Opioids as Analgesics

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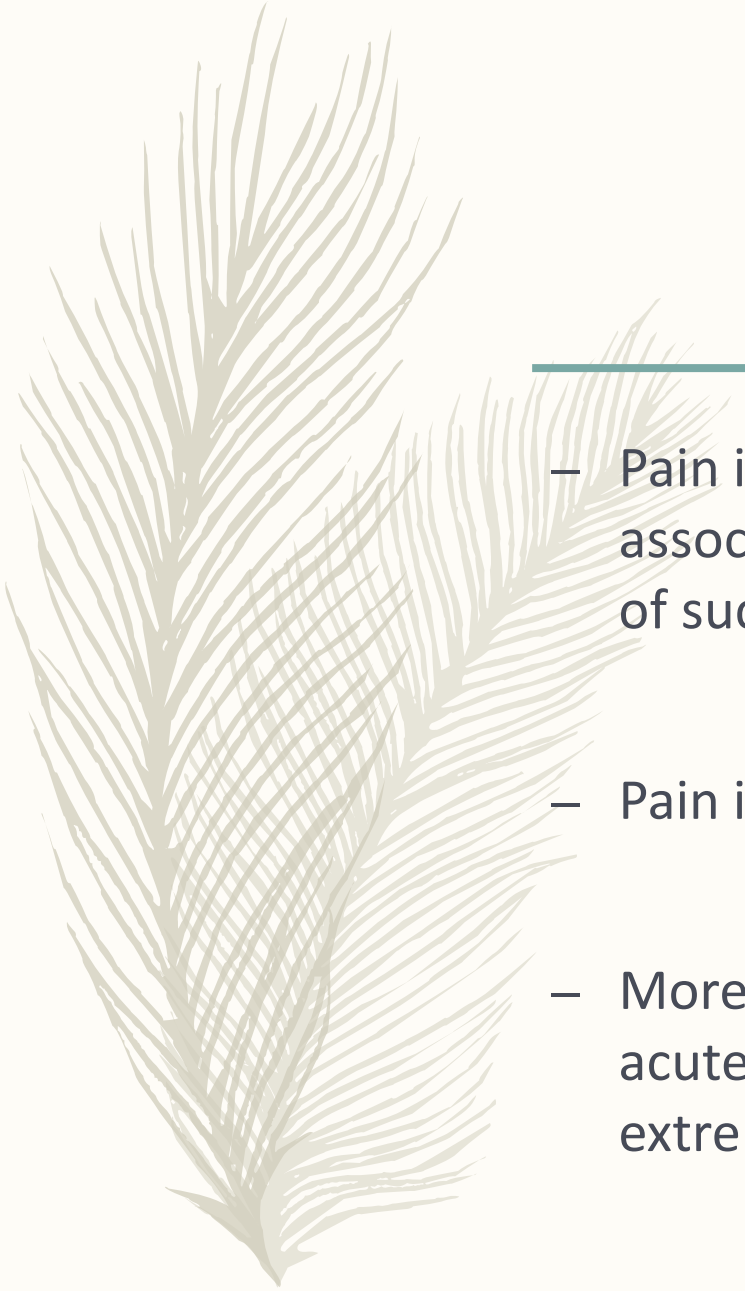


- Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”
- Pain is a hallmark of many acute and chronic conditions.
- More than 80% of patients who undergo surgical procedures experience acute pain, 75% of which report the severity as moderate, severe, or extreme

- Nociception, or the sensation of pain, is composed of four basic processes:
- transduction, transmission, modulation, and perception.

- *Transduction* is the process by which noxious stimuli are translated into electrical signals at peripheral receptor sites (i.e., free nerve endings located throughout the skin, muscle, joints, fascia, and viscera).

- *Transmission* is the propagation of the electrical signal along primary afferent nerves, through the dorsal horn of the spinal cord to the central nervous system (CNS).

- *Modulation* happens throughout the CNS and results in either an increase or a decrease in transmission.

- *Perception* is when the sensory (physical) and affective (psychological) components of the nociceptive message are integrated into the patient's overall experience.

