Therapeutic Class Overview
Fentanyl Immediate-Release

Therapeutic Class

- **Overview/Summary:** Pain is one of the most common symptoms associated with cancer.[1] Patients with cancer experience both chronic and acute pain, and it is important to distinguish the two from each other when determining appropriate management strategies. Acute or breakthrough pain is commonly defined as a transient increase in pain intensity over otherwise stable pain (background pain) in a patient receiving chronic opioid therapy, and is a common and distinct component of cancer pain.[2,3] In this specific patient population, breakthrough pain is considered a clinical problem and supplemental opioid doses are used to manage painful episodes.[1,3] Any of the available short-acting opioids have the potential to be utilized for the management of breakthrough pain; however, immediate-release fentanyl products are Food and Drug Administration (FDA) approved for the management of breakthrough cancer pain. Moreover, these agents are specifically indicated for use in patients who are already receiving and who are tolerant to around-the-clock therapy for their underlying persistent cancer pain (opioid-tolerant).[4-9] According to the FDA, patients considered opioid-tolerant are those who are regularly taking daily doses of at least 60 mg oral morphine, 30 mg oral oxycodone, 8 mg oral hydromorphone, 25 mg oral oxymorphone, 25 µg transdermal fentanyl per hour, or an equianalgesic dose of another opioid for one week or longer.[10] Six different dosage formulations of immediate-release fentanyl are currently available: a buccal film (Onsolis®), buccal tablet (Fentora®), nasal spray (Lazanda®), sublingual spray (Subsys®), sublingual tablet (Abstral®) and a transmucosal lozenge (Actiq®). Currently, only the fentanyl citrate transmucosal lozenge is available generically.[11] Clinical trials have consistently demonstrated the well-established effectiveness of immediate-release fentanyl in the management of breakthrough pain in patients with cancer; however, there is limited evidence regarding head-to-head trials among the different formulations.

Table 1. Current Medications Available in the Therapeutic Class[4-9]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Fentanyl, sublingual spray (Subsys®)	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain†	Sublingual spray: 100 µg 200 µg 400 µg 600 µg 800 µg 1,200 µg (2x600 µg) 1,600 µg (2x800 µg)	-
Fentanyl citrate, buccal film (Onsolis®)	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain†	Buccal film: 200 µg 400 µg 600 µg 800 µg 1,200 µg	-
Fentanyl citrate, buccal tablet (Fentora®)	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain†	Buccal tablet: 100 µg 200 µg 400 µg 600 µg 800 µg	-
Fentanyl citrate, nasal spray (Lazanda®)	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain†	Nasal spray: 100 µg/spray 400 µg/spray	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Fentanyl citrate, sublingual tablet (Abstral®)	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain†	Sublingual tablet: 100 µg 200 µg 300 µg 400 µg 600 µg 800 µg	-
Fentanyl citrate, transmucosal lozenge (Actiq®*)	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain‡	Transmucosal lozenge: 200 µg 400 µg 600 µg 800 µg 1,200 µg 1,600 µg	✔

*Generic available in one dosage form or strength.
†Abstral®, Fentora®, Lazanda®, Onsolis® and Subsys® are Food and Drug Administration (FDA) approved for use in patients ≥18 years of age.
‡Actiq® is FDA approved for use in patients ≥16 years of age.

Evidence-based Medicine

- One Cochrane Review of four randomized-controlled trials evaluating transmucosal fentanyl citrate for breakthrough pain (BTP) in patients with cancer demonstrated that treatment significantly improved pain intensity compared to placebo, immediate-release morphine sulfate and previous BTP medication at 15 and 30 minutes post dose.[2]
- A meta-analysis compared fentanyl buccal tablets, sublingual tablets and transmucosal lozenges to both placebo and immediate-release morphine sulfate. Authors of this study found that the probability of each formulation being 'superior' to placebo, with regard to pain intensity difference (PID) over 60 minutes was 97, 72 and 66% for buccal tablets, sublingual tablets and transmucosal lozenges, respectively. The probability of immediate-release morphine sulfate being 'superior' to placebo was 61%. When compared directly to morphine sulfate, none of the fentanyl preparations had significantly greater PID scores.[12] In addition, Davies et al and Fallon et al both found fentanyl nasal spray to have significantly greater PID scores as early as 10 and 15 minutes, respectively, when compared to immediate-release morphine sulfate (P<0.05).[13,14]
- One open-label, cross-over study evaluated the efficacy of fentanyl nasal spray compared to fentanyl transmucosal lozenge. The primary efficacy endpoint, the time to onset of "meaningful" pain relief, was 11 minutes for the fentanyl nasal spray group and 16 minutes for fentanyl transmucosal lozenge group. The adjusted mean PID_{10} and PID_{30} scores were also significantly greater for the fentanyl nasal spray group compared to the fentanyl lozenge group (P<0.001).[15]
- The results of a meta-analysis by Vissers et al demonstrated that differences in PID_{15} scores favoring fentanyl nasal spray were 1.2 (95% confidence interval, 0.8 to 1.5) relative to the buccal tablet and 1.3 (95% confidence interval, 0.9 to 1.6) relative to the transmucosal lozenge. The significant difference in pain intensity scores favoring fentanyl nasal spray was maintained up to 45 minutes compared to the buccal tablet and up to 60 minutes compared to the transmucosal lozenge.[16]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The World Health Organization promotes the three-step analgesic ladder as a framework for the rational use of analgesic medications in the treatment of cancer pain.
        - Step I specifies the use of non-opioid analgesics.
        - Step II recommends adding an opioid for mild to moderate pain.

        - Step III includes the use of an opioid for moderate to severe pain, with or without non-opioids. If needed, adjuvant drugs can be used at each step.[17]
    - According to the National Comprehensive Cancer Network (NCCN), rescue doses of short-acting opioids should be provided to patients with cancer pain that is not relieved by regularly scheduled, around-the-clock opioid doses.[1]
    - None of the current clinical guidelines give preference to one formulation over the other. The NCCN adult cancer pain guidelines state that consideration should be given to transmucosal fentanyl (without preference given to one method of drug delivery) in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of a long-acting, around-the-clock opioid analgesic.[1]

- Other Key Facts:
    - Currently, only the fentanyl citrate transmucosal lozenge (Actiq®) is available generically.[11]

References

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Therapeutic Class Review
Fentanyl Immediate-Release

Overview/Summary

Pain is one of the most common symptoms associated with cancer.[1] Cancer pain or cancer-related pain distinguishes pain experienced by cancer patients from that experienced by patients without malignancies. Patients with cancer experience both chronic and acute pain, and it is important to distinguish the two from each other when determining appropriate management strategies. Acute or breakthrough pain is commonly defined as a transient increase in pain intensity over otherwise stable pain (background pain) in a patient receiving chronic opioid therapy, and is a common and distinct component of cancer pain.[2,3] In this specific patient population, breakthrough pain is considered a clinical problem and supplemental opioid doses are used to manage episodes.[1,3] Characteristics of breakthrough pain include a rapid onset, severe intensity and a self-limiting course with an average duration of 30 minutes.[2] Patient and caregiver quality of life may be profoundly affected by breakthrough pain, as well as the patient's ability to function.

The World Health Organization has promoted the three-step analgesic ladder as a framework for the rational use of analgesic medications in the treatment of cancer pain. Step I specifies the use of non-opioid analgesics. If this does not relieve the pain, step II recommends adding an opioid for mild to moderate pain. Step III includes the use of an opioid for moderate to severe pain, with or without non-opioids. If needed, adjuvant drugs can be used at each step.[6] Three proposed principles for the management of breakthrough pain include the implementation of primary therapies for the underlying etiology of pain (chemotherapy, radiation, or surgery), optimizing around-the-clock analgesic medications and utilizing specific pharmacological interventions for the breakthrough pain such as supplemental analgesics.[2] According to the National Comprehensive Cancer Network (NCCN), rescue doses of short-acting opioids should be provided to patients with cancer for pain that is not relieved by regularly scheduled, around-the-clock opioid doses.[1]

Any of the available short-acting opioids have the potential to be utilized for the management of breakthrough pain; however, immediate-release fentanyl products (Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis®, Subsys®), due to a fast onset of action, are specifically Food and Drug Administration (FDA) approved for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to around-the-clock therapy for their underlying persistent cancer pain.[5-10] Six different dosage forms of immediate-release fentanyl are currently available; a buccal film (Onsolis®), a buccal tablet (Fentora®), a nasal spray (Lazanda®), a sublingual spray (Subsys®), a sublingual tablet (Abstral®) and a transmucosal lozenge (Actiq®). Currently, only the fentanyl citrate transmucosal lozenge is available generically.

Clinical trials have consistently demonstrated the well-established effectiveness of immediate-release fentanyl in the management of breakthrough pain in patients with cancer, however there is limited evidence regarding head-to-head trials among the different formulations. Currently, none of the current clinical guidelines give preference to one formulation over the other. The NCCN adult cancer pain guidelines state consideration be given to transmucosal fentanyl (various formulations and delivery systems are available, without preference given to one method of drug delivery) in opioid tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of a long-acting, around-the-clock opioid analgesic.[1] According to the FDA, patients considered opioid-tolerant are those who are regularly taking daily doses of at least 60 mg oral morphine, 30 mg oral oxycodone, 8 mg oral hydromorphone, 25 mg oral oxymorphone, 25 µg transdermal fentanyl per hour, or an equianalgesic dose of another opioid for one week or longer.[11]

Medications

Table 1. Medications Included Within Class Review[5-10]

Generic Name (Trade Name)	Medication Class	Generic Availability
Fentanyl, sublingual spray (Subsys®)	Opioid agonist	-
Fentanyl citrate, buccal film (Onsolis®)	Opioid agonist	-
Fentanyl citrate, buccal tablet (Fentora®)	Opioid agonist	-
Fentanyl citrate, nasal spray (Lazanda®)	Opioid agonist	-
Fentanyl citrate, sublingual tablet (Abstral®)	Opioid agonist	-
Fentanyl citrate, transmucosal lozenge (Actiq®)	Opioid agonist	✔

Indications

Table 2. Food and Drug Administration Approved Indications[5-10]

Generic Name	Management of Breakthrough Cancer Pain in Patients Already Receiving and Who are Tolerant to Opioid Therapy for Their Underlying Persistent Cancer Pain*†
Fentanyl, sublingual spray	✔
Fentanyl citrate, buccal film	✔
Fentanyl citrate, buccal tablet	✔
Fentanyl citrate, nasal spray	✔
Fentanyl citrate, sublingual tablet	✔
Fentanyl citrate, transmucosal lozenge	✔

*Actiq® is Food and Drug Administration (FDA) approved for use in patients ≥16 years of age.
†Abstral®, Fentora®, Lazanda®, Onsolis® and Subsys® are FDA approved for use in patients ≥18 years of age.

