

## CHAPTER 5

# INITIATING AND OPTIMIZING OPIOID THERAPY

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Once a decision is made to undertake a trial of opioid therapy, the clinician's obligation should be to implement therapy according to accepted principles of prescribing. These principles have been refined over decades of experience treating patients with cancer pain (table 11).

### **Selecting an opioid**

In the approach to cancer pain management popularized by the World Health Organization, patients with moderate pain who are relatively opioid-naïve should receive an opioid from among a group that has been conventionally used for pain of this severity. In practice, opioid-naïve patients with severe pain also may be offered a trial of one of these drugs. In the United States, this group of medications includes codeine, oxycodone (when combined with aspirin or acetaminophen), hydrocodone (available in combination with acetaminophen or ibuprofen), dihydrocodeine (available in combination with aspirin), and tramadol (either alone or combined with acetaminophen). All of these opioids have a short half-life and short duration of action, typically 2 to 4 hours, and usually are prescribed on an as-needed basis. The total daily dose of those that are combined with a nonopioid coanalgesic should not exceed the maximal safe dose of the latter drug (for example, 4 g of acetaminophen per day and less in patients with known liver disease or high alcohol consumption).

The traditional use of the short-acting combination products for moderate cancer pain is not based on any empirical demonstration of superiority over other treatment approaches, and there is now substantial clinical experience in the use of long-acting, modified-release opioids for pain of this type. These formulations improve the convenience of therapy when the opioid is required repeatedly during the day and should be considered as a potential first-line approach in patients with constant or frequently recurring pain.

Several other opioids, such as oral pentazocine, propoxyphene and meperidine, historically have been used for managing moderate pain. However, these drugs are generally not recommended for long-term opioid therapy.

**Table 11. Principles of opioid prescribing****Selection of opioid**

Consider:

- Severity and pattern of pain
- Age, medical comorbidities, individual differences, previous experience with opioids
- Drug-specific differences
- Available formulations and cost

**Route selection**

- Use the least invasive route possible
- Consider patient convenience and adherence

**Dosing**

- Consider previous dosing requirements and relative analgesic potencies when initiating therapy
- Start with lowest likely effective dose
- Increase the dose incrementally (usually by 30% to 100%), with both the size of the increment and the time interval between increments influenced by the severity of pain and side effects
- Increase the dose until adequate analgesia occurs or dose-limiting side effects are encountered
- Consider dosing schedule (eg, around the clock and/or as needed), depending on temporal patterns of pain
- Consider “rescue” medication for breakthrough pain

**Treatment of side effects**

- Consider treatment of constipation, nausea, mental clouding or somnolence, itch, or other side effects

**Monitoring**

- Monitor treatment efficacy, side effects, and other responses over time and consider modification, if necessary; frequency of follow-up should be individually tailored according to each patient’s clinical and social circumstances

The single-entity pure  $\mu$ -agonist opioids usually are preferred for management of severe pain. In the United States, these medications include:

- Morphine
- Hydromorphone
- Oxycodone
- Oxymorphone
- Fentanyl
- Levorphanol
- Methadone

Few relevant comparative studies of these medications have been conducted, and there is very substantial individual variation in the response to each one. Indeed, sequential opioid trials (ie, opioid rotation [see chapter 7]) may be necessary to identify the drug that yields the most favorable balance between analgesia and side effects. For example, in one prospective survey of 100 consecutive inpatients with cancer pain, 44 patients required trials of 2 or more systemically administered opioid analgesics, and 20 required sequential trials of 3 or more opioids to optimize the balance between analgesia and side effects. Despite the lack of data and the likelihood of individual variation in response, several factors should be considered in selecting an opioid (see table 11). If pain is very severe and rapid oral titration of the dose is needed, the medications that have a short half-life and are available in immediate-release oral formulations (morphine, hydromorphone, and oxycodone) are generally favored because they require a shorter period to approach steady-state plasma concentrations than either the modified-release opioids or medications with a long half-life. If pain is very acute, delivery of a medication with a short half-life by oral transmucosal administration (for fentanyl only) or the intravenous route may be preferable, because these routes provide the fastest onset of effect.

