Opioid Prescribing: Safe Practice, Changing Lives - 2018 Update

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Faculty and Disclosures

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- Contents of This CME Activity
- All sections of this activity are required for credit.
- Assessing Patients and Initiating Opioid Therapy
    - How do you know if opioid therapy is appropriate for your patient?
    - Katherine Galluzzi, DO; Randall Hudspeth, PhD, MBA, APRN-CNP/CNS
- Managing and Monitoring Therapy
    - What steps should you follow to ensure safe use and optimal outcomes?
    - Katherine Galluzzi, DO; Randall Hudspeth, PhD, MBA, APRN-CNP/CNS
- Take-Home Points and General Drug Information
    - A summary of the key clinical points
    - Katherine Galluzzi, DO; Randall Hudspeth, PhD, MBA, APRN-CNP/CNS
- Clinical Case Challenge

Please answer the following questions to assess your performance. Answering these questions again after the activity will allow you to see what you learned and to compare your answers with those of your peers.

Question 1 of 14

Among the risk factors contained in screening tools for predicting aberrant drug-related behavior in patients receiving opioids for chronic pain are family and personal history of substance abuse, legal problems, history of preadolescent sexual abuse, psychological problems and:

- ☐ Age (12-15 years)
- ☐ Age (16-45 years)
- ☐ Age (46-75 years)
- ☐ Age (≥ 76 years)
- ☐ Risk is even across age

Question 2 of 14

Which of the following is most important to consider when determining a starting dosage of an extended-release/long-acting (ER/LA) opioid?

- ☐ Results of urine drug test
- ☐ Patient preference

- Cost of the medications
- Assessment of individual needs
- Starting dosage listed in the package insert

Question 3 of 14

A 55-year-old man who is being treated for chronic low back pain after undergoing laminectomy comes for follow-up evaluation. A trial of oxycodone ER therapy is planned. Completion of which of the following is the most appropriate step before initiation of therapy?

- Oswestry Disability Index
- Roland Morris Disability Questionnaire
- Patient-Prescriber Agreement
- MRI of the lumbar spine
- Routine blood tests

Question 4 of 14

A 63-year-old woman with a history of spinal stenosis and peripheral neuropathy secondary to breast cancer treatment comes for evaluation because of increasingly severe back pain. She reports that the pain started 2 weeks ago after doing yard work. She underwent chemotherapy 12 years ago. Medications include an opioid. Which of the following is the most appropriate next step?

- Assure the patient that the heightened sensitivity to pain is to be expected
- Reevaluate the underlying medical condition
- Refer the patient to physical therapy and administer a short-acting opioid as necessary
- Increase ER/LA opioid therapy dosage for up to 1 month
- Consider adding an adjuvant analgesic for neuropathic pain

Question 5 of 14

Use of ER/LA opioids in pediatric patients <18 years of age deserves special consideration because

- Safety and effectiveness of most ER/LA opioids has not been established in this population
- Many children experience chronic pain conditions with indications for ER/LA opioids
- Starting doses of opioids are reduced by one-third to one-half that in adults
- Opioid risk screening tools have not been validated in this population
- Many state laws require consultation with a pediatric pain specialist or pain clinic

Question 6 of 14

A 59-year-old with long-standing hypertension and Stage 3 chronic kidney disease continues treatment with disease-modifying anti-rheumatoid drugs (DMARDs) for rheumatoid arthritis (RA). Recently she has exhibited increasing pain and further

functional decline likely due to progression of RA and osteoarthritis of the hips, knees and feet as well. She is determined to remain as functional as possible and participates in Aquatherapy and yoga classes. Which of the following pharmaceutical options is the best next step for addressing this patient's pain?

- Acetaminophen 650 mg two tabs q 4 hours prn
- Duloxetine 20 mg daily
- Oxycodone immediate release (IR) 5 mg q 4 hours prn
- Morphine sulfate ER 15 mg q 8 hours
- Ibuprofen 600 mg q 4 hours prn

Question 7 of 14

An inappropriate method to dispose of unused opioid medication is:

- Return the medication to a pharmacy
- Take to a law enforcement-sponsored drug take-back event
- Mix into an undesirable substance before putting in the regular trash
- Dispose of medication in the regular trash
- Flush down the toilet

Question 8 of 14

The most important reason a patient should be counseled to never break, cut, chew, or crush an ER/LA opioid tablet or cut or tear patches is because:

- The medicine will expire
- It is against the law
- The dose will be less than prescribed
- The patient may die

Question 9 of 14

To avoid inadvertent overdose and death, a patient should be counseled to avoid co-administration of an ER/LA opioid with which of the following?

