Texas Vendor Drug Program

Drug Use Criteria: Fentanyl

Publication History

1. Developed: February 2003
2. Revised: **January 2022;** December 2019; December 2017; December 2015; March 2014; May 2012; July 2010; July 2007; January 2006.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

Fentanyl citrate intranasal spray as well as oral transmucosal lozenges, buccal tablets, sublingual tablets, sublingual spray, and transdermal patches are FDA-approved for managing breakthrough cancer pain in patients already receiving and tolerant to opioid therapy for persistent cancer pain. Patients are considered opioid tolerant if they are taking around-the-clock opioids consisting of at least 60 mg of oral morphine daily, 25 mcg of transdermal fentanyl/hour, 30 mg of oral oxycodone daily, 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer. [1-11]

Because of the risk of abuse, addiction, misuse, and overdose, all intranasal and oral fentanyl dosage forms are obtained solely through a restricted distribution program, the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Management Strategy (REMS) Access program, in which only outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors who have registered for the program can prescribe, dispense, and/or obtain intranasal and oral fentanyl.[1-5, 7-11]

Due to pharmacokinetic differences between intranasal, oral transmucosal, buccal, sublingual, and transdermal fentanyl citrate formulations, these products are not interchangeable on a mcg per mcg basis and should not be substituted on a mcg for mcg basis as enhanced or attenuated pharmacologic effects could occur. [1-11]

1.1.1 Transmucosal Lozenges (Actiq®, generic)[1, 7-15]

Patients receiving fentanyl oral transmucosal lozenges for breakthrough pain are prescribed an initial dose of 200 mcg with instructions to allow the lozenge to dissolve over 15 minutes as the product is not designed to be chewed. Until the appropriate dose is reached, patients may find it necessary to use an additional oral transmucosal unit during a single episode. Re-dosing may begin 30 minutes after the start of the previous unit. During the titration phase, no more than two units should be administered for each individual cancer breakthrough pain episode. Patients must wait at least 4 hours before administering fentanyl oral transmucosal lozenges for another episode of breakthrough pain. To limit the number of units during the titration period, patients should be prescribed a maximum supply of six

200 mcg fentanyl oral transmucosal lozenges. At each new dose of oral transmucosal lozenge required by a patient, it is recommended that no more than six units of the titration dose be prescribed. Once a successful dose is identified for a patient, the quantity of lozenges utilized by a patient should be limited to 4 or fewer units per day. If consumption increases to greater than 4 units per day, the dose of the long-acting opiate should be re-evaluated. To discontinue use of fentanyl oral transmucosal lozenges, a downward titration is recommended to minimize potential withdrawal adverse effects.

1.1.2 Buccal Tablets (Fentora®, **generic**) [2, 7-11]

Patients prescribed fentanyl buccal tablets for breakthrough pain should begin therapy with an initial dose of 100 mcg, with the exception of those previously treated with fentanyl oral transmucosal lozenges. Dose conversions between fentanyl oral transmucosal lozenges and buccal tablets are summarized in Table 1.

Table 1. Dosage Conversions for Fentanyl Oral Transmucosal Lozenges and Fentanyl Buccal Tablets

Current Fentanyl Oral Transmucosal Lozenge Dose (mcg)	Initial Fentanyl Buccal Tablet Dose (mcg)
200	100
400	100
600	200
800	200
1200	400 (supplied as 2 x 200 mcg tablets)
1600	400 (supplied as 2 x 200 mcg tablets)

The tablet is placed in the buccal cavity (the space between the upper cheek and rear molar) or under the tongue and should be allowed to dissolve completely over a period of 30 minutes. Tablets should not be split, crushed, chewed or swallowed whole. If there are any tablet pieces remaining after 30 minutes, the patient may swallow them with a glass of water. The same dosage strength may be repeated once during a breakthrough pain episode, administered no sooner than 30 minutes after initiating buccal fentanyl tablet therapy, if pain is not relieved by the first buccal tablet dose. Patients must wait at least 4 hours before administering a fentanyl buccal tablet dose for another episode of breakthrough pain. The fentanyl buccal tablet dose should be increased in patients requiring greater than one breakthrough dose for several consecutive episodes. Patients requiring fentanyl

buccal tablet doses higher than 100 mcg should be titrated in multiples of 100 mcg. Patients may receive up to four 100 mcg tablets at one time placed on each side of the mouth in each buccal cavity (2 tablets per side). Fentanyl buccal tablet dosages greater than 400 mcg should be titrated in 200 mcg increments. Doses should be titrated to achieve adequate analgesia with acceptable side effects, but no more than 4 tablets should be used concurrently for a breakthrough episode. Patients should receive only one buccal tablet dosage strength at a time to minimize confusion and the possibility of overdose. If more than four breakthrough pain episodes happen per day, the long-term opiate maintenance dose should be re-evaluated. To discontinue fentanyl buccal tablet use, a downward titration is recommended to minimize potential withdrawal adverse effects.