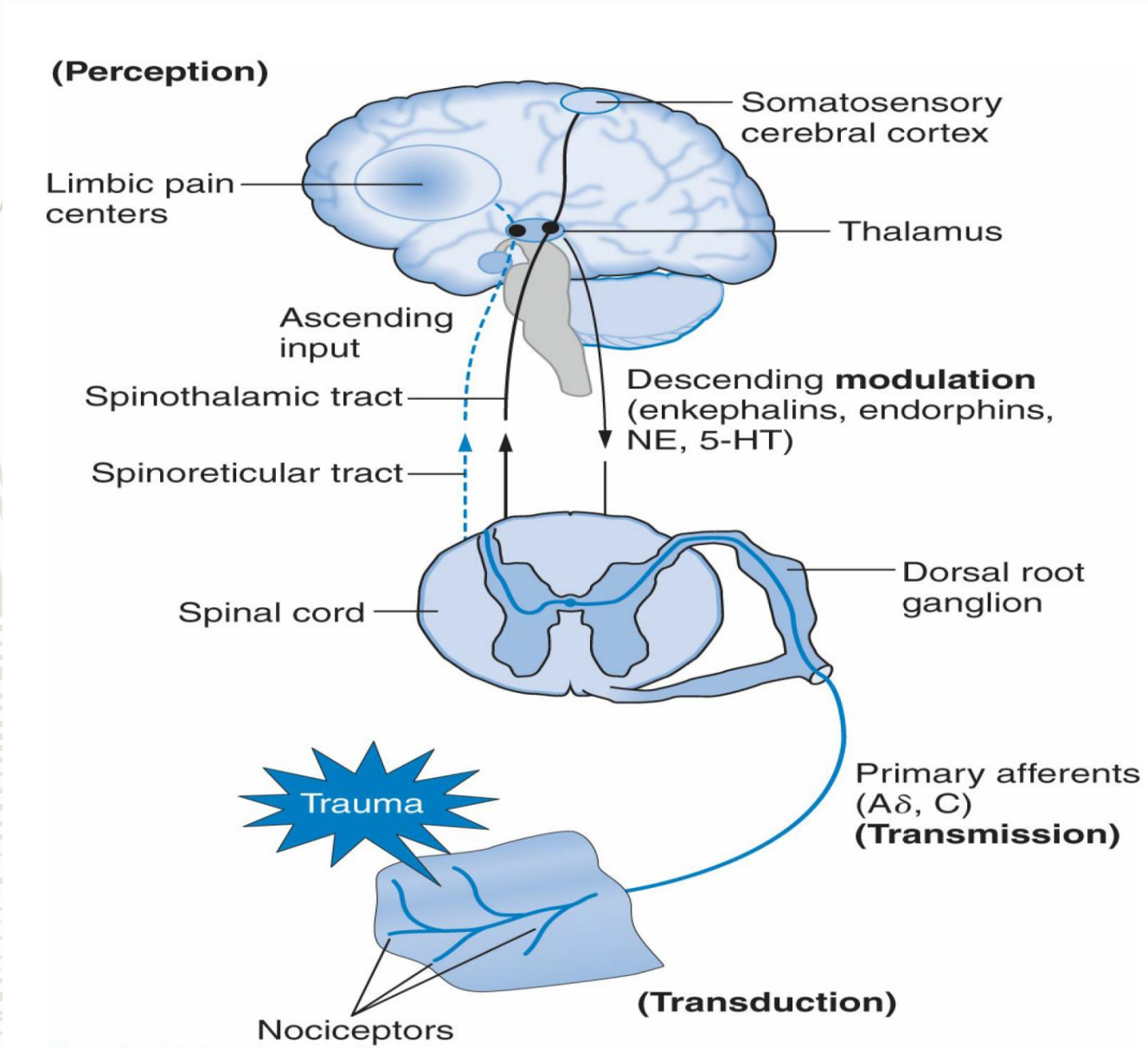


Figure 55-2 Pain pathways. 5-HT, serotonin; NE, norepinephrine.

Post Operative Pain

- After surgery is completed in the operating room, patients are transferred to the PACU for stabilization of respiratory function and pain.
- Most patients emerging from general anesthesia are still quite sedated when they are transferred to the PACU.
- When the anesthetic agents begin to wear off, it is very important to achieve rapid control of severe pain so frequent administration of small intravenous opioid doses is common practice in this setting.

- Currently, there is not a universally accepted standard for titration of intravenous opioids in the PACU.

- Some institutions will allow use of both intravenous fentanyl to gain fast pain control and morphine for a longer duration of action.

- Hydromorphone is an acceptable alternative to morphine for patients with renal insufficiency or intolerable side effects to morphine.

- Morphine is considered the standard for intravenous opioid administration.

- The hydrophilic (i.e., water soluble) property of morphine delays penetration across the blood–brain barrier so the relative time to onset is approximately 6 minutes after an intravenous dose.

- The concentration peak effect (i.e., equilibration time between the plasma and brain) after an intravenous morphine dose is 20 minutes.

