Opioids for the management of breakthrough cancer pain in adults: A systematic review undertaken as part of an EPCRC opioid guidelines project

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Abstract
The usual management of cancer related breakthrough pain is with supplemental doses of analgesics (commonly opioids) at a dose proportional to the total around-the-clock opioid dose. The aim of this review, undertaken as part of a European Palliative Care Research Collaborative (EPCRC) project, to update the EAPC guidelines on opioid analgesics in cancer pain was to determine the evidence for the utility of opioids in the management of breakthrough pain in patients with cancer. Randomized controlled trials of opioids used as rescue medication were identified using electronic search strategies. Outcome measures sought were reduction in pain intensity measured by an appropriate scale, adverse effects, attrition, and patient satisfaction. The date of the final search was 31 July 2009. Eight studies (790 patients) met the inclusion criteria. Most studies investigated rescue medication delivery via the buccal or nasal transmucosal routes. Intravenous morphine has been compared with the transmucosal route and the two found to be effective. The oral route has not been formally tested although found to be an inferior comparator in one study. Most studies showed no meaningful relationship between the effective dose of transmucosal opioid and the around-the-clock scheduled medication or the previous rescue medication, although one study found a fixed proportion of either intravenous morphine or transmucosal fentanyl to be efficacious.

Keywords
Neplasm, pain, opioids, breakthrough pain, transmucosal

Introduction
Breakthrough pain is a heterogeneous pain state first highlighted by Portenoy and Hagen in 1990. The term has been used to describe a phenomenon whereby pain intensity suddenly increases to ‘break through’ the background pain that is otherwise controlled by a fixed schedule ‘around-the-clock’ (ATC) opioid regimen. A number of definitions have appeared in the literature and the lack of consensus on a formal definition has led to difficulties when comparing studies and recommending management strategies. Even the term ‘breakthrough pain’ is not one that is universally agreed with.

The usual approach to managing breakthrough pain is with supplemental doses of opioids, also known as rescue medication. The dose of rescue medication is usually based on the patient’s ATC analgesia and is given before or soon after breakthrough pain has started. The current European Association for Palliative Care (EAPC) recommendation is to use the same as the four-hourly dose of normal-release morphine (approximately 17% of the daily dose) when necessary. The aim of this review was to determine the efficacy of opioid analgesics for the management of breakthrough pain in patients with cancer.

Methods
All published randomized controlled trials, blinded and non-blinded, that assessed the management of
breakthrough pain were included. Randomization was defined as studies that were described by the authors anywhere in the manuscript as ‘randomized’. The study population included adult patients with cancer and breakthrough pain in any setting.

All studies that compared opioid analgesics with placebo or other opioid analgesics, or both, or other active controls were considered regardless of the dose (single or multiple doses) or mode of administration for the relief of breakthrough pain. Patient reported pain and adverse effects were assessed. In addition, requirements for additional rescue analgesia and patient preference were included in the analysis.

To identify studies for inclusion search strategies were developed for each electronic database searched. The subject search used a combination of controlled vocabulary and free text terms based on the following search strategy for searching MEDLINE:

1. (breakthrough or episodic or transient or transitory or incident or flare).mp.
2. (cancer or malignant or neoplasm or neoplasia or tumor or tumour).mp.
3. pain.mp.
4. exp PAIN
5. 3 or 4
6. 1 and 2 and 5
7. limit 6 to (human and (controlled clinical trial or meta analysis or randomized controlled trial))
8. (morphine or fentanyl or hydromorphone, or oxycodone, or pentazocine or methadone or opioid or opiate or opioids or codeine or dextroromamide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).mp.
9. 7 and 8.

The date of the final search was 31 July 2009 and the abstracts of the identified studies were read. If it was clear from the abstract that the study did not meet the selection criteria it was excluded. If it was unclear from the abstract whether the study met the selection criteria then it was read in full, as were all studies that appeared to meet the selection criteria. Justification for excluding studies was documented.