- Alcohol
- Diphenhydramine
- St John's wort
- Aspirin
- Methamphetamine

Question 10 of 14

Which of the following ER/LA opioids is most likely to induce a peak respiratory depression that occurs later and persists longer than the analgesic effect?

- Fentanyl transdermal patch
- Hydromorphone ER
- Methadone
- Oxycodone CR
- Tapentadol ER

Question 11 of 14

When using an equianalgesic table to rotate opioids other than methadone, an important step to account for incomplete cross-tolerance among mu opioid receptor agonists includes:

- Initiate the new opioid at the calculated equianalgesic dose
- Increase the calculated equianalgesic dose by 10%-30%
- Reduce calculated equianalgesic dose by 25%-50%
- Convert and total all opioids to oral morphine equivalents
- Refer to the package insert for appropriate supplemental rescue dose

Question 12 of 14

A 72-year-old grandfather with severe persistent abdominal pain from colon cancer has been taking an IR opioid every 4 hours around the clock. He and his wife care for their 2 young grandchildren, and he states that he can no longer help with their care due to his pain level. He wants to increase the dose of his medication and asks what else he might do to control the pain. Which of the following supports the addition of an ER/LA opioid as treatment for this patient?

- More consistent plasma concentrations
- Fewer adverse events
- Less risk for respiratory depression with the addition of the ER/LA opioid
- Less need for ongoing monitoring

Question 13 of 14

A 67-year-old female with severe knee osteoarthritis has recently been converted from an IR opioid to an ER opioid for pain control. She has chronic obstructive pulmonary disease that has made her a poor surgical candidate. In addition to ER opioid, which second prescription would be the most appropriate to dispense to her?

- Naloxone
- Nortriptyline
- Duloxetine
- Acetaminophen

Question 14 of 14

A positive result of hydromorphone of a urine drug toxicology test for a patient on prescribed morphine can be interpreted as

- Use of heroin in past month
- Proof of supplemental hydromorphone
- Presence of the oxycodone metabolite
- Presence of the morphine metabolite
- Presence of semisynthetic opioids

