



Fast Facts Core Curriculum

Opioid Products

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**FAST FACTS AND CONCEPTS #2
CONVERTING TO TRANSDERMAL FENTANYL
David E Weissman MD and Drew A Rosielle MD**

Quick—what dose of the transdermal fentanyl patch (Duragesic®) is equianalgesic to a 3 mg/hr morphine continuous infusion? Conversions to and from fentanyl transdermal are notoriously tricky, requiring knowledge of the published conversion data, general opioid pharmacology, and a generous dose of common sense. See also Fast Fact #36 on opioid dose conversions.

Step 1: Calculate the 24 hr morphine dose: $3 \text{ mg/hr} \times 24 \text{ hrs} = 72 \text{ mg IV morphine/24 hrs}$.

Step 2: Convert the IV dose to the equianalgesic oral morphine dose using a ratio of:
 $1 \text{ mg IV} = 3 \text{ mg oral}$. Thus, $72 \text{ mg IV} = 216 \text{ mg po/24 hours}$.

Step 3: Convert the oral morphine dose to transdermal fentanyl. There are two methods:

Method 1 – Standard Table. Look up the FDA prescribing information for transdermal fentanyl (Reference 1, pp 29-30). It says that 135-224 mg of morphine per 24 hours = 50 mcg/hr patch. Note: this range of morphine is very broad which may result in significant under-dosing.

Method 2 - Alternate Formula. In 2000, Brietbart, et al published an alternative method, based on the results of a multi-center trial by Donner, et al, that relied on a fixed dose conversion ratio to calculate the fentanyl transdermal dose. Brietbart recommended the ratio of:
 $2 \text{ mg oral morphine/24 hr} = 1 \text{ mcg/hr of transdermal fentanyl}$ —rounded to the nearest patch size. In the case example above, 216 mg of oral morphine per day is approximately equianalgesic to the 100 mcg/hr fentanyl patch.

Note: using this formula, 25 mcg/hr of transdermal fentanyl is roughly equivalent to 50 mg oral morphine/24 hours. This dose may be excessive when used in the opioid naïve or the elderly.

Key Considerations

- All equianalgesic ratios/formulas are approximations; clinical judgment is needed when making dose or drug conversions.
- The FDA Prescribing Information indicates that their table should only be used when converting from another opioid to transdermal fentanyl.
- The risk of sedation/respiratory depression with transdermal fentanyl is probably increased in the elderly or patients with liver and renal impairment due to its long half-life, thus, choose the lower end of the dosing spectrum.
- When in doubt, go low and slow, using prn breakthrough doses generously while finding the optimal dosage of a long-acting drug.

- The 'Alternate Formula' by Brietbart, et al is best used by experienced practitioners as it tends to give higher fentanyl patch doses than the FDA PI.

Other teaching points about Duragesic:

- Start at the lowest dose, 12 mcg/hr, in an opioid naïve patient; there is no maximum dose.
- Therapeutic blood levels are not reached for 13-24 hours after patch application and drug will be continue to be released into the blood for at least 24 hours after patch removal.
- Opioid withdrawal symptoms can occur during dose conversions—care must be taken to avoid this by use of breakthrough opioids.
- Some patients will need to have their patches changed every 48 hours.
- The recommended upward dose titration interval is no more frequently than every 72 hours.
- Place patches on non-irradiated, hairless skin.
- Direct heat applied over the patch can increase drug absorption with increased toxic effects.
- There are no data that cachectic patients have reduced efficacy due to loss of subcutaneous fat; albeit cachectic patients may require higher dosing (6).

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FAST FACTS AND CONCEPTS #50
CHOOSING AN OPIOID COMBINATION PRODUCT
David E Weissman MD

Introduction

There are over 50 different opioid combination products, available in a range of tablet strengths and liquids. Opioid combination products are typically used for moderate pain that is episodic (e.g. breakthrough pain) on a PRN basis. These products contain either acetaminophen, aspirin or ibuprofen, with an opioid: codeine (e.g. Tylenol #2-4), hydrocodone (e.g. Lorcet, Lortab, Vicodin, Vicoprofen), oxycodone (e.g. Percocet, Percodan, Tylox, Roxicet) or propoxyphene (e.g. Darvocet, Wygesic). Other formulations also may contain caffeine and/or a barbiturate. This Fast Fact will review information for rationally choosing among the various products.

Intrinsic Analgesic Potency

Milligram for milligram, oxycodone and hydrocodone are the most potent opioids in this group; they are roughly equianalgesic to each other. Codeine is less potent and propoxyphene the least potent of the group; propoxyphene products are probably no more potent than aspirin or acetaminophen alone.

