 patients receiving fixed-schedule oral opioids for the management of cancer-related pain.[81] Patients reported statistically significant improvements in daily functioning as measured by the modified Brief Pain Inventory over a 28-day observation period (mean combined score of 18 at the study end vs 50.4 at enrolment; $p < 0.0001$). In addition, there was a significant reduction in the percentage

of patients reporting high levels of pain-related disability (defined as a modified pain disability score >40) at the end of the study compared with enrolment (73.0% vs 12.1%). Furthermore, the prevalence of anxiety and depression was significantly reduced during the study period, as measured by the Hamilton Anxiety and Depression Scale.

3.5 Intranasal Fentanyl Spray

The INFS Instanyl® was developed by Nycomed and was approved in the EU in 2009 for BTP in adults with cancer who are receiving and who are tolerant of opioid analgesics for chronic cancer pain. INFS is not available in the US. INFS is available in doses of 50, 100 and 200 μg/spray. Another intranasal fentanyl formulation with pectin has also been developed and this is discussed in the next section.

3.5.1 Pharmacokinetics

The pharmacokinetics of INFS 50–200 μg were assessed in a study of 19 opioid-tolerant patients with cancer and BTP (table III).[58] Median t_{max} values were between 12 and 15 minutes for INFS and the plasma concentration increased in a dose-dependent manner, although C_{max} increased in a manner that was slightly less than proportional to the dose. Importantly, this study demonstrated that the pharmacokinetics of INFS in patients with cancer and BTP were comparable to previous results from studies in healthy volunteers.[58] In a study conducted in patients with pain after oral surgery, the bioavailability of INFS was 89% and $t_{½}$ was ~6.5 minutes.[59]

3.5.2 Clinical Efficacy versus Placebo

The efficacy of INFS 50–200 μg in opioid-tolerant patients with cancer and BTP has been assessed in a phase III, double-blind, randomized, placebo-controlled, crossover study conducted across multiple centres in Europe.[28] A total of 111 patients identified an effective dose of INFS and entered the randomized stage of the study. Compared with placebo, pooled mean PID scores at 10, 20, 40 and 60 minutes were significantly higher ($p < 0.001$) for all INFS doses (PID_{10} scores 1.10 vs 2.36; $p < 0.001$). Fourteen percent of patients required rescue medication while receiving INFS versus 45% of patients administered placebo (p = not significant). The proportion of patients who achieved a clinically meaningful reduction in pain (≥33% or ≥50% reduction) is shown in table IV. Patients' mean global impression of treatment was measured on a five-point scale (where 0 = poor and 5 = excellent). The mean global impression score for INFS (pooled doses) was 1.88 versus 0.95 for placebo ($p < 0.001$); 75.4% of patients reported that they perceived treatment efficacy as good/very good/excellent for INFS compared with 30.9% for placebo.[28]

3.5.3 Clinical Efficacy versus Other Opioids

An open-label, randomized, multicentre study conducted in European countries compared INFS (50–200 μg) with OTFC (200–1600 μg) in 139 opioid-tolerant patients with cancer and BTP who had successfully identified effective analgesia in the preliminary titration phase.[29] Meaningful pain relief in this study was defined by each patient individually with no input from study investigators or healthcare professionals; onset of meaningful pain relief was monitored with a stopwatch from the administration of the first fentanyl dose taken during a single BTP episode. Patients reported that meaningful pain relief was achieved in a median time of 11 minutes with INFS compared with 16 minutes for OTFC. Moreover, 66% of patients reported experiencing a faster onset of meaningful pain relief with INFS versus OTFC ($p < 0.001$).[29] Compared with OTFC, adjusted mean PID was statistically significantly greater for INFS from 10 minutes ($p < 0.001$) through to the final assessment at 60 minutes ($p < 0.01$). $SPID_{0–15}$ and $SPID_{0–60}$ scores were also significantly greater for INFS versus OTFC (treatment differences of 0.82 and 0.70 for the two assessments, respectively; both $p < 0.001$).[29] The proportions of patients achieving ≥33% and ≥50% reductions in pain intensity at 5 and 10 minutes are shown in table IV.