In addition to their Food and Drug Administration approved indication, fentanyl citrate agents may also be used off-label in the management of obstetric pain and for analgesia for mechanically ventilated patients in intensive care units and procedural sedation.[12]

Pharmacokinetics

Table 3. Pharmacokinetics[5-10]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (Hours)
Fentanyl, sublingual spray	76	<7	None	5.0 to 12.0
Fentanyl citrate, buccal film	71	<7	None	14.0
Fentanyl citrate, buccal tablet	65	<7	None	2.6 to 11.7
Fentanyl citrate, nasal spray	Unknown	<7	None	15.0 to 24.9
Fentanyl citrate, sublingual tablet	54	<7	None	5.0 to 10.1
Fentanyl citrate, transmucosal lozenge	50	<7	None	7.0

Clinical Trials

As a well-established opioid, clinical trials have consistently demonstrated the effectiveness and safety of all available dosage forms of immediate-release fentanyl in the management of breakthrough pain (BTP) in patients with cancer. Several trials have compared the agents to placebo and other short-acting opioids (including oxycodone, morphine, hydrocodone, hydromorphone, and codeine). Due to the nature of the disease in which immediate-release fentanyl is utilized, the majority of the efficacy clinical trials are open-label, dose titration trials. Patients typically enrolled in a baseline phase in which the efficacy of their usual BTP medication was assessed and/or the dose of the studied immediate-release fentanyl product was titrated to an effective dose.[13-35]

Trials conducted to compare immediate-release fentanyl to other short-acting opioids have generally shown immediate-release fentanyl products to improve pain relief at a significantly faster rate. One Cochrane Review of four randomized-controlled trials evaluating transmucosal fentanyl citrate for BTP in patients with cancer demonstrated that treatment significantly improved pain intensity compared to placebo, immediate-release morphine and previous BTP medication at 15 and 30 minutes post dose.[2] Another meta-analysis compared fentanyl buccal tablets, sublingual tablets and transmucosal lozenges to both placebo and immediate-release morphine. Authors of this study found that the probability of each formulation being 'superior' to placebo, in regards to pain intensity difference (PID) over 60 minutes, were 97, 72 and 81% for buccal tablets, sublingual tablets and transmucosal lozenges, respectively. The probability of immediate-release morphine being 'superior' to placebo was 61%. When compared directly to morphine, none of the fentanyl preparations had significantly greater PID scores. Additionally, Davies et al. and Fallon et al. both found fentanyl nasal spray to have significantly greater PID scores as early as 10 and 15 minutes, respectively, when compared to immediate-release morphine (P<0.05).

There is limited evidence directly comparing the efficacy among all the various formulations of immediate-release fentanyl products, however there is evidence comparing the fentanyl nasal spray, transmucosal tablet and buccal tablet. One open-label, cross-over study evaluated the efficacy of fentanyl nasal spray compared to fentanyl transmucosal lozenge. The primary efficacy endpoint, defined as the time to onset of "meaningful" pain relief, was 11 minutes for the fentanyl nasal spray group and 16 minutes for fentanyl transmucosal lozenge group. The adjusted mean PID_{10} and PID_{30} scores were also significantly greater for the fentanyl nasal spray group compared to the fentanyl lozenge group (P<0.001). Additionally, a meta-analysis by Vissers et al. found that differences in PID_{15} scores favoring fentanyl nasal spray were 1.2 (95% confidence interval, 0.8 to 1.5) relative to the buccal tablet and 1.3 (95% confidence interval, 0.9 to 1.6) relative to the transmucosal lozenge. The significant difference in pain intensity scores favoring fentanyl nasal spray was maintained up to 45 minutes compared to the buccal tablet and up to 60 minutes compared to the transmucosal lozenge.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Rauck et al[13] Fentanyl sublingual spray (100 to 1,600 µg) vs placebo Fentanyl sublingual spray was titrated up to 1,600 µg until an effective dose was reached. After titration to an effective dose of fentanyl sublingual spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo).	DB, MC, OL, PC, RCT Adult patients with cancer, experiencing persistent cancer or treatment-related pain of no more than moderate severity, receiving ≥60 mg oral morphine, 30 mg oxycodone or 8 mg oral hydromorphone/ day or 25 µg transdermal fentanyl/hour or equivalent	N=130 10 BTP episodes	Primary: $SPID_{30}$ Secondary: $TOTPAR_{30}$, global evaluation of study medication at 30 minutes	Primary: The mean (SE) $SPID_{30}$ score was 640.3 (47.8) for fentanyl sublingual spray and 399.6 (40.8) for placebo; corresponding to a mean treatment difference of 240.7 (37.8) (P<0.0001). A significant difference in SPID values for episodes treated with fentanyl compared to placebo was seen as early as five minutes and maintained for up to 60 minutes. After 30 minutes, 79.3% of patients showed greater improvement with fentanyl sublingual spray compared to placebo (P<0.0001). Secondary: TOTPAR scores from 5 to 60 minutes were significantly greater in episodes treated with fentanyl sublingual spray compared to episodes treated with placebo (P<0.0001 for all time points). The $TOTPAR_{30}$ score in episodes treated with fentanyl sublingual spray was 78.3 compared to 61.0 in episodes treated with placebo (P<0.0001). After 30 minutes, the global evaluation of treatment effectiveness score was 2.8 for fentanyl sublingual spray compared to 2.0 for placebo (P<0.0001). This significant difference was maintained at 60 minutes as well.
Rauck et al[14] Fentanyl buccal film 200 µg vs placebo Patients were provided with a titration kit consisting of five units	DB, MC, PC, RCT, XO Patients ≥18 years of age with pain associated with cancer or cancer treatment, receiving stable opioid therapy equivalent to 60	N=151 Up to 14 days or 9 BTP episodes	Primary: $SPID_{30}$ Secondary: SPID at 5, 10, 15, 45, and 60 minutes post dose, pain intensity difference, pain relief, global satisfaction	Primary: Mean±SEM $SPID_{30}$ values for fentanyl buccal film treated BTP episodes were significantly greater than for placebo treated BTP episodes (47.9±3.9 vs 38.1±4.3; P=0.004). Secondary: SPID values for buccal film fentanyl treated BTP episodes were significantly greater than for placebo from 15 minutes through 60 minutes post dose (all P<0.05). The mean pain intensity differences and pain relief for fentanyl treated BTP episodes were significantly greater (improved) than for placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
each of 200, 400, 600, 800 and 1,200 µg doses of fentanyl buccal film. After titration to an effective dose of fentanyl buccal film, patients received nine doses of study medication (six contained fentanyl and three were placebo). If adequate pain relief was not experienced after 30 minutes, patients were instructed to use their usual BTP medication if needed.	to 1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl, that had one to four BTP episodes/day despite persistent opioid therapy and who achieved at least partial relief from opioid therapy			treated BTP episodes beginning at 30 minutes post dose (P<0.05). There was a significantly greater percentage of BTP episodes with a 33 or 50% decrease in pain with buccal film fentanyl compared to placebo starting at 30 minutes post dose (P<0.01). The percentage of BTP episodes when rescue medication was required was significantly lower when treated with buccal film fentanyl (30.0%±3.5%) than when treated with placebo (44.6%±4.4%; P=0.002). More patients rated their overall satisfaction with buccal film fentanyl as 'good', 'very good' or 'excellent' compared to placebo and fewer patients rated their overall satisfaction with buccal film fentanyl as 'poor' or 'fair' compared to placebo. The overall satisfaction with the study drug was greater with fentanyl buccal film compared to placebo (mean score, 2.0 vs 1.5; P<0.001). The most commonly reported adverse events included nausea (9.9%), vomiting (9.9%), and headache (1.2%). Twenty-three patients (15.3%) experienced a serious adverse event. None of the serious adverse events (including four deaths) were considered study drug-related.
Slatkin et al[15] Fentanyl buccal film 200 µg Fentanyl buccal film was titrated up to 2,400 µg until the patient received adequate pain relief. If adequate pain relief was not experienced after 30 minutes, patients were instructed to use their usual BTP medication if	MC, OL Adult patients with chronic cancer pain, who had one to four BTP episodes/day despite the use of a stable scheduled opioid regimen equivalent to at least 60 mg/day of oral morphine	N=220 17 months	Primary: Safety and tolerability Secondary: Global evaluation of medication performance	Primary: One hundred sixty eight of 179 patients (94%) did not require doses above the recommended dose range of 200 to 1,200 µg. The most frequently reported treatment-related adverse events were those commonly associated with the treatment of cancer pain, including opioid use. The most common adverse events considered treatment-related were nausea (8.6%), dizziness (5.5%), constipation (5.0%), somnolence (4.5%), vomiting (2.7%) and headache (2.3%). Three patients (1.4%) experienced stomatitis which was considered potentially related to study drug. All three cases were considered mild and did not require study discontinuation. Eighty-six patients experienced 134 severe adverse events. No serious adverse events (including 50 deaths) were attributed to buccal film fentanyl. Seventeen of 179 patients (7.6%) discontinued the medication due to adverse

