

*Review Article*

# Efficacy of Rapid-Onset Oral Fentanyl Formulations vs. Oral Morphine for Cancer-Related Breakthrough Pain: A Meta-Analysis of Comparative Trials

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## Abstract

**Context.** Breakthrough cancer pain (BTcP) is widely recognized as a clinically significant complication of chronic cancer pain. With most BTcP episodes peaking in intensity within a few minutes and lasting for approximately 30 minutes, speed of onset is crucial for effective pain management. Although the last decade has seen the development of a number of rapid-onset fentanyl preparations, BTcP is still typically managed by supplemental or rescue doses of the patient's around-the-clock medication, such as oral morphine. Importantly, although the fentanyl preparations, such as fentanyl buccal tablet (FBT), sublingual fentanyl citrate orally disintegrating tablet (ODT), and oral transmucosal fentanyl citrate lozenge (OTFC), have all been proven to be efficacious in clinical studies, oral morphine has never been specifically tested in BTcP, other than as a comparator in studies of OTFC and fentanyl pectin nasal spray.

**Objectives.** To determine the relative contributions to pain relief from oral morphine and the fentanyl preparations using placebo as a common comparator.

**Methods.** Relevant studies were identified by review of the literature and used in a mixed-treatment meta-analysis to indirectly compare fentanyl preparations, morphine, and placebo for the treatment of BTcP.

**Results.** Analysis incorporating the five relevant studies identified revealed that although the fentanyl preparations provide superior pain relief vs. placebo in the first 30 minutes after dosing (FBT provided an 83% probability of superior pain relief, ODT 66%, and OTFC 73% vs. placebo), oral morphine performed little better than placebo (56% probability).

**Conclusion.** This mixed-treatment analysis suggests that FBT, ODT, and OTFC might provide more efficacious treatment options than oral morphine for BTcP. *J Pain Symptom Manage* 2013;46:573–580. © 2013 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

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**Key Words**

*Episodic pain, incident pain, breakthrough cancer pain, rescue medication, buccal, sublingual*

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**Introduction**

For many years, opioids have remained the mainstay of treatment for moderate-to-severe cancer pain.<sup>1,2</sup> Chronic pain is usually treated with a fixed schedule, around-the-clock (ATC) regimen, and by adhering to published guidelines, pain can be controlled in 80–90% of patients with cancer.<sup>3</sup> However, despite well-controlled chronic pain, cancer patients may experience breakthrough cancer pain (BTcP), which has been defined as “a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain.”<sup>4</sup> The reported prevalence of BTcP varies widely, from 19% to 95%, depending on the setting, survey methodology, and patients’ different perceptions and descriptions.<sup>5–7</sup> BTcP can occur during all stages of cancer, but it seems to be more frequently experienced by patients with advanced disease.<sup>8</sup>

Despite the significance of BTcP, data from surveys suggest that it is far from optimally treated,<sup>9–11</sup> with many patients not receiving appropriate additional analgesic medication to treat their BTcP. Unsurprisingly, poorly treated BTcP can reduce a patient’s quality of life,<sup>11–13</sup> and they also may have increased levels of anxiety and depression, increased perception of pain severity, and be dissatisfied with their overall pain management.<sup>8</sup> Inadequately relieved BTcP also represents a significant economic burden, with affected patients estimated to incur total medical costs five-fold higher than patients without BTcP.<sup>14,15</sup>

BTcP has traditionally been managed with oral opioids, also known as rescue medication, given in addition to regularly scheduled ATC analgesics.<sup>16</sup> Although not specifically licensed for the management of BTcP, oral, normal-release formulations of morphine are the most widely used, with other oral opioids, such as oxycodone and hydromorphone, sometimes prescribed.<sup>17</sup> The major limitation of this approach is that the onset of action of these drugs may not match the temporal

characteristics of many BTcP episodes.<sup>18,19</sup> A typical BTcP episode arises in a few minutes and lasts for approximately 30 minutes,<sup>18,20</sup> whereas observational studies have shown that the onset of action of normal-release oral opioids may be approximately 30 minutes, with a mean time to peak effect of approximately one hour.<sup>21</sup>

