PC NOW PALLIATIVE CARE NETWORK OF WISCONSIN

Safe and Effective Opioid Prescribing CME Module

Safe and Effective Opioid Prescribing CME Module
Course Description and Learning Objectives

Course Description: Patients with serious illnesses such as advanced cancer, chronic organ failure, or dementia are at risk for poorly controlled pain and dyspnea. Often these patients require opioid therapy in order to manage these symptoms, especially as their underlying advanced illness progresses. In order to prescribe opioids in a safe and effective manner for these patients, clinicians need to have comprehensive clinical knowledge regarding various types of opioids, routes of opioid therapy, dosing of opioid therapy, and how to modify opioid therapy as their symptoms evolve with the underlying illness. In this module, users can attain 1.0 hours of CME credit after successful completion of the following:

A. Content review of ten *Fast Facts and Concepts* covering the following topics:
    a. Best practices for opioid dose escalation in seriously ill patients
    b. Subcutaneous opioids
    c. Opioid dose conversions
    d. Sublingual morphine
    e. Range orders for as needed opioid prescriptions in seriously ill patients
    f. Opioid infusion orders
    g. Oral opioid orders
    h. Clinical pearls for prescribing scheduled II controlled medications such as opioids
    i. Opioid pharmacokinetics
    j. Abuse-deterrent opioid formulations
B. Score of 70% or higher on a 10 question quiz covering this content
C. Completion of a course evaluation.

Learning Objectives: At the conclusion of this course, learners will:

1. Describe starting doses for two oral and two parenteral opioids in palliative care.
2. List three opioid equi-analgesic and dose escalation principles.
3. Describe three principles of writing opioid prescription orders in the inpatient and outpatient settings.

PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #20
OPIOID DOSE ESCALATION

David E Weissman MD

Background A common question from trainees is how fast, and by how much, can opioids be safely dose escalated? I like to use the analogy of furosemide (Lasix) when discussing this topic. I have never seen a resident order an increase in Lasix from 10 mg to 11 mg, yet that is precisely what often happens with opioids, especially parenteral infusions. Like furosemide, dose escalation of opioids should be done on the basis of a *percentage* increase. In fact, this is reflexively done when opioid-non-opioid fixed combination products are prescribed; going from one to two tablets of codeine/acetaminophen represents a 100% dose increase. The problem arises when oral single agents (e.g. oral morphine) or parenteral infusions are prescribed. Increasing a morphine infusion from 1 to 2 mg/hr is a 100% does increase; while going from 5 to 6 mg/hr is only a 20% increase, and yet many orders are written, "increase drip by 1 mg/hr, titrate to comfort." Some hospitals and nursing units even have this as a standing pre-printed order or nursing policy.

Key Points: In general, patients do not notice a change in analgesia when dose increases are less than 25% above baseline. There is a paucity of clinical trial data on this subject. A common formula used by many practitioners is:

- For ongoing *moderate to severe* pain increase opioids doses by 50-100%, *irrespective of starting dose.*
- For ongoing *mild to moderate* pain increase by 25-50%, *irrespective of starting dose*.
- These guidelines assume the patient is tolerating the opioid well (with no or minimal sedation); clinicians will need to be more cautious and should consider expert help for patients with ongoing uncontrolled pain despite sedation from opioids or another cause.

When dose escalating long-acting opioids or opioid infusions, *do not increase the long-acting drug or infusion basal rate more than 100% at any one time*, irrespective of how many bolus/breakthrough doses have been used. These guidelines apply to patients with normal renal and hepatic function. For elderly patients, or those with renal/liver disease, dose escalation percentages should be reduced (see *Fast Facts* # 161 for Opioid use in renal failure and # 260 for Opioid use in liver failure).

The recommended frequency of dose escalation depends on the half-life of the drug.