A patient's response to previous trials of opioid therapy should be reviewed when selecting a new opioid. Given the marked variability in the analgesic effectiveness and occurrence of side effects with each drug, a patient who had a favorable prior experience with a particular opioid should be considered for treatment with this drug again. If the current opioid is well tolerated, it usually is continued unless difficulties in dose titration occur or the required dose cannot be administered conveniently. The exception to this is meperidine; a favorable experience with short-term intravenous exposure for management of acute pain in the past does not prefigure a similar response during oral therapy.

Patients with renal impairment may accumulate the active metabolites of propoxyphene (norpropoxyphene), meperidine (normeperidine), and morphine (morphine-6-glucuronide, morphine-3-glucuronide). Caution is required in the administration of these medications, particularly in the setting of changing renal function.

Some caution is also appropriate in the use of levorphanol or methadone in patients who are difficult to monitor (eg, patients who do not adhere to treatment regimens, those who live alone or at a distance, older patients without highly capable caregivers) and those predisposed to opioid side effects. Since 4 or 5 half-lives with repeated dosing must pass before steady state is

approached, these opioids with a long half-life require relatively close monitoring for a prolonged period, to avoid unanticipated delayed toxicity resulting from gradual drug accumulation in the plasma with repeated administration. This need for monitoring is most critical in patients predisposed to opioid side effects, including patients with advanced age or major organ failure (ie, encephalopathy or disturbances in pulmonary, hepatic, or renal function). Clinically, most problems appear to develop with methadone, which has a highly variable half-life that ranges from less than 24 hours to more than 150 hours.

Availability of modified-release opioids has increased the role of dosing interval as a consideration in opioid analgesic selection. Most standard opioid preparations require a dosing interval of 3 to 4 hours. Methadone often can be administered every 6 hours and even less often in some patients. The modified-release oral formulations are effective at an 8- to 24-hour dosing interval, and the transdermal fentanyl system can be administered at an interval of 48 to 72 hours. These medications have met with great patient acceptance and presumably enhance patient adherence to therapy.

Other drug-specific characteristics also may influence decision making. There is evidence that transdermal fentanyl is less likely to produce constipation, and patients with preexisting constipation or gastrointestinal comorbidities may be especially good candidates for a trial of this formulation. The unique and somewhat difficult pharmacology of methadone supports the conclusion that it should be a second-line agent. Given the theoretical potential for efficacy that may be based, in part, on reversal of opioid tolerance (resulting from the blocking effect on the *N*-methyl-*D*-aspartate receptor caused by the *d*-isomer), it is reasonable to consider a trial of this drug after another has proved ineffective. Finally, patients with a history of addiction might be considered for treatment with opioids that are less likely to be preferred by substance abusers, either because they are not pure  $\mu$ -agonists (eg, buprenorphine, one of the agonist-antagonists) or because they have less potential for abuse and diversion (eg, transdermal fentanyl, methadone).

## Selecting a route of administration

The least invasive and most convenient route that can provide adequate analgesia should be used to administer opioids. For chronic pain, the oral and transdermal routes usually are preferred.

### **Noninvasive routes**

**Oral.** The oral route for opioid delivery is simple and effective in most patients with chronic pain. It should be avoided in

patients with impaired swallowing or gastrointestinal obstruction and also may become problematic if very high doses are needed or rapid onset of action after a dose is essential. Orally administered medications have a slower onset of action and a more delayed time to peak than parenterally administered drugs. Most immediate-release oral formulations have a peak effect that is typically achieved after 60 minutes. The peak effects of the modified-release formulations generally occur between 3 and 5 hours after administration.

**Transdermal.** The transdermal formulation of fentanyl, which delivers 25, 50, 75, or 100  $\mu\text{g}$  per hour, has become widely used for long-term treatment. Some patients prefer this route, and some are good candidates by virtue of impaired swallowing or gastrointestinal disease, nonadherence with oral regimens, or poor response to other opioids. The dosing interval for each transdermal patch is typically 72 hours, but as with other opioids, individual pharmacokinetic variation is large, and patients may require a dosing interval of 48 hours. Transdermal fentanyl is not indicated for management of acute pain, particularly in patients who are relatively opioid naïve.