1.1.3 Sublingual Tablets (Abstral®)[3, 7-11]

Patients prescribed fentanyl sublingual tablets for breakthrough pain should begin therapy with an initial 100 mcg dose, with the exception of those previously treated with fentanyl oral transmucosal lozenges. Dose conversions between fentanyl oral transmucosal lozenges and sublingual tablets are summarized in Table 2.

Table 2. Dosage Conversions for Fentanyl Oral Transmucosal Lozenges and Fentanyl Sublingual Tablets

Current Fentanyl Oral Transmucosal Lozenge Dose (mcg)	Initial Fentanyl Sublingual Tablet Dose (mcg)
200	100
400	200
600	200
800	200
1200	200
1600	400

To administer fentanyl sublingual tablets, the unwrapped tablet should be placed on the floor of the mouth, under the tongue and allowed to dissolve completely. Fentanyl sublingual tablets should not be chewed or swallowed. Patients should be advised to not eat or drink until the tablet is dissolved. In patients with xerostomia, the mouth should be moistened before the tablet is administered. If patients do not achieve adequate analgesia within 30 minutes, a second fentanyl sublingual tablet dose may be administered as directed. No more than two doses should be administered for any breakthrough pain episode. If pain relief for the breakthrough episode is not relieved with the 100 mcg dose, titrate using multiples of 100 mcg or 200 mcg tablets until adequate analgesia is achieved. Doses may be titrated upward to 200 mcg, 300 mcg, 400 mcg, 600 mcg, or 800 mcg per dose. Doses higher than 800 mcg have not been evaluated in clinical trials. If adequate pain relief is not achieved within 30 minutes of the first dose, a second dose of the same strength may be administered. Patients should not use more than 4 tablets at one time. Patients must wait at least 2 hours before administering fentanyl sublingual tablets for another episode of breakthrough pain. Once an effective fentanyl sublingual tablet dose has been determined, patients should be maintained on this dose. If pain is not effectively managed with this dose of fentanyl sublingual tablet, a patient may use a second dose as directed by their health care provider, with no more than two doses being used to treat any breakthrough pain episode. Again, patients must wait at least two hours before treating subsequent breakthrough pain episodes. Fentanyl sublingual tablets should be used for no more than four breakthrough pain episodes per day. If more than four breakthrough pain episodes happen per day, the long-term opiate maintenance dose should be re-evaluated. To discontinue fentanyl sublingual tablet use, a downward titration is recommended to minimize potential withdrawal adverse effects.

1.1.4 Sublingual Spray (Subsys®)[4, 7-11]

With the exception of patients previously treated with fentanyl transmucosal lozenges, treatment with fentanyl sublingual spray should be initiated with a 100 mcg dose. If patients do not achieve adequate analgesia within 30 minutes, a second fentanyl sublingual spray dose of the same strength may be administered. No more than two doses should be administered for any breakthrough pain episode. Patients must wait at least 4 hours before administering fentanyl sublingual spray for another episode of breakthrough pain. Patients should be prescribed only a titration supply of 100 mcg dose units during titration to minimize the number of available units during titration. If pain relief for the breakthrough episode is not relieved with the 100 mcg dose, titrate doses upward to 200 mcg, 400 mcg, 600

mcg, 800 mcg, 1200 mcg, or 1600 mcg per dose. Patients previously treated with fentanyl transmucosal lozenges should receive a modified initial sublingual spray dose, based on the transmucosal lozenge dose that had previously been utilized. Dosage conversions between fentanyl transmucosal lozenges and sublingual spray are summarized in Table 3.