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
needed.				events. Secondary: Rescue medication was required in 10.2% of all BTP episodes treated. Six of 179 patients (3.4%) withdrew from the study due to lack of efficacy. Patient's global perception of study medication performance was rated as 'good,' 'very good,' or 'excellent' in 84.8% of BTP episodes treated, and 'poor' in 1.9% of BTP episodes.
Portenoy et al[16] Fentanyl buccal tablet vs placebo Enrolled patients began with an OL titration phase to identify an effective dose of fentanyl buccal tablet ranging from 100 to 800 µg. After titration to an effective dose of fentanyl buccal tablet, patients received ten doses of study medication (seven contained fentanyl and three were placebo).	PC, RCT, XO Adults with chronic cancer pain receiving 60 to 1,000 mg/day of oral morphine or equivalent or 50 to 300 µg/hour of transdermal fentanyl for at least one week who experienced one to four episodes of BTP per day	N=123 Duration not reported	Primary: $SPID_{30}$ Secondary: Pain relief and pain intensity difference scores, TOTPAR, global medication performance assessment, need for supplemental medication, proportion of episodes in which there were ≥33 or ≥50% improvement in pain intensity scores	Primary: The mean (±SD) $SPID_{30}$ was 3.00 (±0.12) vs 1.80 (±0.14) for fentanyl buccal tablet compared to placebo (*P*<0.0001). Secondary: The mean pain relief and pain intensity difference scores were significantly higher in the fentanyl group compared to the placebo group at each time point (*P*<0.003 at 15 minutes for both; *P*<0.0001 for all other time points for both). TOTPAR scores were significantly higher in the fentanyl group compared to the placebo group at all time points (*P*<0.0001 for all). At 30 minutes after treatment, 48% of fentanyl treated patients had ≥33% improvement in pain intensity score compared to 29% of placebo patients (*P*<0.0001). At the same time point, 24% of fentanyl treated patients had ≥50% improvement in pain intensity score compared to 16% of placebo patients (*P*=0.0023). A significant difference in clinical improvement (≥33%) between the two groups was seen as early as 15 minutes (*P*=0.045). Global performance assessment ratings showed that fentanyl received a significantly higher satisfaction rating than placebo at both 30 and 60 minutes (*P*<0.0001 for both). Supplemental medication was needed in 23% of episodes treated with fentanyl compared to 50% of episodes treated with placebo (RR, 0.47; 95% CI, 0.37 to 0.60).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Two percent of patients withdrew from the study because of application site ulcers of the oral mucosa deemed by the investigators to be related to the study drug.
Slatkin et al[17] Fentanyl buccal tablet Patients were provided with a titration kit consisting of 100, 200, 400, 600, and 800 µg doses of fentanyl buccal tablet. The starting dose and subsequent titration doses were specified in the protocol based on the medications the patient was using to treat BTP immediately before study enrollment. If adequate pain relief was not experienced after 30 minutes, patients were instructed to use their usual BTP medication if needed. After titration to an effective dose of fentanyl buccal tablet, patients were given ten randomly	DB, PC, RCT, XO Patients 18 to 80 years of age with a histologically documented diagnosis of a malignant solid tumor or a hematologic malignancy causing cancer-related pain, a life expectancy ≥2 months; the use of a fixed-dose, around-the-clock opioid regimen for persistent pain (oral morphine ≥60 mg/day, transdermal fentanyl ≥25 µg/hour, or an equivalent dose of an alternative opioid for ≥7 days), an average pain	N=125 Up to 4 weeks	Primary: $SPID_{60}$ Secondary: Pain intensity at 0, 5, 10, 15, 30, 45, 60, 90 and 120 minutes post dose; the percentage of BTP episodes with an improvement in pain intensity scores from baseline ≥33 and ≥50% post dose; pain relief; TOTPAR at 60, 90 and 120 minutes post dose; and proportion of BTP episodes that required the use of supplemental medication	Primary: The $SPID_{60}$ values were significantly greater for BTP episodes treated with fentanyl buccal tablet compared to BTP episodes treated with placebo (mean±SE, 9.70±0.63 vs 4.90±0.50; *P*<0.0001). There were no clinically meaningful differences in $SPID_{60}$ in terms of the different underlying pain pathophysiologies (nociceptive, neuropathic, or mixed). Secondary: As assessed by pain intensity difference, there was a greater reduction in pain intensity following buccal tablet fentanyl than placebo at 10 minutes (0.9 vs 0.5; *P*<0.0001). The difference in pain intensity difference between the two treatments increased at subsequent time points up to 90 minutes post dose and then was maintained through two hours (*P*<0.0001 for each time point). A clinically significant improvement in pain intensity scores from baseline ≥33% occurred in a larger proportion of BTP episodes treated with fentanyl buccal tablet compared to BTP episodes treated with placebo at 10 minutes (16 vs 10%; *P*=0.007), 15 minutes (29 vs 14%; *P*<0.0001) and 30 minutes (51 vs 26%; *P*<0.0001). The differential increased through 60 minutes and was maintained over the two hour observation period (*P*<0.0001 for each subsequent time point). The difference in the proportion of BTP episodes with an improvement in pain intensity ≥50% following buccal tablet fentanyl or placebo was also significant at 10 minutes (7 vs 4%; *P*=0.033), 15 minutes (18 vs 8%; *P*<0.0001), and 30 minutes (38 vs 15%; *P*<0.0001), and continued to increase through two hours (*P*<0.0001). Pain relief was significantly better with fentanyl buccal tablet compared to placebo as early as 10 minutes (0.815 vs 0.606; *P*<0.0001); the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ordered treatment units (seven buccal tablet fentanyl units and three placebo units) in the form of identical tablets.	intensity pain of <7 (11 point numerical scale) for their persistent pain during the 24 hours before consent, a report of one to four BTP episodes/day while taking around-the-clock opioids and the use of an opioid to treat BTP that is at least partially effective			differential increased over time up to 90 minutes and was maintained for two hours (*P*<0.0001 for each time point). Similarly, TOTPAR values were significantly better (*P*<0.0001) following fentanyl buccal tablet compared to placebo at 60, 90, and 120 minutes post dose. Supplemental medication was used for 53/493 (11%) BTP episodes treated with buccal tablet fentanyl compared to 67/223 (30%) episodes treated with placebo (*P* value not reported).
Zeppetella et al[18] Fentanyl buccal tablet vs placebo Combined analysis of patients previously enrolled in Portenoy et al[16] and Slatkin et al[17]. After titration to an effective dose of fentanyl buccal tablet, patients were given ten randomly	DB, PC, RCT Patients ≥18 years of age with a histologically documented diagnosis of a malignant solid tumor or hematological malignancy who were experiencing persistent cancer-related pain and BTP, and who were	N=150 Duration not reported	Primary: Pain intensity, pain relief, global medication performance, use of rescue medication Secondary: Safety and tolerability	Primary: A greater effect was seen on the proportion of the BTP episodes with ≥33 or ≥50% improvement in pain intensity from baseline in the patients administering fentanyl buccal tablet compared to patients administering placebo, starting at the 15 minute time point and continuing to evaluation at 60 minutes (*P*<0.0001 at each time point). At 30 minutes, 59% of the episodes treated with fentanyl buccal tablet and 36% treated with placebo had a ≥2 point improvement in pain intensity, with the relative proportions increasing at 45 minutes to 74 and 44%, respectively (*P*<0.0001 at each time point). The percentage of BTP episodes with at least moderate pain relief also showed a difference, favoring fentanyl buccal tablet over placebo from 15 minutes (*P*=0.0004). At 30 minutes, 47% of the patients who took fentanyl buccal tablet had a least moderate pain relief compared to 28% who took placebo (*P*<0.0001). Respective differences favoring fentanyl buccal tablet over placebo were maintained at 45 minutes (64

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ordered treatment units (seven fentanyl buccal tablet units and three placebo units) in the form of identical tablets.	receiving maintenance opioid therapy for ≥1 week prior to screening			vs 34%; *P*<0.0001) and at 60 minutes (69 vs 39%; *P*<0.0001). At 60 minutes, the mean global medication performance score for fentanyl buccal tablet was 2.1 and 1.2 for placebo (*P* value not reported). Patients were three times more likely to resort to rescue medication for a placebo-treated BTP episode (40 vs 17%; OR, 3.22; 95% CI, 2.43 to 4.28; *P* value not reported). Secondary: The adverse events noted were generally typical of those experienced by patients with cancer who take potent opioids. Most were classified as either mild or moderate in intensity and were transitory. The most common adverse events were nausea and dizziness.
Lennernäs et al[19] Sublingual fentanyl tablet 100 µg vs sublingual fentanyl tablet 200 µg vs sublingual fentanyl tablet 400 µg vs placebo Patients received one	DB, MC, RCT, XO Adult patients with cancer pain that were regularly experiencing at least four episodes of BTP over a period of 14 days and were receiving a fixed-schedule opioid regimen equivalent to 30 to 1,000 mg/day oral morphine or 25 to 300 µg transdermal	N=38 Duration unknown	Primary: Pain intensity difference Secondary: Global assessment of treatment (none, mild, moderate or excellent), need for rescue medication	Primary: A significant overall improvement in pain intensity difference was seen in the fentanyl 400 µg group compared to the placebo group (*P*<0.0001) with the effect first becoming significant after 15 minutes (*P*=0.005). However, a significant difference was not seen in the 100 or 200 µg groups compared to placebo. Secondary: Nine patients reported treatment with fentanyl 400 µg as excellent compared to three with placebo (*P*=0.0146). Five and three patients taking fentanyl 100 and 200 µg, respectively rated treatment as excellent. Significantly fewer patients taking fentanyl 400 µg required rescue medications compared to patients taking placebo (*P*=0.001). Eleven and ten patients required a rescue medication with the 100 and 200 µg doses, respectively (No *P* values reported).