Toxicity

The dose limiting property of all the combination products is the aspirin, acetaminophen or ibuprofen, not the opioid (see below). Patients receiving any of the four opioids may experience classic opioid side effects: nausea, constipation, pruritus or sedation, along with the potential for tolerance and physical dependence with chronic use. Differences in side effect severity among the different opioids is largely idiosyncratic. There is anecdotal experience that codeine is the most, and hydrocodone the least, emetogenic among the four opioids. Propoxyphene's major metabolite is a CNS stimulant, increasing the likelihood of seizures in an overdose situation. It is also cardiotoxic, with lidocaine-like effects. Because of limited efficacy and increased toxicity, propoxyphene is not recommended, especially in the elderly (1). Multiple countries have banned propoxyphene; as of 2009 this is under consideration in the US.

Cost

Generic products are readily available and typically less expensive.

Range of available doses

Codeine products: 15-60 mg codeine/tablet

Oxycodone or hydrocodone: 2.5–10 mg opioid/tablet

Propoxyphene: 50-100 mg propoxyphene/tablet

Acetaminophen doses range from 325–750 mg/tablet

Recommendations for use

- Propoxyphene should rarely, if ever, be prescribed; it should not be used in the elderly.
- Prescribe generic products whenever possible.
- Prescribe only one combination product at any given time. Avoid writing orders that include multiple products (e.g. “X” for mild pain, “Y” for moderate pain, etc). Rather, prescribe only one product, assess efficacy and toxicity, and modify accordingly.
- Prescribe codeine, oxycodone and hydrocodone products at a q4h interval; not q 4-6 or q6h (see Fast Fact #18) (2).
- Pay very close attention to the total daily dose of acetaminophen/aspirin/ibuprofen. Note: the dose of acetaminophen per tablet can range from 325-750 mg. Thus, with a recommended limit of < 4 grams per day, this equals 12 tablets @ 325 mg or 5 tablets @ 750 mg tablet. Patients with renal or liver dysfunction are at higher risk for adverse effects from the non-opioid (3).

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indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.



FAST FACTS AND CONCEPTS #53 SUBLINGUAL MORPHINE

Debra Gordon RN, MS, FAAN, Sean Marks MD, Bridget Protus PharmD

Background The preferred route of administration of analgesics for most patients in pain is oral (PO) considering the longer duration of action and convenience of use in non-hospital settings compared with subcutaneous and intravenous formulations. Soluble tablets of morphine were once commonly used for off-label sublingual (SL) administration in patients who were unable to swallow pills or large quantities of solutions. Although some hospice pharmacies still may be able to compound soluble morphine for sublingual use, the manufacture of soluble tablets of morphine has not been available in the United States since 2007. Instead, most pharmacist experts recommend the use of concentrated oral solution (20 mg/mL) of morphine or oxycodone for this clinical application.

Pharmacology of SL Morphine SL administration of morphine via soluble tablets was used to treat breakthrough pain to hasten analgesic onset and peak; however, available data do not support more rapid absorption of soluble morphine tablets when compared with more traditional oral formulations of morphine (1-3). Indeed, several clinical studies found no substantial advantage to the use of soluble morphine tablets over oral morphine (4-6).

- Mean time to maximum concentration has been shown to be shorter for PO morphine (0.8 + 0.35hr) compared with soluble morphine tablets (1.75 + 1.30 hr), indicating that soluble morphine tablets are likely swallowed and absorbed gastrointestinally rather than through the oral mucosa (3).
- The bioavailability (amount of drug eventually made available to the systemic circulation) of soluble morphine tablets are relatively low: only 9%
- Agents are most readily absorbed through the oral mucosa when they are potent, non-ionized at physiological pH, and lipid soluble (see *Fast Fact* #103). Morphine has a relatively low potency for an opioid, is 90% ionized at the pH of the mouth, and is one of the least lipid soluble opioids. These factors likely explain its poor performance as a SL or buccal medication.

Pharmacology of Concentrated Oral Solutions of Morphine and Oxycodone In lieu of the poor evidence supporting the efficacy of soluble morphine tablets, they are not manufactured in the United States anymore. Instead, the use of

concentrated (20 mg/mL) of oral morphine solution has been more commonly utilized for imminently dying patients who are unable to tolerate pills or significant volumes of an opioid solution.

- The bioavailability of the oral solution is 23.8%.
- Concentrated oral morphine solution is considered to be equianalgesic with soluble morphine tablets.
- The amount of SL absorption of the 20 mg/mL concentrated oral morphine solution is estimated to be only 18-20%. Its clinical effect is more likely due to the dose being swallowed with saliva and absorbed gastrointestinally.
- Oxycodone also comes available as a 20 mg/mL solution. The most concentrated oral solution available for methadone is a 10 mg/mL solution. Hydromorphone is not available in a concentrated oral solution.

Formulation and Dosing

- There are several forms of short acting PO morphine available, however, only the soluble tablets or the concentrated oral solution are suitable for SL use. Nonsoluble morphine sulfate immediate release (MSIR) tablets will not be absorbed sublingually, even when crushed, because they will not liquefy under the tongue.
- A usual starting dose for an opioid naïve patient is 5-15 mg PO or every 3 hours. The equianalgesic ratio of IV to PO morphine is 1:3 (10mg of IV morphine is approximately equianalgesic to 30 mg PO/SL morphine).