Opioid Prescribing: Safe Practice, Changing Lives - 2018 Update

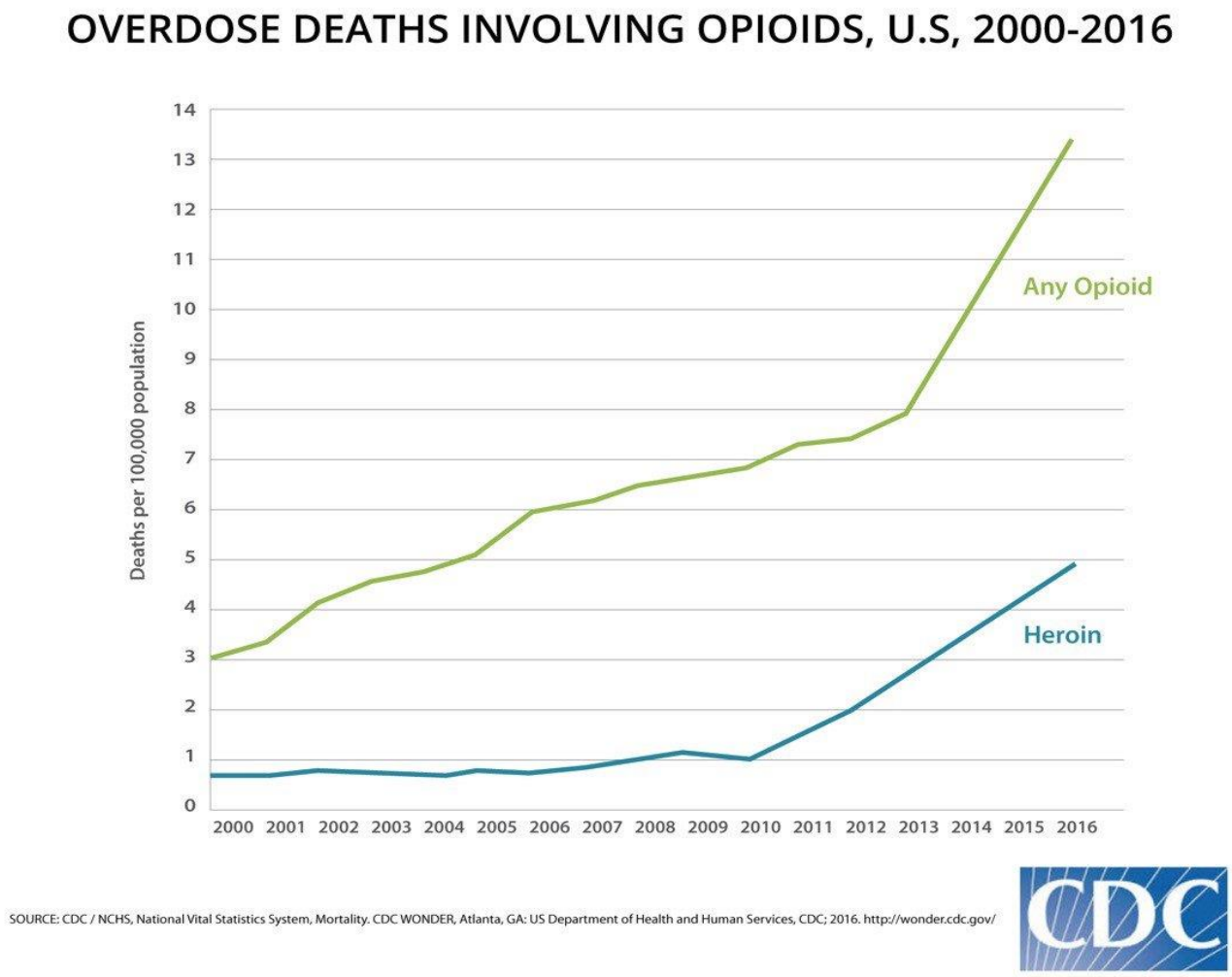
Thank you for answering these questions. They will be repeated at the end of the activity so you can see what you've learned from the activity. We are not providing feedback on these initial questions to avoid influencing your answer choices on the questions presented at the end of the activity.

Assessing Patients and Initiating Opioid Therapy

Introduction: Why Are We Here?

Opioid analgesics can play a valuable role in the management of persistent severe pain in selected patients.[1-3] However, inappropriate prescribing and improper use of these drugs are associated with serious consequences, including overdose, addiction, and death.[1-8] Misuse, abuse, diversion, addiction, and overdose of opioids have created a serious public health epidemic in the United States. Opioid overdose deaths increased steadily in the United States from 2000 to 2015 (Figure 1).[8]

Figure 1. Opioid Overdose Deaths in the United States



Reproduced from Collaborative for REMS Education (CO*RE).

Unfortunately, changes in opioid-prescribing practices contributed to the increase in opioid-related overdose deaths, with the pendulum swinging from underprescribing (and the resulting inadequate pain management) to overprescribing (resulting in unacceptable risks). The goal, of course, is to find a balance between these 2 extremes. One of the keys to reaching this goal is to ensure that opioid analgesics are prescribed only by healthcare professionals who are knowledgeable in the use of these medications. Safe prescribing requires full understanding of the potential benefits and risks of opioid analgesics, which are summarized in Table 1.[9]

Table 1. Potential Benefits and Risks of Opioid Analgesics[9]

Benefits	Risks

• Analgesia
  ○ Adequate pain control
  ○ Continuous, predictable (with
	• Overdose*
	• Life-threatening respiratory depression

ER/LA opioids) • Improved function • Improved quality of life	• Abuse by patient or household contacts • Misuse, diversion, and addiction • Physical dependence and tolerance • Interactions with other medications and substances • Risk of neonatal opioid withdrawal syndrome • Inadvertent exposure/ingestion by household contacts, especially children

ER = extended-release, LA = long-acting.
*The risk is increased with ER/LA formulations because they contain a greater concentration of opioids than immediate-release formulations.

