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An Economic Evaluation of Short-Acting Opioids for Treatment of Breakthrough Pain in Patients with Cancer

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ABSTRACT

Objective: Breakthrough cancer pain (BTCP) represents a considerable economic burden. A decision-analysis model was developed to evaluate the cost-effectiveness of intranasal fentanyl spray (INFS) compared with oral transmucosal fentanyl citrate (OTFC) and fentanyl buccal tablet (FBT) for the treatment of BTCP.

Methods: The model was parameterized for Sweden to estimate the costs and benefits associated with treatments. Expected reductions in pain intensity (PI; measured on a numeric rating scale ranging from 0 to 10) per BTCP episodes were translated into resource use and quality-adjusted life years (QALYs). Relative analgesic efficacy of interventions was derived from a mixed treatment comparison of six randomized controlled trials. The relationship between PI and utility was obtained from a time-trade off study in the general population. Resource use and unit cost data were obtained from the literature and validated by Swedish clinical experts. The base case scenario assumed three BTCP episodes/day, a background PI of 2, and a time horizon of 180 days. Prices of INFS and OTFC were assumed to be equal with FBT ~14% less. Uncertainty in the source data was incorporated by probabilistic sensitivity analyses and different scenario analyses.

Results: With INFS, 55% of BTCP (95% uncertainty interval [UI]: 46–68%) was avoided, which is greater than expected with OTFC (29%; UI 22–38%) or FBT (31%; UI 25–39%). INFS was dominating OTFC (resulting in 0.046 QALY gain and saving 174 Euros with a time horizon of 180 days) and cost-effective versus FBT (incremental cost-effectiveness ratio 12203 Euros/QALY). Despite uncertainty in the source data, there is a >99% probability that INFS is the most cost-effective intervention.

Conclusion: Given inherent limitations of modelling studies, the greater efficacy of INFS translates to cost and QALY advantages over competing interventions in the treatment for BTCP in Sweden.

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Introduction

Breakthrough cancer pain (BTCP) is defined as a transitory exacerbation of pain experienced by a patient who has relatively stable and adequately controlled background pain [1]. The clinical features of BTCP can vary considerably, both between and within individuals. However, it is generally characterized by its fast onset, short duration, and unpredictable but frequent occurrence. In a recent survey, the number of BTCP episodes ranged from one to eight per day, and the average duration was 35 minutes (range, 15–60 minutes) [2]. In another study, the majority of episodes lasted for less than 1 hour [3]. BTCP has been reported to occur in 24% to 95% of patients with cancer, with the wide variation in prevalence attributable to the use of different definitions for BTCP and differences in clinical settings [4,5].

BTCP is associated with considerable morbidity, and has negative physical, psychological, and social consequences. Patients with BTCP have more severe chronic pain, impaired physical function, increased levels of anxiety and depression, and more dissatisfaction with opioid treatment [6–8]. As a result, BTCP results in a significantly impaired quality of life [9]. The occurrence of BTCP also represents a considerable economic burden, although this has not been well studied [10]. In a US survey of 1000 patients with cancer, those with BTCP incurred higher direct medical costs due to increased occurrence of pain-related hospitalizations, emergency room (ER) visits, and physician office visits compared with patients without BTCP [11]. In another US-based survey of 373 cancer outpatients, BTCP was shown to predict higher indirect costs (e.g., transport costs, extra household assistance) as well as direct medical costs [12].

Oral opioids are the usual treatment for BTCP. Although not indicated for BTCP, normal-release morphine sulphate is the most widely used, with other short-acting opioids (e.g., oxycodone, hydromorphone) also sometimes prescribed. However, the clinical characteristics of these treatments do not match the typical BTCP episode. Oral ingestion of opioids is associated with a delay in both onset of action and peak analgesic effect, resulting in inadequate pain control during the first 30 minutes of a BTCP episode [13]. In addition, their duration of effect may be longer than required, resulting in an increased risk of opioid-related adverse effects.