Rescue medication for BTP was used by a greater proportion of patients receiving INFS compared with patients taking OTFC (7.8% vs 4.9%). This difference was ascribed to the study protocol requirement for patients to wait longer before rescue medication could be used after

taking an OTFC dose (45–60 minutes) compared with 20 minutes after the first dose of INFS.[29] This requirement was based on the longer time for administration of the OTFC lozenge. Patients scored their general impression of treatment on a five-point scale (where 0 = poor and 4 = excellent) 60 minutes after administration.[29] The treatment difference for general impression between the two formulations was 0.2 in favour of INFS ($p < 0.001$). It should be noted that the open-label design of this study may have inadvertently favoured INFS, as patients may expect greater benefits from newer formulations and may have had previous experience with the OTFC lozenge. Although double-blinding in this study would have involved the use of placebo sprays and lozenges at the same time as the active dose, this may have assisted in avoiding bias in patients' perceptions of efficacy. In addition to the open-label enrolment protocol, the fact that only 86 patients completed both treatments and the use of onset of "meaningful" pain relief as the primary outcome measure make it difficult to draw firm conclusions regarding the superior efficacy of IFNS over OTFC.

INFS has been indirectly compared with OTFC, FBT and oral morphine in a statistical comparison of the results of studies identified during a systematic review.[82] This study evaluated six published reports and revealed that the fentanyl formulations gave greater pain relief at earlier time points than oral morphine. Morphine did not provide better analgesia than placebo until 45 minutes after dosing, meaning that patients with BTP are unlikely to obtain pain relief sufficiently rapidly with this medication. Reductions in pain intensity with INFS on an 11-point numeric rating scale were clinically meaningful (improvement of ≥2 points) from 30 minutes. Treatment comparison revealed that on an 11-point numeric rating scale, differences in PID_{15} with INFS were 1.2, 1.3 and 1.7 points compared with FBT, OTFC and oral morphine, respectively, although these improvements did not reach statistical significance.[82]

3.5.4 Safety and Tolerability

Aside from the opioid-related adverse events that are usually reported in fentanyl safety analyses, INFS was also associated with dysgeusia, a distortion of taste, and balance problems such as dizziness and vertigo.[28] Ulcers of the nasal mucosa have also been reported with IFNS.[29]

3.5.5 Patient Satisfaction/Preference

In a study comparing the analgesic effects of INFS with those of OTFC, 84 patients with cancer and BTP were questioned on their preferences regarding the two formulations. INFS was favoured by 77.4% of patients compared with 22.6% who preferred the buccal formulation ($p < 0.001$); 90.1% of patients found INFS easy/very easy to use compared with 39.8% for OTFC.[29]

3.6 Fentanyl Pectin Nasal Spray

The fentanyl pectin nasal spray (FPNS) [PecFent® (EU trade name), Lazanda® (US trade name)] was developed by Archimedes Pharma. It was approved in the EU in 2010 and in the US in 2011 for BTP in adults with cancer who are receiving and who are tolerant of opioid analgesics for chronic cancer pain. In January 2011, the Scottish Medicines Consortium accepted the use of FPNS for patients with cancer experiencing BTP as an alternative to other fentanyl formulations or for those who cannot take short-acting opioids. FPNS is available in doses of 100 and 400 μg/spray.

The addition of pectin in FPNS promotes the formation of a gel on contact with calcium cations on the nasal mucosa, prolonging the residence time of fentanyl at the mucosa and giving a rounded pharmacokinetic profile compared with the sharp profile of non-gelling sprays.[60,83] This pectin-based drug delivery system is referred to as PecSys.[83] The high, early C_{max} of the non-gelling sprays is reported to be indicative of a wide coefficient of variation and less predictable efficacy and tolerability.[60] FPNS has demonstrated a slower decline in plasma fentanyl levels compared with non-gelling nasal sprays, suggesting that FPNS provides comparably extended analgesia versus non-gelling intranasal formulations.[60]