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dose of placebo and one of each of the three doses of fentanyl sublingual tablet in random order for four episodes. Treatment periods were separated by a washout period of at least one day.	fentanyl			
Rauck et al[20] Fentanyl sublingual tablet 100 to 800 µg vs placebo Fentanyl sublingual tablet was titrated up to 800 µg until an effective dose was reached.	DB, MC, PC, RCT Patients ≥17 years of age with stable cancer related pain, experiencing one to four episodes of BTP per day and receiving 60 to 1,000 mg oral morphine per day, transdermal fentanyl 50 to 300 µg per hour or equivalent	N=131 10 BTP episodes 12 month safety phase	Primary: $SPID_{30}$ Secondary: Pain intensity difference and pain relief scores	Primary: The mean $SPID_{30}$ in episodes treated with sublingual fentanyl tablets was 49.5 compared to 36.6 in episodes treated with placebo (*P*=0.0004). The significant difference in SPID score was maintained at 60 minutes (*P*=0.0002). Secondary: Treatment of BTP episodes with sublingual fentanyl tablets showed greater improvements in pain intensity difference scores compared to placebo at ten minutes after treatment administration (*P*=0.0055) and was maintained up to 60 minutes. In addition, pain relief scores were significantly greater in episodes treated with sublingual fentanyl tablets compared to placebo at ten minutes (*P*=0.0490). This significant difference was maintained up to 60 minutes. Among patients treated with sublingual fentanyl tablets, 11.2% required rescue medication compared to 27.4% in the placebo group. (No *P* values reported). During the safety phase, the most common treatment-emergent adverse events were nausea, vomiting, headache and somnolence.
Portenoy et al[21] Fentanyl nasal spray 100 to 800 µg	DB, MC, RCT, PC, XO Adult patients with cancer	N=114 10 BTP episodes	Primary: Patient-averaged, $SPID_{30}$	Primary: The mean (±SD) $SPID_{30}$ score was 6.57 (± 4.99) for fentanyl nasal spray and 4.45 (±5.51) for placebo; corresponding to a mean treatment difference of 2.12 (±3.91) (95% CI, 1.21 to 3.03; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Fentanyl nasal spray was titrated up to 800 µg until the patient received adequate pain relief for each BTP episode. After titration to an effective dose of fentanyl nasal spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo).	experiencing at least one to four BTP episodes daily, who were also receiving fixed-dose opioids for pain at a total daily dose equivalent to 60 mg of oral morphine		Secondary: Patient-averaged, summed pain intensity difference scores, patient-averaged, mean differences in pain relief, TOTPAR score, clinically meaningful reduction in pain intensity (≥2), need for additional rescue medication, patient acceptability scores	Secondary: The mean pain intensity score for patient-averaged fentanyl-treated episodes was significantly different from that for placebo-treated episodes at the five minute time point (*P*=0.03), and the difference in pain intensity was sustained over the 10, 15, 30, 45, and 60 minute evaluation time points. Patient-averaged mean differences in pain relief and TOTPAR scores were also significant at 10 minutes and at all measured time-points to 60 minutes. A total of 49% of those treated with fentanyl had a clinically meaningful reduction in pain intensity at 15 minutes (*P*<0.001) and 63% had the same degree of pain relief by 30 minutes. The cumulative SPID scores demonstrated that a significantly higher percentage of patients reported a mean reduction in SPID score ≥2 after fentanyl administration vs placebo administration at each evaluation from 10 to 60 minutes post-treatment dose. Overall, 90.6% of episodes treated with fentanyl nasal spray compared to 80.0% of episodes treated with placebo did not require an additional rescue medication within 60 minutes of breakthrough treatment (*P*<0.001). The overall mean patient-averaged acceptability assessment score was significantly greater for the fentanyl treatment vs placebo at 30 minutes post-treatment (2.63 vs 2.01; *P*<0.0001) and at 60 minutes post-treatment (2.73 vs 2.02; *P*<0.0001).
Taylor et al[22] Fentanyl nasal spray 100 to 800 µg vs placebo Fentanyl nasal spray was titrated up to 800 µg until	DB, MC, RCT, PC, XO Adult patients with cancer experiencing at least one to four breakthrough pain episodes daily, who were also receiving	N=114 10 BTP episodes	Primary: Pain intensity score, SPID score, pain relief score Secondary: Overall patient satisfaction, satisfaction with speed of relief	Primary: Fentanyl nasal spray significantly decreased pain intensity (≥1 point reduction) at all time intervals (5, 10, 15, 30, 45 and 60 minutes) compared to placebo (*P*<0.05 at 5 minutes, *P*<0.0001 at all other intervals). A significant meaningful reduction in pain intensity (≥2 point reduction) was first observed at 10 minutes in 32.9% of fentanyl patients compared to 24.5% of placebo patients (*P*<0.05) and increased to include 50.8% of fentanyl patients at 30 minutes (*P*<0.0001 vs placebo). Significant differences were also observed between fentanyl and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
the patient received adequate pain relief for each BTP episode. After titration to an effective dose of fentanyl nasal spray, patients received ten doses of study medication (seven contained fentanyl and three were placebo). Patients could take a maximum of four doses per day with at least four hours between doses.	fixed-dose opioids for pain at a total daily dose equivalent to 60 mg of oral morphine		and reliability of nasal spray, ease of use and convenience of nasal spray	placebo treated patients in the number of episodes with ≥2 point reduction in SPID score from 10 to 60 minutes (*P*<0.01). In addition, the number of episodes with pain relief score changes ≥1 point and ≥2 points was significantly higher in the fentanyl group compared to placebo from 10 to 60 minutes (*P*<0.0001 and *P*<0.001, respectively). Secondary: Significantly more patients in the fentanyl group reported a higher overall satisfaction score and satisfaction with speed of relief and reliability compared to placebo (*P*<0.0001 for all). A total of 68.5 and 69.9% of patients using fentanyl reported they were either satisfied or very satisfied with ease of use and convenience of the nasal spray, respectively.
Christie et al[23] Fentanyl transmucosal lozenge 200 µg vs fentanyl transmucosal lozenge 400 µg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one Fentanyl transmucosal lozenge unit.	DB, dose titration, MC, RCT Adult patients with cancer using transdermal fentanyl for persistent pain	N=62 Duration not reported	Primary: Pain intensity, pain relief, and global satisfaction compared to usual BTP medication Secondary: Dosing requirements	Primary: Pain scores following fentanyl transmucosal on successful days were compared to pain scores on baseline days following usual BTP medication. Scores at zero minutes were not significantly different for the two groups. At 15, 30 and 60 minutes, transmucosal fentanyl produced markedly lower pain intensity scores and higher pain relief scores than the usual BTP medication (*P*≤0.0002 for each analysis). At 30 minutes, the mean±SD difference between pain intensity scores following usual BTP medication and transmucosal fentanyl was 1.6±1.9. Pain intensity difference values at 15, 30 and 60 minutes were significantly better following transmucosal fentanyl (*P*≤0.001). The 0 to 15 minute pain intensity difference values for transmucosal fentanyl was >2.5 times larger compared to the usual BTP medication (2.35 vs 0.91; *P*=0.0001), which is consistent with a faster onset of action. Also, transmucosal fentanyl produced a pain relief score at 15 minutes that was >2 times higher compared to the usual BTP medication (1.90 vs 0.82; *P*=0.001). At 30 minutes, the mean±SD difference between

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On each study day, as many as 4 units could be taken sequentially (one every 30 minutes) for up to 2 BTP episodes/day. Patients' usual BTP medication included codeine, hydrocodone, hydromorphone, morphine, oxycodone, propoxyphene, tramadol, or no medication.				values following each treatment was 0.95±1.20. Global satisfaction ratings were significantly higher following transmucosal fentanyl compared to usual BTP medication (2.6 vs 2.0; *P*=0.0001). Secondary: Of the 62 patients enrolled, 47 (76%) were successfully titrated to a unit dose of transmucosal fentanyl that effectively treated their BTP. Four patients were unable to control their BTP with the highest transmucosal fentanyl dose of 1,600 µg and 11 patients withdrew from the trial; six of these withdrawals were due to a side effect. Patients who found a successful dose of transmucosal fentanyl were titrated to a mean dose of approximately 600 µg, with no statistically significant difference in the final dose between the patients who began with 200 µg and those who began with 400 µg (667 vs 825 µg, respectively; *P*=0.58).
Farrar et al[24] Fentanyl transmucosal lozenge 200 µg vs placebo Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode. After titration to an	DB, MC, PC, RCT, XO Patients ≥18 years of age with cancer who had sufficient pain to require at least the equivalent of 60 mg/day of oral morphine or 50 µg/hour transdermal fentanyl, and had ≥1 BTP episode/day for which they took	N=89 Duration not reported	Primary: Pain intensity, pain relief, and use of rescue medication at 15 minute intervals over a 60 minute period Secondary: Not reported	Primary: Transmucosal fentanyl produced significantly larger changes in pain intensity and better pain relief than placebo at all time points (two-sided *P*<0.0001). Episodes of BTP treated with placebo required the use of rescue medication more often than episodes treated with transmucosal fentanyl (34 vs 15%; RR, 2.27; 95% CI, 1.51 to 3.26; *P*<0.0001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
effective dose of fentanyl transmucosal lozenge, patients were given ten randomly ordered treatment units (seven fentanyl transmucosal lozenge units and three placebo units) in the form of identical lozenges. If adequate pain relief was not achieved with a single dose of transmucosal fentanyl after 30 minutes, patients were instructed to take a dose of their usual BTP medication. Patients' usual BTP medication included hydrocodone, hydromorphone, morphine, oxycodone, and other medications.	additional opioids			
Hanks et al[25] Fentanyl transmucosal lozenge 200 µg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one	MC, OL Patients stabilized on a long-acting opioid (60 to 1,000 mg/day of oral morphine, 50 to 300 µg/hour of transdermal	N=57 Duration not reported	Primary: SPID and TOTPAR up to 60 minutes Secondary: Not reported	Primary: SPID values were significantly higher following transmucosal fentanyl compared to conventional medication at all time points (*P*<0.001 for all). Transmucosal fentanyl produced better pain relief scores than conventional medication beginning at the 15 minute time point (1.49 vs 0.89; *P*<0.001) and continuing at the 30, 45, and 60 minute time points (*P*<0.001 at all time points). TOTPAR values were also significantly higher at each time point evaluated (*P*<0.001 for all).