These limitations have encouraged the search for new treatment options that better reflect the temporal characteristics of BTCP, having a fast onset of action and a short duration of effect. Unlike morphine, the opioid fentanyl is highly lipophilic and is rapidly absorbed across the mucosal surface, resulting in a faster onset of action. The first fentanyl formulation specifically developed to treat BTCP was oral transmucosal fentanyl citrate (OTFC; Actiq, Cephalon, Frazer, PA), a solid drug matrix on a handle. More recently an intranasal fentanyl spray (INFS; Instanyl, Nycomed, Zurich, Switzerland), an oral transmucosal fentanyl buccal tablet (FBT; Effentora, Cephalon), and a sublingual fentanyl tablet (Abstral®, Orexo AB, Uppsala, Sweden) have become available. All fentanyl products are indicated for the treatment of BTCP in adult patients who receive maintenance opioid therapy for their chronic cancer pain. In placebo-controlled trials, OTFC, FBT, and INFS were all found to be effective analgesics with rapid pain relief for the treatment of BTCP [14–17]. OTFC was shown to provide greater reduction in pain intensity and increased pain relief compared with morphine [18]; however, in a recent randomized controlled trial (RCT), more patients attained faster pain relief with INFS compared with OTFC [19].

Decision making in health care requires robust information on the comparative cost-effectiveness of new and existing treatments. Mixed treatment comparisons (MTCs) provide a means to evaluate competing health-care interventions in the absence of direct head-to-head trials, and are becoming increasingly valuable in economic evaluation [20–22]. We conducted a Bayesian MTC of INFS, OTFC, FBT, and normal-release morphine. Six RCTs were eligible for inclusion in this meta-analysis: INFS versus placebo [17], INFS versus OTFC [19], FBT versus placebo (n=2) [15,16], OTFC versus placebo [14], and OTFC versus morphine sulphate immediate release (MSIR) [18]. In this MTC, INFS provided greater reduction in pain for all time points before 60 minutes versus OTFC and all time points before 45 minutes versus FBT [23].

The results of this MTC were used as the basis of the economic evaluation, which compares the cost-effectiveness of INFS, OTFC, and FBT for the treatment of BTCP in a Swedish-based model using a payer perspective.

Methods

A decision-analysis model was developed to estimate the cost-effectiveness of INFS, OTFC, and FBT for the treatment of BTCP. Sublingual fentanyl tablet was excluded because there were insufficient clinical trial data. Normal-release morphine was also excluded because it is not indicated for BTCP. For INFS, OTFC and FBT, the expected reductions in pain intensity (PI) of BTCP episodes were translated into cost savings and gains in quality-adjusted life years (QALYs).

Model concept

The basic concept of the model for measuring BTCP that was avoided with treatment is shown in Figure 1. This includes a defined level of background pain and number of BTCP episodes per day.

Without treatment, the PI of BTCP decreases over the course of the episode. With treatment, the PI of the BTCP episode decreases more rapidly, with the total area under the curve (AUC) during the episode (representing the total BTCP experienced) being reduced. The area between the PI curves for treatment and placebo reflects the amount of BTCP avoided by the intervention. Assuming a certain number of episodes per day, the percentage BTCP avoided with treatment can be calculated for a defined time horizon.

Model inputs and assumptions

The patient population for the decision model was assumed to be similar to those reported in the six RCTs in the MTC. These are patients whose background pain before the start of a BTCP epi-