- Short-acting oral single-agent opioids (e.g. morphine, oxycodone, hydromorphone), can be safely dose escalated every 2 hours.
- Sustained release oral opioids can be escalated every 24 hours.
- For methadone, levorphanol, or transdermal fentanyl no more frequently than every 72 hours is recommended.
- **Note:** transbuccal fentanyl products have specific guidelines for dose escalation. See the manufacturers' prescribing information and *Fast Fact* #103

See related analgesic *Fast Facts*:
#18 Oral opioid dosing intervals
51 Opioid combination products
70 PRN range orders
74 Good and Bad analgesic orders
215 Opioid poorly-responsive cancer pain

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #28
SUBCUTANEOUS OPIOID INFUSIONS

David E Weissman MD

Background
A parenteral opioid infusion is the standard of care for managing moderate-severe pain or dyspnea when the oral/rectal route is unavailable and/or frequent dose adjustments are needed. As death nears, the burden of maintaining intravenous (IV) access, especially in the home setting, can be enormous. An alternative delivery route supported by major pain societies such as European Association of Palliative Care is the subcutaneous (SQ) route for continuous infusions, Patient Controlled Analgesia (PCA), or intermittent bolus opioid injections.

Drugs
Morphine, hydromorphone (Dilaudid), fentanyl, and sufentanil can all be safely administered as SQ bolus doses or continuous SQ infusion. Methadone infusions cause frequent skin irritation; one case series reported successful use of methadone with concurrent dexamethasone infusion and frequent site rotation.

Dosing equivalents
Dose conversion ratios between the IV and SQ route for all the above listed opioids are not well established. For morphine, the ratio appears to be close to 1 mg IV = 1mg SQ.

Pharmacokinetics
SQ infusions can produce the same blood levels as chronic IV infusions. There is no data to suggest that cachectic, febrile or hypotensive patients have problems with drug absorption.

Volume and Drug Choice
The limiting feature of a SQ infusion is the infusion rate; in general, SQ tissue can absorb up to 3 ml/hr. At low opioid requirements morphine is generally the drug of choice based on availability and cost; a switch to hydromorphone is indicated for a high opioid requirement due its higher intrinsic potency (approximately 4-6 times as potent as morphine), thus the need for a smaller infusion volume.

Administration
Use a 25 or 27 gauge butterfly needle—place on the upper arm, shoulder, abdomen or thigh. Avoid the chest wall to prevent iatrogenic pneumothorax during needle insertion. The needle can be left indefinitely without site change unless a local reaction develops—typically, patients can keep the same needle in place for up to one week at a time.

Toxicity
Local skin irritation, itching, site bleeding or infection can occur. Of these, skin irritation is the most common, managed by a needle site change.

Patient acceptance
Patients readily appreciate the ease of SQ administration as an alternative to IV access.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #36
CALCULATING OPIOID DOSE CONVERSIONS

Robert Arnold MD and David E Weissman MD

Introduction A variety of published conversion tables exist to provide clinicians a rough guide for making calculations when switching between different opioid routes or preparations. Listed below are methods for common conversions using standard published conversion ratios. The examples assume a change in drug or route at a time of stable pain control using equianalgesic doses. See *Fast Fact* #2 about conversions involving transdermal fentanyl; #75 and #86 about methadone; and #181 about oxymorphone.

Caution: Published values in equianalgesic tables should be considered a rough clinical guide when making dose conversions; substantial inter-individual variation exists. The final prescribed dose needs to take into account a patients' age, renal, pulmonary and hepatic function; their current pain level and opioid side effects such as sedation; as well as prior and current opioid use.

Opioid Equianalgesic Conversion Ratios for use with the following examples:
Morphine 10 mg parenteral = Morphine 30 mg oral = Hydromorphone 1.5 mg parenteral = Hydromorphone 7.5 mg oral = Hydrocodone 30 mg oral = Oxycodone 20-30 mg oral (see Reference 1).

A. Change route, keeping drug the same (e.g. oral to IV morphine)
Example: Change 90 mg q12 Extended Release Morphine to Morphine by IV continuous infusion

1. Calculate the 24 hour current dose: 90mg q 12 = 180 mg Morphine/24 hours
2. Use the oral to parenteral equianalgesic ratio: 30 mg PO Morphine = 10 mg IV Morphine
3. Calculate new dose using ratios: 180/30 x 10 = 60 mg IV Morphine/24 hours or 2.5 mg/hour infusion
4. Some experts recommend starting the new opioid at 75% of the calculated dose to account for inter-individual variation in first pass clearance.