More recently, formulations of fentanyl, delivered via the oral transmucosal route, have been developed and licensed specifically for the management of BTcP. Commercially available oral transmucosal fentanyl products approved in the U.K. and Ireland for BTcP include fentanyl buccal tablet (FBT, Effentora<sup>®</sup>; Cephalon UK, Ltd./Teva UK, Ltd., Harlow, UK); sublingual fentanyl citrate orally disintegrating tablet (ODT, Abstral<sup>®</sup>; ProStrakan Group plc, Galashiels, UK); and oral transmucosal fentanyl citrate lozenge (OTFC, Actiq<sup>®</sup>; Flynn Pharma, Ltd., Dublin, Ireland). Clinical studies<sup>22–25</sup> have shown that fentanyl formulations have an onset of action of 15 minutes or less. Most of these studies were placebo controlled,<sup>22–25</sup> although OTFC has been compared with oral morphine.<sup>26</sup> We wanted to determine the relative contributions to pain relief from morphine and oral fentanyl preparations in comparison with placebo.

**Methods**

We searched for randomized trials that evaluated FBT, ODT, and OTFC with either placebo or oral morphine in the management of opioid-tolerant adult cancer patients with BTcP. The search was undertaken in PubMed from 1980 to October 2011 using the following search terms: “breakthrough cancer pain,” “incident pain,” “pain flare,” “morphine,” and “fentanyl,” limited by English language, and randomized, controlled human clinical trials. The search was supplemented by manual searching of bibliographies of short-listed articles. Cephalon UK, Ltd. provided copies of available clinical study reports for FBT and OTFC.

We used mixed-treatment meta-analysis to indirectly compare the fentanyl preparations, morphine, and placebo for BTcP. This methodological approach has been previously used to compare the fentanyl preparations against each other;<sup>27</sup> in this article, we report an analysis comparing these preparations and morphine with placebo. The overall likelihood (probability) of superior pain relief, as measured by differences in pain intensity difference (PID) scores, compared with placebo was calculated for the 15- to 60-minute interval post-dosing, and split from 15 to 30 minutes and 45 to 60 minutes. In support of these probability estimates, which are based on the sampling distribution of efficacy comparisons, outcomes also were expressed as a mean difference in PID between treatments with 95% credible levels (CRLs). A 95% CRL can be interpreted as the range of values that includes 95% of the probability distribution of the mean. For interpretation purposes, and although derived differently, the 95% CRL may be considered analogous to a 95% confidence interval used in traditional, frequentist analyses.

A fixed-effect model with normal prior and posterior distributions was used, with all analyses performed in WinBUGS (Bayesian inference Using Gibbs Sampling, The BUGS Project, Medical Research Council Biostatistics Unit, Cambridge, UK) 1.4.3 statistical software.<sup>27–29</sup>

## Results

### Included Studies

We identified five studies in total (Table 1). Four studies were placebo controlled: two vs. FBT,<sup>22,23</sup> and one each vs. ODT<sup>24</sup> and OTFC;<sup>25</sup> and one study compared OTFC and morphine sulfate immediate-release (MSIR) drugs.<sup>26</sup> We extracted data for the meta-analysis from all five studies relating to PID from baseline at different time points post-dosing (Table 2).<sup>27</sup> There was no evidence of gross heterogeneity across the study populations.

### Mixed-Treatment Meta-Analysis

**Likelihood of Superiority.** When the oral opioids were compared with placebo in the mixed-treatment comparison, there was a 61% probability that MSIR would produce a better outcome than placebo during the first 60

minutes after dosing (a 50% probability represents equivalent efficacy; 67%, a 2:1 likelihood of superior efficacy; 75%, a 3:1 likelihood; 99%, a 99:1 likelihood; and so on; Table 3). The corresponding results for the fentanyl preparations compared with placebo over 60 minutes were: FBT 97%, ODT 72%, and OTFC 81%. The likelihood of superiority of the fentanyl preparations over MSIR during the first 60 minutes after dosing were FBT 68%, ODT 57%, and OTFC 66%.