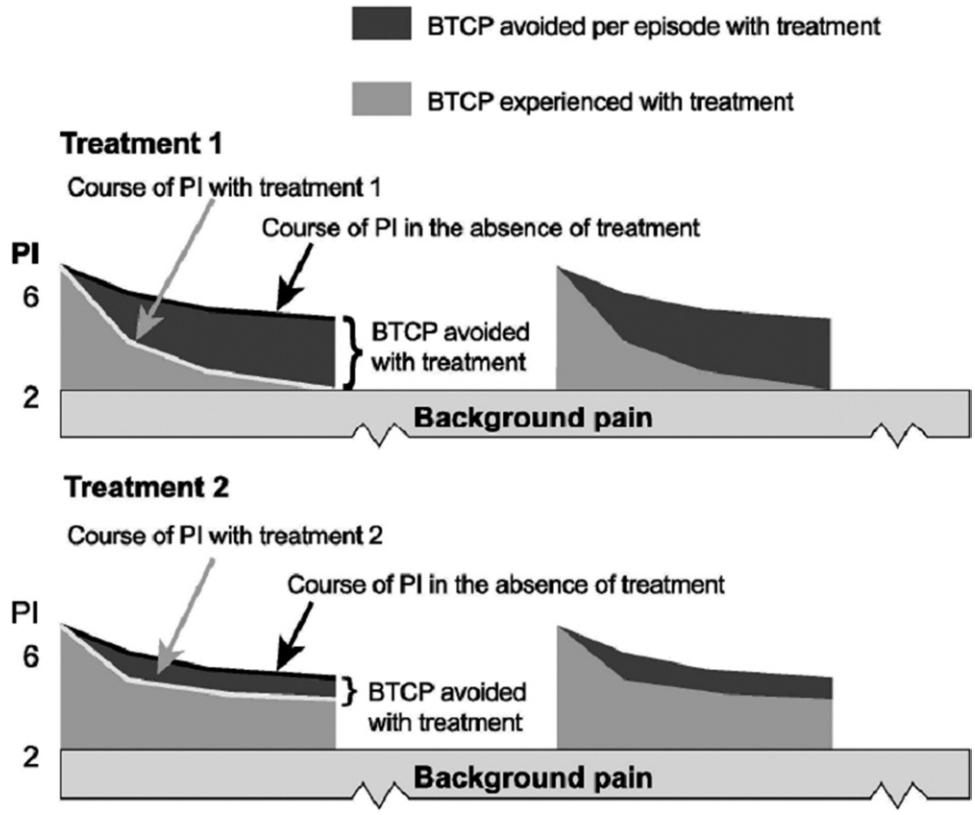

Fig. 1 – Model concept. Pain intensity (PI) courses for two treatments during a breakthrough cancer pain (BTCP) episode are shown, where treatment 1 is more efficacious than treatment 2. For both treatments the light grey area represents the total BTCP experienced upon treatment during the episode. The dark grey area between the PI course in the absence of treatment and the PI course with treatment reflects the amount of BTCP avoided by the treatment. The amount of BTCP avoided by treatment 1 is greater than that of treatment 2.

sode was adequately controlled by opioid treatment and reported to be of no more than moderate severity (≤4 on a 0 [no pain] to 10 [worst pain imaginable] numerical rating scale [NRS], a well established scale to measure pain [24–26]). For the model base case, background PI was set at 2. In trials, the number of BTCP episodes ranged from one to four per day, so a value of 3 was used for the base case. It was also assumed that all BTCP episodes were 1 hour in duration. The majority of patients with BTCP have advanced-stage cancer and a 1-year time horizon was assumed to be adequate, with a life expectancy of 180 days being used for the base case scenario. Effects and costs were not discounted because the time horizon did not exceed 1 year.

Efficacy data was obtained from six RCTs, identified by a systematic literature review, and analyzed with an MTC meta-analysis [23]. Details on the six different RCTs — study design, number of randomized patients, main results regarding pain intensity difference, and limitations — can be found in Table A1 in the Appendix at: doi:10.1016/j.jval.2010.09.007. All studies were randomized, double-blind crossover trials, except the trial by Mercadante et al. [19], which was a randomized, open-label crossover trial.