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transmucosal fentanyl unit. Patients had access to their usual BTP medication. The majority of patients were using IR morphine as their usual BTP medication. If adequate pain relief was not achieved with a single dose of fentanyl transmucosal lozenge after 30 minutes, patients were instructed to take a dose of their usual BTP medication. The efficacy of their usual BTP medication was documented in a run-in phase and patients then changed to fentanyl transmucosal lozenge.	fentanyl, or 8 to 135 mg/day of oral hydromorphone) for ≥3 days prior to enrollment, but experiencing up to four BTP episodes/day, and achieving at least partial relief from BTP using conventional medication			Secondary: Not reported
Payne et al[26] Fentanyl transmucosal lozenge Patients had participated in a previous short-term titration trial of fentanyl transmucosal lozenge	MC, OL Patients requiring either a scheduled oral opioid regimen equivalent to 60 to 1,000 mg/day of oral morphine	N=151 1 to 423 days	Primary: Number of successfully treated BTP episodes, global satisfaction rating, side effects	Primary: Ninety-two percent of BTP episodes were considered successful (defined as a BTP episode for which a patient felt that they had achieved satisfactory pain relief using one transmucosal fentanyl unit [i.e., no additional rescue medication for the episode]). The number of patients dropped substantially from months five to eight (N=53) to months nine to 12 (N=19) and months >12 (N=8). Therefore, though the percentage of BTP episodes treated successfully with transmucosal fentanyl dropped from 90 to 85% after month nine, the declining sample

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(Christie et al[23], Portenoy et al[21], and Farrar et al[24]). Patients began the study at the fentanyl transmucosal lozenge doses that they had found to be effective in the previous titration trials in which they participated.	or 50 to 300 µg/hour of transdermal fentanyl for control of persistent pain, experiencing ≥1 BTP episode/day, and achieving at least partial relief of BTP by use of an opioid in the past		Secondary: Not reported	size makes it difficult to determine whether this is an actual decrease in efficacy. Mean global satisfaction ratings were consistently above three, indicating 'very good' to 'excellent' relief. The satisfaction ratings also remained consistent over time. Common adverse events associated with transmucosal fentanyl were somnolence (9%), constipation (8%), nausea (8%), dizziness (8%), and vomiting (5%). Six patients discontinued therapy due to a transmucosal fentanyl-related adverse event. There were no reports of abuse and no concerns about the safety of the drug raised by patients or families. Secondary: Not reported
Portenoy et al[27] Fentanyl transmucosal lozenge 200 µg vs fentanyl transmucosal lozenge 400 µg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one fentanyl transmucosal lozenge unit. On each study day, as many as four units could	DB, dose titration, MC, RCT Adult patients with cancer-related pain who were receiving a scheduled oral opioid regimen equivalent to 60 to 1,000 mg of oral morphine/day, experienced ≥1 BTP episode per day between 0700 to 1600 hours on the three days	N=65 Duration not reported	Primary: Pain intensity, pain relief, global assessment of drug performance Secondary: Not reported	Primary: For the 48 patients who were successfully titrated to an effective dose of transmucosal fentanyl, the mean pain intensity immediately before the dose of transmucosal fentanyl was approximately 6 on the 0 to10 numerical scale. After 60 minutes, the pain intensity averaged 1.5. The reduction in pain intensity during the 0 to 15 minute time period after the dose was 56% of the total pain intensity decline. Mean pain relief scores at 15 minutes and 30 minutes after the transmucosal fentanyl dose were 2.1 ('moderate' pain relief) and 2.5 ('moderate' to 'lots' of pain relief), respectively. The global performance of the transmucosal fentanyl during the two successful treatment days was 2.9 on the 0 to 4 verbal rating scale. With the exception of a single pain intensity difference recorded at the 60 minute time point, there were no significant differences between patients randomized to the 200 vs 400 µg starting doses in any of these outcome variables.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
be taken sequentially (one every 30 minutes) for up to two BTP episodes/day between 0700 to 1600 hours. Patients' usual BTP medication was used to treat all other BTPs on these study days.	immediately preceding screening, and achieved at least partial relief of this BTP by the use of an oral opioid rescue dose			Secondary: Not reported
Davies et al[28] Fentanyl nasal spray vs IR morphine Fentanyl nasal spray was titrated up to 800 µg until the patient reached an effective dose that treated two consecutive BTP episodes. After titration to an effective dose, ten episodes of BTP were randomly treated with fentanyl nasal spray and encapsulated placebo or IR morphine and nasal spray placebo (five episodes of each).	DB, DD, MC, XO Patients with a diagnosis of cancer, who were receiving fixed-schedule opioid regimens at a total daily dose ≥60 mg/day oral morphine or equivalent and one to four episodes per day of moderate to severe cancer BTP	N=110 10 BTP episodes	Primary: Pain intensity score, SPID, pain relief score, TOTPAR, onset of clinically meaningful pain relief (≥2 point reduction in pain intensity score), patient acceptability score (overall satisfaction, satisfaction with speed of relief and satisfaction with reliability), adverse events Secondary: None reported	Primary: After ten minutes, fentanyl nasal spray had greater pain intensity difference scores and a higher proportion of episodes showing clinically meaningful pain relief compared to IR morphine (P<0.05 for both). After 15 minutes, 52.3% of patients taking fentanyl had a TOTPAR score ≥33% compared to 43.5% of patients taking morphine (P <0.01). This significant difference was maintained until 60 minutes. Patient-averaged acceptability assessment scores were greater for fentanyl nasal spray than for morphine for all questions at 30 minutes (P <0.01) and 60 minutes (P <0.01). More treatment-emergent adverse effects were reported to be associated with fentanyl than with morphine. Only eight patients (six fentanyl and two morphine) experienced adverse effects that resulted in discontinuation of the drug (No P values reported). Secondary: None reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fallon et al[29] Fentanyl nasal spray 100 to 800 µg vs IR morphine Fentanyl nasal spray was titrated up to 800 µg until the patient received adequate pain relief for each BTP episode. IR morphine dose was determined as one-sixth of the total daily oral morphine dose equivalent of the patient's background opioid medication. After titration to an effective dose, ten episodes of BTP were randomly treated with fentanyl nasal spray and encapsulated placebo or IR morphine and nasal spray placebo (five episodes of each).	DB, DD, MC, RCT, XO Adult patients with cancer that were receiving fixed-schedule opioid regimens at a total daily dose equivalent to ≥60 mg/day oral morphine and experiencing one to four BTP episodes per day	N=110 10 BTP episodes	Primary: Pain intensity difference after 15 minutes Secondary: Patient- and episode-averaged pain intensity difference, SPID, pain intensity score, pain relief score, TOTPAR score, onset of analgesia (≥1 point reduction in pain intensity and pain relief), onset of clinically meaningful pain relief (≥2 point reduction in pain intensity and pain relief or 33% reductions in pain intensity and SPID), need for rescue medication	Primary: The mean (±SD) pain intensity difference score after 15 minutes was 3.02 (±0.21) for fentanyl nasal spray compared to 2.69 (±0.18) for IR morphine (P<0.05). Fentanyl nasal spray had significantly greater pain intensity difference scores compared to IR morphine from 15 minutes through 60 minutes after initial dose (P<0.05). Secondary: After treatment of BTP, fentanyl nasal spray treated episodes had significantly lower pain intensity scores compared to IR morphine treated episodes from 30 minutes through 60 minutes (P<0.05). In addition, patient-averaged pain relief scores were significantly higher from 30 minutes through 60 minutes in patients who took fentanyl nasal spray compared to IR morphine (P≤0.005). Patient-averaged mean difference in TOTPAR were significant from 15 minutes through 60 minutes (P<0.05) favoring fentanyl nasal spray. The proportion of patients experiencing onset of analgesia and clinically meaningful pain relief was significantly greater in the fentanyl nasal spray group compared to the IR morphine group as early as five minutes and ten minutes, respectively (P<0.05 for both). There was no significant difference in the proportion of patients requiring rescue medication within 60 minutes between fentanyl nasal spray and IR morphine. More treatment emergent adverse events occurred in patients using fentanyl nasal spray (no P value reported). Of the 14 serious adverse events reported, 12 occurred following treatment with fentanyl nasal spray.
Coluzzi et al[30] Fentanyl transmucosal lozenge 200 µg	DB, DD, RCT, XO Adult patients	N=89 Up to 14 days or 10 BTP	Primary: Pain intensity difference at 15, 30, 45 and 60	Primary: Mean pain intensity differences across all time points significantly favored transmucosal fentanyl (P<0.008 for all). Transmucosal fentanyl produced a >33% change in 15 minute pain intensity difference values

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs IR morphine15 to 60 mg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode using one fentanyl transmucosal lozenge unit. On each study day, as many as four units could be taken sequentially (one every 15 minutes) for each BTP episodes/day. After titration to an effective dose of fentanyl transmucosal lozenge, subjects were given ten pre numbered sets of oral transmucosal units and capsules. Every set had one unit and a number of capsules. Five of the sets contained the successful fentanyl transmucosal lozenge dose paired with placebo capsules and five of the	with cancer-related pain who were regularly having one to four BTP episodes/day while using a stable fixed schedule oral opioid regimen equivalent to 60 to1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl and who were using a successful dose of 15 to 60 mg of IR morphine to treat target BTP	episodes	minutes post dose Secondary: Adverse events	for 42.3% of the episodes treated compared to 31.8% for IR morphine (P<0.001). Secondary: Most adverse events reported during the study were considered unrelated or unlikely to be related to study medication. The most frequent drug-related adverse events included somnolence, nausea, constipation, and dizziness. Due to the design of the study it is difficult to attribute an adverse event to either of the study medications.