B. Change drug, keep the same route (e.g. po morphine to po hydromorphone)
There is *incomplete cross-tolerance* between different opioids, but the exact amount will differ. Thus, equianalgesic tables are only approximations. Depending on age and prior side effects, *most experts recommend starting a new opioid at 50% of the calculated equianalgesic dose*, in the setting of well-controlled pain.
Example: Change 90 mg q 12 Extended Release Morphine to oral Hydromorphone*.*

1. Calculate the 24 hour current dose: 90 Q12 x 2 = 180 mg PO Morphine/24 hrs
2. Use the equianalgesic ratio: 30 mg PO Morphine = 7.5 mg PO Hydromorphone
3. Calculate new dose using ratios: 180/30 X 7.5 = 45 mg oral Hydromorphone/24 hours.
4. Reduce dose 50% for cross-tolerance: 45 x 0.5 = 22 mg/24 hours = 4 mg q4h

C. Changing drug and route (e.g. oral morphine to IV hydromorphone)
Example: Change from 90 mg q12 Extended Release Morphine to IV Hydromorphone as a continuous infusion.

1. Calculate the 24 hour current dose: 90 Q12 x 2 = 180 mg PO Morphine/24 hrs
2. Use the equianalgesic ratio of PO to IV morphine: 30 mg po Morphine = 10 mg IV Morphine
3. Calculate new dose using ratios: 180/30 x 10 = 60 mg IV Morphine/24 hours
4. Use the equianalgesic ratio of IV Morphine to IV Hydromorphone: 10 mg Morphine = 1.5 mg Hydromorphone
5. Calculate new dose using ratios: 60/10 x 1.5 = 9 mg IV Hydromorphone/24 hours

6. Reduce dose 50% for cross-tolerance: 9 x 0.5 = 4.5 mg/24 hours = 0.2 mg IV continuous infusion
7. Note: one would also get the same amount of hydromorphone if you directly converted from oral morphine to IV hydromorphone using the 30 mg :1.5 mg ratio

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PALLIATIVE CARE NETWORK OF WISCONSIN

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).

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 #70
PRN RANGE ANALGESIC ORDERS

Debra B Gordon RN-BC, DNP, ACNS-BC, FAAN

Introduction Use of PRN opioid orders with a wide dose range (e.g. 'morphine 2-8 mg IV q2h PRN') is a practice designed to provide flexibility in dosing to meet an individual's unique and changing needs. However, such orders can be a common source of error due to unsafe interpretation. A dose range should be at least 2 times but generally no larger than 4 times, the smallest dose. It is critical that physicians, nurses, and pharmacists share a common understanding of how to properly write, interpret, and carry out PRN range orders.

Considerations for writing and interpreting PRN range opioid orders:

- Avoid therapeutic duplication consisting of more than one type of PRN opioid by the same route. If PRN opioids from different routes are ordered, give clear indication for use (i.e., use oral route unless patient is NPO or vomiting, use IV route prior to dressing change)
- Avoid prescribing a dose based on pain ratings. While severe pain may require more aggressive analgesic treatment a nonlinear relationship has been demonstrated between opioid dose and the visual analog scale. There is high variability in individual responses to opioid doses.
- Reasonable range. A range order should be large enough to provide options for dose titration, but small enough to ensure safety. The maximum allowable difference for analgesic dose range orders should be no more than four times the lowest dose (eg. four times 2 mg is 8 mg).
- Patient's prior drug exposure. If the patient is opioid-naïve, the first dose administered should be the lowest dose in the range; if the patient is opioid tolerant or has received a recent dose with inadequate pain relief and tolerable side effects, utilize a dose on the higher end of the range.
- Prior response. Inquire about this patient's response to previous doses. How much relief did prior doses provide, and how long did it last? Did the patient experience side effects?
- Age. For very young or elderly patients, *start low and go slow*.
- Liver and renal function. If your patient has hepatic or renal insufficiency, anticipate a more pronounced peak effect and a longer duration of action.
- Pain severity. As a general rule, for moderate to severe pain increase the dose by 50-100%; do not increase by >100% at any time. To "fine-tune" the dose once pain is at a mild level, increase or decrease by 25%.
- Anticipated pain duration. Is the pain acute, chronic, or progressive (likely to worsen)? In other words, is the patient likely to require more or less analgesic over time?
- Kinetics. Know the onset, peak, and duration of action for the specific drug ordered. Unlike scheduled long-acting opioid formulations, doses of short-acting opioids can be increased at each specified dosing interval,
- Co-morbidities. Debilitated patients, or those with respiratory insufficiency, may be at more risk for hypoxia.
- Use of other sedating drugs. When other CNS depressants are administered in combination with opioids, the dose of each medication required to achieve the desired effect may be 30-50% less than if either drug was administered alone.
- Combination drugs. Limit doses of combination drugs: opioids with acetaminophen or an NSAID. Average adults should not receive more than 4000 mg of acetaminophen in 24 hours. If substantial upward dose titration is required or anticipated, use opioid-only preparations.
- Avoid administration of a partial dose. Partial doses at more frequent intervals may result in ineffective pain relief and create time delays in the ability to administer a full dose within the allowed range (i.e. giving oxycodone 5mg every hour when the order reads 5-15mg every 3 hours).