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**FAST FACTS AND CONCEPTS #75
METHADONE FOR THE TREATMENT OF PAIN
Gail Gazelle MD and Perry G Fine MD**

Introduction Methadone, a potent opioid agonist, has many characteristics that make it useful for the treatment of pain when continuous opioid analgesia is indicated. Although available for decades, its use has gained renewed interest due to its low cost, inactive metabolites, and many routes of administration. This Fast Fact will introduce methadone's pharmacology and clinical use as an analgesic.

Pharmacology Unlike morphine, methadone is a racemic mix; one stereoisomer acts as a NMDA receptor antagonist, the other is a mu-opioid receptor agonist. The NMDA mechanism plays an important role in the prevention of opioid tolerance, potentiation of opioid effects, and is the theoretical basis for its use in neuropathic pain syndromes, although this latter impression is largely anecdotal.

Methadone is highly lipophilic with rapid GI absorption and onset of action. It has a large initial volume of distribution with slow tissue release. Oral bioavailability is high, ~ 80%. Unlike morphine there are no active metabolites and biotransformation to an active drug is not required. The major route of metabolism is hepatic with significant fecal excretion; renal excretion can be enhanced by urine acidification (pH <6.0). Unlike morphine, no dose adjustment is needed in patients with renal failure since there are no active metabolites.

Prescribing Methadone is available in tablet, liquid and injectable forms; oral preparations can be used rectally. Parenteral routes include IV bolus dosing or continuous infusion. Any clinician with a Schedule II DEA license can prescribe methadone for pain; a special license is only required to prescribe methadone for the treatment of addiction. In some jurisdictions, it is necessary to apply the words "for pain" on the prescription.

Cautions Unlike morphine, hydromorphone, or oxycodone, methadone has an extended terminal half-life of up to 190 hours. This half-life does not match the observed duration of analgesia (6-12 hours) after steady state is reached. This long half-life can lead to increased risk for sedation and respiratory depression, especially in the elderly or with rapid dose adjustments. Rapid titration guidelines for other opioids do not apply to methadone. Given recent reports that high-dose methadone may be associated with development of QT interval prolongation and Torsades de Pointes, EKG monitoring may be appropriate when changes in dosage are made (depending upon life expectancy and goals of care).

Pediatrics With close monitoring by an experienced prescriber, methadone has been used safely in children, although the safety, effectiveness, and the pharmacokinetics of methadone in

patients below the age of 18 years have not been established by the Food and Drug Administration.

Potency An important property of methadone is that its apparent potency, compared to other opioids, varies with the patient's current exposure to other opioids. See below for a suggested dosing guide for opioid tolerant patients (Reference 1).

Daily oral morphine dose equivalents Conversion ratio of oral morphine to oral methadone

<100 mg	3:1 (i.e. 3 mg morphine = 1 mg methadone)
101-300 mg	5:1
301-600 mg	10:1
601-800 mg	12:1
801-1000 mg	15:1
>1001 mg	20:1

Due to incomplete cross-tolerance, it is recommended that the initial dose is 50-75% of the equianalgesic dose.

Key Points

- Compared to morphine, methadone is inexpensive, safe in renal failure, will provide a longer duration of action, and has a theoretic advantage in neuropathic pain, although the latter point has not been reliably demonstrated.
- Because of its long and variable elimination half-life methadone is not an ideal opioid when rapid dose adjustments are needed; do not increase oral methadone more frequently than every 4 days.
- Dose conversion to:from other opioids and methadone is complex and particularly more dangerous than other opioids; consultation with pain or palliative specialists familiar with methadone use is recommended.
- Patient and family education is essential as they may misinterpret prescription of methadone to mean that their physician believes that they are an addict.

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FAST FACT AND CONCEPT #80
CONTROLLED RELEASE OXYCODONE
David E Weissman MD

Background Controlled release oxycodone (CRO) has received considerable attention in the lay press over the past several years. Much of the coverage has been negative, related to the illicit use of CRO due to diversion outside of legitimate medical practice. Within legitimate medical practice, CRO is an effective long-acting oral opioid product, very similar to controlled release morphine. This Fast Fact reviews CRO usage in palliative care.

Indication CRO is indicated for moderate to severe pain requiring continuous, around-the-clock analgesia for an extended period of time in patients ≥ 18 years of age. The Food and Drug Administration have not established the safety and effectiveness in pediatric patients, although it has been used successfully in select pediatric populations.