The MTC provided estimates of the reduction of PI during BTCP episodes in the absence of treatment [23], based on the four studies with a placebo arm [14–17] (Fig. 2). Studies recorded PI on a 0 to 10 NRS, and a pooled estimate was calculated with a fixed effect model. The PI difference (PID) for INFS, OTFC and FBT relative to placebo was then estimated for different time points after the start of the BTCP episode (Fig. 2). In Kress et al. [17], the PID for INFS was reported for 10, 20, and 40 minutes, whereas PID was reported for every 15 minutes in OTFC and FBT trials. To accommodate this difference in time

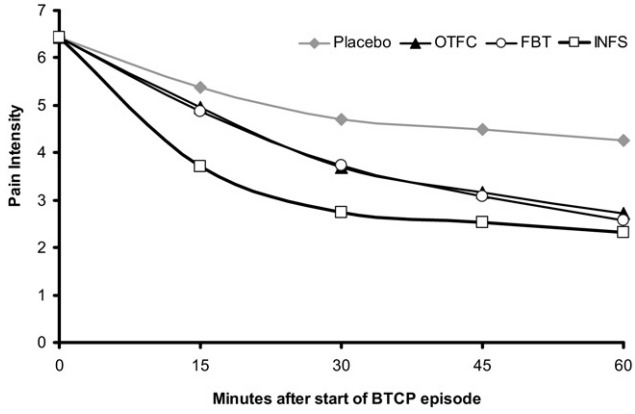

Fig. 2 – Pain intensity levels during a breakthrough cancer pain (BTCP) episode with placebo, oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT), and intranasal fentanyl spray (INFS).

points, INFS averages at 10 and 20 minutes and at 20 and 40 minutes were used to estimate the 15- and 30-minute time points, respectively. In Mercadante et al. [19], the PID for INFS was reported for 5-, 10-, 15-, 20-, 30-, and 60-minute time points. The INFS average at 30 and 60 minutes was used to estimate the 45-minute time point.

In the clinical trials [14–19], the PI during the BTCP episode did not always return to the background PI level within 60 minutes (see Fig. 2). In the absence of data beyond 60 minutes, PI curves were cut-off at this time point and background PI level was assumed.

Utilities and QALYs

Utilities were incorporated into the model in order to estimate QALYs for a specific PI course as well as the QALY gain by treatment. In the absence of published utility values for BTCP, a direct utility elicitation study was performed using a time trade off (TTO) approach [27]. Utility values were generated for a hypothetical patient with advanced stage cancer, with an initial PI of 6 at the start of a BTCP episode, background PI of 2, and three BTCP episodes per day, corresponding to the patient population in the model base case. Eight profiles were generated, each represented a possible course of PI over a 1-hour BTCP episode. The profiles ranged from a PI trajectory that changed little over the duration of an episode (profile 1, defined as PI>4 at 30 minutes and PI>4 at 1 hour), to a PI trajectory that reduced quickly (profile 8, defined as PI 3-3.9 at 5 min and PI 2-2.9 at 1 hour). Variants of baseline characteristics for one profile (profile 2, defined as PI>4 at 30 minutes and PI 3-3.9 at 1 hour) were tested to evaluate the sensitivity of the utility estimates to differences in background PI, BTCP episode frequency, and PI at episode start.

The TTO exercise was conducted in a sample of 99 members of the United Kingdom general public. To derive utility estimates, subjects were asked whether they would rather spend 10 years in each PI profile followed by death, or less than 10 years in full health and then death, with the time in full health varied until a point of indifference was reached. To avoid question order effects, the order in which the PI profiles were presented was varied. The utility of each PI profile was then derived on an interval scale from 0 to 1 using the following equation:

Ui = time in full health/time in PI profile i; with i = PI profile.

The mean utilities for all the PI profiles were logically ordered, ranging from 0.348 for the PI profile with the slowest PI resolution (profile 1), to 0.679 for the profile with fastest resolution (profile 8). The utility estimates for the PI profile 2 variants did not significantly alter the mean utility for that profile. Because the eight PI profiles could not represent all possible courses of PI, a mathematical function (linear ordinary least squares regression: utility = −0.1237*AUC + 0.9536; $R^2 = 0.93$) was used to derive a relationship between utility and each possible AUC in the model.

