North East Treatment Advisory Group

Novel oramucosal (Abstral®, Effentora®) and nasal (Instanyl®) fentanyl for breakthrough pain associated with cancer

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September 2009

Summary

- Three new fentanyl products have recently become available for the relief of breakthrough pain associated with cancer. All involve novel modes of delivery for fentanyl with two providing oramucosal delivery via sublingual (Abstral®) and buccal routes (Effentora®), and one providing mucosal delivery via the intranansal route (Instanyl®).

- The evidence base supporting their efficacy is generally poor. Few studies have been published, most comparisons are against placebo, and methodological and protocol faults have been identified. However, they do appear to produce meaningful and relatively rapid analgesia.

- As with evidence of efficacy, evidence for safety is also poorly available. No important specific safety concerns were highlighted in the clinical studies except for mouth ulceration due to the buccal tablet formulation.

- However, each product is associated with complicated initiation, titration, and maintenance dose instructions. It is not possible to transfer patients from an alternative product/drug to one of the new products without re-titration of the dose. Concerns have been raised regarding the suitability of such products for wider use outside of specialist care where observation may not be as intense and where prescribers will be less familiar with these products. Fentanyl is associated with a relatively high incidence of adverse effects and treatment complications.

- Most episodes of breakthrough pain are currently managed with oral morphine solution, although for some patients the onset of analgesia may be too slow to produce meaningful and timely analgesia. However, morphine solution still appears to be an effective product for most patients, and it is one of the least costly strong opioids suitable for breakthrough pain relief at less than £1 per episode. The new fentanyl products all cost between £5 and £6 per dose and evidence indicates that a second dose or additional analgesia is often required for an episode of breakthrough pain.

Introduction and background

Pain is a common symptom associated with cancer, particularly during the more advanced stages. A number of different analgesic drug groups, and drugs within each group, are used to manage cancer associated pain. The final step in pain management is generally considered to be the use of opioid drugs, which are highly effective analgesics but are associated with some problems such as: addiction, adverse effects such as drowsiness and constipation, negative connotations, and non-familiarity with prescribers leading to potential dosing errors and safety concerns. [1-3]

The ideal opioid analgesic does not yet exist, although evidence indicates that for the majority of patients with cancer associated pain morphine is effective, safe, and well tolerated. [4] However, there does appear to be a minority of patients for whom morphine is not suitable due to intolerance manifesting principally as excessive drowsiness, hallucinations and other psychological disturbances, and intractable constipation. Consequently a number of alternative opioid drugs are now available, with some of the more commonly prescribed being oxycodone, hydromorphone, buprenorphine, and fentanyl. [5]

The latter drug, fentanyl, had previously been available in only two presentations that were in use in primary and palliative care: a lozenge for oromucosal administration and a patch for transdermal administration.[5] The former is used infrequently whereas the latter accounts for about one fifth of all prescriptions for strong opioids in primary care (not necessarily for cancer associated pain). [6] The use of transdermal fentanyl has been highlighted as greater than would be expected based on clinical and cost-effectiveness alone, and it is not without certain safety concerns of its own. [4]

Fentanyl is a synthetic and highly lipophilic opioid. After transmucosal delivery up to 50% of the dose is rapidly absorbed from mucosal membranes. The remainder is swallowed and slowly absorbed from the gastrointestinal tract with extensive first-pass metabolism occurring via this route. Fentanyl has a short duration of action compared with other opioids, although this is thought to be due to extensive tissue redistribution as opposed to differences in metabolism and excretion. Consequently, due to preferential distribution of fentanyl into adipose tissues, it has a relatively long elimination half-life reflecting a slow release from tissue depots. [7]

Despite the regular use of modified release opioid preparations, sometimes at comparatively high doses, patients may still experience acutely painful episodes. These episodes are collectively known as ‘breakthrough pain’ and are typically unpredictable. Breakthrough pain has been defined as ‘a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, experienced by patients who have relatively stable and adequately controlled background pain’. It is typically of rapid onset, severe in intensity, and generally self-limiting with an average duration of 30 minutes. [8]

Breakthrough pain is usually managed by providing patients with a quantity of a standard (as opposed to modified) release strong opioid preparation which can be consumed as soon as the pain is felt or expected, with resultant analgesic control. Commonly used preparations include morphine solution (Oramorph®) and standard tablets or capsules containing morphine, oxycodone, or hydromorphone as well as some more novel preparations such as fentanyl lozenges (Actiq®). Morphine is the most commonly used analgesic for breakthrough pain, and it would appear to be adequate for the majority of patients. However, an often cited problem is its relatively slow onset of action. The peak plasma concentration of oral morphine occurs between 15 and 60 minutes after ingestion, with analgesia usually occurring after this with some time lag, typically at about 30 minutes. Morphine solution may have a quicker onset of action compared with standard solid dose forms. Oral standard morphine has duration of action of between three and six hours. [7,9]

In early 2009 two new presentations of oral fentanyl became available: a buccal tablet (Effentora®) and a sublingual tablet (Abstral®) both designed for oromucosal drug administration. Later in 2009 it is anticipated that a nasal spray delivering fentanyl to the nasal mucosa, with subsequent systemic absorption, will be available (Instanyl®). This not only represents a novel method of drug delivery for fentanyl, but also a UK first for a licensed analgesic delivered by this route. All three preparations are licensed only for the treatment of breakthrough pain associated with cancer in patients who are already managed with background opioid analgesia. [10,11]

The North East Treatment Advisory Group has been requested to conduct an appraisal of these new fentanyl products by the Palliative Care Clinical Group of the North East Cancer Network. This request has the support of the North East Cancer Drugs Approval Group. The Palliative Care Clinical Group has stated specific concerns regarding the safe introduction of these products into clinical practice.