Pharmacology Oxycodone is a semi-synthetic opioid that interacts with both mu- and kappa-opioid receptors, but behaves in most respects identically to morphine. CRO has greater oral bioavailability than morphine, and a bi-phasic absorption pattern, with peaks at 37 minutes and 6.2 hours. Peak pain relief occurs in one hour. Unlike morphine, oxycodone has minimally active metabolites, demonstrating little to no analgesic or anti-analgesic properties. Oxycodone should be used with caution in patients with renal and liver impairment and avoided in hemodialysis patients. CRO can lead to all the traditional opioid side effects. Anecdotal reports suggest less nausea, hallucinosis, and nausea compared to morphine, although these observations have not been substantiated in controlled trials.

Equianalgesic Information Studies comparing round the clock immediate-release oxycodone to controlled-release oxycodone products demonstrate equivalent results. The conversion factor between morphine and oxycodone has been controversial, but the most commonly accepted data suggests that 30 mg of morphine is equivalent to 20 mg of oxycodone. Since all equianalgesic values are rough guidelines, prescribers need to use their clinical judgment in determining the most appropriate starting dose (see Fast Fact #36).

Dosage The starting dose of CRO in an opioid naïve patient is 10 mg q12 hours; it can be dose escalated every 24-48 hours (see Fast Fact #20). CRO must be taken intact; pills cannot be cut or crushed without risk of rapid absorption and subsequent overdose. CRO is not approved for rectal administration.

Cost CRO is more expensive than generic long-acting morphine; there is currently no generic CRO product on the market.

Diversion CRO has been associated with greater diversion to the illicit drug market than morphine. Illicit users will commonly crush the tablet and then chew, snort, or dissolve the product in water for intravenous injection. CRO can bring \$1-per-milligram or more on the illicit market.

Summary CRO oxycodone is an effective long-acting oral opioid. Due to cost and concerns about diversion, controlled release morphine is the drug of first choice for a long-acting oral opioid product. There are no data that CRO offers any analgesic benefit compared to morphine. Data for the use of CRO in the pediatric palliative population is lacking.

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FAST FACTS AND CONCEPTS #103
ORAL TRANSMUCOSAL FENTANYL CITRATE
Debra Gordon RN, MS, FAAN and Mark Schroeder MD

Introduction Oral transmucosal fentanyl citrate (OTFC, Actiq[®]) is a solid formulation of fentanyl that resembles a lozenge on a handle. It is intended for oral transmucosal administration. Fentanyl is also available as an oravescent buccal tablet (Fentora[®]), a sublingual tablet (Abstral[™]), a buccal film (Onsolis[™]), a nasal spray (Lazanda[™]), and a sublingual spray (Subsys[™]), – these products are all dosed differently. Do not interchange these products on a mcg-per-mcg basis – these products are all dosed differently. Do not interchange these products on a mcg-per-mcg basis. This Fast Fact only discusses OTFC (Actiq[®]).

Indications OTFC is indicated for breakthrough cancer pain in patients 16 years or older already receiving and who are tolerant (receiving at least equivalent of 60 mg oral morphine per 24 hours) to opioid therapy for underlying persistent cancer pain. Off-label pediatric use has been described in the literature especially among cancer patients who are opioid tolerant.

Pharmacology Compared to morphine and hydromorphone fentanyl is a lipid-soluble opioid and, when placed in saliva under normal conditions of the mouth, is 80% non-ionized making it the only opioid suitable for transmucosal absorption. Fentanyl is ~ 100 times more potent than morphine. However, bioavailability of OTFC depends on the fraction of the dose that is absorbed through the oral mucosa (~25%) and the fraction that is swallowed (~75%; but swallowed dose is only partially bioavailable). OTFC can produce a rapid onset of analgesia, even during unit consumption (fentanyl begins to cross the blood-brain barrier in as little as 3-5 minutes), with peak effect at 20-40 minutes after the start of administration. Total duration of activity is 2 to 3 hours. The amount of fentanyl absorbed from each single dose remains stable over multiple administrations. This fact, combined with fentanyl's short half-life, reduces the risk of a cumulative increase in serum level with repetitive doses.

Prescribing Information

OTFC is available in 200, 400, 600, 800, 1200, & 1600 mcg dosage strengths. Do not substitute ACTIQ[™] on a mcg per mcg basis for other oral fentanyl products including the oravescent buccal tablet (Fentora[™]).

OTFC should always be started at 200 mcg dose and then individually titrated based on patient response; there is no conversion factor for OTFC and the patient's existing opioid requirement. If the first 200 mcg dose is inadequate, the patient should wait for 15 minutes (30 minutes after start of first unit) and take a second unit. If pain is relieved after the second dose of 200 mcg, the dose to use for the next episode of breakthrough pain would be 400 mcg. The patient should be instructed not to take more than two units per pain episode during the initial titration period. OTFC has typical opioid dose-related side effects: somnolence, nausea, and dizziness. OTFC (along with all other transmucosal immediate-release fentanyl products) are available in the outpatient setting only through a Risk Evaluation and Mitigation Strategy (REMS) program. Enrollment in the program is mandatory for outpatients, prescribers, pharmacies, and distributors.