Resource use and costs

Drug acquisition costs and costs for other health-care resource use (general practitioner [GP] visits, home care, and hospital stay) were included in the model. Drug acquisition costs were based on 2008 Swedish pharmacy selling prices [28]. OTFC is priced on a per treatment basis (€9.3 [Euros], Swedish krona [SEK] 103.57 per BTCP dose). INFS was not available in 2008, but has been launched since then at price parity with OTFC. Thus, the same cost for INFS and OTFC per BTCP episode was used in the model. FBT is not currently available in Sweden so the cost was estimated based on the United Kingdom, where it is priced approximately 14% less than OTFC (€8.1, SEK 89.47).

A review of the literature found only a single study on the impact of BTCP on health-care resource consumption. This was a US telephone survey in which resource use (GP visits, emergency room [ER] visits, and hospital admissions) were compared for patients with and without BTCP [11]. Annual probabilities of resource consumption as well as the frequency of use were reported, as was the average length of stay (LOS) per hospitalization. These data were validated by clinical experts as applicable to the Swedish situation, although ER visits were substituted with specialized home care (resource use and costs assumed to be similar). Unit costs for Sweden were determined as €76 (SEK 845) per GP visit, €196 (SEK 2182) per home care visit, and €370 (SEK 4110) per hospital inpatient day (Södra Samverkansnämnden price list, 2007). Unit costs display cross-regional variation in Sweden, and a conservative approach was taken in the current model by using the lowest reported costs (Malmö University Hospital, ward day). Using these unit costs, the total costs of resource consumption were calculated. It was assumed that the resource consumption of patients with BTCP receiving placebo (i.e., no active treatment) was equivalent to that of patients with BTCP from the US survey. It was also assumed that the reduction in resource use had a linear relationship with the percentage of BTCP avoided.

Direct non-medical costs (e.g., travel to hospital) are not part of the payer perspective and therefore not modeled. Indirect non-medical costs were not included either because it was assumed patients with BTCP would not have additional productivity loss or other non-medical opportunity costs, given that they were unlikely to be in employment because of the advanced stage of their underlying disease. It was also assumed that any indirect medical costs were more likely to be attributable to cancer rather than BTCP.

An expert meeting with four independent Swedish physician-specialists in geriatrics, palliative care, and anesthesiology (two clinical experts) was held to validate the concepts and assumptions underlying the model and the data regarding resource use.

Model outcomes

Outcome parameters were percentage of BTCP avoided, drug costs, costs for resource use (GP visits, specialized home care, and hospital stay), and QALYs gained. For the current model, the primary estimate for cost-effectiveness was the incremental cost per QALY gained.

Table 1 – Model parameters and distributions applied for the probabilistic sensitivity analysis.

Parameter	Mean	Uncertainty range	Reference	Distribution type
BTCP episodes per day	3	2.25–3.75	[23]	Normal
Background pain level	2	1.5–2.5	[23]	Normal
Efficacy			[23]	Normal
INFS				
15 mins	1.66	1.38–1.95		
30 mins	1.95	1.63–2.27		
45 mins	1.95	1.50–2.39		
60 mins	1.94	1.47–2.41		
OTFC				
15 mins	0.42	0.04–0.79		
30 mins	1.01	0.57–1.45		
45 mins	1.32	0.82–1.82		
60 mins	1.52	0.95–2.10		
FBT				
15 mins	0.51	0.29–0.73		
30 mins	0.96	0.62–1.30		
45 mins	1.41	1.07–1.75		
60 mins	1.67	1.30–2.04		
Utility uncertainty				
Slope	−0.12	−0.14–−0.10	Calculation	Normal
Intercept	0.95	0.88–1.03	*	
Resource use (no BTCP)				
Probability of GP visit	0.37	0.27–0.47	[11]	Beta
Probability of home care	0.22	0.14–0.31	[11]	Beta
Probability of hospitalisation	0.22	0.14–0.31	[11]	Beta
Length of hospital stay (days)	4.10	3.28–4.92	Assumption	Normal
Resource use (BTCP)				
Probability of GP visit	0.56	0.49–0.64	[11]	Beta
Probability of home care	0.33	0.26–0.40	[11]	Beta
Probability of hospitalisation	0.37	0.29–0.44	[11]	Beta
Length of hospital stay (days)	7.10	5.68–8.52	Assumption	Normal

BTCP, breakthrough cancer pain; FBT, fentanyl buccal tablet; GP, general practitioner; INFS, intranasal fentanyl spray; OTFC, oral transmucosal fentanyl citrate.