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sets were placebo fentanyl transmucosal lozenge paired with enough capsules to provide the patient's successful dose of IR morphine. For any non-target BTP episodes, patients used their usual supply of IR morphine.				
Mercadante et al[31] Fentanyl transmucosal lozenge, dose proportional to basal daily opioid dose vs intravenous morphine, dose proportional to basal daily opioid dose Patients were planned to receive fentanyl transmucosal lozenge and intravenous morphine for each couple of BTP episodes between 0700-1900 hours. The order of administration was randomized.	RCT, XO Adult patients with cancer-related pain, receiving opioids regularly at doses >60 mg/day of oral morphine equivalents, had acceptable pain relief, and presented ≤2 pain flares/day	N=25 Duration not reported	Primary: Pain intensity at zero (T0), 15 (T1), and 30 (T2) minutes post dose; and opioid-related symptoms Secondary: Not reported	Primary: In BTP episodes treated with intravenous morphine, pain intensity decreased from 6.9 (95% CI, 6.6 to 7.2) to 3.3 (95% CI, 2.7 to 3.8) and 1.7 (95% CI, 1.2 to 2.3) at T1 and T2, respectively. This reduction was >33% in 39 (74%) and in 46 (87%) episodes at T1 and T2, respectively, and >50% in 29 (55%) and in 40 (75%) episodes at T1 and T2, respectively. In BTP episodes treated with transmucosal fentanyl, pain intensity decreased from 6.9 (95% CI, 6.6 to 7.2) to 4.1 (95% CI, 3.6 to 4.7) and 2.4 (95% CI, 1.8 to 2.9) at T1 and T2, respectively. This reduction was >33% in 30 (57%) and 45 (85%) episodes at T1 and T2, respectively, and >50% in 20 (38%) and in 40 (75%) episodes at T1 and T2, respectively. A statistical difference between the two treatments was found at T1 (*P*=0.013), whereas at T2 the difference did not attain a statistical significance (*P*=0.59). At T1, a decrease of 41.1% and 51.7% in pain intensity was observed after transmucosal fentanyl and intravenous morphine, respectively (*P*=0.026). At T2, a decrease of 65.9% and 73.8% in pain intensity was recorded after transmucosal fentanyl and intravenous morphine, respectively (*P*=0.136). No differences between the two groups were observed in the number of episodes with a reduction of >33 and >50% at T1 (*P*=0.66 and *P*=0.39) and T2 (*P*=0.23

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and *P*=0.20), respectively. Acute adverse effects occurring after intravenous morphine and transmucosal fentanyl were comparable and correspond to those commonly observed with opioid therapy. Moderate adverse effects in BTP episodes treated with transmucosal fentanyl and intravenous morphine were nausea, drowsiness and confusion. Secondary: Not reported
Jandhyala et al[32] Fentanyl buccal tablet, sublingual tablet or transmucosal lozenge vs IR morphine vs placebo	MA (five studies)	N=Not available Duration unknown	Primary: Likelihood of superior pain relief (based on pain intensity difference) Secondary: Not reported	Primary: The probability of greater pain relief than placebo during first 60 minutes after dosing was 61% for IR morphine, 97% for fentanyl buccal tablet, 72% for fentanyl sublingual tablet and 66% for fentanyl transmucosal lozenge. The probability of greater pain relief than placebo during first 30 minutes after dosing was 56% for IR morphine, 83% for fentanyl buccal tablet, 66% for fentanyl sublingual tablet and 73% for fentanyl transmucosal lozenge (No *P* values reported). Mean pain intensity difference scores 60 minutes after dosing compared to placebo were 0.44 (95% CI, -2.07 to 2.95) for morphine, 1.16 (95% CI, 0.09 to 2.23) for the buccal tablet, 0.81 (95% CI, -1.40 to 3.04) for the sublingual tablet and 0.88 (95% CI, -0.76 to 2.55) for the transmucosal lozenge. The mean pain intensity difference scores compared to IR morphine were 0.75 (95% CI, -1.92 to 3.41) for the buccal tablet, 0.35 (95% CI, -3.00 to 3.63) for the sublingual tablet and 0.48 (95% CI, -1.34 to 2.34) for the transmucosal lozenge. Secondary: Not reported
Zeppetella et al[33] Opioid analgesics vs	MA (4 RCTs) Patients of any age with cancer and BTP who	N=393 Duration not reported	Primary: Reduction in pain intensity, adverse effects, attrition, patient	Primary: Results from four trials demonstrated that fentanyl transmucosal lozenge was superior to placebo, IR morphine, and previous rescue medication with a WMD of -0.68 (95% CI, -1.03 to -0.34) for pain improvement at 15 minutes and -0.91 (95% CI, -1.23 to -0.59) for pain

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo or opioid analgesics All RCTs were concerned with the use of transmucosal fentanyl in the management of BTP. Two trials examined the titration of transmucosal fentanyl, one trial compared transmucosal fentanyl to IR morphine and one trial compared transmucosal fentanyl to placebo. Previous rescue medication included hydrocodone, hydromorphone, morphine, oxycodone, and propoxyphene.	were treated with opioids for cancer pain		satisfaction, and quality of life Secondary: Not reported	improvement at 30 minutes. Transmucosal fentanyl was superior in providing pain relief at 15 minutes (WMD, 0.54; 95% CI, 0.40 to 0.69) and 30 minutes (WMD, 0.61; 95% CI, 0.47 to 0.75). Compared to previous rescue medication and placebo, transmucosal fentanyl was also superior for global performance (WMD, 0.76; 95% CI, 0.58 to 0.95). *Fentanyl transmucosal lozenge dose titration:* Of the 62 patients on around-the-clock transdermal fentanyl, 47 (76%) were able to titrate transmucosal fentanyl to a safe and effective dose to treat their BTP. Three patients administering around-the-clock transdermal fentanyl withdrew during the titration phase because of treatment-emergent adverse effects and four patients titrated to the 1,600 µg dose without obtaining adequate relief. The mean±SD successful transmucosal fentanyl dose was 587±335 µg. Of the 67 patients on around-the-clock oral opioids, 48 (74%) were able to titrate to a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. Eight patients administering around-the-clock oral opioids withdrew during the titration phase because of treatment-emergent adverse effects and five participants titrated to the 1,600 µg dose without adequate obtaining relief. The mean±SD successful transmucosal fentanyl dose was 640±374 µg. It was determined that the optimal dose of transmucosal fentanyl cannot be predicted by the total daily dose of fixed scheduled opioids. The most common adverse events associated with transmucosal fentanyl were somnolence, nausea, dizziness, and vomiting. An OL comparison of transmucosal fentanyl and usual BTP medication demonstrated that transmucosal fentanyl produced significantly better pain relief at all time periods in patients administering around-the-clock transdermal fentanyl or oral opioids (P<0.0001 for both). Patient rated global satisfaction of transmucosal fentanyl was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significantly higher compared to usual BTP medication (around-the-clock transdermal fentanyl, 2.6 vs 2.01; *P*=0.0001 and around-the-clock oral opioids, 2.74 vs 2.09; *P*=0.0002). *Transmucosal fentanyl vs placebo:* Of the 130 participants, 93 (72%) were able to titrate and find a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. The mean±SD successful transmucosal dose was 789±468 µg. Ninety two patients agreed to enter a DB, randomized phase in which results from 86 patients demonstrated that transmucosal fentanyl produced significantly better pain relief than placebo as evidenced by better pain intensity and pain relief scores for all time points (*P*<0.0001). Patient rated global performance of transmucosal fentanyl was significantly better compared to placebo (1.98 vs 1.19; *P*<0.0001) and patients-treated with transmucosal fentanyl required significantly less additional BTP medication (15 vs 34%; *P*<0.0001). Of the original 92 patients, 74 (80%) chose to continue transmucosal fentanyl following the trial. The most frequent adverse effects included dizziness, nausea, somnolence, constipation, asthenia, confusion, vomiting, and pruritus. *Transmucosal fentanyl vs normal release morphine:* Of the 134 patients, 93 (69%) were able to titrate to a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. Five patients titrated up to the 1,600 µg dose without obtaining adequate relief. Transmucosal fentanyl was significantly superior to IR 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). Additionally, significantly more (*P*<0.001) more BTP episodes treated with transmucosal fentanyl had a >33% change in pain intensity at 15 minutes. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Mercadante et al[34] Fentanyl nasal spray 50 to 200 µg vs fentanyl transmucosal lozenge 200 to 1,600 µg Enrolled patients entered a one week screening phase in which background pain intensity, BTP episodes, and use of rescue medication was assessed. Patients were then randomized to receive fentanyl nasal spray followed by fentanyl transmucosal lozenge, or vice versa, and entered a five to eight week titration phase in which an effective dose of the study drug was determined. Patients then entered a <2 week efficacy phase during which six BTP episodes were treated with the identified effective dose of fentanyl nasal	OL, XO Patients ≥18 years of age, with a life expectancy ≥3 months, who were experiencing ≥3 BTP episodes/week, but ≤4 BTP episodes/day and receiving stable opioid treatment for background pain (oral hydromorphone, morphine, oxycodone, or transdermal fentanyl) at a dose equivalent to 60 to 500 mg/day of oral morphine for ≥1 month prior to the study	N=139 8 to 11 weeks	Primary: Time to onset of 'meaningful' pain relief Secondary: Pain intensity, patient's general impression of drug efficacy and safety	Primary: The median time to onset of 'meaningful' pain relief was 11 minutes for intranasal fentanyl and 16 minutes for transmucosal fentanyl (*P* value not reported). Secondary: Statistically greater proportions of episodes treated with intranasal fentanyl compared to transmucosal fentanyl achieved ≥33 and ≥50% pain intensity reduction up to 30 minutes post dose. The proportion of BTP episodes treated with intranasal fentanyl and transmucosal fentanyl achieving a pain intensity reduction of ≥33% at five and ten minutes were 25.3 and 6.8% (*P*<0.001) and 51.0 vs 23.6% (*P*<0.001), respectively. The proportion of BTP episodes treated with intranasal fentanyl and transmucosal fentanyl achieving a ≥50% pain intensity reduction at 5 and 10 minutes were 12.8 vs 2.1% (*P*<0.001) and 36.9 vs 9.7% (*P*<0.001), respectively. The adjusted mean general impression score for treatment of the BTP episode as assessed by the patient at 60 minutes following the administration of intranasal fentanyl and start of transmucosal fentanyl use respectively was 2.1 (95% CI, 2.0 to 2.3) compared to 2.0 (95% CI, 0.1 to 0.2; *P*<0.001). Seventy nine (56.8%) patients experienced ≥1 adverse event in the titration and efficacy phase. The only adverse event occurred in ≥5% of patients in either treatment group was nausea.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
spray/transmucosal lozenge.				
Vissers et al[35] Fentanyl nasal spray vs fentanyl transmucosal lozenge vs fentanyl buccal tablet vs oral morphine vs placebo	MA (six RCT) Adult cancer patients suffering from BTP, treated with opioid analgesics for management of background pain	N=Not available Duration unknown	Primary: Mean pain intensity difference Secondary: Not reported	Primary: Relative to placebo, fentanyl nasal spray provided a 1.7 (95% CI, 1.4 to 1.9) reduction in pain relief after 15 minutes, while the lozenge provided a 0.4 (95% CI, 0.0 to 0.8) reduction and the buccal tablet provided a 0.5 (95% CI, 0.3 to 0.7) reduction. Differences in pain intensity difference scores favoring fentanyl nasal spray were 1.2 (95% CI, 0.8 to 1.5) relative to the buccal tablet, 1.3 (95% CI, 0.9 to 1.6) relative to the transmucosal lozenge and 1.7 (95% CI, 1.1 to 2.3) relative to oral morphine. The significant difference in mean pain intensity difference scores favoring fentanyl nasal spray was maintained up to 45 minutes compared to the buccal tablet and up to 60 minutes compared to the transmucosal lozenge. According the author's analysis fentanyl nasal spray displayed >99% probability of providing the greatest pain reduction at 15 minutes out of all the interventions in the study. Secondary: Not reported