Patient Information Consumption Technique and Storage Place unit next to buccal mucosa, between cheek and gum, moving the unit gently side to side. 15 minutes is the ideal amount of time to consume a unit to achieve the desired onset and peak effect. OTFC units are designed for one time administration. Patients should be instructed to remove the unit from their mouth if excessive opioid-related side effects develop. The following factors will decrease transmucosal absorption:

- Reduced saliva.

- Use of liquids that reduce oral pH prior to OTFC administration (coffee, cola, fruit juices).
- Placement of OTFC on tongue or gums (lowered absorption at these sites).
- Chewing OTFC.

Instruct patients to utilize the manufacturer's safety containers to store the dosage units, and discard any unused portion of the OTFC by dissolving it under hot tap water. Partially used units should not be stored and re-used. The drug should be stored at room temperature, and not be frozen. The Average Wholesale Price is \$564 for thirty 200 mcg lozenges.

This Fast Fact was adapted with permission from the University of Wisconsin Hospital & Clinics, Madison, WI Pain Patient Care Team 'Pain Management Fast Facts – 5 Minute Inservice' series.

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FAST FACTS AND CONCEPTS #185
TOPICAL OPIOIDS FOR PAIN
Juliet Jacobsen MD, DPH

Background Clinical experience and preliminary research have suggested that topical opioids can be effective local analgesics. This Fast Fact reviews the mechanism of action, research data, and dosing information on topically applied opioids.

Mechanism of action The insight that opioids exert a local analgesic effect is based on several observations: 1) opioid receptors have been found on peripheral nerves and inflamed tissue, 2) morphine and its metabolites are largely undetectable systemically when applied topically to skin ulcers (suggesting the analgesic effect is local), and 3) peripheral opioid injections for local analgesia, such as intra-articular morphine after knee surgery, have been found to be effective in several trials. Of note, animal studies suggest that opioids can accelerate wound healing by up-regulating nitric-oxide synthase. The relevance of this for humans is unknown and there is no consensus regarding whether or not topical opioids benefit or impede wound healing in humans.

Research data Several small case series have shown rapid relief using topical opioids in patients with pain due to skin infiltration of tumor, skin ulcers of malignant and non-malignant origin, severe oral mucositis, knee arthritis, and tenosynovial pain. Most studies have evaluated morphine, although diamorphine and methadone have also shown efficacy.

Skin ulcers: Three randomized, double-blinded, placebo-controlled studies totaling 34 patients assessed the efficacy of topical opioids for treating painful ulcers (mostly sacral pressure ulcers). These studies found significantly lower pain scores in patients treated with topical opioids compared with placebo. In general, pain decreased 2-3 points on a 0-10 pain scale. Another blinded, controlled trial of 18 patients showed topical morphine to be no more effective than placebo. This study's outcome however was complete pain relief, not just significant analgesic response as in the other studies. Itching and burning are common side effects reported by both patients receiving morphine and placebo vehicle-gel. No systemic side effects were reported.

Mucositis: A dose-response relationship has been reported for patients with painful oral mucositis; rinses with 0.2% morphine solution showed better pain relief than those with 0.1%. One non-blinded, randomized study of 26 patients that compared morphine mouthwash (an oral rinse of 0.2% morphine solution) with "magic" mouthwash (a mixture of equal parts lidocaine, diphenhydramine, and magnesium aluminum hydroxide) found significantly decreased duration and intensity of pain in the morphine mouthwash group.

Administration Topical opioid gels and mouthwashes are not available commercially and need to be prepared by a compounding pharmacist.

Gel: Most studies used a mixture of 10 mg of morphine sulfate injection (10 mg/ml) in 8 gm of Intrasite gel. Patients are instructed to cover their wound with the gel (usually using 5-10 ml) and then loosely dress it with gauze. Duration of analgesia varies widely; preparations usually need to be applied one to three times per day. Both morphine sulfate and diamorphine hydrochloride mixed with Intrasite gel have been found to be stable irrespective of temperature and light exposure for up to 28 days.

Mouthwash: The morphine mouthwash which has been studied is an oral rinse of 15 ml of 0.2% morphine solution (2000 mg morphine chloride diluted in 1000 ml of water). It can be taken every 3 hours as needed. Patients should be instructed to hold the mouthwash in their mouth for 2 minutes then spit out. They should be counseled carefully to not swallow the mouthwash to avoid systemic effects from the morphine. Because of this it is most useful for patients with predominantly oral (not esophageal) pain.

Conclusion There are limited trial data to support the use of topical morphine gel and mouthwash for painful cutaneous ulcers and oral mucositis. In patients taking systemic opioids the added benefit of topical ones (e.g. limited systemic side effects) is diminished.