* Least squares mean used: correlation between both utility uncertainty parameters has been taken into account.

Alternative scenarios

In addition to the base case scenario (background PI = 2, three BTCP episodes/day, time horizon 180 days, price of OTFC and INFS assumed to be equal), alternative scenarios were also considered. These were the same as above but with either (a) background PI = 3, or (b) including drug costs only.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) allows for multiple uncertainty across the input parameters to be assessed (unlike one-way sensitivity analysis which only assesses the impact of uncertainty for each input separately). In this model, sources of parameter uncertainty were identified and characterized as probability distributions. Parameters and distributions of the variables included in the PSA are summarized in Table 1. A distribution of the (incremental) costs and benefits (QALYs) was determined by sampling a value from each input parameter distribution, calculating the results with the model and repeating this process 1000 times. Results are presented with a point estimate and 95% uncertainty intervals (95% UIs). Uncertainty intervals reflect confidence intervals of model parameters and also uncertainty for parameters based on expert opinion.

Results

INFS, OTFC, and FBT were all superior to placebo, with the percentage of total BTCP avoided reported as 55% with INFS (95% UI 46%–68%), 29% with OTFC (95% UI 22%–38%), and 31% with FBT (25%–39%) (Table 2).

Total costs for all treatments are reported in Table 2. For all treatments, approximately 90% of overall costs were attributable to drug acquisition. For the placebo arm, the majority of the costs associated with resource use were related to hospital stay (81% of total costs).

In the base case analysis, INFS dominates OTFC (Table 3). INFS is expected to avoid an additional 25% of BTCP compared with OTFC, corresponding to a cost savings of €174 (SEK 1932) and a 0.046 QALY gain. Despite the uncertainty in the source data, the PSA shows there is a more than 99% probability that INFS is cost-effective relative to OTFC. For a willingness-to-pay (WTP) of €45,000 (SEK 500,000), a generally accepted maximum benchmark value for a QALY gained in Sweden [29], there is a >99% probability that INFS is the most cost-effective intervention.

Table 2 – Model outcomes and cost estimates by treatment for the base case scenario.

	Value (95% uncertainty intervals)			
	Placebo	INFS	OTFC	FBT
Model outcomes				
% BTCP avoided versus placebo	—	55% (46%, 68%)	29% (22%, 38%)	31% (25%, 39%)
QALYs	0.167 (0.148, 0.183)	0.266 (0.251, 0.281)	0.220 (0.203, 0.235)	0.223 (0.209, 0.237)
Cost estimates				
Drug acquisition costs	0	€5034	€5034	€4348
GP costs	€93 (78, 109)	€49 (36, 59)	€69 (57, 82)	€68 (56, 81)
Home care costs	€68 (53, 85)	€44 (34, 54)	€55 (44, 68)	€55 (43, 67)
Hospital stay costs	€715 (516, 950)	€407 (289, 532)	€550 (396, 716)	€540 (398, 704)
Total resource use costs	€877 (680, 1112)	€500 (375, 629)	€674 (514, 845)	€662 (508, 828)
Total costs	€877 (690, 1112)	€5534 (5408, 5663)	€5708 (5548, 5878)	€5011 (4832, 5176)

BTCP, breakthrough cancer pain; FBT, fentanyl buccal tablet; GP, general practitioner, INFS, intranasal fentanyl spray; OTFC, oral transmucosal fentanyl citrate; QALYs, quality-adjusted life years.
All costs over 180 days. 1 SEK = €0.09.

Assuming INFS has price parity with OTFC and FBT is priced 14% less, INFS is expected to have higher costs but greater efficacy than FBT. An additional 24% of BTCP is avoided, resulting in a QALY gain of 0.043 (Table 3). The cost per QALY for INFS versus FBT is estimated at €12,203 (SEK 135,585). At a WTP of €45,000 (SEK 500,000), there is a >99% probability that INFS is cost-effective compared with FBT.