3.6.1 Pharmacokinetics

Summary pharmacokinetic data for FPNS are detailed in table III. In a pharmacokinetics study of fentanyl intranasal spray preparations that

form gelling matrices on contact with the nasal mucosa, FPNS was compared with two other novel intranasal preparations and OTFC. The study was conducted in 18 healthy volunteers and comprised a randomized, single-dose, open-label, four-way crossover design.[84] In this study, the t_{max} for FPNS was ~20 minutes and the C_{max} was 337 pg/mL. The other gelling formulations evaluated in this study had a higher C_{max} and a shorter t_{max} than FPNS, but it was posited that such pharmacokinetics were likely to lead to increased rates of adverse events.[84] Indeed, the two nonpectin gel formulations did have poorer tolerability profiles in this study, leading to FPNS being pursued as a novel intranasal spray formulation.[84]

The pharmacokinetics of FPNS (100, 200, 400 and 800 μg) and OTFC have been compared directly in a single-dose, open-label, five-period, crossover study of 16 opioid-naive healthy subjects.[60] FPNS demonstrated a dose-independent t_{max} that was significantly reduced compared with OTFC (15–21 minutes vs 90 minutes; $p < 0.01$). The C_{max} of FPNS increased in a dose-proportional manner (352 pg/mL and 2844 pg/mL for the 100 μg and 800 μg doses, respectively) and was significantly higher for FPNS versus OTFC ($p < 0.001$).

3.6.2 Clinical Efficacy versus Placebo

In a randomized, placebo-controlled study of 83 opioid-tolerant patients with cancer and BTP, clinically relevant reductions of ≥2 points in absolute pain intensity (measured on an 11-point numeric scale) were observed within 10 minutes in 33% of BTP episodes treated with FPNS versus 25% of patients given placebo ($p < 0.05$). Clinically meaningful improvements in pain relief were also recorded at 10 minutes with FPNS (33% vs 24% for placebo; $p < 0.01$).[31] Rescue medication use was required within 60 minutes in 9% of BTP episodes treated with FPNS compared with 20% of episodes treated with placebo ($p < 0.001$).[31] In the same study, FPNS demonstrated significantly greater mean $SPID_{30}$ scores compared with placebo (6.57 vs 4.45; $p < 0.0001$).[30] Compared with placebo, a significantly greater proportion of patients treated with FPNS reported onset of analgesia (≥1 point reduction in pain intensity score) from 10 minutes (38.4% vs 56.2%; $p < 0.01$). The reduction in pain intensity became clinically meaningful (≥2 point reduction) for 49% of FPNS-treated patients at 15 minutes and 63% at 30 minutes.[30] Clinically meaningful pain relief was reported by a significantly higher proportion of patients receiving FPNS versus placebo from 10 minutes (32.9 vs 24.5; $p = 0.01$). Rescue medication within 60 minutes was required during 9.4% of BTP episodes treated with FPNS compared with 20.0% of episodes treated with placebo ($p < 0.001$).[30]

In a long-term (16-week), open-label study of ~350 patients with cancer pain and BTP, rescue medication was required for only 6% of BTP episodes treated with FPNS.[85] Moreover, the FPNS dose was stable with long-term use (4 months) and less than 10% of patients required an increase in initial dose.[85]

3.6.3 Clinical Efficacy versus Other Opioids

FPNS has recently been compared with oral immediate-release morphine sulphate in a double-blind, multiple-crossover study of 110 patients with chronic cancer pain and BTP.[32] Compared with morphine sulphate, clinically meaningful improvements in pain intensity (≥2-point reduction on an 11-point numeric scale) were reported for a significantly higher proportion of FPNS-treated BTP episodes from 10 minutes (45.4% vs 52.4%; $p < 0.05$). In addition, clinically meaningful pain relief (score ≥2 on a 5-point numeric scale) was reported during significantly fewer BTP episodes treated with morphine sulphate than FPNS from 15 minutes (53.4% vs 60.2%; $p < 0.05$).[32] From 30 minutes, the differences between FPNS and morphine sulphate in terms of changes in pain parameters were static or began to diminish.[32] Rescue medication was required within 60 minutes in 3.0% and 3.8% of FPNS- and morphine sulphate-treated BTP episodes, respectively ($p = 0.57$).[32]

