



Fast Facts Core Curriculum

Opioids Writing Orders

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FAST FACTS AND CONCEPTS #18 SHORT-ACTING ORAL OPIOID DOSING INTERVALS

David E Weissman MD

Background Oral opioids are among the most commonly prescribed drugs in palliative care. Despite national analgesic guidelines, the use of excessive intervals for short-acting oral opioids continues to pose a significant barrier to good analgesic care. Understanding the pharmacological rationale for dosing intervals is key to proper prescribing and patient counseling.

Short-Acting Oral Opioids Short-acting products are administered as either single agents (oral morphine, hydromorphone, oxycodone and codeine) or as combination products containing acetaminophen, aspirin or ibuprofen. For all these products, the peak analgesic effect occurs in 60-90 minutes with an expected total duration of analgesia of 2-4 hours. Standard reference sources generally cite a 4 hour dosing interval for the single-agent opioids, but 4-6 or 6 hour intervals for combination products (PDR, Micromedex). However, the Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guideline (1994) recommends dosing intervals for all short-acting opioids at an interval or every 3-4 hours, an interval more consistent with patient reports of pain relief and the half-life of oral opioids.

Is there a danger to more frequent drug administration? There is no danger of dosing intervals as often as every 2 hours for single agent products (e.g. morphine), *in patients with normal renal function and who are currently tolerating the opioid without sedation*, as the peak effect will be reached in 60-90 minutes and there is rapid renal excretion. For combination products, the concern is excessive acetaminophen. Thus, if patients need opioids on an every four hour basis, it is appropriate to change to single agents without acetaminophen and/or add a long-acting opioid product so as to keep the total daily acetaminophen dose at less than 4 grams.

Note: Transmucosal fentanyl citrate and oral oxymorphone have different pharmacokinetics than the agents mentioned above and are dosed differently – see *Fast Facts* #103 and #181.

Summary

- Prescribe the products listed above at intervals *no greater* than every 4 hours.
- Closely monitor daily acetaminophen intake when combination products are used.
- Provide explicit patient/family counseling regarding safe and allowable dosing intervals.
- Review your institutional opioid policies – ask if there is a hospital policy or guidelines for oral opioid dosing intervals; if not, such guidelines should be developed to help guide practice.

See related analgesic *Fast Facts*:

20 Opioid dose escalation

51 Opioid combination products

70 PRN range orders

74 Good and bad analgesic orders

82 Why patients do not take their opioids

94 Writing discharge/outpatient opioid prescriptions

#161 Opioid use in renal failure

#198 Regulatory issues for prescribing Scheduled II opioids at the end of life

#248 Counseling patients on side effects and driving when starting opioids

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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% dose 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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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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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 oxycodone.

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 patient's 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: $180/30 \times 10 = 60$ 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: $180/30 \times 7.5 = 45$ mg oral Hydromorphone/24 hours.
4. Reduce dose 50% for cross-tolerance: $45 \times 0.5 = 22$ 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: $180/30 \times 10 = 60$ 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: $60/10 \times 1.5 = 9$ mg IV Hydromorphone/24 hours
6. Reduce dose 50% for cross-tolerance: $9 \times 0.5 = 4.5$ 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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FAST FACTS AND CONCEPTS #51

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

1. Propoxyphene should rarely, if ever, be prescribed; it should not be used in the elderly.
2. Prescribe generic products whenever possible.
3. 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.
4. Prescribe codeine, oxycodone and hydrocodone products at a q4h interval; not q 4-6 or q6h (see *Fast Fact #18*) (2).
5. 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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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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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 preferred dosing 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 #92 PATIENT CONTROLLED ANALGESIA IN PALLIATIVE CARE

ERIC PROMMER MD

Introduction Patient Controlled Analgesia (PCA) is a technique allowing patients to self-administer parenteral analgesics. The primary advantage of PCA is to shorten the interval from the time of patient-defined need to the time of actual analgesic administration. PCA is an effective, safe, and well-accepted treatment for post-operative pain, sickle cell crisis pain (as young as age 4), and cancer pain. In general, PCA will provide the same degree of analgesia compared to other delivery systems with the same or less total amount of medication. PCA allows for more immediate relief of incident (breakthrough) pain and can provide patients with a greater sense of personal control over their pain.

Indications The primary indication for PCA is the patient who requires parenteral analgesia (e.g. severe pain and/or oral/transdermal/rectal route not useable) and has *incident pain* or other pain patterns that are not predictable. PCA is also indicated for use as a method of rapid dose titration and dose finding in acute, severe pain. Relative contraindications include patients who a) do not have the cognitive ability to understand how to use a PCA device, or b) have an anticipated need for parenteral opioids less than 24 hours.

