Opioid Pharmacology and Considerations in Pain Management

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FACULTY:
Anne Zichterman, PharmD, BCPS
Assistant Professor, Department of Pharmacy
University of Tennessee College of Pharmacy

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GOAL:
To educate pharmacists about the variations in opioid pharmacology and effective clinical strategies for pa

LEARNING OBJECTIVES:
After completing this article, the pharmacist will be able to:

1. Compare and contrast the differences between opioids and their pharmacologic profiles that may le
2. Assess the advantages and disadvantages of available routes of administration.
3. Implement effective pain management using as-needed and scheduled regimens, dosage titration,
4. Develop management strategies for adverse effects, and distinguish the difference between toleran

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Throughout the past century, the availability of opioids has expanded to include semisynthetic opiate deriv oxycodone, and oxymorphone) and synthetic opioid analogs (e.g., tramadol, fentanyl, meperidine, methad These drugs bind to three types of opioid receptors: mu, delta, and kappa.[1] When selecting an opioid anal potency and efficacy, speed of onset, duration of effect, route of administration, and adverse effect profile. these aspects, and knowledge in this area may aid the practitioner in tailoring therapy for effective and saf

Opioids for Mild-to-Moderate Pain

Codeine: Codeine, like morphine, is a naturally occurring opiate. It is a weak analgesic and should be use codeine for severe pain is extremely limited due to its lack of potency; a 60-mg dose produces less analge

Some researchers have proposed that codeine is a pro-drug with analgesic activity dependent on its conv 2D6 (CYP2D6) enzyme.[2-4] If a patient is taking a drug that inhibits the CYP2D6 enzyme (e.g., a phenothia paroxetine),[4] codeine's efficacy may be reduced. Additionally, up to 10% of the population lack the CYP2 with codeine-containing products.[3]

Codeine is not recommended for patients with impaired renal function; serious adverse effects have been setting.[4,5]

Hydrocodone: Hydrocodone is only available in combination with non-opioids. Compared with codeine, it longer duration of action.[4,6] Hydrocodone is a prodrug metabolized by CYP2D6, with analgesic effects dep hydromorphone. Consequently, drug interactions with CYP2D6 inhibitors and genetic enzyme deficiencies

Dose titrations are limited by the non-opioid content, which makes using this agent for severe or escalating

combination products contain at least 500 mg of acetaminophen; at these dosages, the maximum 4-g dos ingestion of eight tablets. If taken as commonly prescribed (one or two tablets every four to six hours), pati of acetaminophen. According to one study, 42% of acute liver failure cases in the United States resulted fr who unintentionally overdosed, 63% used opioid-containing compounds, most commonly hydrocodone.[7] P use of products containing acetaminophen and check ingredients of OTC pain relievers and cold remedies

Propoxyphene: Propoxyphene is usually used alone (Darvon) or in combination with acetaminophen (Da codeine and hydrocodone and more closely resembles the phenylheptylamine opioid methadone.[2] It is a w over using acetaminophen alone. However, propoxyphene may cause adverse effects, such as dizziness a

Propoxyphene is metabolized to norpropoxyphene, which may cause irreversible cardiac toxicity and arrhy 30 to 34 hours and accumulates with repeated dosing.[4] Thus, propoxyphene is not recommended for the t patients with renal insufficiency.[6,9]

Tramadol: Tramadol is a weak opioid analgesic that may be useful for chronic pain. It comes in three form combination with acetaminophen (Ultracet), and as an extended-release tablet (Ultram ER) for once-daily includes weak binding to mu receptors and inhibition of norepinephrine and serotonin reuptake.[4] The non- usefulness of tramadol for neuropathic pain.[10] Due to a high incidence of nausea and vomiting, dosages m weeks, thereby limiting its effectiveness for acute pain.[6,10]

Since seizures have been described with tramadol administration, concurrent use of monoamine oxidase i reuptake inhibitors (SSRIs), and tricyclic antidepressants should be avoided.[11] To lower the risk of adverse mg/day; however, seizures have been reported within the recommended dosing range.[4] Dosages should b or for patients with renal or hepatic dysfunction.[11]

Tramadol is not a controlled substance and is less likely to produce significant tolerance, physical depende should be cautious when prescribing this drug for patients recovering from substance abuse disorders.[6]

Opioids for Moderate-to-Severe Pain

Morphine: Morphine is the prototype pure mu-receptor agonist. It is extensively used and is available in a immediate- and sustained-release products.