In the critical appraisal of studies the aspects of quality considered were: whether the treatment was randomized, whether the process of randomization was described, and whether withdrawals and dropouts were described and then appropriately handled in the analysis. The quality of each study was quantified using a validated scoring system.4

A data collection form was used for the review and the following data was collected:

Publication details
Participants: number subjects at baseline, gender, age
Trial quality characteristics
Description of intervention
Outcome data
The number of patients and number of adverse effects reported.

In the analysis a comparison was calculated of weighted mean difference for pain intensity difference at either 10 or 15 minutes after drug administration.

Results

Identified studies

Electronic searching identified 125 studies. Eleven studies appeared to fit the inclusion criteria; however, on reading the papers it was found that two were not randomized and one was a duplicate French version, leaving eight primary references.5-12 Two studies were randomized, double-blind dose titration studies and allowed only open label comparison of the investigational drug and previous rescue medication.6,7 The remaining studies tested the investigational drugs either against placebo5,9,11,12 or an alternative opioid.5,10

Oral transmucosal fentanyl citrate studies. Oral transmucosal fentanyl citrate (OTFC) consists of a fentanyl-impregnated sweetened and hardened lozenge on a plastic handle and has been designed for the management of breakthrough pain. The lozenge is applied to the buccal mucosa and as it dissolves in the saliva a proportion (approx 25%) is absorbed across the buccal mucosa, the remainder of the drug is swallowed and a further 25% is absorbed through the gastrointestinal tract.13 OTFC is available in six doses; 200, 400, 600, 800, 1200 and 1600 μg.

Christie et al.6 and Portenoy et al.7 employed a randomized, double-blind dose titration methodology in patients utilizing either transdermal6 or oral7 ATC opioids to identify the dose of OTFC for each patient adequate to treat one episode of breakthrough pain. Both studies, which between them enrolled 252 patients, were divided into two phases. In phase 1 breakthrough pain and the performance of the usual rescue medication was assessed for two consecutive days. In phase 2, patients were randomized to start with either 200 μg or 400 μg of OTFC and titrated to the effective dose.
and the performance of the drug was then evaluated. During each day of phase 2 four OTFC units could be taken sequentially (one every 30 minutes) for up to two episodes of pain. If more than one unit was necessary the investigator could order titration to the next largest OTFC. Dose unit could also be decreased at the discretion of the investigator. Blinding was further enhanced by ignoring the need to increase the OTFC dose in one-third of instances according to a randomization schedule. Data were used to examine the success of the titration process, the existence of a dose–response relationship with OTFC, the comparison of outcomes during the two days of baseline treatment and the two days with OTFC once patients had titrated to an effective dose.

Farrar et al.\(^5\) compared OTFC with placebo in a multicentre, randomized double-blind study design. One hundred and thirty patients were recruited to phase 1 of the study where OTFC was substituted for their usual rescue medication. All patients were commenced on 200 \(\mu g\) of OTFC; if more than one unit was required to successfully manage the pain a larger unit was used for subsequent pains. Once the successful dose was determined patients entered phase 2 of the study where they were given 10 sequentially numbered oral transmucosal units; seven contained OTFC at the same dose found to be successful in phase 1 and three were placebo units. Patients were asked to use the lozenges in a predetermined order. If pain relief was inadequate within 30 minutes they were asked to take their previous rescue medication.

Coluzzi et al.\(^8\) compared OTFC and normal release morphine for the management of breakthrough pain. One hundred and thirty-four patients entered the study having identified a successful dose of normal release morphine to treat their target breakthrough pain for at least three consecutive days. Phase 1 of the study was an open label OTFC titration to determine the dose that successfully treated the target breakthrough pain with acceptable adverse effects. Patients were commenced on 200 \(\mu g\) of OTFC and once a successful dose was found patients entered phase 2 when they were given 10 pre-numbered oral transmucosal units and capsules. Five units contained the successful dose of OTFC with placebo capsules and five units contained placebo oral transmucosal lozenge and the patients’ pre-trial successful dose of normal release morphine capsules.