- Major morphine metabolites include morphine-3-glucuronide (M3G) and morphine-6-nglucuronide (M6G).
- The M3G metabolite is inactive but M6G crosses the blood– brain barrier and has potent analgesic activity.
- Therefore, the analgesic and ventilatory depressant effects of morphine and M6G may not be evident with initial high plasma morphine concentrations.
- Adverse events may occur 40 to 60 minutes after the last intravenous morphine dose.
- Patients with renal insufficiency will have M6G metabolite accumulation and be at increased risk for respiratory depression so morphine use is not recommended in this population

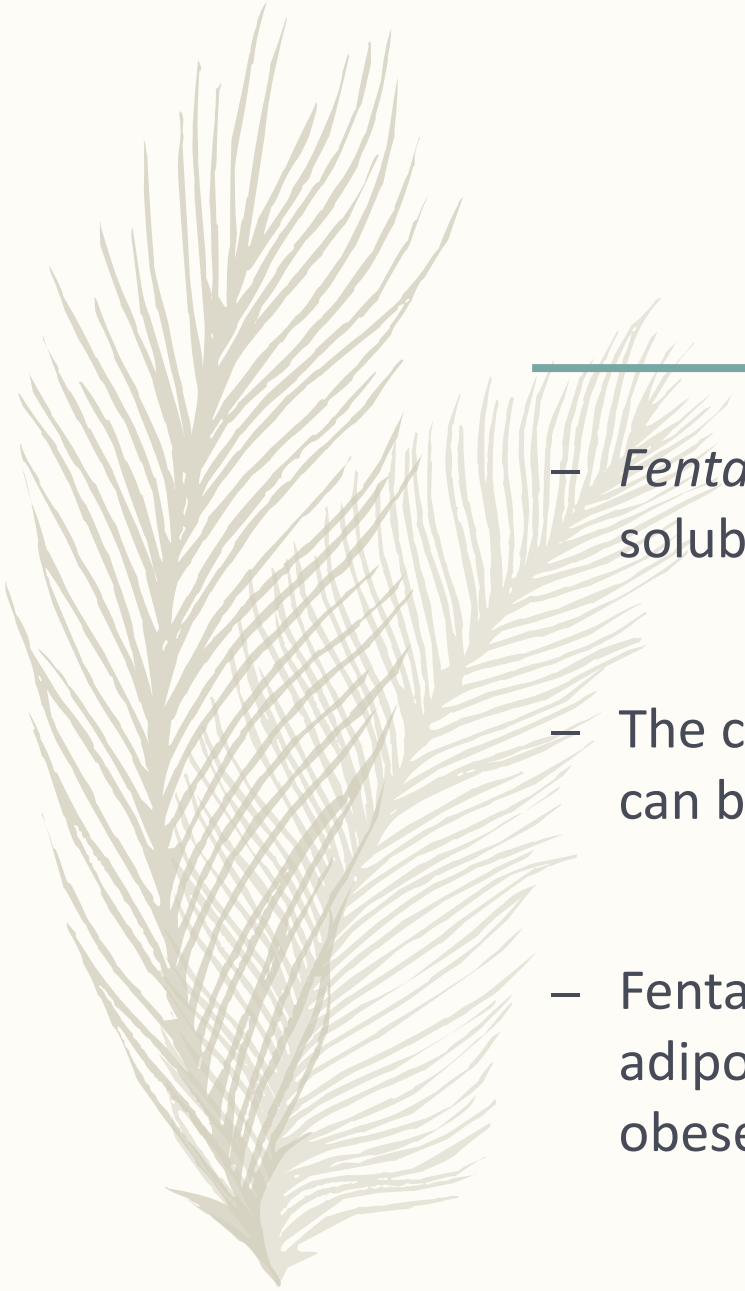
- *Hydromorphone* is commonly used in patients who cannot tolerate morphine or have a history of renal insufficiency.

- Hydromorphone is a hydrogenated ketone analogue of morphine with slightly higher lipid solubility.

- The concentration peak effect after intravenous hydromorphone administration is between 8 and 20 minutes.

- Hydromorphone has a similar metabolic pathway to morphine producing hydromorphone-3-glucuronide (H3G) and hydromorphone-6-glucuronide (H6G).

- However, hydromorphone metabolites are devoid of analgesic activity but H3G has been showed to accumulate in animal models leading to dose-dependent myoclonus



- *Fentanyl* is a synthetic phenylpiperidine compound with high lipid solubility resulting in rapid transfer across the blood–brain barrier.
- The concentration peak effect after intravenous fentanyl administration can be seen within 4 to 6 minutes.
- Fentanyl is a good option for rapid pain control but may accumulate in adipose tissue with multiple doses; therefore, it is not the best choice for obese patients

Table 55-7

Postoperative Transition of Opioid Doses for Naive Patients >50 Kg[30,42,48]