For the first 30 minutes after dosing, the likelihood of superiority over placebo was 56% for MSIR. Superiority estimates over placebo for the fentanyl preparations were 83% for FBT, 66% for ODT, and 73% for OTFC (Table 3). A similar pattern was observed for the 45–60 minutes post-dosing interval, with superiority over placebo marginally increased for all of the opioids ( $\leq 10\%$  increase in likelihood). When the fentanyl preparations were compared with MSIR over the first 30 minutes post-dosing, the likelihood of superiority estimates were 58% for FBT, 56% for ODT, and 62% for OTFC. The likelihood of superiority over MSIR was similar for the 45–60 minute interval post-dosing (ODT 2% drop and OTFC unchanged), apart from an 8% rise in probability for FBT (to 66%).

**Pain Intensity Differences.** The mean PIDs were consistently better for all of the opioids than placebo at all recorded time points (Table 3). However, the differences observed with the fentanyl preparations were consistently around double those observed with MSIR. Across the first 60 minutes after dosing, the mean PID (95% CRL) vs. placebo was 0.44 (–2.07, 2.95) for MSIR compared with 1.16 (0.09, 2.23) for FBT, 0.81 (–1.40, 3.04) for ODT, and 0.88 (–0.76, 2.55) for OTFC. Improvements in pain relief were apparent within 30 minutes of treatment, with the PID being larger for the fentanyl preparations than for MSIR during this period (vs. placebo: MSIR 0.31 [95% CRL –2.93, 3.57]; FBT 0.73 [–0.51, 1.97]; ODT 0.69 [–2.08, 3.44]; and OTFC 0.75 [–1.28, 2.78]).

The PID benefit of the fentanyl products over MSIR when compared with placebo was maintained when the fentanyl treatments were compared with MSIR (Table 3). When compared with MSIR over the first 60 minutes

Table 1  
**Randomized Controlled Trials of Strong Oral Opioids in the Management of BTcP Identified in the Literature Search**

Study	Oral Opioid	Study Design <sup>a</sup>	Patient Number	Time Points Analyzed (Min)	Primary Efficacy Outcome	Secondary Efficacy Outcomes (All in Favor of Fentanyl vs. Comparator)
Portenoy et al. <sup>22</sup>	FBT 100–800 µg vs. placebo	Multicenter, double-blind, randomized, placebo-controlled 2 phases: open-label titration followed by 3-wk double-blind	Titration: 123 Double-blind: 77	15, 30, and 60	SPID <sub>30</sub> (mean ± SE) 3.0 ± 0.12 for FBT vs. 1.8 ± 0.18 for placebo ( <i>P</i> < 0.0001)	PR and PID at each time point, TOTPAR, GMP assessment, proportion of episodes ≥33% or ≥50% improvement in PI scores at each time point, and use of rescue medication
Slatkin et al. <sup>23</sup>	FBT 100–800 µg vs. placebo	Multicenter, double-blind, randomized, placebo-controlled 2 phases: open-label titration followed by 3-wk double-blind	Titration: 129 Double-blind: 87	5, 10, 15, 30, 45, 60, and 120	SPID <sub>60</sub> (mean ± SE) 9.7 ± 0.63 for FBT vs. 4.9 ± 0.50 for placebo ( <i>P</i> < 0.0001)	PR and PID at each time point, TOTPAR, GMP assessment, proportion of episodes ≥33% or ≥50% improvement in PI scores at each time point, and use of rescue medication
Rauck et al. <sup>24</sup>	ODT 100–800 µg vs. placebo	Multicenter, double-blind, randomized, placebo-controlled 3 phases: open-label titration followed by 2-wk double-blind efficacy phase and an open-label long-term safety phase	Titration: 131 Double-blind: 66 Long-term: 72	10, 15, 30, and 60	SPID <sub>30</sub> (mean) 49.5 for ODT vs. 36.6 for placebo ( <i>P</i> = 0.0004)	SPID at 60 min, PID and PR at each time point, GMP assessment, responders (%), and use of rescue medication
Farrar et al. <sup>25</sup>	OTFC 200–1600 µg vs. placebo	Multicenter, double-blind, randomized, placebo-controlled 2 phases: open-label titration, then double-blind phase	Titration: 93 Double-blind: 92	15, 30, 45, and 60	PID ( <i>P</i> < 0.0001) and PR scores ( <i>P</i> < 0.0001) better for OTFC vs. placebo at all time points	GMP and use of rescue medication
Coluzzi et al. <sup>26</sup>	OTFC 200–1600 µg vs. MSIR 15–60 mg	Multicenter, double-blind, randomized, multiple crossover 2 phases: open-label dose-titration, then double-blind phase	Titration: 134 Double-blind: 93	15, 30, 45, and 60	15 min PID score better for OTFC vs. placebo ( <i>P</i> ≤ 0.008)	PI, PID, PR, GMP, and use of rescue medication