**Sublingual.** A sublingual preparation of buprenorphine is available in some countries, but in the United States, prescriptive authority is limited to persons with special certification for its use in addiction therapy. Sublingual absorption occurs to some extent with any opioid, but bioavailability is very poor with drugs that are not highly lipophilic, such as morphine. Although there is considerable experience in the use of sublingual administration of concentrated oral morphine solution during the care of patients at the end of life, it is likely that most of the effects obtained by this route occur following enteral absorption after swallowing. Lipophilic opioids, such as fentanyl and methadone, are relatively well absorbed sublingually, and sublingual administration of an injectable formulation may be a useful approach in some patients who transiently lose the option of oral dosing.

**Rectal.** The rectal route usually is considered for patients who are relatively opioid nontolerant and become temporarily unable to take oral medications. In the United States, rectal suppositories containing morphine, hydromorphone, or oxymorphone are available. There also is anecdotal experience with rectal administration of controlled-release morphine or oxycodone tablets. The potency of opioids administered rectally is believed to approximate oral dosing. However, absorption is variable, and relative potency may be higher or lower than expected, depending on a variety of factors, including location of the suppository (low in the

rectum, where the blood supply is systemic, or high in the rectum, where blood flows through the portal circulation) and contents of the rectum at the time of dosing.

**Oral transmucosal.** An oral transmucosal formulation of fentanyl citrate is available for breakthrough pain. The fentanyl, which is incorporated into a hard lozenge, is rapidly absorbed through the oral mucosa. This formulation has been shown to have an onset of pain relief similar to intravenous morphine, and its safety and efficacy have been demonstrated in several clinical trials.

**Intranasal and inhaled.** An intranasal formulation of butorphanol is available. This mixed agonist-antagonist drug is not preferred for management of chronic pain. Theoretically, any lipophilic drug could be rapidly absorbed from the nasal cavity, and there is anecdotal experience in the use of others, such as fentanyl. Also, research is ongoing to develop an aerosolized opioid that will be administered through a metered dose inhaler. These formulations potentially could play a role in treatment of acute pain, including breakthrough pain.

### ***Invasive routes***

The parenteral route of administration should be considered for patients who require a very rapid onset of effect, have impaired swallowing or gastrointestinal obstruction, or require high doses that cannot otherwise be conveniently administered. However, because of the cost, invasiveness, and nursing requirements for parenteral administration of opioids, these routes typically are limited to patients who are unable to swallow or to absorb opioid drugs administered by enteral routes.

**Intramuscular.** Repetitive intramuscular injections are painful and offer no pharmacokinetic advantage. Consequently, their use is not recommended. Repeated bolus doses, if required, can be accomplished without frequent skin punctures, through use of an indwelling intravenous or subcutaneous infusion device.

**Subcutaneous.** The clearest indication for using the subcutaneous route is the inability to tolerate the oral route. Repeated bolus injections can be delivered painlessly through a 27-gauge infusion needle that is left under the skin and can remain there for up to a week. Continuous infusions can be performed using morphine, hydromorphone, fentanyl, or oxymorphone and are widely used in populations with far-advanced cancer or other illnesses. Methadone appears to be relatively irritating and is not preferred for subcutaneous infusion. Ambulatory infusion devices vary in complexity, cost, and ability to provide patient-controlled “rescue” doses as an adjunct to a continuous basal infusion.

To maintain the comfort of an infusion site, the subcutaneous infusion rate should not exceed 5 mL per hour.

**Intravenous.** Intravenous opioid infusion is commonly used in the hospital setting. Long-term intravenous infusions are possible if a permanent venous access device is available. As with the subcutaneous route, repeated bolus injections and patient-controlled analgesia may be coadministered with a continuous infusion. Infusions of drug combinations may also be indicated when pain is accompanied by nausea, anxiety, or agitation. In such cases, an antiemetic, neuroleptic, or anxiolytic agent may be combined with an opioid, provided it is nonirritating, miscible, and stable in combined solution. Experience has been reported with infusions of an opioid combined with metoclopramide, haloperidol, scopolamine, cyclizine, methotrimeprazine, chlorpromazine, or midazolam.