Postanesthesia Care Unit
Fentanyl intravenous 25–50 mcg every 5 minutes as needed Morphine intravenous 2–4 mg every 5 minutes as needed Hydromorphone intravenous 0.2–0.4 mg every 5 minutes as needed
Medical/Surgical Hospital Floor
Patient-controlled Analgesia (PCA) Starting Dose
Morphine intravenous 1 mg every 10 minutes Hydromorphone intravenous 0.2 mg every 10 minutes Fentanyl intravenous 25 mcg every 10 minutes
Nurse-Administered Opioid Dose for Patients Unable to Use PCA
Morphine intravenous 2–4 mg every 2 hours as needed

Hydromorphone intravenous 0.25–0.5 mg every 2 hours as needed
Discharge Planning
Hydromorphone 2–4 mg orally every 4 hours as needed Oxycodone 5–10 mg orally every 4 hours as needed (can be combined with acetaminophen 325 mg) Hydrocodone 5 mg with acetaminophen 325 mg—1 to 2 tablets orally every 4 hours as needed
Important
Long-acting opioid formulations are not recommended for acute postoperative pain management unless the patient was taking opioid therapy for chronic pain prior to surgery.

- For postoperative pain management after discharge from the PACU, the oral route is preferred over intravenous administration unless the patient is unable to use this route or has severe uncontrolled pain.

- The use of PCA provides a precise and convenient method for intravenous opioid administration that allows the patient to activate the dose for acute pain management.

- The intravenous PCA route is preferred over nurse-administered intravenous doses because the patient does not have to notify the nurse when more medication is needed, wait until it is given, and then further wait for the peak effect to occur for pain relief

- Self-administration of smaller and more frequent intravenous opioid doses reduces the variation between the peak and trough effect of the dosing interval thus better maintenance of the plasma opioid concentration.

- The PCA dose button is connected to an infusion pump that will allow the administration of an opioid dose when the button is pushed (i.e., demand).

- To prevent over dosage by continual demand, all PCA devices use a lockout interval which is the length of time after a successful patient demand during which the device will not administer another dose even if the patient pushes the button

- Most patients who start intravenous PCA are opioid-naïve meaning that their opioid use the week prior to surgery was less than 60 mg of oral morphine or its equivalent.

- For this reason, the starting dose for intravenous PCA is standardized for opioid-naïve patients

- Use of a continuous opioid infusion for postoperative pain management is generally reserved for patients who are opioid-tolerant and were taking opioid medication around-the-clock prior to surgery.

- Equianalgesic dose calculations are used to determine the dose difference between two opioids to provide the same degree of pain relief

- Respiratory depression remains the most serious adverse event related to opioid therapy often due to excessive amounts or frequent use of opioid medication beyond what is needed to achieve pain control.

- There are many factors that increase the risk of opioid-induced respiratory depression with intravenous PCA related to comorbid medical conditions.

- advanced age >65 years
- Renal insufficiency
- history of sleep apnea
- morbid obesity
- Opioid-naïve patients
- Postoperative pain
- PRN opioid administration

- To prevent respiratory depression in high-risk patients, the lowest possible starting dose of an opioid should be initiated, and use of a continuous infusion should be avoided.

- For all patients, avoid administration of more than one drug with sedating properties at the same time with opioids.

- Medications including antihistamines, benzodiazepines, gabapentin, pregabalin, and skeletal muscle relaxants should be scheduled approximately 2 hours apart to prevent accumulation of sedating side effects.

- For hospitalized patients who experience excessive sedation and cannot be aroused with sternal stimulation, or have a significant decline in breathing, naloxone administration may be needed to reverse the opioid CNS effects.

- Naloxone is a nonselective competitive opioid antagonist of all pharmacologic effects on mu, delta, and kappa receptors.

- After oral administration, naloxone is extensively metabolized in the liver (i.e., >95% first pass effect) and not effective so intravenous, intramuscular, or subcutaneous administration at a dose of 0.4 mg is required for reversal of life-threatening respiratory depression.

- The extent and duration of naloxone reversal of opioid-induced respiratory effects is highly variable and is related to many factors, including the specific opioid used, the opioid dose, administration mode, concurrent medication, underlying disease, and pain.

- Therefore, naloxone administration may need to be repeated every 2 to 3 minutes or given as a continuous infusion until full recovery of respiratory function

Risk of Addiction

- Opioid use behaviors are stratified based on the risk of aberrant drug use.
- Aberrant drug use behaviors may occur along a spectrum from those less suggestive of addiction, such as an occasional, sanctioned increase in the opioid dose by a medical provider, to those that may be more suggestive of addiction, such as injecting oral formulations.
- With respect to gender, women with chronic pain who report significant emotional issues were at increased risk for opioid misuse.
- Multiple literature reports have confirmed there is a strong association between alcohol abuse and opioid addiction

Terms Related to Opioid Use[149,154]

Term	Definition
Misuse	Taking a prescription for a reason or at a dose or frequency other than for which it was prescribed.
	Use of a medication for a nonmedical use, or for reasons other than prescribed. For example, altering dosing or sharing medicines, which has harmful or potentially harmful consequences.