FBT = fentanyl buccal tablet; SPID = sum of pain intensity differences; SE = standard error; PR = pain relief—measured on a five-point numeric scale (0 = none; 4 = complete); PID = pain intensity difference; TOTPAR = total pain relief; GMP = global medication preference—measured on a five-point numeric scale (0 = poor; 4 = excellent); PI = pain intensity—measured on an 11-point numeric scale (0 = no pain; 10 = worst pain); ODT = sublingual fentanyl citrate orally disintegrating tablet; OTFC = oral transmucosal fentanyl citrate lozenge; MSIR = morphine sulfate immediate-release.

<sup>a</sup>In all five studies, opioid-tolerant patients experiencing 1–4 BTcP episodes per day first entered an open-label, dose-titration phase, wherein a single, “successful” dose of the oral fentanyl preparation was identified that provided effective and consistent pain relief of BTcP. This was followed by a double-blind treatment phase in which the patients were randomly assigned to prespecified treatment sequences of the successful dose and placebo/MSIR, sufficient to treat 10 episodes of BTcP.

Table 2  
Source Data for the Mixed-Treatment Comparison Meta-Analysis

Study	PID for Oral Fentanyl Preparation and Control (Placebo or Morphine)															
	15 min				30 min				45 min				60 min			
	Fentanyl		Control		Fentanyl		Control		Fentanyl		Control		Fentanyl		Control	
	PID	Pr.	PID	Pr.	PID	Pr.	PID	Pr.	PID	Pr.	PID	Pr.	PID	Pr.	PID	Pr.
FBT vs. placebo (Portenoy et al. <sup>22</sup> ) <sup>a</sup>	0.90	0.77	0.60	1.13	2.30	0.42	1.40	0.54	3.30	0.30	1.90	0.38	4.00	0.24	2.30	0.27
FBT vs. placebo (Slatkin et al. <sup>23</sup> ) <sup>a</sup>	1.50	0.65	0.80	1.06	2.40	0.40	1.30	0.65	3.00	0.32	1.50	0.65	3.40	0.29	1.60	0.57
Sublingual fentanyl ODT vs. placebo (Rauck et al. <sup>24</sup> ) <sup>b</sup>	2.04	0.51	1.52	0.34	2.93	0.57	2.11	0.22	3.18	0.30	2.31	0.18	3.44	0.30	2.52	0.18
OTFC vs. MSIR (Coluzzi et al. <sup>26</sup> ) <sup>a</sup>	1.86	0.36	1.46	0.51	2.88	0.36	2.40	0.51	3.55	0.35	3.03	0.46	4.03	0.31	3.57	0.40
OTFC vs. placebo (Farrar et al. <sup>25</sup> ) <sup>a</sup>	1.62	0.81	1.02	0.81	2.41	0.52	1.51	0.59	2.88	0.45	1.91	0.40	3.19	0.40	2.13	0.32