Table 3. Dosage Conversions for Fentanyl Oral Transmucosal Lozenges and Fentanyl Sublingual Spray

Current Fentanyl Oral Transmucosal Lozenge Dose (mcg)	Initial Fentanyl Sublingual Spray Dose (mcg)
200	100
400	100
600	200
800	200
1200	400
1600	400

Once an effective fentanyl sublingual spray dose has been determined, patients should be maintained on this dose. If pain is not effectively managed with this dose of fentanyl sublingual spray, a patient may use a second dose as directed by their health care provider, with no more than two doses being used to treat any breakthrough pain episode. Again, patients must wait at least four hours before treating subsequent breakthrough pain episodes. Increase the fentanyl sublingual spray dose only when treatment at the current dose fails to provide pain relief for several episodes. To reduce the risk of overdose, patients should have only one fentanyl sublingual spray dosage strength available at any time. If more than four breakthrough pain episodes happen per day, the long-term opiate maintenance dose should be re-evaluated. In patients with Grade 1 mucositis, fentanyl sublingual spray may result in higher drug serum concentrations. For patients with Grade 2 mucositis, avoid sublingual fentanyl use unless the benefits outweigh the risks of increased drug exposure.

1.1.5 Intranasal Spray (Lazanda®)[5, 7-11]

Fentanyl intranasal spray should be initiated in all patients with a dose of 100 mcg (one spray in one nostril). If adequate analgesia is achieved, this dose will be used to manage future breakthrough pain episodes. If adequate pain relief is not

achieved with the 100 mcg dose, titrate the dose upward in a stepwise manner to 200 mcg (2 x 100 mcg – one spray in each nostril), 400 mcg (4 x 100 mg – two sprays in each nostril or 1 x 400 mcg – one spray in one nostril), or 800 mcg (2 x 400 mcg – one spray in each nostril) per dose until adequate analgesia is achieved with minimal adverse effects. Patients must wait at least 2 hours before administering subsequent fentanyl intranasal spray doses. Safety and efficacy of doses greater than 800 mcg have not yet been determined in clinical trials. Once an effective dose has been established, fentanyl intranasal spray should be used to manage no more than four breakthrough episodes per day. If adequate analgesia is not achieved within 30 minutes of a fentanyl intranasal spray dose or a breakthrough pain episode occurs before the next fentanyl intranasal spray dose (i.e., within 2 hours of a fentanyl intranasal spray dose), a rescue medication may be utilized as dictated by the patient's health care provider. If more than four breakthrough pain episodes happen per day, long-term opiate maintenance doses should be re-evaluated. To discontinue fentanyl intranasal spray use, a downward titration is recommended to minimize potential withdrawal adverse effects.

1.1.6 Transdermal Patch (Duragesic®, generics)[6, 7-11]

To initiate fentanyl transdermal patch therapy in patients prescribed other opioids, discontinue all other **around-the-clock** opioid therapy. **Short-acting opioid agonists may be used as needed for the first 24 hours after initial application. Breakthrough pain may require supplemental doses even after a transdermal dose is established.** Conversion doses from an oral or parenteral fentanyl preparation to fentanyl transdermal patches is summarized in Table 4. **Conversion doses from daily oral morphine dosages to fentanyl transdermal patches is provided in Table 5.** This table does NOT represent equianalgesic doses and is only intended to provide dosage conversions from other opioids to fentanyl transdermal patches, but does NOT provide dosage conversions from fentanyl transdermal patches to other fentanyl/opioid dosage forms as the new opioid dose would be overestimated and may potentially result in a fatal drug overdose.

Table 4. Opioid Dosage Conversion to Fentanyl Transdermal Patch[6-11]

Current Analgesic	Daily Dosage (mg/day)			
Oral morphine	60–134	135–224	225–314	315–404
Intravenous or intramuscular morphine	10–22	23–37	38–52	53–67
Oral oxycodone	30–67	67.5–112	112.5–157	157.5–202
Oral codeine	150–447			
Oral hydromorphone	8–17	17.1–28	28.1–39	39.1–51
Intravenous hydromorphone	1.5–3.4	3.5–5.6	5.7–7.9	8–10
Intramuscular meperidine	75–165	166–278	279–390	391–503
Oral methadone	20–44	45–74	75–104	105–134
	↓	↓	↓	↓
Recommended fentanyl transdermal patch dose	25 mcg/hour	50 mcg/hour	75 mcg/hour	100 mcg/hour

Table 5. Recommended Initial Fentanyl Transdermal Patch Dose Based Upon Daily Oral Morphine Dose[6-11]

Oral Daily Morphine (mg/day)	Fentanyl Transdermal Patch Dose (mcg/hour)
60-134	**25**
135-224	**50**
225-314	**75**
315-404	**100**
405-494	**125**
495-584	**150**
585-674	**175**
675-764	**200**
765-854	**225**
855-944	**250**
945-1034	**275**
1035-1124	**300**