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FAST FACTS AND CONCEPTS #268
LOW-DOSE BUPRENORPHINE PATCH FOR PAIN
Julie W Childers MD and Robert Arnold MD

Background Buprenorphine is an opioid agonist/antagonist that is used sublingually for opioid addiction treatment (see Fast Fact #221). In 2010, the Food and Drug Administration approved a buprenorphine transdermal system (the ‘Butrans®’ patch) for use in the United States. This Fast Fact reviews the use of buprenorphine for pain, with an emphasis on the new low-dose transdermal patch.

Pharmacology Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa- and delta-opioid receptors. It provides analgesia with decreased incidence of sedation, euphoria and respiratory depression compared to other opioids (1). A ceiling effect for pain relief, previously identified in animals and humans, has not been found at the lower doses used for analgesia. In doses available transdermally (up to 70 mcg/hour), buprenorphine does not antagonize the effect of other opioids used for breakthrough pain (2).

Equianalgesic Ratios Buprenorphine is effective parenterally for post-operative pain; 0.3 mg is equianalgesic to 10 mg IV morphine. A trial of sublingual buprenorphine for pain (an off-label use in the U.S.) found that 0.4 mg is as effective for acute pain as 5 mg IV morphine (3). The transdermal buprenorphine to oral morphine equianalgesic ratio has been reported to be between 1:70 to 1:115 (e.g., 100 mg of oral morphine/24 hours ≈ 0.87-1.42 mg transdermal buprenorphine/24hr ≈ 36-59 mcg/hr transdermal buprenorphine). The transdermal buprenorphine:fentanyl ratio is reported to be 0.8 mcg buprenorphine to 0.6 mcg fentanyl (4) (e.g., 20 mcg/hour of transdermal buprenorphine is approximately equivalent to 15 mcg/hour of transdermal fentanyl).

Using the Low-Dose Buprenorphine Patch The U.S. formulation of the buprenorphine transdermal system is recommended for opioid tolerant patients requiring up to 80 mg/day of oral morphine equivalents. The patch is available in strengths of 5, 10, and 20 mcg/hour, and is worn for seven days at a time. The 20 mcg/hour patch is not intended for initial use, but patients accustomed to the patch may be titrated to this dose. The safety and efficacy of transdermal buprenorphine has not been fully established in children. In children >13 years of age, the dosing is felt to be equivalent to adults. Buprenorphine reaches a steady state level 48 hours after application of the first patch, and, with a terminal half-life of 26 hours, levels decline slowly after patch removal. Withdrawal symptoms tend to be milder than with other long-acting opioids (5). Use of more than one patch at a time is not recommended due to risk of QT prolongation, with a mean QTc prolongation of 9.2 ms at a dose of 40 mcg/hour (6). Note: in Europe doses between 70-210 mcg/hour have been used for cancer pain with a different patch system (7).

Initiating the Low-Dose Buprenorphine Patch (Manufacturer’s Recommendations) (6)

Baseline Daily Oral Morphine Equivalent	Starting Patch Dose
<30 mg	5 mcg/hour
30-80 mg	10 mcg/hour
>80 mg/day	Usage not recommended

Clinical Applications The buprenorphine patch has shown to be non-inferior to other opioids in studies of chronic lower back pain, osteoarthritis, and cancer pain (8). Because of its kappa antagonism, it has theoretical advantages in the treatment of neuropathic pain, though evidence for this is limited to case reports (9, 10). It has also been shown experimentally to have antihyperalgesic effects (11). Other advantages of buprenorphine include a decreased risk of respiratory depression and a lack of accumulation in renal failure, including in hemodialysis patients (12). Some studies have reported less constipation, nausea, and sedation with

buprenorphine (13,14). In a trial comparing transdermal buprenorphine in patients over 65 with younger patients, older patients had equivalent analgesia without any differences in accumulation of buprenorphine or its metabolites (15).

Cost The average wholesale price (in 2015) for a month's supply of four 10 mcg patches is \$336.

Summary The low-dose transdermal buprenorphine patch is effective for mild to moderate chronic pain, both malignant and nonmalignant. However, given the dose limitations of the buprenorphine patch as marketed in the U.S., as well as the cost, the usefulness of this medication for most patients and clinicians is very limited. The low-dose buprenorphine patch may be a reasonable second- or third-line option in patients with low opioid requirements who experience intolerable side effects with other opioids.

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FAST FACTS AND CONCEPTS #290
TRAMADOL IN PALLIATIVE CARE**Jennifer Pruskowski PharmD and Robert M Arnold MD**

Background Tramadol is an important medication in palliative care. It is a Step II agent on the World Health Organization's (WHO) pain ladder (1) and has FDA approval for the treatment of moderate to severe pain in adults. This Fast Fact will review tramadol's pharmacology, its benefits, and limitations. Note that tramadol has similarities with tapentadol which is discussed in Fast Fact #228.