To address this increasing public health epidemic, the US Food and Drug Administration (FDA) made the decision to require a Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER)/long-acting (LA) opioid analgesics and the Centers For Disease Control and Prevention (CDC) published guidelines for prescribing opioids for chronic pain.[1,3] The CDC guidelines were developed for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care.[1] The ER/LA opioid REMS is focused on prescriber education. The main goals of the REMS are to help clinicians:

- Understand how to assess patients for treatment with ER/LA opioids
- Be familiar with how to initiate therapy, modify dosages, and discontinue use of ER/LA opioids
- Know how to manage ongoing therapy with ER/LA opioids
- Know how to counsel patients and caregivers about the safe use of ER/LA opioids, including proper storage and disposal
- Be familiar with general and product-specific drug information concerning ER/LA opioids

This activity will present highlights of the REMS for ER/LA opioid analgesics and will include recommendations for the safe use of opioids in general, including recommendations in the CDC guideline for opioid prescribing for chronic pain. Additional information can be found in the Additional Resources section and on the website for the Collaborative for REMS Education (CO*RE).[10,11]

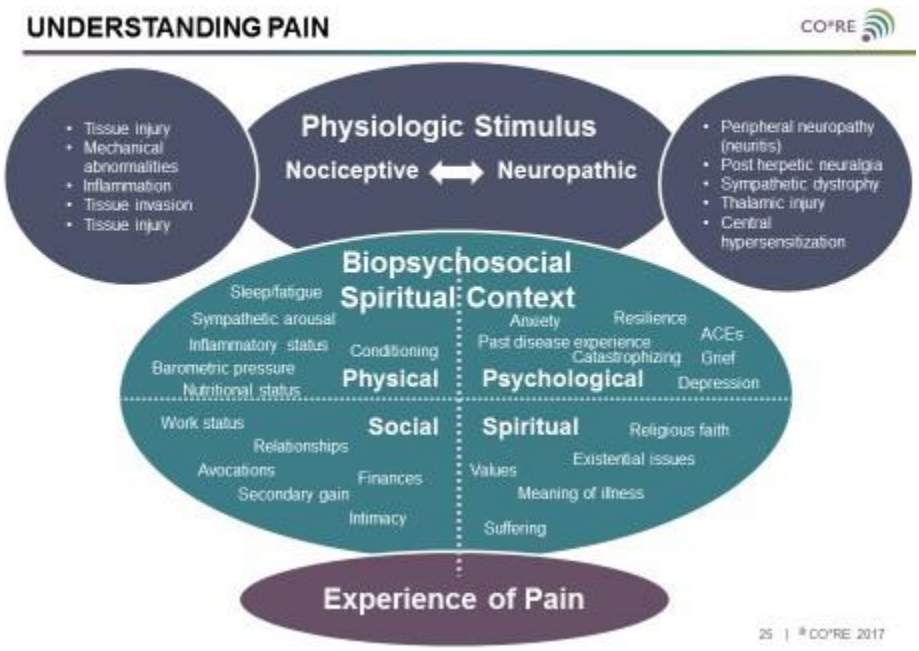
The Contextualization of Pain

Clinicians who prescribe opioids must have adequate understanding of the neuropsychobiology of pain and the many psychological, social, and spiritual variables that may interact to contribute to the patient's experience of pain (Figure 2). It is essential to appreciate the importance and complexity of the impact that chronic pain has on the individual. Anxiety and depression, secondary physical problems, sleep disturbances, and many other factors can affect chronic pain

and in turn be affected by chronic pain. Consequently, the management of chronic pain requires a multimodal approach, which may include some combination of cognitive-behavioral therapy, physical therapy, other interventional treatments such as nerve blocks, and pharmacologic therapy. In general, the goals of treatment are to reduce pain, restore function, and improve the patient's quality of life and sense of well-being.