Abuse	Misuse with consequences involving the use of a substance to modify or control mood or state of mind in a manner that is illegal or harmful to oneself or others. Potentially harmful consequences include accidents, injuries, blackouts, legal problems, and sexual behavior that increases the risk of infectious diseases.
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
Physical dependence	A state of adaptation manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist.
Pseudoaddiction	Condition characterized by behaviors that outwardly mimic addiction but are in fact driven by a desire for pain relief (e.g., constantly watching the clock to dose medication "on time" so pain does not become severe).[151]
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects with time.

Risk Factors for Opioid Addiction[149,150]

Concurrent abuse of alcohol or illicit drugs
Evidence of a deterioration in the ability to function at work, in the family, or socially that appears to be related to drug use
Injecting oral formulations
Multiple dose escalations or other nonadherence with therapy despite warnings
Obtaining prescription drugs from nonmedical sources
Prescription forgery
Repeated resistance to changes in therapy despite clear evidence of physical or psychological effects
Repeatedly seeking prescriptions from other physicians or emergency departments
Selling prescription drugs
Stealing or borrowing drugs from others

Discontinuing Opioid Therapy

- Guidelines strongly recommend that clinicians taper patients from chronic opioids if they have repeated aberrant drug-related behaviors, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects.

- When tapering patients from long-term opioid therapy, the length of time the patient has been taking opioids needs to be considered.

- Approaches to opioid tapering range from a slow 10% dose reduction per week to a more rapid 25% reduction every few days.

Cancer Pain

- Pain is one of the most commonly experienced and feared symptoms of cancer.

- Cancer pain is defined as pain that results from treatment of the disease or the direct impact of tumor growth.

During cancer treatment, 35% to 56% of patients will have pain with up to one-third of those patients having severe pain

Equianalgesic Opioid Dosing[42,179]

Opioid	Equianalgesic Dose (mg)		Duration (hours)	Comments
	Oral (PO)	Parenteral (IV)		
Morphine	30	10	IM/IV/SC 3–4 hours	Standard for comparison of opioid analgesics.
			Oral short-acting 3–6 hours	Morphine not recommended in patients with severe renal impairment.
Hydromorphone (Dilaudid, Exalgo)	7.5	1.5	IM/IV/SC 3–4 hours	Exalgo (extended release) dosed every 24 hours.
			Oral short-acting 3–6 hours	Can be used in patients with renal or liver impairment.
Fentanyl[179]		0.05–0.1	IV/SC 1–2 hours	Refer to Figure 55-7 for transdermal fentanyl conversion example. Equianalgesic conversion ratios have not been established for transmucosal and transbuccal fentanyl formulations. Can be used in patients with renal or liver impairment.
Oxycodone	20		Oral short-acting	OxyContin (controlled release) is dosed every 8 or 12 hours.

			3–6 hours	Can be used in patients with renal impairment.
Buprenorphine (Buprenex, Butrans)[174,175]	0.3 (SL)	0.4		Available as sublingual tablets, sublingual film, transdermal patch, and injection. Suboxone (buprenorphine and naloxone) restricted to treatment of opioid dependence. Partial agonists not recommended for cancer pain management.
Meperidine (Demerol)[42,174]	300	100		Not recommended for routine clinical use by the American Pain Society.[42] Normeperidine is a toxic metabolite that produces anxiety, tremors, myoclonus, and generalized seizures.

SL, sublingual; SC, subcutaneous; PO, oral; IV, intravenous.

TRANSDERMAL FENTANYL

- The transdermal fentanyl patch is an excellent choice for eventual outpatient pain management because it will provide continuous release of opioid and is convenient to use.

- Transdermal fentanyl patches are intended for opioid-tolerant patients with stable chronic pain.

- Opioid-tolerant patients are those who have been taking daily, for a week or longer, at least 60 mg of oral morphine, 30 mg of oral oxycodone, or at least 8 mg of oral hydromorphone or an equianalgesic dose of another opioid

Doses of two different opioids (or two different routes of administration of the same opioid are considered to be equianalgesic if they provide the same degree of pain relief.

There are several published tables for converting morphine to transdermal fentanyl that have been developed by researchers and manufacturers of transdermal fentanyl products.

They provide slightly different dose conversion recommendations.

- Breitbart et al. recommend a 2:1 ratio of oral morphine to transdermal fentanyl (i.e., 2 mg oral morphine/day is equivalent to 1 mcg/hour transdermal fentanyl), resulting in higher transdermal fentanyl doses, which may be excessive for elderly patients.