PID = pain intensity difference, calculated as the difference between pretreatment (baseline) and post-treatment pain intensity scores for individual episodes of BTcP; Pr = precision = 1/variance, variances were calculated from published standard errors and 95% confidence intervals; FBT = fentanyl buccal tablet; ODT = sublingual fentanyl citrate orally disintegrating tablet; OTFC = oral transmucosal fentanyl citrate lozenge.

<sup>a</sup>Data from clinical study report.<sup>30–33</sup>

<sup>b</sup>Data estimated from figure in article<sup>24</sup> (15, 30, 60 min) or extrapolated as midpoint value (45 min).

Table data adapted from Jandhyala and Fullarton.<sup>27</sup>

post-dosing, FBT produced a 0.75 (−1.92, 3.41) improvement in PID, ODT a 0.35 (−3.00, 3.63) improvement and OTFC a 0.48 (−1.34, 2.34) improvement. Summing the PID calculated for MSIR against placebo with the PID calculated for a particular fentanyl preparation against MSIR gave a similar value to the PID derived independently for that fentanyl preparation vs. placebo (Table 3).

## Discussion

This study aimed to compare the efficacy of oral morphine and three oral transmucosal

fentanyl preparations against placebo to provide further insight into their relative merits as treatments for BTcP. As would be expected, all of the opioids provided superior pain relief compared with placebo throughout the first hour after dosing. The mixed treatment analysis also suggested, however, that the oral fentanyl preparations might provide a greater level of pain relief than oral morphine.

When examined across the first hour after dosing, the fentanyl preparations were all superior to placebo: FBT 97% likelihood of superiority, ODT 72%, and OTFC 81%. In comparison, there was a 61% likelihood of oral morphine being superior to placebo

Table 3  
Mean Differences in PID Scores and Resultant Probabilities for an Improved PID vs. Comparator

Comparison	Minutes After Dosing					
	15–30 min		45–60 min		15–60 min	
	Mean PID (95% CRL)	Probability (%)	Mean PID (95% CRL)	Probability (%)	Mean PID (95% CRL)	Probability (%)
MSIR vs. placebo	0.31 (−2.93, 3.57)	56	0.56 (−3.22, 4.38)	60	0.44 (−2.07, 2.95)	61
FBT vs. MSIR	0.45 (−2.97, 3.91)	58	1.06 (−3.11, 5.25)	66	0.75 (−1.92, 3.41)	68
Sum of PID <sup>a</sup>	0.76		1.62		1.19	
FBT vs. placebo	0.73 (−0.51, 1.97)	83	1.59 (−0.14, 3.31)	93	1.16 (0.09, 2.23)	97
ODT vs. MSIR	0.39 (−3.94, 4.61)	56	0.32 (−4.71, 5.40)	54	0.35 (−3.00, 3.63)	57
Sum of PID <sup>a</sup>	0.70		0.88		0.79	
ODT vs. placebo	0.69 (−2.08, 3.44)	66	0.92 (−2.58, 4.39)	67	0.81 (−1.40, 3.04)	72
OTFC vs. MSIR	0.47 (−2.04, 3.01)	62	0.49 (−2.14, 3.20)	62	0.48 (−1.34, 2.34)	66
Sum of PID <sup>a</sup>	0.78		1.05		0.92	
OTFC vs. placebo	0.75 (−1.28, 2.78)	73	1.02 (−1.64, 3.64)	74	0.88 (−0.76, 2.55)	81

PID = pain intensity difference; CRL = credible level; MSIR = morphine sulfate immediate-release; FBT = fentanyl buccal tablet; ODT = sublingual fentanyl citrate orally disintegrating tablet; OTFC = oral transmucosal fentanyl citrate lozenge.