Mercadante et al.\(^10\) compared effectiveness of a fixed dose of OTFC and intravenous morphine for the management of breakthrough pain using a randomized, crossover, controlled methodology.\(^10\) Adult patients with cancer-related pain were eligible if they were receiving opioids regularly at doses of more than 60 mg of oral morphine equivalents, had an acceptable pain relief, and presented no more than two breakthrough pains per day. Patients meeting the inclusion criteria were planned to receive intravenous morphine and OTFC for each couple of breakthrough pain episodes in random order with a wash out period between the episodes of at least 6 hours. Patients who repeated the sequence on another day received the opposite sequence, thus serving as their own control. The rationale in choosing the doses to be administered was based on previous studies\(^13\) and not intended to be equianalgesic.

**Fentanyl buccal tablet studies.** Fentanyl buccal tablet (FBT) incorporates an effervescent reaction to enhance fentanyl absorption through the buccal mucosa and facilitate rapid systemic exposure to the analgesic. Transient pH changes accompany the effervescent reaction, and increase both the rate of tablet dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl. Compared with OTFC, a larger proportion of FBT is absorbed transmucosally (48%) compared with OTFC (22%) and the \(T_{\text{max}}\) was earlier after administration of FBT (47 min) than OTFC (91 min).\(^14\) FBT is available in five doses; 100, 200, 400, 600, and 800 \(\mu g\). Portenoy et al.\(^9\) and Slatkin et al.\(^11\) both compared the FBT with placebo in the management of breakthrough pain and included an initial screening visit, a dose titration phase and a double-blind treatment phase. The studies, which enrolled 252 patients, aimed to identify the dose of FBT for each patient adequate to treat one episode of breakthrough pain using a single unit of FBT. In one study outcome measures were assessed between 15 and 60 minutes,\(^9\) in the other the time points were between 5 and 120 minutes.\(^11\) Patients were provided with a titration kit consisting of 100, 200, 400, 600, and 800 \(\mu g\) doses of FBT; the starting dose was based on the medications the patient was using to treat breakthrough pain immediately before study enrolment. If two successive episodes of breakthrough pain were adequately relieved within 30 minutes using a single tablet of the same FBT dose and no unacceptable adverse effects occurred, patients were considered to have identified an effective FBT dose and could begin the double-blind treatment phase of the study. In phase 2 patients were randomly assigned to one of 18 double-blind dose sequences (seven tablets of the previously identified effective dose of FBT and three matching placebo tablets) to treat 10 breakthrough pain episodes. Patients continued to use their ATC opioid regimen, and if satisfactory relief was not achieved within 30 minutes following study drug administration, they also continued their pre-study supplemental medications.
**Intranasal fentanyl spray studies.** Intranasal fentanyl spray (INFS) is a phosphate buffered fentanyl solution in a multi-dose bottle specifically developed for the management of breakthrough pain. The nasal spray’s pH of 6.4 has been formulated to closely match the physiological environment of the nasal cavity thus lowering the potential for local irritation. The formulation is of sufficient concentration to deliver an analgesic dose in a volume that does not exceed the nasal capacity. In clinical pharmacokinetics studies INFS shows an approximate bioavailability of 90%, with a venous \( T_{\text{max}} \) of 13 min.\(^{15} \) INFS is available in three doses: 50, 100, and 200 μg.

A European study compared INFS against placebo for the management of breakthrough pain in a double-blind, randomized, placebo-controlled, crossover trial.\(^{12} \) Eligible patients were adults with cancer receiving a stable dose of long-term opioid treatment for the control of background pain. Patients were treated at home with their effective dose of INFS (50, 100, or 200 μg) or inactive spray (placebo) in a randomized sequence for 3 weeks, followed by a 10-month, open-label tolerability phase during which they received their effective dose of INFS.