The purpose of this appraisal is to consider the efficacy, safety and cost effectiveness of Effentora®, Abstral® and Instanyl® in order to support a recommendation for prescribers and other clinicians within NHS North East.

Clinical Evidence

In all studies some common outcome measures were used: Pain intensity was measured on an 11-point scale where 0 was 'no pain' and 10 was 'pain as bad as you can imagine' or similar. Pain relief was measured on a 5-point scale where 0 was 'no relief' and 4 was 'complete relief'.

Abstral® sublingual tablets

Abstral® sublingual tablets are available in six different strengths of 100, 200, 300, 400, 600, and 800 micrograms. The tablets are intended for use by placing under the tongue resulting in complete dissolution. About 70% of the dose is absorbed sublingually thus avoiding hepatic metabolism. [10] Complete disintegration of the tablet typically takes less than one minute. [8]

No published phase III studies of Abstral® or a similar preparation were identified. The license application for Abstral® to the European Medicines Agency (EMA) was based largely on the clinical efficacy and safety of Actiq® lozenges with a single bridging study used to demonstrate appropriate pharmacokinetic and pharmacodynamic equivalence. This approach was rejected by the EMA and consequently interim results from two phase III US-based studies were submitted. The sum of the data relating to the use of Abstral® in clinical practice is small. The two phase III studies recruited a total of 219 patients. Results are obtained from an EMA report and abstract data presented in 2009. [12,13]

Both studies were identical in design and duration except that study reference 005 included an efficacy phase of 14 days duration from which the main efficacy results are derived. The efficacy results (n = 61) are displayed in table 1. [12]

All patients were receiving a stable dose of regular opioid analgesia with breakthrough analgesic requirements of between one and four episodes per day. Doses of Abstral® were titrated from 100 micrograms up to a maximum of 800 micrograms. The double-blind efficacy phase of study 005 involved giving patients 10 doses over two days which included three placebo doses in a random sequence. [12]

Table 1. Efficacy results from Abstral® study 005 [12-14]

Outcome (n = 61)		Abstral®	Placebo	Difference	P value
Summed pain intensity difference	30 mins	50	37	13	0.0004
	60 mins	143	105	38	0.0002
Mean pain intensity difference	10 mins	1.2	0.9	0.3	0.0055
	15 mins	2.0	1.5	0.5	0.0011
	30 mins	2.9	2.0	0.9	0.0002
	60 mins	3.4	2.5	0.9	0.0004
Pain relief score	10 mins	1.0	0.8	0.2	0.0490
	15 mins	1.4	1.0	0.4	0.0007
	30 mins	1.8	1.3	0.5	0.0002
	60 mins	2.0	1.5	0.5	0.0022

Patients in both studies were allowed to use rescue medication after 30 minutes if they had not experienced sufficient pain relief. In Abstral®-treated episodes 11% required rescue compared with 27% of placebo-treated episodes. No further clinical data concerning Abstral® appears to be available. [12-14]

Effentora® fentanyl buccal tablets

Effentora® buccal tablets are available in five different strengths of 100, 200, 400, 600 and 800 micrograms. Effentora® has been available in the US since 2006 under the proprietary name Fentora®. Effentora® is a novel formulation for a buccal tablet in that it is actually effervescent. On contact with moisture in the oral cavity the tablet effervesces, thus expediting tablet disintegration. The process of tablet disintegration is claimed to take between 14 and 25 minutes. [10]

Effentora® has been assessed in a number of published articles including two key phase III studies, and is being investigated in numerous ongoing studies. This appraisal will only consider the published evidence. All studies of Effentora® to date are placebo-controlled or open-label non-comparative extension studies.

Following a screening and titration process Portenoy et al randomly allocated treatment sequences of three placebo and seven active doses to 77 adult patients. Patients were instructed to use all 10 doses within 21 days at a maximum rate of four doses per day. Patients were therefore able to take a dose when required for breakthrough pain, as well as their background analgesia, and were instructed to record pain outcomes at intervals up to one hour post-dose. [15] Slatkin et al conducted a study of similar design in 87 adult patients. [16] The results of these two studies are summarised in table 2. Supplemental analgesic medication was used in 23% and 11% of pain episodes in these studies.