Morphine has two biologically active metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuror receptors but acts as a neuroexcitatory agent, contributing to adverse effects such as hyperalgesia, myocl activity; it is at least two to four times more potent than morphine and may significantly contribute to analge are renally eliminated; accumulation of M6G may lead to oversedation and respiratory depression in patien

Morphine is known to induce histamine release, which may lead to hypotension and pruritus.[2] As a hydrop and longer duration compared with more lipophilic opioids (e.g., fentanyl, meperidine). Like most opioids, s amount of orally administered drug that reaches the circulation, giving a parenteral-to-oral dose ratio of 1:3

Hydromorphone: Hydromorphone is five to seven times more potent than morphine but is not more likely common misconception.[6] Hydromorphone has an improved side effect profile over morphine, with less hist metabolite. Consequently, hydromorphone may be a preferable option to morphine for patients with renal i

The use of hydromorphone for chronic pain has been limited by the lack of a sustained-release product. Th suspended and recalled by the FDA due to an interaction with alcohol that caused destruction of the timed currently available in parenteral, oral, and rectal immediate-release formulations. The intravenous and oral hydromorphone also undergoes first-pass metabolism; the parenteral-to-oral dose ratio is 1:5.[6]

Oxycodone: Oxycodone is more potent and causes fewer severe adverse effects (e.g., histamine release Oxycodone is metabolized by CYP2D6 to an active metabolite, oxymorphone, which is now available in ar and hydrocodone, oxycodone is itself a potent analgesic. It is unknown whether oxymorphone significantly oxycodone. Patients with CYP2D6 deficiencies who do not respond well to codeine or hydrocodone may a oxycodone.[3]

Oxycodone is available in combination with non-opioids or alone in immediate- and sustained-release proc renal impairment, oxycodone requires less dosage adjustment and may be a safer alternative to morphine

Oxymorphone: Oxymorphone is approximately twice as potent as oxycodone. It is more lipophilic than m It is available as an injection and as oral formulations: immediate-release (Opana) and sustained-release (half-life than morphine, hydromorphone, and oxycodone, the immediate-release product may be dosed at

Fentanyl: Fentanyl is 100 times more potent than morphine when administered intravenously and is dose acts selectively at the mu receptor, leading to an improved side effect profile with negligible histamine relea is extremely lipophilic, with an almost immediate onset when administered intravenously. In addition, its du opioids, usually lasting only 30 to 60 minutes. Analgesic effects may be prolonged after continuous infusio redistribution of the drug into fat stores; in these cases, the elimination half-life may be extended to 13 to 2 weight loss who take fentanyl chronically may require a dosage reduction.[15] Fentanyl has no pharmacolog safest options for patients with renal failure.[5]

Because of its quick onset and short duration, fentanyl is often used for procedural analgesia. Although the intermittent as-needed (prn) dosing, fentanyl is gaining popularity when used via patient-controlled adminis postoperative pain. A comparative study of opioids administered via intravenous PCA showed that fentany reactions than morphine and hydromorphone.[16] A fentanyl iontophoretic transdermal system for administra FDA and will be available to the public sometime this year. Fentanyl is also available in several other formu oral transmucosal lozenge, and the recently approved Fentora buccal tablet.

Meperidine: Despite its continued use, meperidine is not recommended as a first-line opioid analgesic.[6,9, rapid onset and shorter duration of analgesia (usually 2-3 hours) than other short-acting opioids.[6,17,19,20] T commonly prescribed four- to six-hour dosing interval, resulting in uncontrolled pain before the next dose is which may be related to its lipophilicity and rapid transport into the central nervous system (CNS).[19] It has than other opioid drugs.[6]

The clinical utility of meperidine is limited by its active metabolite, normeperidine. This metabolite is neurot agitation, tremors, and seizures. Normeperidine toxicity is not reversed by administration of the opioid anta worsen the effects by counteracting the depressant effect of meperidine.[4,19] Accumulation of normeperidin its extended half-life, which is five to 10 times longer than the parent drug. Because it is eliminated renally, adverse effects is higher in patients with renal insufficiency.[2,6,19,21]