**Efficacy, safety and tolerability**

**Dose titration: patients on ATC transdermal fentanyl.** Of the 62 patients recruited, 33 (53%) were female, mean ± SD age of all patients was 59 ± 14 years and the commonest cancers were lung (16 patients), breast (7), and prostate (6). The mean ± SD dose of transdermal fentanyl was 103 ± 63. Patients were using a variety of rescue medication, the most common of which were oxycodone (16 patients), morphine (15), hydromorphone (11), hydrocodone (10), and propoxyphene (6). The mean ± SD morphine equivalent of rescue medication was 21 ± 20. The ratio of ATC opioid to rescue medication (determined as morphine equivalent using standard relative potencies) ± SD (range) was 0.22 ± 0.17 (0.03–0.75). The pathophysiology of target breakthrough pains was somatic (34 patients), visceral (29), and neuropathic (16).

Forty-seven (76%) patients were able to titrate OTFC to a safe and effective dose to treat their breakthrough pain; three patients withdrew during titration because of OTFC-related adverse effects and four patients titrated to the 1600 μg dose without obtaining adequate relief. The mean (±SD) successful OTFC dose was 587 ± 335 μg. No relationship was found between the successful dose of OTFC and the total daily dose of ATC transdermal fentanyl, indicating that the optimal dose of OTFC cannot be predicted by the total daily dose of fixed scheduled opioid. An open-label comparison of OTFC and the patients’ usual rescue medication for breakthrough pain showed that OTFC produced significantly better pain relief than regular rescue medication at all time periods (\( p = 0.0001 \)). Patients rated the global satisfaction of OTFC significantly higher than global performance of their regular rescue medication (2.6 vs. 2.01 \( p = 0.0001 \)). The most common adverse effects on days that any OTFC was taken were considered possibly, probably, or almost certainly due to OTFC were somnolence (11 patients), nausea (7), dizziness (6), and vomiting (3), whilst during the final two days of the study when OTFC had been titrated, adverse effects considered possibly, probably, or almost certainly due to OTFC were somnolence (7 patients), nausea (6), and dizziness (3).

**Dose titration: patients on ATC oral opioids.** Of the 67 patients recruited, 65 were randomized to the different starting doses of OTFC. Thirty-seven (57%) patients were women and the mean ± SD age was 53 ± 12 years. The commonest cancers were breast (17 patients), lung (7), colon (6), and head/neck (6). Sixty patients (92%) received modified release morphine as their ATC oral opioid; other ATC oral opioids used were hydromorphone (2 patients), oxycodone (2), and methadone (1), whereas rescue medication varied: morphine (34 patients), oxycodone (14), hydromorphone (8), hydrocodone (6), and codeine (3). The ratio of ATC opioid to rescue medication (determined as morphine equivalent using standard relative potencies) ± SD (range) was 0.15 ± 0.09 (0.04–0.50). The pathophysiology of target breakthrough pains was somatic (28 patients), visceral (15), and neuropathic (22).

Forty-eight (74%) patients were able to titrate and find a safe and effective dose of OTFC using a single unit to treat their breakthrough pain, eight patients withdrew during titration because of OTFC-related adverse effects, and five patients titrated to the 1600 μg dose without obtaining adequate relief. The mean ± SD successful OTFC dose was 640 ± 374 μg. No relationship was found between the successful dose of OTFC and the total daily dose of ATC oral opioid. An open-label comparison of OTFC and the patients’ usual rescue medication for breakthrough pain showed that OTFC produced significantly better pain relief than regular rescue medication at all time periods (\( p = 0.0001 \)). Patients rated the global satisfaction of OTFC significantly higher than global performance of their regular rescue medication (2.74 vs. 2.09 \( p = 0.0002 \)). Dose–response relationships for pain scores (\( p = 0.006 \)) and global performance ratings (\( p = 0.0001 \)) were demonstrated by comparing patients’ response to OTFC at the starting and final dose. The most common adverse effects on days that any
OTFC was taken were somnolence (18 patients), dizziness (9), nausea (6), and headache (3) and during the final two days of the study were somnolence (10 patients), dizziness (4), and nausea (3). Seven patients were hospitalized; in six cases the cause was unrelated to OTFC, in one case the investigator could not rule out a possible relationship to OTFC.