Table 2. Summary results of Effentora® studies by Slatkin [16] and Portenoy [15]

		Slatkin et al [16]		Portenoy et al [15]	
		Effentora®	Placebo	Effentora®	Placebo
Number of patients		n = 78		n = 77	
Number of episodes treated		493	223	493	208
Summed pain intensity score difference at 60 minutes		9.7	4.9	*10.1*	*5.9*
Mean difference in pain intensity score	10 minutes	0.9	0.5	not reported	
	15 minutes	*1.4*	*0.8*	*1.0*	*0.7*
Mean pain relief score	10 minutes	0.8	0.6	not reported	
	15 minutes	*1.2*	*0.8*	*0.7*	*0.5*
Improvement in pain intensity score ≥ 33% (considered minimum for clinical significance)	10 minutes	16%	10%	not reported	
	15 minutes	29%	14%	13%	9%
	30 minutes	51%	26%	48%	29%
	45 minutes	not reported		71%	44%
	60 minutes			75%	48%
Improvement in pain intensity score ≥ 50%	10 minutes	7%	4%	not reported	
	15 minutes	18%	8%	8%	6%*
	30 minutes	38%	15%	24%	16%
	45 minutes	not reported		51%	25%
	60 minutes			64%	35%

All $p < 0.05$ unless indicated (*). Figures in italics are estimates.

Weinstein et al report the results of an open-label extension study with at least 12 months follow-up for all patients. 232 patients were enrolled in the study with just over half coming from the two phase III studies and the remainder newly recruited. [17] Only 42 completed the planned 12-month maintenance phase with a further 16 continuing beyond 12 months. The results demonstrated a clear preference for Effentora® over previous medications, and that initial performance ratings for Effentora® were maintained over the long-term (18 months). The patient drop out rate was high, with most discontinuing treatment due to adverse effects.

Instanyl® intranasl spray

Intranasal fentanyl has been under clinical investigation for a number of years in adult and paediatric patients, for cancer and non-cancer associated pain. The EMA Public Assessment Report (EPAR) on Instanyl® refers to three key phase III studies supporting the license application, [18] of which one has been published and the results of two others are available from conference abstracts. [18a,18b,18c,18d]

Instanyl® will be available in the UK from October 2009. It will be available in small glass bottles adapted for intranasal application. Each bottle will provide either 10 or 20 doses of fentanyl containing 50, 100, or 200 micrograms per actuation. In addition, during 2010, a pack of 10 single-use applicators will be available for each strength to support administration in communal settings. Instanyl® is licensed for the management of breakthrough cancer-associated pain for patients who experience up to four episodes of breakthrough pain per day, and who are already managed with a background opioid analgesic. The licensed dose is one spray, followed by an additional spray if required and no sooner than 10 minutes following the earlier dose. Therefore the maximum number of daily actuations is expected to be eight. [11]

The first two phase III studies, referred to as FT-017 and FT-018 in the EPAR, recruited adult patients with cancer-associated pain managed with a stable dose of background opioid, and experiencing no more than four episodes of breakthrough pain per day and no less than three per week. [18]

FT-017 was a placebo-controlled, double blind, cross-over study. Patients were treated for a total of eight episodes of breakthrough pain within a period of three weeks maximum duration. Of the eight episodes, two were to be treated with placebo, and two with each strength of fentanyl (50, 100 or 200 micrograms per actuation). The order in which patients received the doses was randomly selected. Patients were permitted to administer an additional dose of the same strength per episode if, after at least ten minutes, they did not receive adequate analgesia following the first dose. The proportion of patients requiring rescue medication despite being permitted to take up to two doses of Instanyl® was 33% with 50 micrograms, 25% with 100 micrograms, and 17% with 200 micrograms. This suggests that even with the maximal dose 1 in 6 patients required an additional dose. [19]

Details of study FT-018 have been published in a peer reviewed journal. [20] Patients were recruited from two earlier studies of Instanyl® including FT-017. It consisted of two phases; a double blind, placebo-controlled phase and an open label 10-month follow-up phase to assess safety and tolerability. In the first phase patients had their dose titrated. This dose was then used to treat six episodes of pain, with two to be treated by placebo. The sequence of active treatment and placebo doses was randomly allocated. The second phase involved the provision of the previously titrated dose for the treatment of breakthrough pain episodes, with results extending to four months. [20]

Major protocol violations were later identified at one of the study sites and so all quoted results from studies 017 and 018 are based on the exclusion of this site. [18,20]

Table 3. Summary results of studies 017 and 018 [18,20]

	FT-017-IM [18,19]				FT-018-IM [18,20]			
Enrolled (test dose given)	165				120			
Randomised	159				113			
Intention-to-treat population	152				111			
Mean age, years (range)	62 (32 to 86)				61 (33 to 83)			
Outcome	Placebo	50 µg	100 µg	200 µg	Placebo	50 µg	100 µg	200 µg
Mean pain intensity difference after 10 mins	1.4	1.8	2.2	2.7	1.3	2.0	2.7	2.6
Mean responder rate after 10 mins*	22%	29%	42%	50%	21%	31%	60%	49%
Episodes requiring two doses	79%	75%	70%	58%	84%	69%	62%	76%

* : Response defined as pain intensity difference relative to baseline > 2.0

The Committee on Human Medicinal Products (CHMP) of the EMA was highly critical of studies 017 and 018. Specifically, there were found to be major and significant errors in conduct at two centres, including the centre that recruited the greatest number of patients in each study. Additionally, the study designs were considered to be flawed as they would lead to instances of under- and overdosing of pain episodes compared with a titration study design and did not reflect the proposed actual use of Instanyl®. Nonetheless, following remedial action by the sponsor (Nycomed), and despite persisting concerns, the CHMP concluded that "…. the deficiencies found in the quality system … are unlikely to invalidate the quality of the efficacy and safety data." [18]