PCA devices Most devices have a drug reservoir and infusion system whereby PCA administration can occur with or without a background continuous infusion. Thus, PCA devices need the following orders: 1) **PCA dose** in mg or mcg ('patient initiated dose,' 'patient demand dose,' or 'bolus dose'), 2) **Delay Interval** ('lockout') – in minutes (period during which the patient cannot obtain additional demand medication), 3) **Continuous infusion (CI) Rate** in mg/hr or mcg/hr (if CI is used), and 4) **Hour Limit** – maximum amount of drug to be dispensed in a defined period of time. Often the one hour limit is set to deliver 3-5 times the estimated required hourly dose. (Note: due to the need for frequent dose adjustments, the Hour Limit is often omitted in palliative care.) Most palliative care patients will need both PCA demand and CI dosing. Opioids used in PCA devices include morphine, hydromorphone, fentanyl, and methadone. IV or SQ are the most common routes of administration; PCA can also be used with epidural, intrathecal, or intraventricular opioid administration (see *Fast Facts* #28, 85, and 98).

Dosing in opioid-naïve patients The following information is for morphine, the first-line drug of choice for most patients. **Note:** dosing and delay interval information will differ with other opioids. Start dosing: PCA demand dose = 1-3 mg morphine; Delay Interval = 8-10 min. Initial CI (if any) is dependent on the clinical situation. For instance, 1 mg/hour of IV morphine is approximately equivalent to 35 mg bid of oral morphine ER. This may be excessive for opioid-naïve patients; conversely many opioid-naïve patients with severe pain will easily tolerate this, so the decision to immediately start a CI depends on clinician judgment. If not started immediately, one can initiate a CI after four hours by summing the total demand dose given over 4 hours and converting that into an hourly rate (e.g. if 16 mg is given over four hours, CI would be 4 mg/hour). A new PCA demand dose can then be calculated at 50% of the hourly CI rate (4 mg/hr ÷ 2 = 2 mg PCA demand dose, Delay Interval 8-10 min).

Dosing in non-naïve patients Convert their current total oral/transdermal dose to a total 24 hour IV dose; divide by 24 to give the hourly CI rate in mg/hour (see *Fast Fact* #36 on dose conversions). The PCA demand dose is initially calculated at 50% of the hourly rate.

Risk of Overdose The patient who is pushing his or her own PCA button will fall asleep before serious signs of overdose occur as long as only the patient pushes the button. **Note:** special care is needed for patients with sleep apnea as they will be more sensitive to opioids.

Dose titration and Loading Doses See *Fast Facts* #20 Opioid Dose Escalation, #54 Opioid Infusions in the Imminently Dying Patient, and #72 Opioid Infusion Titration Orders.

Common Sense Cautions These dosing recommendations are rough guidelines—clinicians need to take into account pain severity, patient age, renal and pulmonary function, co-morbid

illness, and other psychoactive medications. When in doubt, it is advised to use a lower CI rate (with upward dose adjustments of the CI rate no more frequently than every 8 hours), while adjusting the PCA dose at frequent intervals (q30-60 minutes) to effectively control pain.

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FAST FACTS AND CONCEPTS #94
WRITING DISCHARGE AND OUTPATIENT OPIOID PRESCRIPTIONS

Colleen Dunwoody MS, RN and Robert Arnold MD

Background Assuring continuity in pain relief in the outpatient setting or following hospital discharge is an important aspect of patient care. Poorly written prescriptions or orders can be inconvenient for the patient as well as the clinician, but can also lead to prescriptions not being filled, inadequate pain control, and patient suffering. This *Fast Fact* will touch on some practical considerations in writing opioid prescriptions. See also *Fast Fact #89* for writing orders for patients in long term care facilities, #74 for a general discussion of proper opioid order writing, and #198 for further discussion of regulatory issues.

Regulations Different states have different rules concerning controlled substances: amount of drug that may be dispensed, number of refills, faxing of orders and telephone prescriptions, and requirements for special prescription forms or blanks. Review your state regulations. See the website below for state-by-state listings.

Legibility The DEA and NPI numbers and your name must be legible. Print your name after your signature or otherwise indicate the spelling of your name on a personalized prescription.

Frequency Consider if the frequency you are prescribing is the *recommended* frequency. Third party payers may not pay for medications prescribed to be taken more frequently than recommended in the literature. For example, transdermal fentanyl patches changed q48 hours and oxycodone ER q8 hours may not be paid by insurers without a specific reason. Oxycodone ER and morphine ER may not, and should not, be dispensed when the frequency is *PRN* or less than 8 hours.

Strength There are more than two dozen combination opioids available; it is good practice to always write the correct strength for combination opioids (e.g. oxycodone/acetaminophen 5 mg/325 mg). Be sure to check the available pill/tablet doses when prescribing long acting opioids. When writing prescriptions for different strengths, it is helpful for both the patient and pharmacist to specify that on the prescriptions. For instance, if someone is taking morphine ER 75 mg q12 hours they would require prescriptions for both morphine ER 60mg tabs and 15mg tabs, one should write: "Morphine ER 15 mg tabs. Take one tab PO q12 hours. Take along with your 60 mg tabs to make a total of 75 mg every 12 hours."