3.6.4 Safety and Tolerability

Typical opioid treatment-related adverse events were reported by approximately one-quarter of patients in a 16-week open-label study of FPNS.[85] One death (out of a total of 80 deaths

during the study) was considered to be possibly related to the use of FPNS. This patient died after peritonitis-complicated bowel perforation, possibly due to opioid-induced constipation.[85] Approximately half of the patients receiving FPNS experienced treatment-emergent adverse events in a placebo-controlled, multiple-crossover study.[30] One event of noncardiac chest pain was judged to be possibly related to the study drug. Mild to moderate nasal tolerability events were reported in ~10 patients in this study (n = 113).[30] Nasal adverse events reported in a study (n = 89) comparing FPNS with immediate-release morphine sulphate included mild obstruction (2.2%) and mild nasal discharge (4.5%).[32]

3.6.5 Patient Satisfaction/Preference

In a study of 16 healthy volunteers administered FPNS as part of a pharmacokinetics analysis, five subjects rated nasal dosing with fentanyl to be slightly or moderately inconvenient.[60] By contrast, in a larger randomized, placebo-controlled, double-blind study in patients with cancer and BTP, satisfaction with the ''convenience of use'' of intranasal fentanyl spray was reported by 70% of patients and satisfaction with ''ease of use'' was reported by 69% of patients.[31]

Compared with oral immediate-release morphine sulphate, patients reported (on a scale of 1–4) that they were significantly more satisfied with FPNS: overall (2.73 vs 3.01 at 60 minutes; $p \leq 0.01$); in terms of speed of pain relief (2.72 vs 3.01 at 60 minutes; $p \leq 0.01$); and in terms of reliability (2.74 vs 3.03 at 60 minutes; $p \leq 0.01$).[32] These higher ratings of patient satisfaction with FPNS versus morphine sulphate were reflected in the high proportion (70%) of patients who chose to continue treatment with FPNS in an open-label extension.[32]

4. Future Formulations

Of the products currently in development for BTP, Taifun® – intrapulmonary fentanyl administered with an inhaler – is closest to obtaining approval. A phase II, randomized, double-blind, placebo-controlled study of intrapulmonary fentanyl 100, 200 and 400 μg in 122 opioid-tolerant patients with cancer and BTP, reported that the active treatment resulted in significant pain relief within ~10 minutes and significantly better SPID scores.[86] A multicentre, phase III safety study of intrapulmonary fentanyl was completed in 2010 and the full results of this and the phase II efficacy study are awaited. Other opioid and non-opioid formulations in development for BTP include subcutaneous hydromorphone, sublingual methadone, and intranasal morphine, ketamine and dexmedetomidine.[13]

5. Discussion

The studies discussed in this review indicate that, with the exception of the findings from a single open-label study, with the limitations inherent of non-blinded analysis, the efficacy and safety profiles of the ROOs for cancer-related BTP are comparable to each other, although OTFC has markedly lower bioavailability. Unfortunately, there are no published double-blind, head-to-head studies from which to draw further conclusions on the clinical differences between and patient preferences for the currently available formulations.

A recent economic evaluation of INFS compared with FBT and OTFC used data from Sweden to model the potential cost:benefit ratios of these formulations.[87] This model revealed that over a time horizon of 180 days INFS dominated OTFC (i.e. conferred benefits in terms of quality-adjusted life-years [QALYs] and cost compared with the buccal formulation) and was cost effective compared with FBT (had an incremental cost-effectiveness ratio of 12 203 Euros/QALY gained).[87] The cost of treatments is an important consideration when making management decisions, particularly for chronic conditions. Additional studies regarding the health economics of treatment for BTP would be welcome, particularly with longer time horizons and across more countries.