Study FT-019 was an open active-comparator cross-over study involving a comparison with Actiq® lozenges. Details are available in abstract [21,22] and from the EPAR. [18] Patients were randomly allocated to treatment with Instanyl® followed by Actiq® or vice versa (total n = 139) with doses titrated prior to each active phase. Patients had a mean age of 62 years, had cancer, and were experiencing up to four episodes of breakthrough pain each day. The results demonstrated a faster onset of pain relief with Instanyl® compared with Actiq®, at all points between 5 and 40 minutes post-administration, although the median total difference between treatments was only 5 minutes (11 vs. 16 minutes). [21] In addition, a separate report states that, compared with Actiq®, about two thirds of patients reported a faster onset of 'meaningful' pain relief and patients reported that the product was easy to use and preferred to Actiq®. [22]

Summary of the clinical evidence

None of these new fentanyl preparations have been robustly investigated with an appropriate active comparator which, according to one widely used reference source, should be oral morphine solution. [9] As would be expected, all demonstrated significant and dose-related responses compared with placebo in patients with cancer-associated pain. All license applications make extensive use of the existing evidence base for fentanyl in general and not specifically the new product. This approach appears to be accepted by the licensing authorities and is probably sufficient. All studies appear to have used an enhanced patient recruitment process which may have distorted the efficacy results in favour of the new treatment. Generally, there is a paucity of published data currently available and so the above evidence summaries are often based upon secondary data sources from the EMA and conference abstract data. The evidence base for Instanyl® suffers in particular with major deficiencies identified by the licensing authority. As most of the Instanyl® studies have not yet been published in peer reviewed journals a significant bias cannot be ruled out. All products appear to produce rapid analgesia in a substantial proportion of patients, with Instanyl® producing a more rapid effect than either Abstral® or Effentora®. However, in the absence of direct comparisons, this indirect comparison should be interpreted cautiously.

Safety

Fentanyl has been in clinical use for many years. It is a potent opioid, estimated to be between 50 and 150 times as potent as morphine by mass. [7,9]

Data available from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) identifies 744 separate reports of adverse effects with fentanyl and associated proprietary brands since 1972. In total 1,696 reactions were reported, including 70 fatalities. None of this data includes Abstral®, Effentora®, or Instanyl®. A reported adverse reaction does not necessarily imply causality. [23]

The National Patient Safety Agency's (NPSA) National Reporting and Learning System had received 4,407 reports of patient safety incidents involving opioid medications by June 2008. Twelve per cent (544) were associated with fentanyl. It is possible that some of the reports to the MHRA and the NPSA are of the same incident. [24]

Abstral® (safety)

Adverse effects with Abstral® are not readily identifiable from primary or secondary sources. The summary of product characteristics lists the following as 'very common' which is defined as affecting >10% of patients: dizziness, somnolence, headache, nausea, and fatigue. Other adverse effects are those generally associated with opioid drugs and their known pharmacological effects. [10] With exposure of up to 12 months, 55 patients out of 219 had

experienced a total of 106 serious adverse events although none were considered related to Abstral®. [13]

Between both studies 270 patients entered the titration phase with 174 completing titration (64%). Of the 96 patients who did not complete titration 29 (30%) were due to adverse events and 17 (18%) due to lack of efficacy. The nature of the adverse events is not described and causal association with Abstral® is not stated. [14]

Effentora® (safety)

In their placebo-controlled study of Effentora® Slatkin et al report that of 175 patients screened, three were not enrolled due to an adverse event. Of 129 patients enrolled, 125 were entered the titration phase of which 14 withdrew due to adverse events (11%). Of 87 patients who entered the double-blind treatment period five withdrew due to adverse events (6%), meaning that of the original 175 patients 22 withdrew due to an adverse event (13%). Adverse events were reported by 83 of 125 patients (66%) who entered the titration phase. Twelve patients (10%) reported adverse events related to the effect of the formulation at the site of application with most being mild and transitory. Serious adverse events were reported in eleven patients although none were considered related to Effentora®. The most common adverse effects were typical of opioid drugs and were nausea (13%), dizziness (11%), fatigue (8%), headache (6%), vomiting (6%), and constipation (6%). [16]

In the placebo-controlled study by Portenoy et al 139 patients were screened, 123 entered the titration phase of which 77 completed, with 12 (10%) withdrawing due to an adverse event. Of the 77 patients who entered the treatment phase 68 completed with three (4%) withdrawing due to an adverse event. Therefore, of 123 patients 15 (12%) withdrew due to an adverse event. The nature of adverse events were to be expected with a potent opioid and included: nausea (22%), dizziness (22%), headache (15%), fatigue (12%), vomiting (11%), somnolence (10%) and constipation (8%). Two patients reported oral ulcers due to Effentora® and both subsequently withdrew. Serious adverse events occurred in 11% of patients and there were seven deaths, with none considered related to Effentora®. [15]