**Intraspinal.** Properly selected patients can benefit greatly from intraspinal opioid administration. A recent randomized trial in the cancer population found that intrathecal drug administration through an implanted programmable pump yielded better pain relief and fewer side effects than conventional analgesic therapy in patients with an extended prognosis.

The clearest indication for intraspinal opioid administration is pain below the midthorax that cannot be adequately relieved by systemic opioids because of development of central nervous system toxicity (eg, intolerable somnolence, confusion). Many methods may be used. If therapy is expected to be given in the relative short term (no longer than several months), the preferred system usually involves placement, in the epidural or intrathecal space, of a catheter that is tunneled subcutaneously and either brought through the skin or connected to a subcutaneous portal. Infusions that are expected to continue for a longer period than this are better accomplished by the intrathecal route using a totally implanted pump.

The preferred opioids for neuraxial infusion are morphine and hydromorphone. Others, such as fentanyl, methadone, and sufentanil, have been used. The opioid can be combined with a local anesthetic agent, such as bupivacaine. Clonidine is commercially available for intrathecal use and has been shown in controlled trials to be more effective for neuropathic than nociceptive pain, and ziconotide is currently being reviewed by the FDA in the United States. Other agents have been tried, but experience is too limited to recommend their use.

### **Switching routes**

During long-term treatment, it may be necessary to switch routes of administration. One survey of patients with advanced cancer,

for example, found that more than half of the patients required 2 or more routes of administration prior to death, and almost a quarter needed 3 or more. All such changes require careful attention to relative potency. It is generally prudent to perform the switch in a gradual, stepwise manner over 2 to 3 days.

## Selecting an initial dose

Opioid-naïve patients with severe pain should generally begin one of the opioids conventionally used for severe pain, at a dose equivalent to 5 to 10 mg of parenteral morphine every 3 to 4 hours. Equivalent doses of these opioids are calculated from the relative potency ratios published in equianalgesic dose tables (see chapter 3).

A switch to a new pure  $\mu$ -agonist opioid, or a new route of administration, can be guided by consulting an equianalgesic table. The doses indicated on this table should be viewed as broad guidelines, the use of which must be tempered by clinical judgment and the condition of the patient (table 12). As a first step, the calculated equianalgesic dose typically is reduced to account for incomplete cross-tolerance between opioids and for individual variation. To be prudent, and respectful of patient variability, the calculated dose also is usually decreased when switching routes with the same drug.

Initial reduction in the calculated dose is typically 25% to 50%, with two important exceptions. First, the dose reduction is larger (ie, 75% to 90%) when switching to methadone. Second, there typically is no reduction required when a switch is made from another opioid to transdermal fentanyl if the equianalgesic dose table provided by the manufacturer is used, because a reduction has already been built into the calculation.

This initial adjustment in equianalgesic dose should be altered on the basis of the patient's condition. Specifically, the reduction in equianalgesic dose should be augmented in patients with relatively good pain control and either severe side effects or serious medical comorbidities. The reduction should be diminished if the patient has severe pain and is not expected to have any undue toxicity from the new opioid. For example, a patient with severe pain and no comorbidities who is being switched from morphine to oxycodone might be started at an oxycodone dose equal to the calculated equianalgesic dose, or just 10% less, whereas a patient with mild pain and severe comorbidities might be started at an oxycodone dose that is 66% to 75% less than the calculated equianalgesic dose.