INFS dominates when compared with OTFC and is more cost-effective than FBT in a scenario that assumes a higher background PI (3 rather than 2) (Table 3). When only drug costs are compared, INFS still dominates OTFC and is more cost-effective than FBT because of the additional QALYs gained.

Discussion

The objective of this study was to evaluate the cost-effectiveness of INFS with OTFC and also FBT for the treatment of BTCP in Sweden. On the basis of this model, and assuming price parity, INFS was dominating OTFC, provided cost savings and an increase in QALYs, and was more cost-effective than FBT.

Efficacy data in this model were derived from an MTC meta-analysis of six RCTs in which INFS provided greater reduction in pain 15 minutes after administration than either OTFC or FBT. This greater efficacy of INFS was maintained for all time points before 60 minutes versus OTFC and all time points before 45 minutes versus FBT [23]. The effect of normal-release morphine was similar to placebo for all time points before 45 minutes after administration.

Although widely used, normal-release morphine is not indicated for the treatment of BTCP and its slow onset of action and extended duration of effect make it an unsuitable choice for the majority of BTCP episodes [13]. Thus, despite the availability of low-cost generics, normal-release morphine is not an ideal option for the effective treatment of BTCP.

When there is insufficient direct evidence from comparative RCTs, a formal indirect comparison provides another method for obtaining data on the relative efficacy of competing interventions. MTC is a method of indirect comparison that combines both direct and indirect evidence and is particularly useful in the context of cost-effectiveness analysis and medical decision making [20–22]. However, the validity of the approach depends on the internal validity and similarity of

Table 3 – Cost-effectiveness of INFS compared with OTFC and FBT.

	Incremental costs, (% UI)	Incremental % BTCP avoided (95% UI)	Incremental utility (QALY) (95% UI)	Costs per BTCP avoided	Cost per QALY gained
Base case scenario vs OTFC	€174 (−276, −98)	25% (17%, 36%)	0.046 (0.029, 0.064)	Dominant	Dominant
Alternative scenario 1: Background PI = 3	€262 (−486, 134)	38% (23%, 66%)	0.046 (0.029, 0.066)	Dominant	Dominant
Alternative scenario 2: Drug costs only	0 (0, 0)	25% (16%, 37%)	0.046 (0.029, 0.065)	NA	NA
Base case scenario vs FBT	€523 (432, 593)	24% (16%, 33%)	0.043 (0.029, 0.059)	€2216	€12203
Alternative scenario 1: Background PI = 3	€441 (237, 554)	36% (22%, 61%)	0.043 (0.029, 0.059)	€1242	€10293
Alternative scenario 2: Drug costs only	€685 (685, 685)	24% (16%, 33%)	0.043 (0.030, 0.059)	€2902	€15979

BTCP, breakthrough cancer pain; FBT, fentanyl buccal tablet; INFS, intranasal fentanyl spray; NA, not applicable; OTFC, oral transmucosal fentanyl citrate; PI, pain intensity; QALYs, quality-adjusted life years; UI, uncertainty interval.
INFS performs better than OTFC (incremental QALY 0.046) but incremental costs are the same since drug costs are similar and resource use costs are not taken into consideration. Because incremental costs are the same, an ICER cannot be calculated. INFS is still the preferred treatment.
1 SEK = €0.09. Dominant means cost-saving and more effective.

the included trials [30]. Although the six trials included in this MTC appear sufficiently similar in patient characteristics and study designs for clinically meaningful conclusions to be drawn, unknown factors may have biased indirect comparisons. Because of the limited number of studies included in the model, any heterogeneity of treatment effects that may be indicative of bias cannot be fully assessed. However, the results of the MTC are consistent with those of the randomized head-to-head comparative trial of INFS and OTFC [19], on which it is in part based, indicating the clinical validity of its findings. In this case, the use of an MTC incorporates and extends beyond the findings of the direct comparative trial of INFS and OTFC by including additional data on the interventions from other studies, as well as comparison with placebo.