An unpublished pooled safety analysis of the Slatkin and Portenoy studies included 248 patients who received treatment with Effentora® for a mean of 6 days. 72% of patients experienced at least one adverse event with 36% considered related to Effentora®. Adverse events leading to treatment cessation occurred in 14% of patients. Serious adverse events occurred in 10% with none considered related to Effentora®. The most common adverse events were dizziness (17%), nausea (17%), headache (10%), fatigue (10%), vomiting (8%), application site reactions (7%), and constipation (7%). The most common effects considered related to Effentora® were dizziness (13%), nausea (8%) and

application site reactions (7%). Three patients discontinued due to application site reactions. [25]

In the long-term safety study of Effentora® reported by Weinstein et al 232 patients were enrolled of whom 197 (85%) entered the 'maintenance' phase following dose titration, of whom only 42 completed with 76 (39%) withdrawing due to adverse events. Only 24 patients entered the 'maintenance extension' phase with 8 (33%) withdrawing due to adverse events. Therefore, of 232 patients enrolled, 84 (36%) withdrew due to an adverse event. However, 'death' is included in these figures, of which the incidence was 60 and all were related to an underlying condition. The 'true' figure of withdrawals due to adverse events is therefore 10%. In total 90% of patients reported at least one adverse event. The most common events (≥10%) are generally associated with opioid drugs or an underlying diagnosis of cancer and include: nausea (37%), vomiting (22%), dizziness (20%), fatigue (16%), constipation (14%), anaemia (14%), headache (14%), and somnolence (13%). Application site reactions occurred in 15 (6%) of patients with four resulting in treatment cessation. Patient surveys indicated a high degree of satisfaction with Effentora® compared with their previous 'breakthrough' analgesia. [17]

In November 2007 the American Food and Drug Administration issued a safety alert specifically concerning Fentora® (Effentora®). The alert stated that serious side effects, including fatalities, had occurred and attributed these to: use in non-opioid tolerant patients, dosing errors, and inappropriate substitution of Fentora® for Actiq®. Several recommendations were made, the majority of which are reflected in the summary of product characteristics. These include information concerning initial doses, dose frequency, defining 'opioid-tolerant', and a reminder that it should only be used for cancer associated pain. [26]

Instanyl® (safety)

All relevant Instanyl® studies made use of test doses to identify those patients who could not tolerate a single maximal dose. Additionally, in two of those studies it was found that investigating staff had been recording adverse effects other than in accordance with good practice.

In study 017 the reported incidence of any adverse events appears to be low, being less than 10% for any treatment group. Nausea and vomiting are reported as the most frequent. [19]

In the report by Kress et al (FT-018) safety results with up to 10 months follow-up are available. 77% of patients reported at least one adverse event and 52% reported at least one serious adverse event (note that cancer progression was included as an adverse event and affected 51% of patients, and 38% of patients died with death counted as a serious event). 46% of patients experienced an adverse event that led to treatment withdrawal. Other adverse events are typical

of strong opioids and include dizziness, nausea, constipation, and vomiting (all ≤ 10%). [20]

The EPAR states that 207 adult patients with chronic cancer pain received treatment for more than 3,000 episodes of breakthrough pain with nasal fentanyl as part of the Instanyl® development programme. The overall incidence of adverse effects in the patient population was substantially lower than expected and has been attributed to deviations from good clinical practice in studies 017 and 018. A retrospective review identified a substantial number of previously unrecorded adverse effects in these studies. [18]

In study 019, which involved a cross-over comparison with Actiq®, no important errors of practice are known. Following treatment of six pain episodes with Instanyl® 46% of patients experienced an adverse event compared with 35% following treatment of six pain episodes with Actiq®. Most were not considered related to study treatment. Serious adverse events affected 14% of Instanyl® patients and 5% of Actiq® patients with none considered related to study treatment. Following Instanyl® treatment 8% of patients withdrew due to an adverse event and 7% following Actiq®. The most common adverse events reported during the study were nausea (12%), vomiting (7%), and constipation (7%). [18,21]

There was only one report concerning nasal ulceration, which rapidly healed following cessation of Instanyl®. There was also one report of respiratory depression following Instanyl®. [18]

In summary, although there are substantial deficiencies in the reporting of adverse events in studies of Instanyl®, those that were reported are typical of fentanyl and other strong opioids and no important new safety concerns arose. [18]

Summary of the safety data

In general the fentanyl products were well tolerated within the constrained and controlled environments of the clinical studies. In the limited clinical evidence base for Abstral®, Effentora® and Instanyl® no unexpected safety concerns were observed. The majority of adverse effects were to be expected with use of a potent opioid generally, or fentanyl more specifically. Against this, patients had serious underlying medical problems and continued treatment with a regular strong opioid analgesic. The one exception is the incidence of application site reactions seen with Effentora®. Intriguingly these reactions were not seen with Abstral®, due perhaps due to the quality of the data sources, but probably due to a more rapid dissolution of Abstral® and the fact that Effentora® tablets are in fact effervescent possibly resulting in greater risk of mucosal irritation.