After any change from one opioid to another or from one route to another, patients must be monitored carefully to assess the

**Table 12. Empirical guidelines for opioid rotation**

1. Use the equianalgesic table to calculate a dose of the new opioid that is roughly equivalent to the dose of the current opioid.
2. Determine the clinically relevant starting point.
  - a. If switching to any opioid other than methadone or fentanyl, decrease the equianalgesic dose by 25% to 50%.
  - b. If switching to methadone, reduce the equianalgesic dose by 75% to 90%.
  - c. If switching to transdermal fentanyl, do not reduce the equianalgesic dose.
3. Consider further dose adjustments on the basis of medical condition and pain.
  - a. If the patient is elderly or has significant organ failure, consider further dose reduction.
  - b. If the patient has severe pain, consider a lesser dose reduction.
4. Calculate a “rescue” dose as 5% to 15% of the total daily dose and administer at an appropriate interval.
5. Reassess and titrate the new opioids according to therapeutic response and side effects.

adequacy of analgesia and to detect the development of side effects. Subsequent dose adjustments are usually necessary.

### **Titrating the dose**

Once an opioid and route of administration are selected, the dose should be increased until adequate analgesia occurs or intolerable and unmanageable side effects supervene. Titration of the opioid dose may be necessary at the start of therapy and repeatedly during the patient’s course of treatment. Inadequate pain relief usually should be addressed through gradual escalation of the dose until adequate analgesia is reported or intolerable and unmanageable side effects limit further dose escalation. Adherence to this guideline requires repeated assessment and the ongoing management of side effects.

The concentration-response relationship for opioid drugs is best characterized as a log-linear relationship. Accordingly, dose increments are best considered as percentages of the existing dose, rather than any absolute amount. A dose increment of 30% to 50% is safe and usually large enough to observe a meaningful change in effects. If pain is severe and the patient is not predisposed to opioid toxicity, a higher increment—up to 100% of the existing dose—may be considered.

An alternative approach to dose titration is possible in patients who receive a coadministered, as-needed opioid dose (such as an oral rescue dose or patient-controlled analgesia) during fixed-schedule administration of an oral, transdermal, or parenteral opioid. The total amount of supplemental drug used during the

previous day or two can be summed and converted into the fixed-schedule administration. Whatever the amount, safety is assured if the patient has tolerated it during the previous day.

The use of a percentage dose increment applies irrespective of the specific opioid or route of administration. When patients are receiving a drug by fixed-schedule dosing (such as a long-acting, modified-release oral formulation, a transdermal formulation, or a continuous infusion) and a drug by as-needed administration, both the fixed-schedule drug and the as-needed drug should be increased concurrently.

In most cases, gradual dose escalation identifies a favorable balance between analgesia and side effects that remains stable for a prolonged period. There is no ceiling effect to analgesia provided by the pure  $\mu$ -agonist opioids, and the maximal dose is immaterial as long as the patient attains a favorable balance of analgesia, other functional goals, and side effects. This implies that the opioid responsiveness of a specific pain can be ascertained only if the dose is gradually increased until treatment-limiting side effects occur.

In clinical practice, the range of opioid doses required by patients is enormous. Occasionally, doses can become extremely large (equivalent to grams of morphine per day) during the process of dose titration. The absolute dose is irrelevant, however, as long as therapy is not compromised by dose-limiting toxicity, cost, or excessive inconvenience produced by the number of pills. In a retrospective study of 100 patients with advanced cancer, the average daily opioid requirement was equivalent to 400 to 600 mg of morphine given parenterally, but approximately 10% of patients required more than 2,000 mg and 1 patient required more than 30,000 mg per 24 hours. According to most surveys, patients with chronic nonmalignant pain usually require less than a dose equivalent to few hundred milligrams of oral morphine per day. If a patient requires a relatively high dose, careful assessment is needed to ensure that the outcomes, including analgesia and side effects, are consistently favorable and the drug is taken responsibly.

Although doses typically stabilize for prolonged periods during long-term management, dose escalation is usually required at intervals to maintain analgesia. Studies of patients with pain due to medical illness have indicated that the need for a dose increase usually can be explained by some change in clinical status. In this setting, analgesic tolerance cannot be invoked as the dominant factor in the need for opioid dose escalation.

This observation has two important implications. First, concerns about tolerance should not impede the use of opioids.