Pharmacology The analgesic effects of tramadol are likely due to mu-opioid agonist activity, and weak monoamine reuptake inhibition (specifically blocking norepinephrine and serotonin) in the CNS. Tramadol is a prodrug and must be metabolized via CYP2D6 to its pharmacologically active metabolite (O-desmethyl tramadol) (2). It is excreted 90% in the urine; therefore specific dosing adjustments are necessary in renal impairment (CrCl <30 mL/min). There are also dosing adjustments in the elderly and end-stage liver failure. Clinicians should be aware of tramadol's significant drug interactions with other CYP2D6 inhibitors (fluoxetine, paroxetine and amitriptyline) and CYP3A4 inhibitors (ketoconazole and erythromycin), which increase the risk of seizures and serotonin syndrome.

Dosing Tramadol is available as both generic and proprietary formulations: a 50 mg immediate-release (IR) tablet and 100 mg, 200 mg, and 300 mg extended-release (ER) tablet (Ultram ER®). Immediate-release tramadol also comes formulated with acetaminophen. Tramadol should be started at 25 mg/day in the morning and increased by 25-50 mg every 3 days. The maximum daily dose of tramadol is 400 mg/day (50-100mg every 4-6 hours). In patients with renal impairment (CrCl <30 mL/min), the dosing interval is 12 hours with a maximum daily dose of 200 mg/day. The maximal recommended dose for adult patients with cirrhosis is 50 mg every 12 hours. For elderly patients over 75 years old, the total daily should not exceed 300 mg/day. Approximately 120 mg of oral tramadol is equivalent to 30 mg of oral morphine (3). Oral morphine tablets are roughly half the cost of tramadol IR tablets, and one-sixth the price of tramadol ER tablets.

Adverse Drug Reactions Tramadol's adverse drug reaction profile is similar to other opioids, although it has a lower incidence of respiratory depression (4) and likely has a lower abuse potential. An early comparative study suggested that tramadol has less abuse potential than morphine (5) and more recent preclinical studies suggest that abuse-related behavioral effects of tramadol may be of lesser magnitude than other mu-opioid receptor agonists (6). However, there have been several reports of its abuse and misuse (7). Hence, in August of 2014 tramadol was made a Schedule IV controlled medication.

Cautions Tramadol carries four specific cautions: Seizures have been reported with higher than recommended dosage and with concomitant use of SSRI/SNRIs, MAOIs, triptans, and other drugs that reduce the seizure threshold (8). Serotonin-syndrome may occur only with the concomitant use of other serotonergic drugs and is characterized as a triad of clinical changes: cognitive (mental-status changes, agitation and hallucinations), neuromuscular (hyperreflexia, incoordination) and autonomic (tachycardia, labile blood pressure). Although the prevalence of serotonin-syndrome is unknown, the majority of cases present within 24 hours (and most within 6 hours), of a change in dose or initiation of a serotonergic medication (9).

A large population cohort study from the UK comparing tramadol with codeine found a significantly increased risk of hospitalization from hypoglycemia, especially in the first 30 days of initiation and non-diabetic patients (10).

Lastly in May of 2010, the FDA strengthened the warning for suicide risk for patients at high risk (defined as those who are addiction-prone, taking tranquilizers, or antidepressant drugs)(11).

Research Data Most of the literature examining tramadol's role in palliative care involves the management of cancer pain (12). In comparison studies, tramadol was favored over sublingual buprenorphine due to the lower prevalence of adverse drug reactions, but morphine was preferred in patients with more severe pain (13). It has been shown to be safe and effective following surgical procedures, for neuropathic pain (14), as well as a variety of other pain conditions.

Summary Tramadol has an important position as a Step II agent on the WHO pain ladder, where it is effective for a variety of syndromes in patients with mild to moderate pain intensity. Its recommended dosing adjustments, potential ceiling effect, cost, pertinent drug-interactions, and risk for significant adverse drug reactions may limit its chronic use in patients with significant pain.

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**FAST FACTS AND CONCEPTS #307
OPIOID PHARMACOKINETICS**

Jennifer Pruskowski, PharmD, and Robert M Arnold, MD

Background Pharmacokinetics is the science of what the body does to a drug after administration, in contrast to pharmacodynamics -- the effect of a drug on the body. Knowledge of opioid pharmacokinetics parameters is critical for the safe and effective administration.

Absorption The proportion of active drug (whether given intravenously or absorbed from the gastrointestinal, respiratory, or cutaneous system) that enters the systemic circulation is defined as bioavailability. The wide bioavailability range amongst different opioids is partially attributable to differences in first pass metabolism, when the drug is metabolized directly by the liver from the gastrointestinal tract before it reaches the systemic circulation. Clinicians should be aware of the bioavailability for the opioid being prescribed because it indirectly affects PO: IV conversion ratios.

Distribution refers to the movement of drug between the blood and various tissues in the body. The parameter used to describe this movement is the volume of distribution (Vd). The targeted tissue for opioids is the central nervous system (CNS). To activate the targeted receptors, opioids must cross the blood-brain-barrier (1). Those opioids with a higher Vd are usually more lipophilic, and more likely to distribute faster and more strongly both into and out of the blood-brain-barrier. In clinical practice these opioids also tend to have a quicker onset, and shorter duration of analgesic action.