Acetaminophen Identify whether the 3000-4000 mg/day maximum will be exceeded when writing the frequency. Pay extra attention to combination products via which the patient may be receiving extra acetaminophen. Most pharmacists will not dispense doses likely to exceed this recommended maximum daily dose. If there is any doubt one should write "...not to exceed X pills in 24 hours."

Tampering Write the number after the numeric '10' (ten) to prevent someone altering the prescription (e.g. changing 10 to 40 by changing a 1 to a 4).

Substitutions and Corrections Pharmacists will not correct an improperly written prescription, and some may not accept prescriptions that have obvious corrections (e.g. items crossed out) because there is no way of knowing who did the correction. Nor will a prescription for an opioid be filled when written on a prescription printed with "*not for controlled substances*". Pharmacists also will not make substitutions; if you write for 'morphine ER 80 mg,' the pharmacist will not fill it since the medicine is not available as an 80 mg tablet.

Communication When prescribing opioids that are infrequently used or in high doses, communicate with the pharmacist *before the patient is discharged or leaves your office* to assure

availability. Pharmacists prefer communication from physicians and nurses in advance so medications can be stocked.

** In 2011, the FDA and acetaminophen manufacturers announced plans to lower the recommended maximum daily dose from 4000 mg to 3000 mg/day due to rare instances of hepatotoxicity for patients receiving 4000 mg daily. As of June 2015 the official prescribing information has not been updated to reflect those announced changes. However, in 2014, the FDA urged all acetaminophen drug manufacturers to halt production of combination products with more than 325 mg of acetaminophen per dosage in order to help curb acetaminophen toxicity.

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FAST FACTS AND CONCEPTS #215 OPIOID POORLY-RESPONSIVE CANCER PAIN

Tamara Sacks MD, David E Weissman MD, and Robert Arnold MD

Background Relief of cancer pain from opioids is rarely all or nothing; most patients experience some degree of analgesia alongside opioid toxicities. When the balance of analgesia versus toxicity tips away from analgesia, the term 'opioid poorly-responsive pain' is invoked. While opioid poorly-responsive pain is not a discreet syndrome, it is a commonly encountered clinical scenario. This *Fast Fact* reviews key points in its assessment and management.

Differential Diagnosis of Opioid Poorly-Responsive Pain

1. *Cancer-related pain*
 - a. Cancer progression (new fracture at site of known bone metastases).
 - b. Causes of pain (eg. neuropathic pain, skin ulceration, rectal tenesmus, muscle pain) that are known to be less responsive to systemic opioids or opioid monotherapy.
 - c. Psychological/spiritual pain related to the cancer experience (existential pain of impending death).
2. *Opioid pharmacology/technical problems*
 - a. Opioid tolerance (rapid dose escalation with no analgesic effect).
 - b. Dose-limiting opioid toxicity (sedation, delirium, hyperalgesia, nausea – see *Fast Facts* #25, 142).
 - c. Poor oral absorption (for PO meds) or skin absorption (e.g. transdermal patch adhesive failure).
 - d. Pump, needle, or catheter problems (IV, subcutaneous, or spinal opioids).
3. *Non-cancer pain*
 - a. Worsening of a known non-cancer pain syndrome (diabetic neuropathy).
 - b. New non-cancer pain syndrome (dental abscess).
4. *Other psychological problems*
 - a. Depression, anxiety, somatization, hypochondria, factitious disorders.
 - b. Dementia and delirium both can effect a patient's report of and experience of pain.
 - c. Opioid substance use disorders or opioid diversion.

Management Strategy

1. *Initial Steps*
 - a. Complete a thorough pain assessment including questions exploring psychological and spiritual concerns. If substance abuse or diversion is suspected, complete a substance abuse history (see *Fast Facts* #68, 69).
 - b. Complete a physical examination and order diagnostic studies as indicated.
 - c. Escalate a single opioid until acceptable analgesia or unacceptable toxicity develop, or it is clear that additional analgesic benefit is not being derived from dose escalation. If this fails, consider:
 - i. Rotating to a different opioid (e.g. morphine to methadone).
 - ii. Changing the route of administration (e.g. oral to subcutaneous).
 - d. Treat opioid toxicities aggressively.
 - e. Use (start or up-titrate) adjuvant analgesics, especially for neuropathic pain syndromes.
 - f. Integrate non-pharmacological treatments such as behavioral therapies, physical modalities like heat and cold, and music and other relaxation-based therapies – see *Fast Fact* #211.
2. *Additional steps* – Pain refractory to the initial steps requires multi-disciplinary input and care coordination.
 - a. Hospice/Palliative Medicine consultation to optimize pain assessment, drug management, and assessment of overall care goals.
 - b. Mental health consultation for help in diagnosis and management of suspected psychological factors contributing to pain.

- c. Chaplain/Clergy assistance for suspected spiritual factors contributing to pain.
- d. Interventional Pain and/or Radiation Oncology consultation.
- e. Rehabilitation consultations (Physiatry, Physical and Occupational Therapy) to maximize physical analgesic modalities.
- f. Pharmacist assistance with drug/route information.

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