Two of the most commonly used routes of administration—oral and intramuscular—are problematic. Signif levels of normeperidine that are considerably higher when the drug is given orally. However, oral bioavailal required when using this route.[4] The American Pain Society (APS) recommends avoiding oral meperidine avoided, since absorption of meperidine is erratic and can vary by 50% or more (even when administered

Meperidine inhibits the reuptake of norepinephrine and serotonin, and is contraindicated for coadministrati syndrome is increased with concurrent use of serotonin-receptor agonists and SSRIs.[10,19]

Meperidine is not recommended for PCA administration due to the high doses needed for acceptable anal of adverse effects.[21] Although intermittent intravenous dosing of meperidine may be required in patients w such as morphine or hydromor-phone,[20] its use for PCA may be obsolete given the availability of the struc

Meperidine is often used for pain associated with pancreatitis, because it is thought to cause less spasm a opioids. Pancreatitis treatment guidelines have listed meperidine as the opioid of choice, even as recently studies that supported the use of meperidine used animals or small sample sizes and did not use compara contrast, more recent studies indicate that at equianalgesic dosages, all opioids cause an increase in bile p evidence for any benefit with meperidine use.[6,19-21,23] The most recent practice guideline for acute pancre Gastroenterology does not recommend the use of any particular opioid.[24] Due to the risk of toxicity, meper pancreatic pain.

Because of its unique toxicity profile, meperidine is not an appropriate choice for chronic pain, elderly patie seizure disorders. The maximum recommended daily dosage is 600 mg per day, for less than 48 hours.[10, patients who have allergic reactions to other opioids such as morphine or hydromorphone; for the treatmer product-induced rigors; or for treatment of postanesthesia shivering.[20]

Methadone: Methadone's pharmacology is unique; unlike other opioids, methadone is a racemic mixture (d)-isomers. The l-isomer gives methadone its opioid activity, while the disomer is an *N*-methyl-D-aspartate norepinephrine and serotonin reuptake inhibitor.[25] As the NMDA receptor has been demonstrated to play a tolerance, it is likely that the d-isomer of methadone is at least partially responsible for its increased potenc opioids.[1,6] Changing to methadone may benefit patients who require high doses of opioids but also experie mechanism, methadone may also have increased efficacy for neuropathic pain.[25,26]

Methadone's unique mechanism and low cost have contributed to a renewed interest in its use. Howeve predispose patients to developing serious adverse effects. Methadone has the longest and most variable h 12 to 190 hours (the usual half-life is approximately 24 hours). The duration of analgesia is much shorter th every four to eight hours at the beginning of treatment and every six to 12 hours at steady state.[1,6,26,27] As life-threatening sedation and respiratory depression within three to five days after starting methadone thera Methadone is highly lipophilic and redistributes to fat stores; significant weight loss may necessitate dosag

Methadone is metabolized by CYP3A4, with minor activity at CYP2D6. High doses may cause QTc interva effect may be worsened by drug interactions with CYP3A4 inhibitors or other QTc interval-prolonging age avoiding use of high dosages or the 40-mg dispersible tablets for pain, which are only indicated for detoxifi addiction.[29] Caution should be used whenever initiating or adjusting a methadone regimen, especially in pa disease or are taking additional medications that may prolong the QTc interval.

Methadone's low cost and long half-life may provide an advantage for patients who cannot tolerate or aff dosing regimens for pain are scheduled every six to eight hours, as opposed to the once-daily regimens us opioid dependence.[25] Methadone may be highly effective when used by practitioners who are familiar with indiscriminate use may be hazardous if its safety profile is not appreciated and toxicity carefully managed. 2003 indicated that in five of six states, methadone outnumbered oxycodone or hydrocodone in opiate-rela Health and Human Services has attributed the rise in deaths to increased use of methadone as an analge closely followed by a knowledgeable physician and receive thorough instruction on how to take methadone

Levorphanol: Levorphanol is considered a second-line opioid for patients with moderate-to-severe chroni release opioids. Like methadone, levorphanol has a long half-life (usually 12-15 hours), and accumulation respiratory depression. Duration of analgesia is usually four to six hours, with typical dosages scheduled a exhibits NMDA receptor antagonism and may provide benefit for the treatment of neuropathic pain.[32] Levo administration. The oral formulation is available only as a 2-mg tablet, which makes titration difficult.