- A study by Donner et al. suggested a dose ratio of 60 mg/day oral morphine is equal to 25 mcg/hour transdermal fentanyl, which falls between the manufacturer's table and the study recommendations by Breitbart et al.

- The Donner conversion ratio is used in most references because it is less likely to cause underdosing or overdosing

- Patients who have been on opioid therapy for a prolonged time are likely to exhibit *tolerance* to the therapeutic effect.

- However, when switched to a different opioid, the level of tolerance may change (i.e., diminished tolerance to the new opioid) owing to the pharmacokinetic properties of the new opioid.

- This change in sensitivity to the new opioid is called incomplete cross-tolerance.

- Most opioid doses need to be reduced by 25% to 50% after the conversion calculation to account for the incomplete cross tolerance.
- The exception to this is methadone and fentanyl.
- Conversion ratios for methadone and fentanyl have already accounted for incomplete cross tolerance, so no further reductions are generally needed

- After the initial transdermal patch is applied, it will take 12 hours to reach the minimal effective blood concentration and up to 36 hours to achieve the maximal concentration.

- The transdermal fentanyl patch must be changed every 72 hours to maintain the steady-state blood concentration.

- Elderly, cachectic, or debilitated patients may have altered pharmacokinetics (i.e., more rapid rate of release) as a result of poor subcutaneous fat stores, thus requiring the transdermal fentanyl patch be changed every 48 hours

Step 1:
Determine the 24-hour total of the opioid that will be converted. For L.V., the 24-hour total of intravenous hydromorphone is 14 mg.

Step 2:
Select the equianalgesic dose ratio that corresponds to the opioid and route that will be converted from Table 55-20. Ratio calculations should be set up to correlate the actual dose with the equianalgesic equivalent as shown below:

$$\frac{\text{"X" mg total daily dose of new opioid}}{\text{mg total daily dose of current opioid}} = \frac{\text{equianalgesic factor of new opioid}}{\text{equianalgesic factor of current opioid}}$$

For conversion of L.V.'s hydromorphone dose, 1.5 mg intravenous hydromorphone is equianalgesic to 30 mg oral morphine:

$$\frac{\text{"X" mg total daily dose of new opioid}}{\text{14 mg intravenous hydromorphone}} = \frac{\text{30 mg oral morphine}}{\text{1.5 mg intravenous hydromorphone}}$$

Step 3:
Cross multiply the ratio to determine the total daily dose of oral morphine.

$(1.5)(X) = (14)(30)$
$1.5X = 420$
$X = 280$ mg of oral morphine

Step 4:
Determine L.V.'s transdermal fentanyl patch dose equivalent to 280 mg oral morphine using the conversion ratio of 60 mg/day oral morphine to 25 mcg/hour transdermal fentanyl will be used for the calculation.

$$\frac{\text{"X" mg total daily dose of new opioid}}{\text{280 mg oral morphine/day}} = \frac{\text{25 mcg/hour transdermal fentanyl}}{\text{60 mg oral morphine/day}}$$

$(60)(X) = (280)(25)$
$X = 116$ mcg/hour transdermal fentanyl

Figure 55-7 Conversion of L.V. from intravenous hydromorphone to transdermal fentanyl.

TRANSITION TO TRANSDERMAL FENTANYL

- Reducing the intravenous hydromorphone(or other oioids) continuous infusion by 50% should occur 6 hours after the initial transdermal fentanyl patch is placed.

- Discontinuation of the IV hydromorphone continuous infusion and PCA dose should occur 12 hours after the initial transdermal fentanyl patch placement

OPIOID THERAPY FOR BREAKTHROUGH PAIN MANAGEMENT

- Breakthrough pain can be classified as *spontaneous* pain (i.e., frequently idiopathic, occurring with no known stimulus), *incident* pain (i.e., secondary to a stimulus that the patient may or may not be able to control), or *end-of-dose* failure (i.e., pain at the end of the dosing interval of the ER/LA opioid).

- *Incident* pain can be reduced by instructing the patient to take a dose of short-acting opioid 30 minutes before activity.

- *Spontaneous* breakthrough pain should be treated by administering a short-acting opioid as soon as the pain is experienced.

- For patients on ER/LA opioid formulations experiencing *end-of-dose* failure, APS guidelines recommend supplementary doses of a short-acting opioid equivalent to 5% to 15% of the total daily dose to be taken every 2 hours as needed.