Patients requiring fentanyl transdermal patch therapy and taking an opiate not listed in Table 4 should calculate the previous 24-hour analgesic requirement and convert the quantity to an equianalgesic oral morphine dose and use Table **4 or an additional dosage conversion chart such as the "Table 2. Morphine**

Milligram Equivalent (MME) Doses for Commonly Prescribed Opioids" table provided in the "CDC Guideline for Prescribing Opioids for Chronic Pain-United States, 2016" to identify an appropriate transdermal fentanyl patch conversion dose. The fentanyl transdermal patch dose should be titrated to a dose that provides adequate analgesia and minimal adverse reactions. The patch should be changed every 72 hours. If adequate analgesia is not achieved, the initial dose can be titrated after three days; subsequent dosage titrations should not be made more frequently than every six days. In the event that breakthrough pain occurs, a dosage adjustment may be necessary as well as rescue medication administration with an immediate-release analgesic. A small percentage of adult patients may not have adequate pain control with an every 72 hour dosage scheme and may require an every 48 hour dosing regimen. The patch should be applied to non-irritated, non-irradiated skin on a flat surface; avoid exposing the patch to external heat sources.

1.1.7 Off-Label Uses [7, 17-19]

Although not FDA-approved, a few small studies have evaluated oral transmucosal fentanyl lozenge use for migraine headache pain management refractory to conventional treatment in patients with a history of parenteral opioid use in the Emergency Department (ED). These studies found the drug to be effective in reducing pain intensity scores and number of ED visits. **Additional outpatient off-label use has been investigated in opioid-naïve patients with cancer, moderate to severe osteoarthritis with an inadequate response to weak opioid analgesic therapy, and pain associated with sickle cell anemia. The use of fentanyl patches in opioid-naïve patients with cancer is contraindicated, but two studies demonstrated successful use in this patient population. Short-term treatment with transdermal fentanyl significantly improved pain and functionality in patients with moderate to severe pain due to knee or hip osteoarthritis in two trials. However, opioid medications are conditionally recommended against for use in patients with osteoarthritis of the knee, hand, or hip while recognizing use may be appropriate when alternative options have failed. Current recommendations for the management of pain in sickle cell disease recommend against the use of chronic opioid therapy (COT) in children and adults unless the pain is refractory to multiple other therapies. Shared decision making should be used to determine the continuation of COT in patients who are well functioning and receiving a perceived benefit in**

therapy. Continuation of COT is not recommended in patients who are functioning poorly or are at high risk for opioid abuse or toxicity.

1.1.8 Dosage Limits

The lowest effective fentanyl transmucosal, buccal, intranasal, or sublingual dose should be administered to patients with renal or hepatic dysfunction, as well as those patients receiving concurrent CYP3A4 inhibitor drugs.

Patient profiles containing prescriptions for greater than 6 units of fentanyl oral transmucosal lozenges during a transition phase will be reviewed. Patient profiles containing prescriptions for more than one strength of buccal, nasal, sublingual, or transmucosal fentanyl concurrently for greater than two months will be reviewed. Patient profiles containing prescriptions for greater than four doses per day of fentanyl intranasal spray or fentanyl sublingual tablets will be reviewed. Patient profiles documenting treatment of more than 4 breakthrough episodes daily with fentanyl buccal, transmucosal, or sublingual dosage forms will be reviewed (see **Table 6**).[1-5, 7-11]

Table 6. Adult Maximum Oral/Intranasal/Transdermal Fentanyl Dosages [1-11]

Fentanyl Dosage Form	Dosage Strengths	Maximum Dose
buccal tablet (Fentora®, **generic**)	100 mcg, 200 mcg, 400 mcg, 600 mcg, or 800 mcg per tablet	800 mcg/dose; no more than 4 tablets at one time per breakthrough episode, and no more than 2 doses per breakthrough pain episode; if more than 4 breakthrough episodes per 24 hours occur once maintenance dose determined, long-acting opioid dose should be re-evaluated
intranasal spray (Lazanda®)	100 mcg, **300 mcg,** or 400 mcg per actuation	800 mcg/dose; if more than 4 breakthrough episodes per 24 hours occur once maintenance dose determined, long-acting opioid dose should be re-evaluated