Agonist-Antagonist Derivatives: Pentazocine, nalbuphine, and butorphanol are kappa receptor agonists buprenorphine exhibits partial activity at the mu receptor and antagonism at the kappa receptor; it is often these agents cause less respiratory depression than pure mu-agonist opioids, the ceiling effect for analges severe pain. Administration may cause opioid withdrawal in patients who are already receiving pure muag of psychomimetic effects such as confusion and hallucinations; these may be particularly severe with use patients with renal impairment.[2,4] These agents are not recommended for the treatment of moderate-to-se formulations of buprenorphine (Subutex, Suboxone) have been approved only for the maintenance of opio certified physicians in office-based treatment programs.[33]

Route of Administration

Patients may require different routes of administration, especially if they are unable to ingest or tolerate ora release opioids are available in a variety of formulations and may be administered via several routes. Altho intraspinal (including intrathecal and epidural) administration and PCA are additional methods of delivery.

Oral: Due to efficacy and convenience, oral administration is preferred. Immediate-release tablets like hyd may be crushed for ease of administration. Liquid formulations of morphine, hydromorphone, oxycodone, a Sustained-release products such as oxycodone (Oxycontin), oxymorphone (Opana ER), and morphine (M since the timed-release mechanism will be destroyed, resulting in a potentially lethal overdose. Controlled- Avinza) may be opened, and the beads of medication can be sprinkled on soft food for patients who have

Intravenous: The intravenous route provides the most rapid onset but also a shorter duration than oral or time-to-peak effect depends on the lipophilicity of the opioid (ranging from five minutes for fentanyl to 15-3

Subcutaneous: Subcutaneous administration may be an alternative if intravenous access cannot be obta either continuously or intermittently. Subcutaneous boluses have a slower onset and lower peak effect tha must be limited. For this reason, hydromorphone may be preferred over morphine, as it is available as a m

Intramuscular: Intramuscular injections are painful, may exhibit wide fluctuations in absorption, and can le against the use of intramuscular administration of analgesics.

Rectal: Several immediate-release opioids may be administered via this route, including morphine, hydror absorption of opioids is variable and highly dependent on suppository placement; if inserted past the recta

may be avoided.[10] Sustained-release morphine tablets may be administered rectally every 12 hours using
however, some patients may require slight dosage reductions. This technique has often been used in the p

Transdermal: Transdermal administration of fentanyl may be useful for patients with chronic pain who car
patch (Duragesic) is designed to provide analgesia for 72 hours, although some patients may experience b
48 hours. This formulation is unique and carries a number of warnings not shared by other sustained-relea
large amount of medication, and starting an opioid-na&#65533;ve patient on a fentanyl patch could result in overn
depression. As such, the fentanyl patch should be used only for opioid-tolerant patients (defined as a daily
other opioid equivalent, every day for at least a week). Patients with acute pain or those who have not con
candidates for treatment with the transdermal fentanyl patch.[6,10,34]

Transdermal fentanyl does not work immediately upon placement of the patch. There is a delay of 12 to 16
hours for blood levels to drop by half once the patch is removed.[6] The lag time for effect and prolonged titr
considered when selecting a sustained-release opioid for a terminally ill patient whose analgesic requirem

Heat can increase absorption of fentanyl, resulting in a potentially lethal overdose.[10,34] Fever over 104&#65533;F
third, necessitating an increase in monitoring for toxicity. Patients should be cautioned not to apply a heatir
blanket) directly to the patch.[6]

Oral Transmucosal and Buccal: The fentanyl oral transmucosal lozenges (Actiq) and fentanyl buccal tab
management of breakthrough cancer pain in patients who are tolerant to opioid therapy. Both are contrainc
patients who are opioid na&#65533;ve. These formulations allow for an extremely fast onset of action&#65533;within five
over oral short-acting opioids, which take longer to work.