Metabolism The most important area of opioid pharmacokinetics is metabolism. The metabolism process may involve the Cytochrome (CYP) P-450 enzymes, particularly CYP 2D6 and 3A4, or other enzymes such as UDP-glucuronyltransferase (2). The spectrum of interpatient analgesic variability and clinically significant drug interactions of opioids are mostly due to the CYP enzymes.

Interpatient Variability CYP 2D6 influences the metabolism of codeine, hydrocodone, oxycodone, and tramadol, and has been found to have many genetic polymorphisms. Based on phenotypic profiles, patients can be poor, intermediate, or extensive metabolizers (3). This can potentially lead to inadequate analgesia or over-sedation. Fentanyl and methadone are primary metabolized by CYP 3A4. Although CYP 3A4 also has many genetic polymorphisms, none have been shown to be of major clinical relevance (4). UDP-glucuronyltransferase, the primary enzyme responsible for the metabolism of morphine, hydromorphone, oxymorphone, and tapentadol, does not possess significant interpatient variability.

Clinically Significant Drug Interactions There are three types of CYP P-450 enzyme subcategories: substrates, inhibitors, and inducers. Substrates require P-450 enzymes for metabolism. When enzyme inhibitors or inducers are concomitantly administered with substrates, the serum levels of these substrates are altered. Enzyme inhibitors may increase opioid serum levels leading to over-sedation; enzyme inducers may decrease opioid serum levels leading to inadequate analgesia. Table 1 summarizes drug interactions between opioids and commonly prescribed medications (5).

Enzyme	Substrates	Inhibitors	Inducers
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CYP 3A4	Codeine, fentanyl, methadone, oxycodone, tramadol	Amiodarone, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, itraconazole, ketoconazole, nefazodone, ritonavir, verapamil, voriconazole	Carbamazepine, dexamethasone, efavirenz, modafinil, oxcarbazepine, phenobarbital, phenytoin, rifampin, St. John's wort, troglitazone
CYP 2D6	Codeine, hydrocodone, methadone, morphine, oxycodone, tramadol	Amiodarone, bupropion, celecoxib, chlorpromazine, citalopram, diphenhydramine, doxepin, duloxetine, escitalopram, fluoxetine, haloperidol, hydroxyzine, metoclopramide, paroxetine, quinidine, ritonavir, sertraline, terbinafine, thioridazine	None reported

Excretion The vast majority of opioids are excreted as metabolites through the kidneys, with the exception of methadone which is primarily excreted via bile. Patients with renal and/or liver dysfunction may have altered drug clearance (see Fast Facts #161 and #260). Clinicians should be aware of opioid-individual terminal elimination half-lives ($T_{1/2}$), as these dictate the speed of opioid titrations. When given consistently, opioids reach steady state after four $T_{1/2}$. Opioid titrations should be avoided until the opioid regimen has reach steady state.

Summary Table 2 summarizes the pharmacokinetic parameters of commonly used oral opioids. These parameters are critical for the safe and effective use of these medications, as they commonly translate into individual pharmacodynamics properties (6-17).

Opioid (Route)	Absorption	Distribution	Metabolism		Excretion	
			Major Metabolism Enzyme(s)	Active Metabolite	Urine (%)	$T_{1/2}$ (Hours)
Codeine (PO)	53	3-6	CYP3A4 and 2D6	Morphine	90	3
Fentanyl (TDS)	N/A	4-6	CYP3A4	None	75	20-27
Hydrocodone IR (PO) δ	NR	NR	CYP2D6 and 3A4	Hydromorphone	26	3.3-4.4
Hydro-morphine IR (PO)	24	4	UGT	Unknown	75	2-3
Methadone (PO)	36-100	1-8	CYP3A4, 2D6, 2B6, 2C19	None	<10	7-59
Morphine IR (PO)	<40	4	UGT	M6G	90	2-4

Oxycodone IR (PO)	60-87	2.6	CYP3A4 and 2D6	Oxymorphone	19-64	2-4
Oxymorphone IR (PO)	10	1.94-4.22 L	UGT	6-OH	33-38	7-9
Tramadol IR (PO)	75	2.6	CYP3A4 and 2D6	M1	90	6.3
Tapentadol IR (PO)	32	540 +/- 98 L	UGT	None	99	4-5

Key: PO: oral; TDS: transdermal system; IR: immediate-release; δ : hydrocodone IR is available only in combination with acetaminophen; Vd: Volume of distribution; L: liters; N/A: non-applicable; CYP: Cytochrome enzyme; UGT: UDP-glucuronosyltransferase; M6G: Morphine-6-glucuronide; 6-OH: 6-OH-Oxymorphone; M1: O-desmethyltramadol; NR: not reported

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