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, RCT=randomized controlled trial, RR=relative risk, SD=standard deviation, SE=standard error, SEM=standard error of the mean, WMD=weighted mean difference, XO=crossover
Other abbreviations: BTP=breakthrough pain, IR=immediate-release, SPID=Summed Pain Intensity Differences, TOTPAR=Total Pain Relief

Special Populations

Table 5. Special Populations[5-10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Fentanyl, sublingual spray	No dosage adjustment required in the elderly, but monitor for respiratory depression and central nervous system effects when titrating. Safety and efficacy in children <18 years of age have not been established.	Monitor for respiratory depression and central nervous system effects when used in patients with renal dysfunction.	Monitor for respiratory depression and central nervous system effects when used in patients with hepatic dysfunction.	C	Yes (% not reported).
Fentanyl citrate, buccal film	No dosage adjustment required in the elderly, but use with caution. Safety and efficacy in children <18 years of age have not been established.	Use with caution.	Use with caution.	C	Yes (% not reported).
Fentanyl citrate, buccal tablet	No dosage adjustment required in the elderly, but use with caution. Safety and efficacy in children <18 years of age have not been established.	Use with caution.	Use with caution.	C	Yes (% not reported).
Fentanyl citrate, nasal spray	No dosage adjustment required in the elderly, but use with caution. Safety and efficacy in children <18 years of age have not been established.	Use with caution.	Use with caution.	C	Yes (% not reported).
Fentanyl citrate, sublingual tablet	No dosage adjustment required in the elderly, but use with caution.	Use with caution.	Use with caution.	C	Yes (% not reported).

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children <18 years of age have not been established.				
Fentanyl citrate, transmucosal lozenge	No dosage adjustment required in the elderly, but use with caution. Safety and efficacy in children <16 years of age have not been established.	Use with caution.	Use with caution.	C	Yes (% not reported).

Adverse Drug Events

Table 6. Adverse Drug Events (%)[5-10]

Adverse Event	Fentanyl, Sublingual Spray	Fentanyl Citrate, Buccal Film	Fentanyl Citrate, Buccal Tablet	Fentanyl Citrate, Nasal Spray	Fentanyl Citrate, Sublingual Tablet	Fentanyl Citrate, Transmucosal Lozenge
Blood and Lymphatic System Disorders						
Anemia	-	-	13 to 32	-	-	-
Neutropenia	-	-	0 to 8	-	-	-
Central Nervous System						
Abnormal gait	-	-	-	-	-	0 to 5
Anxiety	6	2 to 5	-	-	-	0 to 15
Confusion	-	0 to 14	3 to 16	-	-	0 to 13
Depression	-	0 to 11	1 to 15	-	-	2 to 9
Dizziness	7	0 to 12	3 to 11	2 to 6	0 to 6	0 to 17
Dysgeusia	-	-	-	-	0 to 14	-
Insomnia	-	0 to 7	3 to 11	-	-	0 to 8
Somnolence	10	1 to 11	0 to 15	-	0 to 9	7 to 20
Gastrointestinal						
Abdominal pain	-	0 to 9	3 to 15	-	-	-
Constipation	5 to 10	4 to 14	8 to 26	1 to 10	0 to 10	0 to 20
Diarrhea	-	0 to 12	0 to 16	-	-	-
Dry mouth	-	2 to 7	-	-	0 to 6	-
Stomatitis	-	-	-	-	0 to 8	-
Nausea	10 to 13	0 to 32	9 to 42	2 to 9	0 to 17	11 to 45
Vomiting	10 to 16	0 to 28	0 to 37	1 to 13	-	6 to 31
Infections and Infestations						
Pneumonia	-	-	2 to 16	-	-	-
Metabolism and Nutrition Disorders						
Anorexia	-	2 to 9	5 to 11	-	-	-
Decreased appetite	-	0 to 7	-	-	-	-
Dehydration	-	4 to 12	0 to 21	-	-	-
Hypokalemia	-	-	0 to 15	-	-	-
Respiratory						
Cough	-	0 to 7	3 to 9	-	-	-
Dyspnea	10	4 to 13	0 to 19	-	0 to 8	2 to 22

Adverse Event	Fentanyl, Sublingual Spray	Fentanyl Citrate, Buccal Film	Fentanyl Citrate, Buccal Tablet	Fentanyl Citrate, Nasal Spray	Fentanyl Citrate, Sublingual Tablet	Fentanyl Citrate, Transmucosal Lozenge
Skin						
Hyperhidrosis	-	-	-	-	0 to 14	-
Pruritus	-	-	-	-	-	0 to 5
Rash	-	-	-	-	-	4 to 8
Other						
Accidental injury	-	-	-	-	-	4 to 9
Accidental overdose	-	-	-	-	0 to 14	-
Arthralgia	-	-	0 to 8	-	-	-
Asthenia	10	0 to 14	5 to 16	-	-	0 to 38
Back pain	-	-	0 to 11	-	-	-
Cancer pain	-	-	2 to 16	-	-	-
Fatigue	-	1 to 12	2 to 20	-	0 to 6	-
Headache	-	0 to 10	2 to 15	-	0 to 10	3 to 20
Hypotension	-	0 to 5	-	-	-	-
Peripheral edema	-	-	5 to 32	-	-	-
Pyrexia	-	-	-	5 to 7	-	-
Weight decreased	-	0 to 13	-	-	-	-

-Event not reported or incidence <5%.

Contraindications[5-10]

Due to the potential for life-threatening hypoventilation and death in opioid non-tolerant patients, fentanyl immediate-release products are contraindicated in opioid non-tolerant patients, and in the management of acute or postoperative pain. Additionally, fentanyl immediate-release products are contraindicated in patients with a known intolerance or hypersensitivity to fentanyl or to any of the products' components.

Black Box Warning for fentanyl sublingual spray and fentanyl citrate buccal film, buccal tablet, nasal spray, sublingual tablet and transmucosal lozenge[5-10]

WARNING
WARNING: Risk of Respiratory Depression, Medication Errors and Abuse Potential. • Due to the risk of fatal respiratory depression, these medications are contraindicated in opioid non-tolerant patients and in management of acute or postoperative pain, including headache/migraines. • Keep out of reach of children. • Use with CYP3A4 inhibitors may cause fatal respiratory depression. • When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product. • When dispensing, do not substitute with any other fentanyl products. • Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. • Available only through a restricted program called the Transmucosal Immediate-Release Fentanyl Risk Evaluation and Mitigation Strategy Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program.

Warnings/Precautions

Table 7. Warnings and Precautions[5-10]

Warnings and Precautions	Fentanyl, Sublingual Spray	Fentanyl Citrate, Buccal Film	Fentanyl Citrate, Buccal Tablet	Fentanyl Citrate, Nasal Spray	Fentanyl Citrate, Sublingual Tablet	Fentanyl Citrate, Transmucosal Lozenge
Administer with extreme caution in patients who may be particularly susceptible to intracranial effects of carbon dioxide retention (e.g., those with increased intracranial pressure or impaired consciousness)	✔	✔	✔	✔	✔	✔
Because of the risk of misuse, abuse, addiction and overdose, the medication is only available through a restricted program under a Risk Evaluation and Mitigation Strategies (REMS) called the Transmucosal Immediate Release Fentanyl (TIRF) REMS ACCESS program	✔	✔	✔	✔	✔	✔
Concomitant use with other central nervous system depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages may produce increased depressant effects; patients on concomitant central nervous system depressants must be monitored for a change in opioid effects and may require a dose adjustment of the opioid medication	✔	✔	✔	✔	✔	✔
Concomitant use with potent inhibitors of cytochrome P450 3A4 may increase fentanyl levels, resulting in an increased depressant effect	✔	✔	✔	✔	✔	✔
Contains an amount of medication which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant	✔	✔	✔	✔	✔	✔
Do not substitute with other fentanyl products; different products are not bioequivalent	✔	✔	✔	✔	✔	✔
May produce bradycardia; use with caution in patients with bradyarrhythmias	✔	✔	✔	✔	✔	✔
More than 10% of patients report application site reactions	-	-	✔	-	-	-

Warnings and Precautions	Fentanyl, Sublingual Spray	Fentanyl Citrate, Buccal Film	Fentanyl Citrate, Buccal Tablet	Fentanyl Citrate, Nasal Spray	Fentanyl Citrate, Sublingual Tablet	Fentanyl Citrate, Transmucosal Lozenge
Not recommended for use in patients who have received monamine oxidase inhibitors within 14 days	✔	✔	✔	✔	✔	✔
Opioid analgesics impair the mental and/or physical ability required for potentially dangerous tasks (e.g., driving a car or operating machinery); patients should be warned on these dangers and counseled accordingly	✔	✔	✔	✔	✔	✔
Opioids may cause respiratory depression; the dose should be titrated with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to hypoventilation	✔	✔	✔	✔	✔	✔
Respiratory depression is the chief hazard of opioid agonists; it is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients	✔	✔	✔	✔	✔	✔

Drug Interactions

Table 8. Drug Interactions[5-10,12]

Generic Name	Interacting Medication or Disease	Potential Result
Fentanyl, fentanyl citrate	Central nervous system depressants	Concomitant use with other central nervous system depressants may produce increased depressant effects; patients on concomitant central nervous system depressants must be monitored for a change in opioid effects and may require a dose adjustment of the opioid medication.
Fentanyl, fentanyl citrate	CYP3A4 inhibitors	Concurrent use may result in increased fentanyl concentrations resulting in increased or prolonged adverse effects; patients should be monitored for an extended period of time and dosage increases should be done conservatively.
Fentanyl, fentanyl citrate	CYP3A4 inducers	Concurrent use may result in decreased fentanyl concentrations resulting in decreased analgesia; dosages should be adjusted accordingly.
Fentanyl, fentanyl citrate	Monoamine oxidase inhibitors	Concurrent use of fentanyl citrate within 14 days of a monoamine oxidase inhibitor should be avoided due to reports of unpredictable but severe adverse effects.
Fentanyl citrate*	Agents used to treat allergic rhinitis (e.g., oxymetazoline)	Co-administration with a vasoconstrictive nasal decongestant leads to a lower peak plasma concentration of fentanyl leading to less effective pain management; titration should be avoided under such circumstances to avoid incorrect dose identification.