Fentanyl Dosage Form	Dosage Strengths	Maximum Dose
sublingual tablet (Abstral®)	100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, or 800 mcg per tablet	800 mcg/dose; no more than 4 tablets at one time per breakthrough episode, and no more than 2 doses per breakthrough pain episode; if more than 4 breakthrough episodes per 24 hours occur once maintenance dose determined, long-acting opioid dose should be re-evaluated
sublingual spray (Subsys®)	100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, or 1600 mcg per spray	1600 mcg/dose; no more than 2 doses per breakthrough pain episode; if more than 4 breakthrough episodes per 24 hours occur once maintenance dose determined, long-acting opioid dose should be re-evaluated
transmucosal lozenge (Actiq®, generic)	200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, or 1600 mcg per lozenge	no more than 2 units/lozenges per breakthrough pain episode; no more than 4 lozenge units/day; if more than 4 breakthrough episodes per 24 hours occur once maintenance dose determined, long-acting opioid dose should be re-evaluated
transdermal patch (Duragesic®, generic)	12 mcg/hr, 25 mcg/hr, 37.5 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr	maximum dose not identified; dosages titrated every 3 days after initial dose, then every 6 days thereafter; most patients controlled with every 72 hour administration; a small percentage require every 48 hour administration

1.2 Pediatrics [1-11]

Fentanyl citrate transmucosal lozenges are FDA-approved for use in adolescents 16 years and older. Fentanyl transdermal patch is FDA-approved for use to manage chronic severe pain in opioid-tolerant pediatric patients 2 years of age and older requiring around-the-clock opiate therapy. Fentanyl nasal spray as well as oral fentanyl buccal tablet, sublingual spray, and sublingual tablet safety and efficacy

have not been established in patients below 18 years of age. Pediatric fentanyl maximum dosage recommendations are summarized in **Table 7**.

Table 7. Pediatric Maximum Transmucosal/Transdermal Fentanyl Dosages [1-11]

Fentanyl Dosage Form	Dosage Strengths	Maximum Dose
transmucosal lozenge (Actiq®, generic)	200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, or 1600 mcg per lozenge	*16 years and older:* no more than 2 units/lozenges per breakthrough pain episode; no more than 4 lozenge units/day; if more than 4 breakthrough episodes per 24 hours occur once maintenance dose determined, long-acting opioid dose should be re-evaluated
transdermal patch (Duragesic®, generic)	12 mcg/hr, 25 mcg/hr, 37.5 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr	*2 years and older:* maximum dose not identified; dosages titrated every 3 days after initial dose, then every 6 days thereafter

Although not FDA-approved, oral fentanyl citrate has been studied in non-opioid tolerant patients as young as 2 years of age for various indications including surgical procedure pain, wound dressing changes in burn patients, and sedation in single doses ranging from 10-20 **mcg**/kg given prior to procedures with mixed efficacy rates. Similarly, intranasal fentanyl has been effectively utilized in pediatric patients as young as 6 months of age for non-FDA approved uses (e.g., analgesia, burns, postoperatively) at doses of 1-2 mcg/kg with success.[20-29]

1.4 Opioid Reversal Agents [30-35]

Naloxone is an opioid receptor antagonist that is FDA approved for reversal of opioid-induced respiratory and central nervous system depression. Naloxone is supplied as a nasal spray marketed as Narcan® 4 mg/0.1 mL nasal spray, Kloxxado® 8 mg/ 0.1 mL nasal spray, Evzio® 0.4 mg/ 0.4 mL auto-injector solution for injection, LifEMS Naloxone® 2 mg/ 2 mL solution for injection, and generic formulations of the solution for injection are available.

In July of 2020 the U.S. Food and Drug Administration made the recommendations that healthcare professionals should discuss the

availability of naloxone products and consider prescribing naloxone to patients who are prescribed opioid pain relievers and are at increased risk of opioid overdose. Patients at risk of opioid overdose include patients who are co-prescribed benzodiazepines or other drugs that depress the central nervous system, patients with a history of opioid use disorder (OUD), or who have experienced a previous opioid overdose. Healthcare professionals should also consider prescribing naloxone to patients who have other household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose. In 2016, the state of Texas, in association with the Texas Pharmacy Association, obtained a physician-signed standing order that allows pharmacists to dispense naloxone products to patients after completing Texas-accredited training. This allows for the sale and possession of naloxone products without a prescription in the state of Texas.