There is no strict dose conversion ratio from other immediate-release opioids to the fentanyl lozenges and
the lowest dosage of each (Actiq 200 mcg lozenge or Fentora 100 mcg buccal tablet). Doses of the lozeng
interchangeable; the Fentora buccal tablets have faster and higher absorption than the Actiq lozenges, an
proportionally.[35]

As-Needed Versus Scheduled Dosing

The disadvantage of administering analgesics on a prn basis is that pain must be a problem before it can b
result in high peaks and low troughs, causing alternating periods of uncontrolled breakthrough pain and to
up&#65533; with the pain. If pain is present for most of the day, then sustained-release or long-acting opioids adm
preferable to maintain consistent plasma levels.[10]

Sustained-release and long-acting products may limit episodes of breakthrough pain, improve compliance,
Several products are available (**TABLE 1**). If cost is a concern, or if other methods are not successful, met
since their long duration of action is independent of dosage formulation. The dose of the sustained-release
previous 24-hour opioid requirement. The APS recommends treating patients for 48 hours with an immedia
thirds of the estimated daily requirement to the sustained-release regimen.[10]

When sustained-release opioids are used, an immediate-release opioid should be provided for prn rescue
equal 10% to 15% of the total daily requirement.[10] If four to six rescue doses are required in a 24-hour per
increased.[6] A sustained-release opioid should never be used as a prn medication, since the delivery mech
immediately.[10]

Titration

There is no ceiling effect for pure opioids. Dosage requirements vary widely among patients, and opioids s analgesia or until side effects occur. Dosage increases of 10% to 20% during the first few days, or 30% to appropriate. Elderly patients or those with comorbidities, such as pulmonary or CNS diseases, may require duration of analgesia has been reported for older patients, who commonly experience prolonged eliminatic

The duration of action and time to steady state must be considered when titrating an opioid dosage. The o typically within 45 minutes, with maximum effect occurring at one to two hours. If a patient has not achieve time, a second dose of an immediate-release opioid may be administered.[10] Because transdermal fentany the first dosage adjustment may be made after three days, with subsequent increases every six days.[10,34]

Table 1

Sustained-Release and Long-Acting Opioids

Drug		Dosing Interval
Morphine	MS Contin	8-12 hrs
	Oramorph-SR	8-12 hrs
	Kadian	12-24 hrs
	Avinza*	24 hrs
Oxycodone	OxyContin	8-12 hrs
Oxymorphone	Opana ER	12 hrs
Fentanyl	Duragesic	48-72 hrs
Methadone		6-8 hrs
Levorphanol		6 hrs

** The maximum dosage of Avinza is 1,600 mg/day due to fumaric acid content, which may cause renal toxicity.*

Dosage Conversion

When switching to another opioid, the dosage may be determined by using an equianalgesic chart (**TABLE** incomplete, and calculated dose equivalents should be reduced by 30% to 50% (see **PATIENT CASE** for a dose reduction is not necessary when changing between routes with the same opioid. Equianalgesic dose variation may occur. Clinicians should remain attentive to the patient during the first few days after changir analgesia or adverse effects.[10]

Conversion to methadone does not involve the use of a single equianalgesic dose ratio. Methadone increa other opioids are used. Due to this effect, some practitioners recommend an empiric 75% to 90% decrease methadone. An alternative method that determines methadone dosing ratios based on the daily requireme 3).[35]

Several dose equivalency ratios have been described for converting oral opioids to transdermal fentanyl. T 25 mcg per hour increment to 45 mg per day of oral morphine.[10]

Table 2

Equianalgesic Chart

	Equianalgesic Dose (mg) Oral	Parenteral
Codeine	200	130
Hydrocodone	30	[illegible]
Morphine	30	10
Hydromorphone	7.5	1.5
Oxycodone	20	[illegible]
Oxymorphone	10	1
Fentanyl	[illegible]	0.1
Meperidine	300	75
Methadone	10	5
Levorphanol	4 (acute)	2 (acute)
	1 (chronic)	1 (chronic)

Note: For repeated dosing, IV and IM dose ratios are assumed to be equivalent. For single dosing, the IV dose may be lowered to half the IM dose to achieve the same peak effect.

Source: References 6, 10.

Table 3

Conversion Ratio of Oral Morphine to Oral Methadone

Daily oral morphine dose (mg)	Conversion ratio, oral morphine to oral methadone (mg)
<100	3:1
101-300	5:1
301-600	10:1
601-800	12:1
801-1000	15:1
>1001	20:1

Note: Reduce calculated dose by 30% to 50% to account for incomplete cross-tolerance. Dose ratios do not apply to conversions from methadone to another opioid.

Source: Reference 43.

Patient Case: Opioid Conversion

A patient is receiving a hydromorphone IV infusion of 1.2 mg/h, and the physician wishes to convert to a regimen of sustained-release oral oxycodone.