**OTFC vs. placebo.** Of the 130 patients recruited 93 (72%) were able to titrate and find a safe and effective dose of OTFC using a single unit to treat their breakthrough pain. The mean ± SD successful OTFC dose was 789 ± 468 µg. The reasons for not completing the titration were patient choice (15 patients), disease progression (12), and adverse effects (10). Of the 93 patients eligible for randomization, 51 (55%) were female, mean ± SD age of all patients was 54 ± 12 years and the commonest cancers were breast (21 patients), lung (17), and colorectal (12). Most patients were using either oral morphine (63 patients) or transdermal fentanyl (21) as their ATC opioid; the other ATC opioids were methadone (5 patients) and oxycodone (3). The mean ± SD daily morphine equivalent dose of oral ATC medication was 166 ± 137 mg and for transdermal fentanyl was 102 ± 58 µg/h. Patients were using a variety of rescue medication, the commonest of which were oxycodone (16 patients), morphine (15), hydrocodone (11), hydromorphone (10), and propoxyphene (6). The mean ± SD morphine equivalent of rescue medication for each breakthrough pain episodes was 18 ± 18 mg. The ratio of oral and transdermal ATC opioid to rescue medication ± SD (range) was 0.14 ± 0.13 (0.02–0.71) and 0.11 ± 0.05 (0.03–0.2) respectively. The pathophysiology of target breakthrough pains was somatic (48 patients), visceral (29), neuropathic (13), and unknown (2).

Ninety-two patients agreed to enter the randomized double blind phase; seven withdrew during this phase because of adverse effects. Eighty-six patients generated assessable data from 730 episodes of breakthrough pain. OTFC produced significantly better pain relief than placebo as evidenced by better pain intensity and pain relief scores for all time points ($p < 0.0001$). Patients rated the global performance of OTFC better than placebo (1.98 vs. 1.19, $p < 0.0001$) and required significantly less additional rescue medication when using OTFC than when using placebo (34% vs. 15%, $p < 0.0001$). Of the original 92 patients, 74 (80%) chose to continue to treat their breakthrough pain with OTFC following the trial. The most frequent opioid related adverse effects reported for all 130 patients initially enrolled in the trial as possibly related to OTFC were dizziness (22 patients), nausea (18), somnolence (11), constipation (7), asthenia (6), confusion (5), vomiting (4), and pruritus (4).

**OTFC versus normal release morphine.** Of the 134 patients recruited 93 (69%) were able to titrate and find a safe and effective dose of OTFC using a single unit to treat their breakthrough pain. The commonest reasons for not completing the titration were protocol violation (17 patients) and adverse effects (14); in five patients adverse effects were OTFC related. Five patients titrated to the 1600 µg dose without obtaining adequate relief. Of the 93 patients eligible for randomization, 89 used at least one set of study medication and of these 47 (53%) were male, mean ± SD age of all patients was 55 ± 11 years and the commonest cancers were lung (15 patients), breast (14), and colorectal (13). Patients ATC opioids included morphine (43 patients), transdermal fentanyl (28), oxycodone (14), methadone (3), and hydrocodone (1). Patients were using a variety of rescue medication, the commonest of which were morphine (66 patients), oxycodone (11), hydrocodone (4), hydromorphone (3), and propoxyphene (1). The pathophysiology of target breakthrough pains was somatic (46 patients), visceral (25), neuropathic (17), and unknown (1).