<sup>a</sup>Sum of PIDs for MSIR vs. placebo plus fentanyl preparation vs. MSIR.

over one hour post-dosing. When looked at in terms of PID scores, the fentanyl preparations provided around double the pain relief of oral morphine when compared with placebo (mean PID difference at one hour: FBT 1.16, ODT 0.81, OTFC 0.88 vs. 0.44 for MSIR). Although the fentanyl preparations appeared superior to oral morphine across the whole hour (approximately 2:1 ratio in favor of fentanyl), the opioids were comparatively more superior within the first 30 minutes post-dosing, albeit with a slight advantage for the fentanyl preparations (mean likelihood of superiority at 30 minutes vs. MSIR: FBT 58%, ODT 56%, OTFC 62%). This is of potential importance because most BTcP episodes occur within 30 minutes. It also should be noted that there was considerable overlap in the CRLs for the resultant PID scores for each treatment. However, despite this overlap in CRLs, review of the PID scores generated in the analysis revealed that summing the PID for MSIR vs. placebo with the PID for a fentanyl preparation gave a remarkably consistent result to that from the independent placebo analysis. This lends further credibility to the results when compared with that of MSIR. Our results are consistent with a previous mixed-treatment comparison of intranasal fentanyl and other opioids for BTcP, which showed a greater pain reduction for the fentanyl preparation over oral morphine.<sup>34</sup>

The small number of studies available, particularly with regard to comparison of the fentanyl preparations with oral morphine/MSIR, is a limitation of this mixed-treatment comparison. Obtaining the raw numbers for the PID scores in the Rauck et al.<sup>24</sup> study (ODT vs. placebo) also would have been useful to improve the precision of the outputs, although they would not be expected to change the results materially. Although indirect comparisons can potentially be biased by differences in study design and sample populations, including variability in inclusion and exclusion criteria and definitions of effective dose, the randomized, controlled trials used in this analysis were performed according to methodologically comparable protocols. Visual inspection of the data also indicated that there was no significant heterogeneity between the placebo-controlled studies that would preclude their combination in a mixed-treatment comparison. However,

the possibility of systematic differences between data sources that were not detected by heterogeneity analysis cannot be ruled out. Although a well-documented and recognized technique for meta-analysis, it also should be recognized that Bayesian sampling was carried out by a computerized process that could infuse some (albeit small) level of machine bias, despite the use of 10,000 sample points in every analysis.

The results of the mixed-treatment comparison provide additional information on the comparative efficacy of the oral fentanyl preparations and oral morphine in the treatment of BTcP. Another key consideration when deciding on the most effective treatment for a patient is the balance between efficacy and tolerability. It could potentially be argued that the prolonged duration of action of oral morphine in comparison with the fentanyl preparations might result in an extended opportunity for adverse events.<sup>4,19</sup> At present, however, most available data come from placebo-controlled studies, as described herein, and focus on the efficacy of the preparations, and not on tolerability, with all products reported to cause "typical" opioid adverse events, such as nausea, vomiting, dizziness, constipation, and somnolence.<sup>22-26</sup> The only comparative data are from the Coluzzi et al.<sup>26</sup> study, which, because of the study design, had patients receiving concomitant ATC medication as well as OTFC and MSIR during the double-blind phase, making it difficult to attribute any adverse events to a specific product. Indirect evidence from patient preference surveys, which take into account the mode of administration and efficacy as well as tolerability, indicate that the fentanyl preparations might have some advantages over oral morphine beyond efficacy. For example, in a longer-term follow-up study of two double-blind studies,<sup>22,23</sup> 88% of the patients were reported to prefer FBT over their previous BTcP medication.<sup>35</sup> Further work, however, is needed to formally assess the comparative tolerability of the various preparations, to help put the results of this efficacy analysis into the wider clinical context.

This study suggests that although oral morphine remains an adequate treatment option for BTcP, there might be clinical advantages to using one of the oral transmucosal fentanyl preparations in some patients.

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