Example: Opioid naïve patient arrives with the order 'Morphine sulfate 2-6 mg IV every 2h PRN pain.' Give 2 mg for first dose. Reassess within 30 minutes. If adequate relief, reassess within next 2 hours. If

no side effects but inadequate relief – may give 4 mg more in 30 minutes or when time to peak effect has passed from first dose. Total dose therefore is 6 mg in a 2-hour period.

Document patient response to PRN dosing:

- Reassess pain relief, side effects and adverse events produced by treatment, and the impact of pain and treatment effects on patient function, once sufficient time has elapsed to reach peak effect: 15-30 minutes after parenteral drug therapy or 1 hour after oral administration of a PRN analgesic or non-pharmacologic intervention.
- Reassessments may be done less frequently for patients with chronic stable pain or for patients who have exhibited good pain control without side effects after 24 hours of stable therapy.

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FAST FACTS AND CONCEPTS #72
OPIOID INFUSION TITRATION ORDERS

David E Weissman MD

Introduction This *Fast Fact* will discuss appropriate ways to write opioid infusion titration orders. See *Fast Fact* # 34 for further information on the appropriate symptom management during a ventilator withdrawal.

A bad example: '*Morphine 2-10mg/hour, titrate to pain relief.'* This order is commonly written for terminally ill patients and in the context of terminal ventilator withdrawals.

What is wrong with this order?

1. It places full responsibility for dose titration upon the nurse.
2. It provides no guidance regarding how fast to titrate (e.g. every hour, every shift?) or dose titration intervals (e.g. for poorly treated pain, should the dose be raised from 2 to 3 mg, 2 to 10 mg, other?).
3. It poses the potential for overdosage by too zealous dose escalation and provides only one option for poorly controlled pain – increasing the continuous infusion rate.
4. Given that it takes at least 8 hours to achieve steady-state blood levels after a basal dose change, it makes no pharmacological sense to dose escalate the basal dose more frequently than q 8 hours.

A better way to write this order: *'Morphine 2 mg/hour and morphine 2 mg q 15 minutes for breakthrough pain (or 2 mg via PCA dose). RN may dose escalate the PRN dose to a maximum of 4 mg within 30 minutes for poorly controlled pain.'*

Why is this better?

1. This order is preferred as it provides a basal rate and a breakthrough dose. The breakthrough dose has a peak effect within 5-10 minutes. Thus, if the breakthrough dose is inadequate it can be safely increased, as often as every 15-30 minutes, to achieve analgesia – without a need for rapid upward titration of the basal rate.

2. Reassess the need for a change in the basal rate no more frequently than every 8 hours; use the number of administered bolus doses as a rough guide when calculating a new basal rate. However, never increase the basal rate by more than 100% at any one time. When increasing the basal rate, always administer a loading dose so as to more rapidly achieve steady-state blood levels.

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PALLIATIVE CARE NETWORK OF WISCONSIN

FASTS FACTS AND CONCEPTS #74
ORAL OPIOID ORDERS: GOOD AND BAD EXAMPLES

David E Weissman MD

Introduction This *Fast Fact* will illustrate poorly written opioid orders and provide preferred alternatives.