The mean ± SD normal release morphine and OTFC doses for the 93 patients enrolled to the double blind phase of the study was 31 ± 13.5 mg and 811 ± 452 µg respectively. There was no relationship between the normal release morphine and OTFC doses ($R^2 = 0.065$) nor between the successful dose of rescue medication (either normal release morphine or OTFC) and ATC oral or transdermal opioid. In the primary efficacy analysis (for patients who have at least one evaluable episode for each study drug; $n = 75$) OTFC was significantly superior to normal release morphine in terms of pain intensity difference ($p < 0.008$) and pain relief ($p < 0.009$) at each time point, and global performance rating ($p < 0.001$). In addition, significantly ($p < 0.001$) more pain episodes treated with OTFC had a greater than 33% change in pain intensity at 15 minutes than normal release morphine, implying faster onset of action with OTFC. The most frequent reported adverse effects in 134 patients were somnolence (20 patients), nausea (18), constipation (14), and dizziness (10). All adverse effects occurred during either OTFC titration or the double blind phase, at which time patients were receiving ATC opioid, OTFC, and normal release morphine, consequently it is difficult to attribute an adverse effect specifically to OTFC or normal release morphine. Eighteen patients withdrew from the study due to adverse effects, six of which were considered at least partly due to study medication.

**OTFC vs. intravenous morphine.** Of the 25 patients recruited the mean age was 59 years, and 52% were female. The pathophysiology of breakthrough pains
was somatic (9 patients), visceral (4), neuropathic (4), and mixed (8). The background opioid morphine dose was 120 mg (95% confidence interval, CI, 96–144). All patients had their background pain under control (mean 2.9, 95% CI 2.3–3.6). Patients completed 53 couples of breakthrough pain episodes each randomly treated with intravenous morphine and OTFC, during admission; 25 couples were intravenous morphine/OTFC sequences, and 28 were OTFC/intravenous morphine sequences.

In breakthrough pain episodes treated with intravenous morphine, pain intensity decreased from 6.9 (95% CI 6.6–7.2) to 3.3 (95% CI 2.7–3.8) and 1.7 (95% CI 1.2–2.3) at 15 and 30 min, respectively. In episodes treated with OTFC, pain intensity decreased from 6.9 (95% CI 6.6–7.2) to 4.1 (95% CI 3.6–4.7) and 2.4 (95% CI 1.8–2.9) at 15 and 30 min, respectively. This reduction was more than 33% in 30 (57%) and 45 episodes (85%) at 15 and 30 min, respectively. A statistical difference between the two treatments was found at 15 min but not 30 min. No differences between the two groups were observed in the number of episodes with a reduction of more than 33% and 50% at 15 and 30 min, respectively. The outcome was not related to the background regimen. Adverse effects occurring after intravenous morphine and OTFC were comparable and corresponded to those commonly observed with opioid therapy. Moderate adverse effects in episodes treated with OTFC were: nausea (4 episodes), drowsiness (7), and confusion (1). Moderate adverse effects in episodes treated with intravenous morphine were: nausea (2 episodes), drowsiness (10), and confusion (3). No severe adverse effect was recorded.

**FBT versus placebo.** Of the 252 patients enrolled in the studies, 164 (65%) achieved a successful dose and entered the double-blind treatment phase. Of the 84 patients who discontinued treatment during the titration phase, 28 (11% of those enrolled) withdrew because of lack of efficacy and 26 (10%) because of adverse events. During double-blind treatment, 150 of the 164 patients fulfilled the criteria for efficacy analysis. The mean age ± SD was 55.2 ± 12.6 years, 47% were men and 84% Caucasian. Baseline pain was predominantly neuropathic in 20% of patients, nociceptive in 46% and mixed in 34%; the location of pain varied widely. The mean dose of baseline ATC medication was 232.9 mg/day of oral morphine equivalents. The mean dosage of rescue medication (oral morphine equivalents) was 23.9 mg/breakthrough pain episode. Among the 150 patients included in the efficacy analysis, the successful dose of FBT was 100 µg for 13 patients (9%), 200 µg for 20 (13%), 400 µg for 33 (22%), 600 µg for 32 (21%), and 800 µg for 52 (35%).