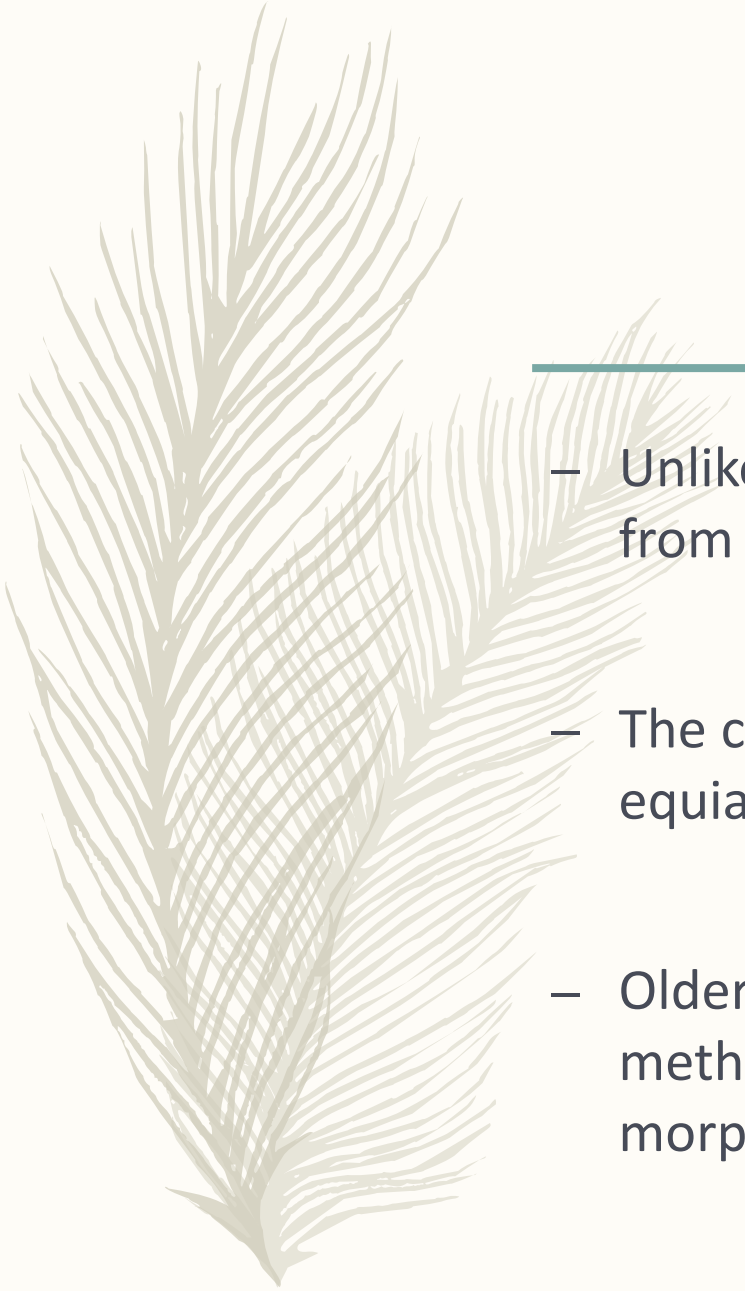
- Short-acting opioid/acetaminophen products have a maximal dose to prevent liver toxicity with acetaminophen, thus creating a ceiling limit on the analgesic efficacy.

Equianalgesic Doses for Actiq (Transmucosal Fentanyl) and Fentora (Buccal Fentanyl)[180]

Current Actiq Dose (mcg)	Initial Fentora Dose (mcg)
200	100
400	100
600	200
800	200
1,200	400
1,600	400

METHADONE DOSE CALCULATION

- Methadone is an opioid agonist with analgesic activity at mu and delta receptors.
- Additional mechanisms of action that make it unique from other opioids and a good option for neuropathic pain include 5-HT and NE reuptake inhibition and antagonist effects at the NMDA receptor.
- Rotation to methadone is recommended when a patient has an inadequate response to other opioids or experiences intolerable side effects such as delirium, myoclonus, or nausea



- Unlike short-acting opioids, methadone has a long half-life that ranges from 15 to 60 hours with a duration of action of 6 to 12 hours.
- The conversion to methadone is not proportional like other opioid equianalgesic dose calculations.
- Older opioid dosing tables list a single conversion factor of 20 mg of oral methadone (or 10 mg IV methadone) equianalgesic to 30 mg of oral morphine.

- The single methadone conversion factor was intended for acute pain and does not account for chronic use.

- The conversion ratios vary with the morphine dose.

- Contemporary tables contain three or more morphine-to-methadone ratios to adjust for the magnitude of the methadone dose potency with higher morphine daily dose requirements for chronic noncancer and cancer pain.

Morphine-to-Methadone Equianalgesic Dose Ratio[182]

Oral morphine dose (mg/day)	<100	101–300	301–600	601–800	801–1000	≥1001
Oral morphine-to-oral methadone ratio	3:1	5:1	10:1	12:1	15:1	20:1

- Guidelines recommend when switching to methadone from higher doses of another opioid, start methadone therapy no higher than 30 to 40 mg/day, with initial dose increases of no more than 10 mg/day every 5 to 7 days.