2 Duration of Therapy [1-11]

Therapy duration for fentanyl oral transmucosal lozenges, fentanyl buccal tablets, fentanyl sublingual tablets, fentanyl sublingual spray, fentanyl nasal spray, and fentanyl transdermal patches is limited to the need for pain management in patients with cancer already receiving opioids and tolerant to opioid therapy.

3 Duplicative Therapy [1-11]

Concurrent therapy with fentanyl oral transmucosal lozenges, buccal tablets, sublingual tablets, sublingual spray, or nasal spray and other forms of fentanyl as well as other CNS depressants should be prescribed cautiously, if at all. If concurrent therapy is necessary, patients should be monitored for signs of respiratory depression as well as excessive sedation.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for fentanyl are summarized in **Table 8**. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 8. Fentanyl Drug-Drug Interactions [1-11, 36]

Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
amiodarone	concurrent use may result in cardiac toxicity (e.g., bradycardia, low cardiac output) and increased risk of fentanyl toxicity (e.g., respiratory and CNS depression) as amiodarone inhibits CYP3A4	if combination utilized, monitor patients closely for enhanced pharmacologic/toxic effects	major (DrugReax) 3-moderate (CP)
CNS depressants (e.g., skeletal muscle relaxants, haloperidol, other opioids)	potential for additive CNS effects, including respiratory depression, excessive sedation or coma	use cautiously together; modify fentanyl doses as necessary and observe patients for enhanced CNS adverse effects	major (DrugReax) 2-major (CP)
CYP3A4 inducers (e.g., rifampin, barbiturates, carbamazepine, phenytoin, aprepitant, efavirenz)	may increase fentanyl clearance and reduce fentanyl systemic concentrations leading to decrease effectiveness as fentanyl is a CYP3A4 substrate	monitor fentanyl efficacy in patients prescribed CYP3A4 inducers concurrently; adjust doses as necessary when CYP3A4 inducer added, deleted, or changed to therapeutic regimen	moderate (DrugReax) 2-major, 3-moderate (CP)

Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
CYP3A4 inhibitors (e.g., aprepitant, protease inhibitors, macrolides, azole antifungals, efavirenz)	may decrease fentanyl clearance and increase fentanyl systemic concentrations leading to potential for enhanced pharmacologic/toxic effects as fentanyl is a CYP3A4 substrate	monitor for enhanced fentanyl pharmacologic/toxic effects and adjust doses as necessary	strong inhibitors - contraindicated, inhibitors - major (DrugReax) 2-major, 3-moderate (CP)
MAOIs (e.g., phenelzine, procarbazine, linezolid)	concurrent administration may potentiate severe, unpredictable opioid effects including CNS depression and hypotension	fentanyl should not be prescribed during or within 14 days of MAOI administration	major (DrugReax) 2-major (CP)
mifepristone	adjunctive administration may result in increased fentanyl serum levels and the potential for enhanced pharmacologic/ serious adverse effects as fentanyl is a CYP3A4 substrate and mifepristone is a CYP3A4 inhibitor	avoid concurrent administration	contraindicated (DrugReax) 1-severe (CP)
nasal decongestants (e.g., oxymetazoline) and intranasal fentanyl	combined administration of intranasal fentanyl with vasoconstrictive nasal decongestants results in reduced fentanyl absorption through the nasal mucosa, reduced Cmax and delayed Tmax, and the potential for reduced effectiveness in pain management	use combination cautiously; avoid intranasal fentanyl dose titration in patients using vasoconstrictive decongestants as inappropriate maintenance dose may be calculated; interaction does not occur with other fentanyl dosage forms	2-major (CP)
opioid antagonists (e.g., naloxone, naltrexone)	may precipitate withdrawal symptoms and/or decrease fentanyl effectiveness	use with caution only when necessary and monitor for signs of fentanyl withdrawal/loss of efficacy	naltrexone: contraindicated (DrugReax) 2-major (CP)

Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]
serotonergic agents (e.g., selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors)	concurrent use increases risk for serotonin syndrome or neuroleptic malignant syndrome-like reactions as both agents have serotonergic properties	administer cautiously together; observe for signs/symptoms of serotonin syndrome (e.g., agitation, confusion, hyperthermia, shivering)	major (DrugReax) 2-major (CP)

[#]CP = Clinical Pharmacology
CNS = central nervous system; Cmax = maximum serum concentration; CYP = cytochrome P450; MAOIs = monoamine oxidase inhibitors; Tmax = time when maximum serum concentration is reached

5 References

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