During the double-blind treatment phase the 150 enrolled patients experienced 1417 episodes of breakthrough pain, which they treated with FBT (986 episodes) or placebo (431 episodes). The mean PI score at baseline was 6.6. Twenty-one patients discontinued this phase, eight (5%) withdrew due to adverse events, and seven (4%) withdrew their consent. A total of 248 patients constituted the safety analysis set. In one study the primary outcome measure was SPID₃₀ and the mean ± SE SPID₃₀ for FBT was 3.0 ± 0.12 versus 1.8 ± 0.18 for placebo (p < 0.0001); measures of pain relief (PR), pain intensity difference (PID), summed pain intensity difference (SPID), summed total PR, and patient ratings of global performance of medication significantly favoured FBT over placebo at all time points. In the second study the primary outcome measure was SPID₆₀, which also significantly favoured FBT vs. placebo (mean ± SE, 9.7 ± 0.63 vs. 4.9 ± 0.50, p < 0.0001). Secondary measures in this study also favoured FBT: PIDs and PR showed significant differences versus placebo at 10 minutes (0.9 versus 0.5; 0.815 vs. 0.606, respectively, p < 0.0001) and all subsequent time points (p < 0.0001). The adverse events noted in both studies were generally typical of those experienced by patients with cancer utilizing potent opioids. Most adverse events were classified as either mild or moderate in intensity and were transitory. The most common adverse events were nausea 43 patients (17%), dizziness 41 (17%), headache 26 (10%), fatigue 25 (10%), vomiting 21 (8%), constipation 17 (7%), asthenia 14 (6%), and somnolence 12 (5%). Application site abnormalities considered to be related to treatment were seen in 18 patients (7%) and led to the discontinuation of three patients. Serious adverse events were recorded for 10% of 25/248) of patients and all were considered by the investigators to be related to underlying conditions.

**INFS versus placebo.** A total of 120 patients were enrolled and achieved an effective dose; 113 were randomized and 111 were included in the intent-to-treat (ITT) analysis set (56 males, 55 females; mean ± SD age, 60.6 ± 9.5 years). The most frequently reported primary tumour sites were the breast (18 patients) and lung or respiratory system (17). The opioid medications most frequently used to treat background pain were fentanyl (60 patients) and morphine (48). The majority of patients were receiving low doses (equivalent to oral morphine ≤180 mg/d) of background pain opioid medication, while 23 (20.7%) and 13 (11.7%) were receiving intermediate doses (>180–360 mg/d) and high doses (>360 mg/d), respectively. The most frequently used pre-trial rescue medication was oral morphine (101/111) patients.

The majority (98.2%) of the 111 patients in the ITT set had six episodes of breakthrough pain treated with
INFS and two episodes for which placebo was administered (110 patients). Eighteen patients were titrated to a dose of 50 μg of INFS; 48 patients to 100 μg; and 45 patients to 200 μg. Use of INFS at all doses was associated with adjusted mean (95% CI) $\text{PID}_{10}$ scores that were significantly higher than those with placebo (2.36 [2.16–2.56] vs. 1.10 [0.84–1.36], respectively; adjusted difference, 1.26 [1.03–1.48], $p < 0.001$). Mean PID scores with INFS (pooled doses) were significantly higher compared with those with placebo at 10, 20, 40, and 60 minutes after administration (all, $p < 0.001$). The mean PID scores at 20, 40, and 60 minutes were significantly higher with each dose of INFS compared with placebo (at all time points, $p < 0.05$ for 50 μg vs. placebo and $p < 0.001$ for 100 and 200 μg vs. placebo). Mean PID scores were significantly increased with increases in dose and time after administration with INFS compared with placebo (all, $p < 0.001$). The prevalence of adverse effects was 22/111 (19.8%) during the efficacy period, during which the most frequently reported adverse effects were nausea (5 patients) and vertigo (2). No serious adverse effects were considered related to the study drugs. In all, 108 patients entered the extension period, with a mean duration of exposure to INFS of 134.9 days. Progression of underlying malignant disease was the most common adverse effects reported during this period (55 patients); this event was not considered treatment related.