In practice, deviations in use from the licensed instructions may arise with consequent safety problems particularly as each product is associated with complicated instructions regarding dose titration and frequency, and licensed

constraints on minimum background opioid requirements, breakthrough pain requirements, and maximum daily doses. Indeed, this appears to have occurred in America with Effentora® where the product has been available since 2006, and for which the FDA issued a safety alert only 12 months after its launch. [26]

Genuine safety concerns have been raised with fentanyl in the recent past. Some of these are related as much to the mode of delivery as to the drug itself. [27] There is a sound hypothetical problem with accumulation of fentanyl unless the preparations are used according to instructions, which limit repeat doses of Abstral® to two per episode of pain and up to eight per day, Effentora® to one dose per four hours and up to four doses per day, and Instanyl® to two sprays per episode per four hours and up to eight sprays per day. [10,11]

Unless fentanyl preparations are used with a higher degree of scrutiny than is required for other strong opioids, they may present additional safety issues.

An additional review of the safety and efficacy of Abstral®, Effentora®, and Instanyl® has recently been published by the London New Drugs Group and this document can be freely accessed via an NHS net connection. [28]

Practical and other considerations

- The three fentanyl products considered in this appraisal all have in common the ability to bypass absorption from the gastrointestinal tract. This has advantages for some patients who have problems swallowing or have an obstructed, damaged, or otherwise impaired gastrointestinal tract. Importantly though, it means that the drug, in this case fentanyl, can be absorbed rapidly and without undergoing first-pass metabolism. This is an advantage as it increases the proportion of the dose that makes it into the systemic circulation whilst at the same time minimising the amount of drug that is consumed.

- There are no objective rules or algorithms for converting existing use of breakthrough analgesia into an appropriate dose for any of the new fentanyl products, including those patients who are already using fentanyl lozenges (Actiq®). Consequently, all patients must be titrated to an appropriate dose. This process requires close monitoring, patient and carer education, and may expose the patient to a period of inadequate analgesic cover. [10,11]

- Prescribers may initially have to manage patients with breakthrough pain more intensively with fentanyl compared with morphine as fentanyl doses require individualised dose titration compared with a standard estimate/algorithm for morphine. [9-11]

- Fentanyl transdermal patches are widely used for cancer-associated analgesia. Before the availability of these new fentanyl products the only fentanyl medicine available for breakthrough pain was Actiq® lozenges. Prescribing data indicates that this product is used infrequently within NHS

North East, accounting for a total of 941 items (36,146 doses) and only 0.3% of all analgesic strong opioid items prescribed in primary care in 2008-09. Conversely, fentanyl patches are widely used and account for about 1 in 5 of all prescriptions for strong modified-release opioids (344,330 patches). [6] This leads to the assumption that many patients using fentanyl patches will be prescribed a non-fentanyl opioid for breakthrough pain relief thus negating some of the advantages that use of fentanyl patches may offer, such as reduced incidence and severity of constipation. Therefore these new products mean that a greater number of patients can be managed entirely with the same analgesic.

- Each of the new fentanyl preparations presents a new route of administration for their particular dose form. However, oromucosal delivery of fentanyl has been possible for a number of years with Actiq® lozenges. Additionally, other buccal and sublingual opioids have also been available for some time, such as buprenorphine.

- Instanyl® represents the first licensed intranasal analgesic of any class to become available in the UK. Unlicensed nasal opioid preparations are rarely used within palliative care, usually only within specialist centres.

- Patients, and in many situations carers, will require additional education and training regarding the correct use of these products. Some individuals may not be able to adequately comprehend the dose instructions.

- Restrictions on repeat dosing may mean that these preparations are unsuitable for some patients, or may mean that additional analgesia is required (e.g. morphine solution).

- Abstral® and Effentora® may be unsuitable or problematic for patients experiencing dry mouth (xerostomia) or oral mucositis (inflammation of the membranes of the oral cavity) although treatment is not necessarily contra-indicated.

- The Scottish Medicines Consortium has accepted Abstral® and Effentora® for use within NHS Scotland, restricted to instances where other short-acting opioids (e.g. oral morphine) are deemed unsuitable. [29,30]