1. Determine the total daily dose of hydromorphone for the previous 24 h.

Hydromorphone IV 1.2 mg/h x 24 h = hydromorphone IV 28.8 mg

2. Determine the equivalent dose of oxycodone for the daily requirement.

Hydromorphone IV 28.8 mg ÷ 1.5 (equivalency dose for hydromorphone IV) = 19.2 mg equianalgesic dose units

19.2 mg equianalgesic dose units x 20 (equivalency dose for oxycodone po) = oxycodone 384 mg

3. Reduce the oxycodone dose for incomplete cross-tolerance.

Oxycodone 384 mg x 70% (i.e., 30% reduction) = oxycodone 269 mg

The new regimen of oxycodone may be Oxycontin 120 mg twice daily (total daily dose, 240 mg), which closely approximates the calculated total daily dose of 269 mg.

Management of Adverse Effects

Opioids share a common side effect profile, including sedation, constipation, nausea, vomiting, pruritus, m Tolerance develops to most opioid adverse effects within a few days. Patients taking opioid therapy should of side effects.

If opioids cause unwanted side effects, clinicians can change the dosage, schedule, or route. If analgesia s time interval may be decreased. Alternatively, sustained-release formulations may decrease peak effects a side effect profile.[10] Patients with liver cirrhosis may have reduced metabolism and require extended dosin opioids to a nonoral route of administration may decrease the incidence of nausea and vomiting or myoclo

Opioid rotation, or changing to another opioid, may reduce side effects and/or improve efficacy if a patient most opioids share adverse effects at equianalgesic dosages, some opioids have slight advantages over c effects such as constipation and histamine release. Occasionally, patients may tolerate certain opioids bet differences in opioid receptor subtypes.[10,37,38] Opioid rotation may also decrease adverse effects caused b Patients with renal insufficiency should be changed to an opioid that lacks active metabolites (TABLE 4). A be avoided for patients with liver dysfunction.[36]

Table 4

Opioid Selection in Renal Failure

Not Recommended for Use	Use with Caution	Safest in Renal Insufficiency
Meperidine	Hydromorphone	Fentanyl
Codeine	Oxycodone	Methadone
Morphine	Oxymorphone	

Propoxyphene

Source: References 5, 14.

Multimodal therapy with the addition of nonpharmacologic treatments (e.g., heat, cold, relaxation technique non-opioid analgesics (e.g., nonsteroidal anti-inflammatory drugs or other adjuvant drugs) may improve pa dosage. Combination pharmacotherapy relies on multiple mechanisms of action and is often more effective

If the previous methods fail, adjuvant medications may be used for symptomatic treatment of adverse effec

Sedation: Sedation and cognitive impairment are more likely to occur when opioid therapy is initiated or d despite opioid rotation and dosage reductions, therapy with psychostimulants may be considered. Caffeine and modafinil have all been used for this purpose.[10]

Constipation: Tolerance does not develop to this adverse effect. Patients on chronic opioid therapy shoul stimulant laxative (e.g., senna or bisacodyl) to increase bowel motility. Stool softeners such as docusate m as monotherapy. Other classes of laxatives can be expensive and may not be effective.[6,10] Bulk-forming la avoided, since concurrent therapy with opioids may result in impaction.[6] Constipation may be avoided by u be associated with a lower incidence of this adverse effect than oral sustained-release opioids such as mo

Nausea/Vomiting: Nausea and vomiting may be avoided by using a nonoral route of administration for the tolerance to this side effect. However, nausea and vomiting may occasionally persist. Chronic nausea is ob morphine for chronic cancer pain. If changing the opioid or route of administration is not helpful, antiemetic studies to indicate the superiority of one antiemetic over another. Recommended agents include metoclopr phenothiazines, transdermal scopolamine, ondansetron (or another 5-HT3 antagonist), and dexamethasor

Pruritus: Morphine and codeine have a high incidence of histamine release and pruritus. Changing to fent negligible histamine release, may avert this problem.[10] Antihistamines are commonly recommended to trea evidence for success with paroxetine.[37]

Myoclonus: Myoclonus is uncontrolled twitching or jerking, usually of the arms or legs, that may be cause adverse effect may occur with high-dose opioid therapy.[6,37] Oral morphine causes a threefold higher incide morphine, implicating the role of higher M3G concentrations resulting from first-pass metabolism. Opioid ro myoclonus persists, adjuvants such as baclofen, diazepam, clonazepam, midazolam, valproic acid, and da