There are a number of factors to take into account when considering whether the results of the studies reviewed here are applicable to the wider clinical population. For example, the patient populations in these studies were ''enriched'' or

"preselected for response" due to very specific enrolment criteria and a need for titration to an effective fentanyl dose.[25] Without careful titration and patient selection, it is unlikely that clinicians will observe the same high levels of pain relief in their own practices. However, such patient selection and titration with fentanyl is vital to avoid safety risks. Instances of serious illness and death have occurred in opioid non-tolerant patients treated with fentanyl, patients who have misunderstood their dosing schedule and patients who have substituted one fentanyl formulation with another.[40] Fentanyl formulations cannot be used interchangeably due to their different pharmacokinetic profiles.

Consideration of the pharmacokinetic profiles of fentanyl formulations is fundamental in choosing the most appropriate treatment for each patient as they can indicate the likely onset of action and the potency of the effect of the medication (C_{max} and bioavailability). Most pharmacokinetic studies of fentanyl have been performed in healthy volunteers, but it should be remembered that patients requiring relief from BTP may be using concomitant medications or may have hepatic impairment and therefore the pharmacokinetics of fentanyl may differ substantially in clinical practice.[67] To date, the pharmacokinetics of INFS and SLF have been reported in patients with cancer and BTP; in these studies, INFS and SLF demonstrated pharmacokinetics that were comparable between patients and healthy volunteers.[57,58]

Patients with BTP frequently have a high burden of morbidity due to both their disease and to treatments for the disease and for chronic pain. These aspects have, to date, made it difficult for investigators to assess the safety profile of ROOs – differentiating between treatment-emergent adverse events and underlying morbidity is not simple. In addition, the usefulness of any "background" assessment of the safety of ROOs in healthy subjects during pharmacokinetics studies is limited by the use of naltrexone to stop subjects from experiencing opioid-associated effects, such as respiratory depression. There is, therefore, a possible gap in our knowledge regarding the true safety and tolerability profiles of ROOs in patients with BTP.

The transmucosal and intranasal routes have been a focus for drug development in patients with chronic pain and BTP due to ease of use and the absorption and bioavailability profiles over time, which closely match the dynamics of BTP. A recent Delphi survey of 33 Danish general practitioners assessed which characteristics of INFS and OTFC led to clinicians prescribing/not prescribing these formulations.[88] Reasons for prescribing OTFC included the possibility of self-administration and its utility as a medication for frequent dosing in patients with BTP; reasons for choosing an alternative to OTFC included patient confusion, high cost and the occurrence of dry mouth and nausea.[88] Furthermore, other studies have reported that some patients find the appearance of the OTFC lozenge embarrassing as it makes them look childish.[7,35] Results of the Delphi study indicated that benefits associated with INFS were the potential for it to be administered by family members (reducing direct patient treatment burden) and being suitable for use in patients with dry mouth. Reported rationales for not prescribing INFS were application side effects (such as nasal irritation) and issues with the nasal mucosa, such as colds and influenza or disease pathology.[88]

Studies that discuss the disadvantages and advantages of different routes of administration for BTP in general,[35] or with fentanyl specifically,[88] serve to highlight the potential for individualizing treatments for BTP. Because the use of BTP treatments is influenced by patient-centric factors, such as underlying disease characteristics, patient preferences and ease of administration, the available formulations for BTP can be prescribed according to the needs of the patient and should improve the clinical response as a result. There is potential for other administration routes to be used for the treatment of BTP, and it is likely that future research will focus on expanding the options available to patients by exploring these alternatives and also on optimizing the bioavailability of fentanyl through currently available modalities. ROOs are recommended for the treatment of most BTP episodes in opioid-tolerant patients with cancer, particularly those episodes that are unpredictable, of an extremely

intense nature or very short duration, or have a rapid steep climb to peak intensity.

Conclusion

The last 5 years have seen the introduction of a range of fentanyl-based ROOs with different administration routes for the management of BTP in opioid-tolerant patients with cancer. Given the absence of data from double-blind, head-to-head trials, it is not currently possible to conclude that any formulation is superior to another. Based on available data, mainly from placebo-controlled trials, the current formulations appear to be comparable in terms of efficacy and safety. It is likely that factors such as disease characteristics, patients' preference and ease of administration will continue to be key determinants in deciding the most appropriate formulation for individual patients.

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