*Fentanyl citrate, nasal spray only.

Dosage and Administration[5]

Fentanyl immediate-release products are available in a number of different dosage form and delivery systems, none of which are equivalent on a µg per µg basis. Therefore, patients cannot be switched on a µg per µg basis between available fentanyl products. Only prescribers enrolled in the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) program may prescribe fentanyl immediate release products on an outpatient basis.[5-10]

Table 9. Dosing and Administration[5-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Fentanyl, sublingual spray	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain: Sublingual spray: initial, 100 µg; maintenance, once titrated to an effective dose, patients should use one unit of the appropriate strength per BTP episode waiting at least four hours before treating another BTP episode; maximum, two doses per breakthrough episode to treat no more than four episodes of BTP per day	Safety and efficacy in children <18 years of age have not been established.	Sublingual spray: 100 µg 200 µg 400 µg 600 µg 800 µg 1,200 µg (2x600 µg) 1,600 µg (2x800 µg)
Fentanyl citrate, buccal film	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain: Buccal film: initial, 200 µg; maintenance, once titrated to an effective dose,	Safety and efficacy in children <18 years of age have not been established.	Buccal film: 200 µg 400 µg 600 µg 800 µg 1,200 µg

Generic Name	Adult Dose	Pediatric Dose	Availability
	patients should use one unit of the appropriate strength per BTP episode waiting at least two hours before treating another BTP episode; maximum, 1,200 µg per dose to treat no more than four episodes of BTP per day		
Fentanyl citrate, buccal tablet	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain: Buccal tablet: initial, 100 µg for patients not being converted from Actiq®; maintenance, once titrated to an effective dose, patients should generally use only one unit of the appropriate strength per BTP episode waiting at least four hours before treating another BTP episode; maximum, two units for any BTP episode	Safety and efficacy in children <18 years of age have not been established.	Buccal tablet: 100 µg 200 µg 400 µg 600 µg 800 µg
Fentanyl citrate, nasal spray	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain: Nasal Spray: initial, 100 µg spray in one nostril; maintenance, patients should use the following titration steps (titration steps, 100 µg (1x100 µg dose), 200 µg (2x100 µg dose; one per nostril), 400 µg (1x400 µg), 800 µg (2x400 µg dose; one per nostril)) to identify the least effective dose, once identified patients should only use one dose per BTP episode waiting at least two hours before treating another BTP episode; maximum, 800 µg per dose to treat no more than four episodes of BTP per day	Safety and efficacy in children <18 years of age have not been established.	Nasal Spray: 100 µg / spray 400 µg / spray
Fentanyl citrate, sublingual tablet	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain: Sublingual tablet: initial, 100 µg; maintenance, once titrated to an effective dose, patients should generally use only one unit of the appropriate strength per BTP episode waiting at least two hours before treating another BTP episode; maximum, 800 µg per breakthrough episode to treat no more than four episodes of BTP per day	Safety and efficacy in children <18 years of age have not been established.	Sublingual tablet: 100 µg 200 µg 300 µg 400 µg 600 µg 800 µg
Fentanyl citrate, transmucosal lozenge	Management of breakthrough cancer pain in patients already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain:	Safety and efficacy in children <16 years of age	Transmucosal lozenge: 200 µg 400 µg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Transmucosal lozenge: initial, 200 µg; maintenance, once titrated to an effective dose, patients should generally use only one unit of the appropriate strength per BTP episode waiting at least four hours before treating another BTP episode; maximum, two units for any BTP episode	have not been established.	600 µg 800 µg 1,200 µg 1,600 µg

BTP=break through pain

Clinical Guidelines

The National Comprehensive Cancer Network (NCCN) adult cancer pain guideline notes that appropriate pain management includes long-acting medications for continuous pain and short-acting opioids for breakthrough pain. Transmucosal fentanyl products are mentioned as effective options in opioid tolerant patients that have adequate around-the-clock pain management.[1]

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
National Comprehensive Cancer Network: **Adult Cancer Pain (2013)**[1]	• Pain is one of the most common symptoms associated with cancer. • The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization which suggests that patients with pain be started on acetaminophen or a non-steroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid" and then to a "strong opioid", such as morphine. • This guideline is unique it that it contains the following components: o Pain intensity must be quantified by the patient (whenever possible), as the algorithm bases therapeutic decisions on a numerical value assigned to the severity of pain. o A formal comprehensive pain assessment must be performed. o Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect. o Psychosocial support must be available. o Specific educational material must be provided to the patient. • The pain management algorithm distinguishes three levels of pain intensity, based on a 0 to 10 numerical rating scale: severe pain (7 to 10), moderate pain (4 to 6) and mild pain (1 to 3). • Pain associated with oncology emergency should be addressed while treating the underlying condition. • Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support as well as patient and family education. • Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids. • Opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids. • Opioid-naïve patients experiencing mild pain intensity should receive non-opioid analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids.

Clinical Guideline	Recommendations
	• Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain. Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. • Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). • Fentanyl, hydromorphone, morphine, and oxycodone are the opioids commonly used in the United States. An individual approach should be used to determine opioid starting dose, frequency and titration in order to achieve a balance between pain relief and medication adverse effects. • In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice. • Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. • Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. • Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid tolerant patients. It is usually the drug of choice for patients who are unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. • Consider transmucosal fentanyl (various formulations and delivery systems available) only in opioid tolerant patients for brief episodes of acute exacerbation of pain not attributed to inadequate dosing of around the clock opioids. • Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. • Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration. • The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing. • The methods of administering analgesics that are widely accepted within clinical practice include "around the clock", "as needed", and "patient-controlled analgesia."

Clinical Guideline	Recommendations
	• "Around the clock" dosing is provided to chronic pain patients for continuous pain relief. A "rescue dose" should also be provided as a subsequent treatment for patients receiving "around the clock" doses. Rescue doses of short acting opioids should be provided for pain that is not relieved by regularly scheduled, "around the clock" doses. Opioids administered on an "as needed" basis are for patients who have intermittent pain with pain-free intervals. The "as needed" method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic "on demand". • For opioid-naïve patients experiencing pain intensity ≥4 or a pain intensity <4 but whose goals of pain control and function are not met, an initial dose of 5 to 15 mg of oral morphine, 2 to 5 mg of intravenous morphine or equivalent is recommended. • Patients should be reassessed every 60 minutes for oral medications and every 15 minutes for intravenous medications. If pain remains unchanged or is increased, opioid dose is increased by 50 to 100%. If inadequate response is seen after two to three cycles of the opioid, changing the route of administration from oral to intravenous or subsequent management strategies can be considered. • If the pain decreases to 4 to 6, the same dose of opioid is repeated and reassessed again in 60 minutes for oral medications and 15 minutes for intravenous medications. If the pain decreases to 0 to 3, the current effective dose is administered "as needed" over the initial 24 hours before proceeding to subsequent management strategies. • No single opioid is optimal for all patients. When considering opioid rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse effects, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. • For opioid-tolerant patients (those chronically receiving opioids on a daily basis) experiencing breakthrough pain of intensity ≥4, a pain intensity <4 but whose goals of pain control and function are not met, in order to achieve adequate analgesia the previous 24 hour total oral or intravenous opioid requirement must be calculated and the new "rescue dose" must be increased by 10 to 20%. • The Food and Drug Administration (FDA) defines tolerance as receiving at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer. • Subsequent treatment is based upon the patient's continued pain rating score. All approaches for all pain intensity levels must be administering regular doses of opioids with rescue doses as needed, management of constipation coupled with psychosocial support and education for patients and their families. • Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or in some cases to counter the adverse events associated with opioids. • Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. • If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an extended-

Clinical Guideline	Recommendations
	release oral medication (if feasible) or another extended-release formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by extended-release opioids. • Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. • Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. • Opioids alone may not provide the optimal therapy, but when used in conjunction with non-opioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. • The term adjuvant refers to medication that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch. • Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement and are particularly important in treating neuropathic pain that is resistant to opioids. • Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain. • Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic interventions. Attention should also be focused on psychosocial support and providing education to patients and families.

Conclusions

Immediate-release fentanyl products, including fentanyl and fentanyl citrate, are short-acting opioids Food and Drug Administration (FDA) approved for the management of breakthrough cancer pain in patients who are already receiving and who are tolerant to around-the-clock therapy for their underlying persistent pain.[5-10] Currently available formulations of immediate-release fentanyl, include the generically available transmucosal lozenge (Actiq®) and the branded buccal film (Onsolis®), buccal tablet (Fentora®), nasal spray (Lazanda®), sublingual spray (Subsys®) and sublingual tablet (Abstral®). Immediate-release fentanyl has a fast onset of action, making it optimal for the management of cancer-related breakthrough pain as this type of pain is characterized by a rapid onset, severe intensity and a self-limiting course. Currently, Abstral®, Actiq®, Fentora®, Lazanda®, Onsolis® and Subsys® are the only short-acting opioids specifically FDA approved for use in the management of cancer pain.

The effectiveness of these products are well documented by clinical trials.[13-35] Additionally, none of the current clinical guidelines distinguish among the different immediate-release fentanyl formulations. There are limited head-to-head trials comparing efficacy among all dosage forms, however, there is evidence that fentanyl nasal spray when compared to the fentanyl lozenge was associated with a faster median time to "meaningful" onset of pain relief by approximately five minutes.[34] In addition a meta-analysis concluded that that fentanyl nasal spray displayed greater than a 99% probability of providing the greatest pain reduction at 15 minutes relative to either the buccal tablet or transmucosal lozenge.[35] According to the National Comprehensive Cancer Network (NCCN) adult cancer pain guidelines, consideration should

be given to transmucosal fentanyl (without preference given to one method of transmucosal drug delivery) in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of a long-acting, around-the-clock opioid analgesic.[1]

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