Respiratory Depression: Opioids exert a depressant effect on the respiratory center, which can slow brea arrest. Pain is a powerful stimulus to counter this effect.[5] Respiratory depression is rare in patients receivir

It can usually be avoided by careful titration but may occur in opioid na&#65533;ve patients who require high dosa &#65533;No patient has succumbed to respiratory depression while awake.&#65533; If a patient becomes overly sedated emergent situations, the opioid antagonist naloxone may reverse the effect. The duration of naloxone is m minutes), and repeated doses are often needed. Patients should be monitored closely for at least three ho analgesic blood concentrations.[11] Prolonged naloxone opioid antagonism has been reported in patients wi extra care should be given to monitoring when metabolite accumulation is suspected.[39]

Opioid Allergy

True opioid allergies are rare.[6,40] Patients frequently confuse common side effects, such as nausea or pru
to describe their reaction may help to clarify whether the reported allergy involves anaphylaxis or a side ef

There are three classes of opioids: phenanthrenes, phenylpiperidines, and phenylheptylamines (TABLE 5
reaction to a natural phenanthrene like codeine or morphine may not exhibit the same reaction to a semisy
oxycodone could be tried in this case. However, if the reaction is severe or if the patient describes an anap
breathing, switching to an opioid from another chemical class (such as fentanyl or methadone) may be ind
incidence of cross-allergy in these instances is unknown.[40]

Table 5

Chemical Classes of Opioids

Phenanthrenes	Phenylpiperidines	Phenylheptylamines
Natural	Fentanyl	Methadone
Codeine	Meperidine	Propoxyphene
Morphine		
Semisynthetic		
Hydrocodone		
Hydromorphone		
Oxycodone		
Oxymorphone		

Source: References 2, 40.

Tolerance, Physical Dependence, and Addiction

Tolerance occurs when a constant opioid dosage produces a decreasing effect. With the exception of cons
induced side effects (e.g., respiratory depression, sedation, nausea). Tolerance to analgesic effects may o
and is usually characterized by a decrease in the duration of analgesia. After this time, however, tolerance
patient has been stabilized on an opioid regimen and a dosage escalation is required, the development of
Cross-tolerance among opioids is not complete, for either analgesic effects or toxicity.[6,10]

Physical dependence is a predictable pharmacologic effect that is manifested by the development of a with
discontinuation of therapy. It is often confused with addiction; however, physical dependence is unrelated t
of drugs, including steroids and antihypertensive agents. Physical dependence may be anticipated in patie

opioid for more than two weeks. A withdrawal syndrome may be avoided by tapering doses by 10% to 20%

Addiction is a psychological dependence, rather than dependence related to a property of the drug. The AI compulsive drug use characterized by a continued craving for an opioid and the need to use the opioid for definitions characterize addiction as "continued use despite harm." Patients with addiction disorders ma focus of their life and exhibit aberrant drug-seeking behaviors.[10]

The incidence of addiction in patients treated with opioids is widely debated and often overestimated. A fre 0.01% is not likely representative of the true incidence in the population, as it was based on a retrospective prior history of substance abuse from the final analysis.[41] Subsequent studies have corroborated that the r substance abuse (either drugs or alcohol) is low, and most experts agree that fear of opioid addiction shou appropriate opioid therapy.[42] Patients who have active or prior history of substance abuse disorders are at and may require care by specialists. The prevalence of addiction among patients treated with opioids in ch between 3.2% and 18.9%.[10]

Pseudoaddiction is a term used to describe aberrant behavior by patients who are not truly addicted to opi use deception or illicit methods to obtain medication due to the fear of uncontrolled pain. Demanding beha analgesics are not always predictive of addiction and may instead result from a desire for pain relief. Pseu addiction in that once patients are effectively treated, aberrant or drug-seeking behaviors cease.[6,10]

Conclusion

Opioids have been considered the mainstay of cancer pain management,[37] and they are increasingly usec noncancer pain. As understanding of the pharmacology of this class of drugs becomes more sophisticated adverse effects and variations in individual response. Pharmacists can use this knowledge as part of a mu selection of opioids, identify correct dosages and schedules, and monitor for adverse effects. Counseling p overall treatment success.

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