Scenario 1: Episodic (non-continuous) moderate-to-severe pain
Bad Example: *'Oxycodone w/ acetaminophen (Percocet), 1-2 PO q 4-6hour PRN severe pain, and acetaminophen w/codeine (Tylenol #3) 1-2 PO q4-6 PRN moderate pain.'*

Discussion: This order has several problems.

1) The duration of short-acting opioids is typically 3-4 hours - rarely 6 hours. Studies document that when given a range, nurses and doctors are most likely to give the lowest dose at the longest interval, leading to inadequate analgesia.
2) Only one opioids/non-opioid combination should be prescribed at a time: assess for response and change to different product if the first agent does not produce the desired effect.
3) The use of descriptors ('mild,' 'moderate,' 'severe') allows for subjective interpretation of pain severity by the nurse, rather than judging pain severity directly based on patient report. There is a very poor correlation of pain ratings between patients and clinicians.
4) Should both drugs be used, there is risk of exceeding 4 grams/day of acetaminophen.

Preferred Order: '*Oxycodone w/ acetaminophen, 1-2 tabs PO q 4 hours PRN pain*.'

Scenario 2: Order for an oral long-acting opioid
Bad Example: *'Morphine extended-release 60 mg q 6 hours and transdermal fentanyl patch 25 mcg/hour, changed q 72 hours.'*

Discussion: This order has two problems. First, none of the oral long-acting products (e.g. MS Contin, OxyContin, Kadian) should be prescribed less than Q8h; Q12 is the recommended starting interval, although many patients need a q8h interval. Second, there is no rationale for using two different long-acting products at the same time. Prescribe only one drug, then dose escalate to desired effect or unacceptable toxicity. Remember to always prescribe a PRN product for breakthrough pain. While the oral long-acting products can be dose escalated every 24 hours, the transdermal fentanyl patch can only be safely dose escalated every 2-3 days. Thus, it is a poor choice for poorly controlled pain

Preferred order: '*Morphine extended-release 150 mg q 12 hours.'* (The dose of 150 mg q12 hours is derived from the following equianalgesic relationships: morphine 60 mg q6 hours is 240 mg/day; transdermal fentanyl 25mcg/hr = approximately 60 mg/day of oral morphine. 240 + 60 = 300 mg or 150 mg q12 hours. See *Fast Fact* #2.)

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FAST FACTS AND CONCEPTS #198
REGULATORY ISSUES FOR PRESCRIBING SCHEDULE II OPIOIDS AT THE END OF LIFE

Neil M. Ellison MD

Background Schedule II opioids (e.g. morphine, oxycodone, methadone, hydromorphone) play a major role in the management of symptoms at the end of life. Because of possible abuse, trafficking, and diversion of opioids, federal statutes mandate that appropriate safeguards be adhered to by prescribing clinicians and dispensing pharmacists. There are regulations that are important to understand for patients in hospice and long-term care settings, or who may have rapidly changing symptoms at home. This *Fast Fact* will review US federal regulations regarding prescribing Schedule II drugs for adult and pediatric patients. **Note:** a) some states may impose additional restrictions – check with your state licensing boards for specifics, and b) individual pharmacists may enforce these regulations with variable stringency.

Prescription Information Prescriptions for Schedule II opioids must be written, dated, and signed on the day issued, and include the full name and address of the patient, the drug name, strength, quantity prescribed, and directions for use. The name, address, and Drug Enforcement Agency (DEA) registration number of the practitioner must also be included.

Refills and Prescription Series Refills are not allowed on Schedule II opioids; however there are no federal regulations limiting the number of days a prescription can cover (many state or local professional standards have limited this to a 30 or 90 day supply). It is permissible to write a prescription series for up to a 90 day supply of medication. For example, at a single office visit a patient can be given 3 prescriptions, each for 30 days worth of the same drug, with two of the prescriptions noting: "Do not fill until [1 or 2 months, respectively, from the issue date]."