Comparison of pain intensity difference at either 10 or 15 minutes after drug administration is shown for the identified studies in Figures 1, 2, and 3. Given the different methodologies not all studies have data for both time points.

**Discussion**

Breakthrough pain is a heterogeneous phenomenon commonly managed with orally administered normal release opioids. It has been standard practice to use the same opioid for the treatment of background and breakthrough pain, but in different formulations, such as modified release morphine for background pain and normal release morphine for breakthrough pain. Although this may seem rational during titration of uncontrolled background pain there is no evidence to suggest it is necessary for breakthrough pain. Indeed the studies identified in this review suggest that fentanyl can be used successfully in patients using a variety of oral ATC opioids including morphine, oxycodone, hydromorphone, and methadone.

Only eight randomized controlled studies on the use of opioids in the management of breakthrough pain were identified in this review. Most were industry sponsored studies undertaken for registration of transmucosal opioids products specifically developed for the management of breakthrough pain. The studies identified investigating buccal and nasal delivery of opioids demonstrated that these routes can be safely used to provide analgesia and can have an onset of action within 10 minutes of administration. Comparison of transmucosal and parenteral opioids showed superiority for later at 15 minutes; the two routes were equally effective at 30 minutes. Adverse effects were typical of those experienced by cancer patients using potent opioids; however, all patients were also taking concomitant ATC opioids thus it was not possible to definitively separate the effects of transmucosal opioids alone. Adverse effects were generally mild and tolerable, serious adverse events were commonly considered by the investigators to be related to underlying conditions. Other buccal, sublingual and nasal preparations have been developed but data were not available at the time of this review.

When prescribing opioids for either background or breakthrough cancer pain, the oral route is preferred often because it is convenient and usually inexpensive. Normal release formulations of oral opioids are commonly used for breakthrough pain but despite this the oral delivery of rescue medication has not been formally tested, except in one study comparing OTFC against oral morphine that found the latter to be an inferior comparator.

Although one study found fixed doses of intravenous and transmucosal opioids to be effective for breakthrough pain, most found no correlation between the ATC opioid dose and transmucosal or oral rescue opioid doses. This finding does not appear to support the previous EAPC recommendation on the use of rescue medication, which recommends the equivalent four-hourly dose of morphine be administered for breakthrough pain. It is not clear whether the recommendation related to end-of-dose pain resulting from uncontrolled background pain or breakthrough pain as in the text the recommendation the authors state that optimal dose for breakthrough pain may only be determined by titration. As breakthrough pain can vary in severity, duration, aetiology, and pathophysiology it is possible the dose may also vary. Some clinicians have therefore recommended individualization and titration for both oral and transmucosal rescue opioids. Although all the identified studies are randomized direct comparison is of limited value as there is significant variation between studies in parameters such as baseline pain intensity, titration protocols, study endpoints, and use of rescue medication. Figures 1, 2, and 3 therefore give only an indication of efficacy within the individual studies; double-blind, double-dummy, head-to-head studies would be required to make
**Figure 1.** Weighted mean pain intensity difference at 10 minutes following transmucosal fentanyl or comparator.

**Figure 2.** Weighted mean pain intensity difference at 15 minutes following transmucosal fentanyl or comparator.

**Figure 3.** Weighted mean pain intensity difference at 15 minutes following oral transmucosal fentanyl citrate or intravenous morphine.
a judgement as to relative efficacy of individual formulations.

**Conclusion**

In conclusion, this review identified eight studies describing the use of transmucosal and parental opioids in the management of breakthrough pain. Most studies reported the utility of transmucosal fentanyl products and confirmed their efficacy, safety, and tolerability provided that they are first titrated to a successful dose in the individual patients already using opioids as ATC medication. One study demonstrated the utility of parenteral morphine and its faster onset of action compared with transmucosal fentanyl. More evidence is required to support the use of oral opioids for the management of breakthrough pain.

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