Clinically significant tolerance may or may not ever occur, and if it does, analgesia usually can be recaptured through dose escalation. Second, worsening pain in a patient receiving a stable dose of opioids should be assessed as presumptive evidence of a new process, such as disease progression or increasing psychologic distress or delirium. This potential for a changing opioid requirement over time underscores the need for repeated assessment. Given the inherently subjective nature of the critical end points (ie, adequate analgesia and intolerable side effects), careful patient assessment is essential.

### **Scheduled versus as-needed dosing**

Because experts generally agree that the more effective approach to pain management is to prevent the recurrence of pain than to abort it once it appears, by-the-clock dosing has replaced as-needed dosing in treatment of continuous or frequently recurring pain. As-needed dosing still plays a role, however, and should be considered during initiation of therapy in opioid nontolerant patients, in those with rapidly changing pain, and in patients with intermittent pains separated by pain-free intervals. (Given the risk of gradual accumulation, methadone is often started with 1 to 2 weeks of as-needed dosing and at least a 6-hour interval between doses.) As-needed administration of a rescue drug also is commonly combined with fixed-schedule administration to manage intermittent breakthrough pains. This is considered a standard of care in management of cancer pain and an option to consider in management of nonmalignant pain syndromes. In most cases, the rescue drug can be the same as the drug administered by fixed-schedule dosing. If a rapid onset of action is essential, treatment with the oral transmucosal fentanyl formulation should be considered. The long and variable half-life of methadone complicates its use as a rescue drug, and an alternative opioid with a short half-life is usually offered to supplement a methadone regimen.

On the basis of clinical experience, the size of the most effective rescue dose usually is selected to be equivalent to 5% to 15% of the total daily opioid dose. The lower end of this range is used if the patient is medically frail or has moderately intense breakthrough pain. The upper end is used if the breakthrough pains are anticipated to be severe and the risk is not excessive, considering factors such as advanced age or major organ failure that predispose to opioid toxicity.

Use of oral transmucosal fentanyl presents an exception to the 5% to 15% rule for rescue medication. In several clinical trials, there was no relationship between the effective dose of oral transmucosal fentanyl and the total daily opioid dose. Therefore, oral

transmucosal fentanyl should be initiated at one of the lower available doses (200 or 400 µg) and the dose should be titrated until the appropriate dose is identified.

In cancer care and for acute pain management (eg, postoperative care), oral rescue doses typically are offered at intervals up to every 1 to 2 hours as needed, and parenteral rescue doses can be offered at intervals up to every 15 to 30 minutes. As noted, the number of rescue doses required daily can be used to guide the size of the increment in the regularly scheduled dose as it is titrated upward. Use of rescue doses for pain flares in management of noncancer chronic pain syndromes remains controversial but, if determined to be indicated, is generally restricted to a few doses per day.

### **Rate of dose titration**

The severity of the pain should determine the rate of dose titration. Patients with very severe pain who need rapid relief can be managed by repeated parenteral dosing every 15 to 30 minutes until pain is partially relieved. After parenteral loading using an opioid with a short half-life, an approximate hourly maintenance dose can be calculated by dividing the total loading dose by twice the elimination half-life of the drug. For example, the starting maintenance dose for a patient who has required an intravenous loading dose of 30 mg of morphine sulphate (half-life, approximately 3 hours) would be 5 mg per hour, (ie,  $30 \text{ mg} \div [3 \text{ hours} \times 2]$ ). Patients with less severe pain can undergo more gradual dose escalation. Aggressive dose titration is rarely indicated in patients with a stable chronic-pain syndrome treated in the outpatient setting.

### **Treatment of side effects**

Treatment of opioid-induced side effects is an integral part of effective opioid administration (see chapter 6). Successful amelioration of symptoms both enhances patient comfort and improves the likelihood that a favorable balance between analgesia and side effects will be found.

### **Risk assessment and management strategies**

These pharmacologic principles must be complemented by proactive and ongoing efforts to assess and manage another potential set of negative outcomes, specifically outcomes associated with abuse, addiction, and diversion (see chapter 10). This is true in all populations, particularly those that include patients at relatively high risk. Given the prevalence of substance abuse in US society, it is best to incorporate risk assessment and

management as part of the routine approach to opioid therapy in all patient populations.

**Suggested readings**

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