Emergency prescriptions Emergency prescriptions can be phoned into a pharmacist. The pharmacist must make a reasonable effort to determine that the verbal authorization came from a registered practitioner and that the quantity prescribed and dispensed is limited to the amount adequate to treat the patient during the emergency period. This is often interpreted as a three day supply, but there is no regulation specifying how many days or doses constitute an emergency prescription. The prescribing clinician must quickly supply the pharmacy with a written prescription (postmarked within seven days if mailed). This prescription must have "Authorization for emergency dispensing" written on it as well as the date of the verbal order.

Facsimile prescriptions A facsimile prescription is sufficient for a Schedule II opioid used for direct parenteral administration (e.g. intravenous or spinal use), or for oral opioids for patients residing in a long-term care facility (LTCF) or who are receiving hospice care (even if at home). The script must note the patient's status (e.g. "Resides in LTCF," "Patient in hospice"). In other circumstances, written, not facsimile prescriptions, are required.

Partial dispensing Partial dispensing is allowed if the pharmacist is unable to supply the full quantity at one time. The remaining portion of the prescription must be filled within 72 hours. For patients in a LTCF or with a terminal illness, partial quantities up to 60 days from the issue date may be dispensed. The script must designate the patient is 'terminally ill' or in a LTCF.

Pharmacist changes to prescriptions Pharmacists may independently add or change the patient's address. After consultation with the prescriber, pharmacists may also add or change the dosage form, drug strength, drug quantity, directions for use, and issue date. While the aforementioned changes are permissible, many pharmacists will request a rewritten prescription.

Patients with an addictive disease or in a drug treatment program Opioid addiction and pain can co-exist at the end of life. Clinicians approved for Schedule II prescribing by their DEA license can

prescribe any Schedule II drug in the inpatient and outpatient settings (including buprenorphine and methadone) for pain and symptom relief, even if the patient is enrolled in an opioid maintenance program. Clinicians are strongly advised to seek specialist help in these situations (from both pain and addiction specialists) as well as to work collaboratively with the patient's treatment program. To better identify cases of opioid misuse or diversion, it is recommended that at least one prescriber from every hospice have access to a prescription drug monitoring program. Standardized protocols on how to approach cases of suspected drug abuse and diversion in the home are also recommended for hospice organizations.

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PALLIATIVE CARE NETWORK OF WISCONSIN

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 be 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
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,	Amiodarone, bupropion, celecoxib, chlorpromazine, citalopram, diphenhydramine, doxepin, duloxetine, escitalopram, fluoxetine,	None reported

	morphine, oxycodone, tramadol	haloperidol, hydroxyzine, metoclopramide, paroxetine, quinidine, ritonavir, sertraline, terbinafine, thioridazine	

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 ½), as these dictate the speed of opioid titrations. When given consistently, opioids reach steady state after four T½. 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**	
	Bioavailibility (%)	Vd (L/kg unless noted)	Major Metabolism Enzyme(s)	Active Metabolite	Urine (%)	T ½ (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-morphone 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
Oxymor-phone 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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FAST FACTS AND CONCEPTS #329
ABUSE-DETERRENT OPIOID FORMULATIONS
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Background In response to the mounting public health crisis regarding opioid related deaths from misuse, the Food and Drug Administration (FDA) haThers issued guidance to pharmaceutical manufacturers on the development of abuse-deterrent formulations of opioids (1). This *Fast Fact* will focus on the different types of abuse-deterrent opioid formulations and their role in palliative care.

Opioid Abuse in the Palliative Care Population Opioid abuse is the intentional, nontherapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect (2). Opioids may be ingested, either whole or crushed, inhaled, via snorting, smoking, or vaping, or injected in an attempt to more quickly achieve a euphoric "high" (1,3). Previous literature suggests that 29-46% of palliative care patients possess risk factors for opioid misuse defined as a positive score (≥4 points) on the Screener and Opioid Assessment for Patients with Pain version 1.0—Short Form (SOAPP-SF) (4,5).