- For most patients, the recommended methadone dose interval is every 8 hours.

- Older adults or frail patients may need methadone dosed every 12 hours to reduce the occurrence of side effects such as sedation.

- Because methadone has a long terminal half-life, it will take 4 or more days to achieve steady state.

- Unless patientis experiencing severe pain, the methadone dose should not be increased before 5 days

Step 1:
Determine the 24-hour total of the opioid that will be converted. For L.V., the transdermal fentanyl 100 mcg/hour patch will need to be converted to oral morphine. In addition, L.V. is using 150 mg/day of immediate-release oral morphine.

The conversion ratio of 60 mg/day oral morphine to 25 mcg/hour transdermal fentanyl will be used for the calculation.

$$\frac{\text{"X" mg total daily dose of new opioid}}{\text{100 mcg/hour transdermal fentanyl}} = \frac{\text{60 mg/day oral morphine}}{\text{25 mcg/hour transdermal fentanyl}}$$

(25)(X) = (100)(60)
X = 240 mg oral morphine
Therefore, the total daily dose of oral morphine is 390 mg (240 mg + 150 mg)
The conversion ratio of X = 200 mg/day oral morphine

Step 2:
Select the equianalgesic dose ratio from the methadone table that corresponds to a total daily morphine use of 390 mg using the Donner method in step 1.[161,169]

According to the methadone dose Table 55-22, morphine doses in the range of 301–600 mg correspond to a 10:1 ratio (oral morphine to oral methadone).

$$\frac{\text{"X" mg total daily dose of new opioid}}{\text{390 mg total daily dose oral morphine}} = \frac{\text{1 mg oral methadone}}{\text{10 mg oral morphine}}$$

(10)(X) = (390)(1)
10X = 390
X = 39 mg of oral methadone/day
If the total daily dose of 340 mg oral morphine is used for the calculation, the total daily dose of methadone would be 34 mg.

Figure 55-8 Conversion of L.V. from transdermal fentanyl to oral methadone.

- Methadone can cause prolongation of the QTc interval and increase the risk for development of torsades de pointes (potentially fatal arrhythmia).

- Factors associated with QTc prolongation are methadone doses greater than 100 mg/day, hypokalemia, low prothrombin level (suggestive of reduced liver function), and drug interactions involving the cytochrome P-450 3A4 enzyme.

- Consensus guidelines have been published on cardiac monitoring for patients taking methadone.
- The guidelines recommend pretreatment screening, electrocardiogram (ECG) evaluation, and risk stratification for QTc intervals exceeding 500 ms.
- For a QTc interval exceeding 500 ms, the consensus guidelines recommend reducing or discontinuing methadone

OPIOID SIDE EFFECT MANAGEMENT

- Appropriate use of opioids requires minimizing the occurrence of side effects including sedation, nausea, vomiting, pruritus, myoclonus, and cognitive impairment.

- In cancer patients, multiple factors may contribute to the emergence of opioid side effects such as renal insufficiency, nausea, and vomiting caused by changes in gut motility or chemotherapy, sedation owing to metabolic disturbances, and concomitant use of other sedatives or antiemetics

- Tolerance to most of the opioid side effects develops in 3 to 7 days.

- If the side effects do not diminish with time, treatment may include switching to a different opioid or adding another medication to counteract the undesired effect.

Pharmacologic Treatments for Opioid-Related Side Effects[185]

Side Effect	Treatment
Constipation	Stool softener, laxative, methylnaltrexone, oral naloxone, naloxegol
Sedation	Methylphenidate, modafinil
Pruritus	Diphenhydramine, hydroxyzine
Nausea	Prochlorperazine, haloperidol, metoclopramide, ondansetron, antihistamine
Dysphoria	Haloperidol, opioid rotation
Cognitive impairment	Methylphenidate, modafinil, opioid rotation
Myoclonus	Clonazepam, dose reduction, opioid rotation

REFRACTORY CANCER PAIN MANAGEMENT

- Neuraxial opioid administration (epidural or intrathecal) can be used to treat cancer pain that is refractory to conventional therapy with opioids and coanalgesic medications.

- Medication selection is based on the patient's allergy history and response to a screening trial.
- Opioids (e.g., morphine, hydromorphone, fentanyl), local anesthetics (e.g., bupivacaine, ropivacaine), clonidine, ziconotide, and baclofen are commonly used in neuraxial regimens

- Oral cannabinoid formulations (dronabinol and nabilone) are approved by the FDA for chemotherapy-induced nausea and vomiting refractory to conventional antiemetic therapy.

- Several studies of the endogenous cannabinoid receptors (CB1 and CB2) have demonstrated efficacy in the management of pain.