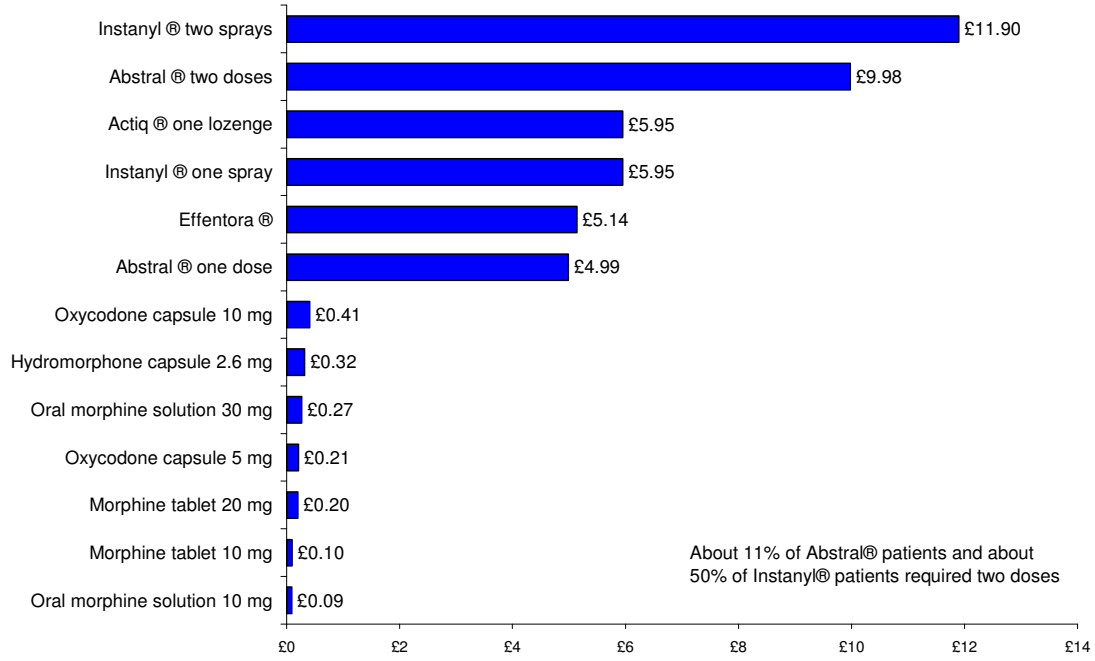
Economic assessment

Both Abstral® and Effentora® utilise a dose-independent pricing structure where the cost of any strength is the same per unit (tablet) at £4.99 and £5.14 respectively. [31] Instanyl® is available in packs containing either 10 or 20 doses of one of three different strengths and will cost £5.95 per actuation so that 10-dose bottles cost £59.50 and 20-dose bottles cost £119.00. Because each dose/actuation costs the same regardless of strength variations in the number of actuations administered will have a directly proportional effect on the overall cost (i.e. a dose increase resulting in use of twice as many sprays will result in double the cost). In the Instanyl® clinical studies approximately half of patients required two actuations per episode of pain, resulting in a mean cost per episode of about £9. In a similar way, the dose of Abstral® permits up to two tablets per episode of pain. In studies of Abstral® 11% of patients required a second dose resulting in a mean price per episode of £5.54. [14]

It may be assumed that use of the new fentanyl products will be a substitution for an existing treatment option and there will be no direct increase in the overall use of opioids for breakthrough analgesia. However, advances in medical care and demographic and environmental changes mean that the number of patients requiring treatment for cancer-associated pain may increase.

Figure 1 shows the costs per dose based on treatment of a single episode of breakthrough pain as well as the cost of some alternatives.

Figure 1. Cost per episode of breakthrough pain of some common strong opioid and fentanyl preparations [31]



Use of Abstral®, Effentora®, or Instanyl® in preference to Actiq® will represent a modest saving. However, use in preference to a non-fentanyl alternative such as morphine solution or tablets represents a substantial (approximately 20 to 50 fold) increase in cost.

It is not possible to accurately quantify the proportion of recorded opioid use in primary care that is used for breakthrough cancer-associated pain as opposed to non-cancer pain or for background analgesia in cancer and non-cancer.

The cost of drugs prescribed or purchased other than via an NHS community dispensing contract will incur value added tax, currently 15% until January 2010 and then 17.5% thereafter. The costs stated in this report **do not** include VAT.

The absence of a common meaningful outcome across the studies of Abstral®, Effentora®, and Instanyl®, and from a suitable source regarding morphine, mean no useful indirect comparisons can be made. At an incremental cost of about £5 per dose compared with morphine, the maximum daily incremental cost would be £20 based on the treatment of four episodes per day each with a single dose, and if this was repeated over a year the incremental cost would be £7,300 per annum. At this rate of use over this period (four doses per day per annum) the new treatment would have to be at least 36% more effective in absolute terms than oral morphine to meet the conventional incremental threshold of £20,000 per quality adjusted life year. This scenario is unlikely because it would be unusual for a patient to require such a rate of breakthrough pain relief over such a prolonged period. Therefore the figures stated should be interpreted as maximum possible values.

Points to consider

- Abstral®, Effentora®, and Instanyl® are effective analgesics for cancer-associated breakthrough pain. The principal advantage that they hold over other equally effective and cheaper analgesics is the speed of analgesic onset. In this respect, Instanyl® is probably the most effective. Comparative studies with oral morphine have not been published.

- The evidence base supporting the above statements and use of the products within their licensed indications is generally poor. Few studies are published, most comparisons are placebo-controlled, and study designs poorly represent practical or licensed use.

- The evidence base does not identify any major safety concerns with Abstral®, Effentora®, or Instanyl® when they are used correctly, for example within a controlled study. However, use of the products in practice is far from straight forward with doses requiring careful titration regardless of prior patient opioid exposure. Indeed, within 12 months of its availability on the American market the FDA were sufficiently concerned to issue a drug alert concerning Effentora®. The clinical studies also indicate a surprisingly high rate of

intolerance to the new fentanyl products, as evidenced by the cumulative number of study discontinuations including those exposed to 'test doses'. This may be due to the constraints of the study but raises concerns about appropriate use in practice. An additional concern is with local reactions attributable to Effentora®. Although affecting only ~ 5 to 10% of patients a significant number of these subsequently discontinue due to administration site reactions. Abstral® does not appear to result in similar affects although there is less evidence available to support that conclusion.