Opioid Abuse-Deterrent Categories
1. Physical/Chemical Barriers: Physical barriers, such as polymers and high resistance coatings, can prevent mechanical manipulation, such as chewing, crushing, cutting, or grinding, of the medication. Chemical barriers, such as gelling agents, can resist dissolution of the opioid using common solvents (water, alcohol, or other organic solvents).
2. Agonist/Antagonist Combinations: The addition of an opioid antagonist, most commonly naloxone or naltrexone, can interfere with the euphoria and analgesia associated with opioid abuse. Pharmaceutical designers often aim to sequester the antagonist so that it only becomes clinically active if the product is crushed for injection or snorting.
3. Aversion: Substances can be added to the product to produce an unpleasant effect, such as irritation to the nasal mucosa, if the dosage form is manipulated or is used at a higher dosage than directed.
4. Delivery System: Certain drug release and delivery methods, such as sustained-release depot injections and subcutaneous implants, can offer resistance to abuse as they cannot be tapered to quickly release the opioid and produce a drug high.
5. New Molecular Entities and Prodrugs: These opioids require enzymatic activation, different receptor binding, slower penetration into the central nervous system, or other novel effects to thereby provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid by continuing to have controlled release of the drug even if it is crushed.

Opioid Abuse-Deterrent Formulations There are several brand-name extended release (ER) opioid formulations available with FDA-approved labeling describing abuse-deterrent properties (6,7). There is one immediate release oxycodone agent with abuse deterrent properties, but it does not possess FDA-approved labeling (8). Moving forward, the FDA has issued guidance on the development of generic versions of these abuse-deterrent opioids formulations (9).

Brand (generic)	US Market	Abuse-Deterrent Properties	Comparative Cost to Dose Equivalent Long Acting Morphine
OxyContin® (oxycodone ER) (9)	Approved: 1950 Reformulated: 4/5/2010	*Physical/Chemical Barrier* • Difficult to crush or break • Resistant to chemical extraction techniques • Forms a viscous gel when dissolved	2 times

Targiniq ER® (oxycodone/ naloxone ER) (10)	Approved: 6/23/2014	*Agonist/Antagonist Combination* • Naloxone released if crushed	*Not yet available in the US*
Embeda® (morphine/ naltrexone ER) (11)	Approved: 8/13/2009	*Agonist/Antagonist Combination* • Naltrexone released if crushed	7 times
Hysingla ER® (hydrocodone ER) (12)	Approved: 11/20/2014	*Physical/Chemical Barrier* • Difficult to crush or break • Resistant to chemical extraction techniques • Forms a viscous gel when dissolved	8 times
MorphaBond ER® (morphine ER) (13)	Approved: 10/2/2015	*Physical/Chemical Barrier* • Multiple abuse barriers.	*Not yet available in the US*
Xtampza ER® (oxycodone ER) (14)	Approved: 4/26/2016	*Physical/Chemical Barrier* • Multiple abuse barriers.	4 times
Troxyca ER® (oxycodone/ naltrexone ER) (15)	Approved: 8/19/2016	*Agonist/Antagonist Combination* • Naltrexone released if crushed	*Not yet available in the US*

Evidence To be considered abuse-deterrent by the FDA, formulations must undergo long term epidemiological study to assess their clinical abuse potential (17). Most often this is done utilizing a drug-liking and a subjective feeling of getting "high" scale of 0-100, where 0 represents maximum disliking, 50 represents a neutral response, and 100 represents maximum liking. FDA approved abuse deterrent agents showed statistically significant decreases in drug-liking and drug high when compared to other opioid formulations (10-16). Retrospective reviews found that 3.5 years after the reformulation of OxyContin®, opioid abuse, doctor-shopping, the amount of OxyContin® dispensed, and OxyContin-related fatalities were reduced (18,19). However, heroin overdoses increased by 23% during that same time (18). There is concern that even if these formulations reduce opioid-specific abuse, they may contribute to a shifting pattern of heroin abuse. No palliative care specific studies have yet been conducted.

Cost Effectiveness There is a lack of robust, controlled trials to determine if the expense of these formulations is justified. Most of these formulations are not covered by insurance policies. One cross-sectional study of Oklahoma Medicaid claims suggested that abuse-deterrent opioids may be related to slightly lower overall health care costs for members with ICM-9 codes associated with opioid abuse; this finding was not replicated among members without comorbidities of addiction (19).

Summary Abuse-deterrent opioids may have a role in the palliative care population, however cost may limit their use. These opioid formulations should be limited to opioid-appropriate patients who are at risk for opioid-specific problems.

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