The utility estimates in the model were based on establishing a relationship between PI level and a utility score. In order not to overload the participants in the TTO exercise, it was decided that utilities for a maximum of eight PI profiles (and three variants of profile 2 to evaluate differences in background PI, episode frequency, and PI at episode start) would be generated, resulting in a range of utilities from 0.348 to 0.679. However, this does not represent all possible PI profiles that could exist for a BTCP episode. A regression model was used to estimate the cumulative utility and QALY associated with area under the curve for the BTCP experienced with each treatment option in the model.

The TTO method used to generate utilities is a well established method [27]. There is a difference between the utility assessment (10 years) and the time horizon in the model (1 year).

Ten years is an appropriate timescale for a trading exercise in cancer patients completed by members of the general public, i.e., to enable meaningful trade-offs between time spent in the health state in question and longer time in perfect health in order to derive a utility that can then be applied to the episodes of breakthrough pain over the course of a year. Although the study was performed in a UK population, the subjects represented a cross section of the public from a European country whose values and preferences can be assumed to be similar to those in Sweden. There are no other available utilities for BTCP, but utilities for conditions where pain is a large component are in a similar range. For example, UK population utilities for fibromyalgia have been estimated to be in the range of 0.45 to 0.82 [31], and values associated with pain have been reported for patients with severe rheumatoid arthritis with ~0.65 for a PI of 2, and ~0.45 for a PI of 6 [32].

A possible limitation with this model is the lack of published data on the resource use of BTCP. For the current model, we used data from the US study by Fortner et al [11], which compared the level of resource use of cancer patients with and without BTCP. It is important to note that this was a retrospective observational study for which data were collected through telephone interviews. Such an observational study can be biased for a number of reasons, including selection bias (participation in the survey might have been associated with the level of resource use), information bias (only three types of resource use were identified), and recall bias (recollection might be related to BTCP). In addition, it was assumed that patients with BTCP in the survey by Fortner et al. [11] were equivalent to the non-treated patients in the current model with regard to resource use, and that resource use displayed a linear relation to the percentage of BTCP avoided. Despite this potential bias, both the resource use data and the assumptions made were validated by independent clinical experts for the Swedish setting. Furthermore, the actual impact of resource use in the model is limited, because 90% of the total costs are related to drug acquisition costs. In the scenario in which resource use costs were excluded and only drug costs were considered, INFS remained the more cost-effective treatment option compared with OTFC or FBT.

In addition to INFS, several other new fentanyl formulations for the treatment of BTCP have recently been launched or are at late stages of development. Oral transmucosal FBT (Effentora) is available in some European countries, but is not yet available in Sweden.

FBT was included in the model on the basis of pricing in the United Kingdom. Sublingual fentanyl citrate (Abstral) is available in Sweden, but was not included in the MTC on which this model was based because there was only limited clinical data available (its approval was primarily based on pharmacokinetic data). Other fentanyl products, including a bioerodible mucoadhesive (BEMA) fentanyl disc and a dry powder fentanyl inhaler, are also likely to be available in the near future. Like sublingual fentanyl citrate, these products were not included in the current model because clinical trial data were not available, but may need to be considered in the future.

Safety was not included in the model. This was primarily because no differences in adverse events were expected given that the active ingredient in the interventions (fentanyl) is the same. In addition, patients who experience adverse effects may have been withdrawn from trials before randomization because all trials included an initial titration phase to determine the most effective tolerable dose. A further reason that safety was not included is that it is difficult to distinguish adverse effects related to treatment of BTCP from those attributable to opioid treatment for background pain.

Conclusions

In conclusion, treatment with INFS provides a faster onset of pain relief and greater reduction in BTCP than achieved with OTFC or FBT. This improvement in analgesic efficacy with INFS seems to translate into savings in health-care resource use and medical costs as well as improved quality of life for patients with BTCP. Based on this model analysis, INFS can be considered a cost-effective option compared with OTFC and FBT for the treatment of BTCP in Sweden.

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Supplementary Material

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.jval.2010.09.007.

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