- The actual incremental cost per dose is about £5 compared with morphine, the most commonly used opioid for breakthrough pain. This is fairly modest, although the relative increase in costs is about 20 to 50-fold. If levels of use remain at about the same rate as Actiq® the net impact on NHS North East will be small, and indeed if used as a substitute to Actiq® will even present savings. However, if the new products assume a greater share of the market in a similar fashion to that seen with the use of fentanyl patches then they could present a significant financial burden.

- Use of proprietary names on prescriptions as opposed to generic descriptions ('branded prescribing') has been specifically recommended by the Palliative Care Pharmacists Network with Abstral® and Effentora®. [32] Branded prescribing is also a widely disseminated recommendation regarding the prescribing of any strong opioid drug. [9]

Audit, follow-up, and monitoring

Local medicines management teams including those in primary care, acute hospitals, and specialist centres such as hospices and respite centres, should continually ensure that prescribing of Abstral®, Effentora®, and Instanyl® meets the recommendation issued by the North East Treatment Advisory Group. Instances where prescribing is appropriate but does not meet the recommendation should be fully documented in the patients' medical notes. Periodic audits (e.g. once every 24 months) should be performed in localities with relatively high levels of use. Primary care medicines management teams may wish to consider shared-care arrangements for their locality as there are safety and monitoring issues regarding these products.

The Palliative Care Network Clinical Group has indicated a willingness to audit use of new fentanyl preparations including some assessment of patient preference and adverse events.

Acknowledgement
The Regional Drug and Therapeutics Centre (Newcastle) has provided assistance in data collation, interpretation and presentation.

Author's declaration
The author has participated in an advisory board for a company that markets modified-release morphine capsules.

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Characteristics of normal-release oral opioids used for breakthrough pain

Preparation	Approx. time to onset	Approx. duration of effect	Main advantages	Main disadvantages	Cost per dose (recommended doses from APS 2003 if not licensed for breakthrough pain***)
Established preparations					
Oramorph® (morphine oral liquid)	20 to 30 mins	4 hrs	Cheap Healthcare professionals experience of use.	Dose form less convenient than tablets. Unpleasant taste. Relatively slow onset of action for BTP.	< £1 (20mg)
Sevredol® (morphine tablets)	Variable reports. Clinical experience 20 to 30 mins	4 hrs	More convenient than liquid. Healthcare professionals experience of use.	Relatively slow onset of action for BTP. No 5mg tablet.	< £1 (20mg)
Oxynorm® liquid (oxycodone oral liquid)	20 to 30 mins	4 to 6 hrs	Good strength range available. Healthcare professionals experience of use.	More expensive than morphine. Advantages of oxycodone over morphine not demonstrated in clinical trials. Relatively slow onset of action for BTP.	< £1 (10mg)
Oxynorm® capsules (oxycodone capsules)	20 to 30 mins	4 to 6 hrs	Healthcare professionals experience of use.	More expensive than morphine. Advantages of oxycodone over morphine not demonstrated in clinical trials. Relatively slow onset of action for BTP.	< £1 (10mg)
Alfentanil buccal/nasal spray (unlicensed product). 140 mcg/spray	'Almost immediate'*. Clinical experience indicates < 5 mins	15 to 20 mins*	Quick acting with short duration	Unlicensed product lack of official data. Many patients find it difficult to use.	£2 (~35p/spray) Usual dose 2 to 12 sprays*
Actiq® (transmucosal fentanyl lozenge/'lollipop')	5 to 10 mins	1 to 2 hrs	Rapid onset of action with shorter duration of effect than morphine or oxycodone.	Many patients find it difficult or tiresome to use. Less effective if dry, sore mouth. Relatively expensive.	£6 per single dose unit

Characteristics of normal-release oral opioids used for breakthrough pain (continued from previous page)

Newer preparations					
Abstral® (fentanyl sublingual)	10 mins	Effective at 1 hour post dose**	Relatively rapid onset of action with shorter duration of effect than morphine or oxycodone Convenient non-invasive dose form.	No comparator trials with other opioids used in BTP Relatively expensive.	£5 per single dose unit
Effentora® (fentanyl buccal)	10 mins	Effective at 2 hours post dose**	Relatively rapid onset of action with shorter duration of effect than morphine or oxycodone. Convenient, non-invasive dose form.	No comparator trials with other opioids used in BTP Relatively expensive. Time restriction on treating subsequent BTP episodes.	£5 per single dose unit
Preparations on the horizon					
Bio-erodible muco-adhesive (BEMA) fentanyl discs	Early reports indicate faster absorption of fentanyl than with Actiq with some good data demonstrating efficacy in treating BTP.				
Nasal fentanyl preparations (Instanyl & Nasalfent)	Early reports demonstrate efficacy in treating BTP.				
Fentanyl multidose dry powder inhalers	At least three preparations in pipeline using differing technologies to deliver fentanyl via the inhaled route. Early reports demonstrate good efficacy in treating BTP.				
Patient self administered analgesia via 'pen' devices.					

* Unlicensed product , anecdotal evidence only as no official data. ** Manufacturer's data. *** APS – American Pain Society.

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