In addition, the assessment of pain control must be done in the context of treating the whole patient. Ballantyne and Sullivan raised the question of whether a reduction in pain intensity is the right goal for the management of chronic pain.[12] For some patients, maintaining low pain scores will require continuous or escalating doses of opioids at the cost of worsening function and quality of life. Pain intensity scales do not necessarily reflect the extent of tissue damage, and patients' experience of their pain intensity is shaped by many factors, including psychosocial and emotional variables.

Figure 2. The Complexity of Pain



ACE = adverse childhood experiences
Reproduced from CO*RE.

Assessing Patients for Opioid Analgesic Therapy

Deciding whether a trial of an opioid analgesic is appropriate for your patient requires a comprehensive evaluation that includes pain assessment and patient history, physical examination and appropriate workup, and risk assessment. This evaluation should be made and documented before starting opioid therapy.[2,3]

Pain Assessment and Patient History

A comprehensive evaluation of the patient's pain is essential. Strategies that can be used to determine pain intensity, pain-related disability, and distress include interviews, standardized questionnaires, diaries, behavioral observation, physical and psychosocial assessment, and discussion with family members, significant others, and caregivers.[13,14] Questionnaires and inventories are available to assess specific pain domains (Table 2).[13,14]

Table 2. Domains of Pain to Assess[13,14]

- Location of pain
- Intensity of pain
- Quality of pain: eg, dull, stabbing, hot-burning, shooting, aching, piercing, tingling, numb, radiating (use patient's words when possible)
- Onset/duration of pain
- Variations/patterns/rhythms of pain: eg, the pain is constant, intermittent, episodic/recurring
- What relieves the pain? eg, sitting, lying down, standing, heat, cold, rest, distraction, exercise, movement
- What causes or increases the pain? eg, sitting, lying down, standing, heat, cold, rest, exercise, movement
- What are the effects of pain? eg, sleep, movement, energy, lifestyle, personal relationships, work, emotions, concentration, appetite, motivation, ADLs, instrumental ADLs
- Patient's pain and functional goals: eg, comfortable sleep, comfort at rest, comfort with movement, able to perform ADLs, QoL, acceptable level of pain intensity on a 0-to-10 scale
- Current pain and function

ADL = activity of daily living; QoL = quality of life.

The patient's pain treatment history includes the nonpharmacologic and pharmacologic strategies used and their effectiveness. It is important to confirm that the patient has had an adequate trial of nonopioid treatments and/or complementary therapies and to evaluate his or her past and current opioid use. Pay close attention to the dosage and duration of past and current treatment and establishing whether the patient is opioid tolerant. Regarding current opioid use, prescribers should query state prescription drug-monitoring programs (PDMPs) to confirm the patient's report of prescribed controlled substance use and to determine whether the patient has been treated by more than 1 provider.[2,3] It can be useful to contact past providers to confirm the patient's self-report and to obtain previous assessments.

Identify all drugs the patient is taking. Also evaluate the patient's history of nonpharmacologic methods of pain relief, such as physical therapy, surgical interventions, psychotherapy, relaxation, biofeedback, osteopathic or chiropractic manual treatments, transcutaneous electrical nerve stimulation, heat/cold application, occupational therapy, distraction, exercises, and stretching.[14]

When evaluating the patient's past medical history, look for illnesses that may affect the response to opioids, such as pulmonary disease, constipation, nausea, and cognitive impairment, and illnesses that may affect the metabolism of opioids, such as hepatic or renal disease.[2,13] Keep an eye out for illnesses that are possibly associated with substance abuse disorders; these include hepatitis, HIV infection, tuberculosis, cellulitis, sexually transmitted diseases, trauma/burns, cardiac disease, and pulmonary disease.

The Physical Examination

Of course, the physical examination is an essential part of the evaluation of pain and may help identify the cause of a patient's pain. The standard components of the examination include:

- General: vital signs, appearance, and pain behaviors
- Neurologic examination
- Musculoskeletal examination: inspection, gait and posture, range of motion, palpation, percussion, auscultation, and provocative maneuvers
- Cutaneous or trophic findings

The physical findings need to be considered in the context of the patient's history and the results of diagnostic tests that may be needed to evaluate the underlying pain condition.[15] These findings may help clarify whether the pain might be treated more effectively with nonopioid therapy.

Assessing the Patient's Risk of Abuse

Obtain a complete history of current and past substance use. Risk factors for opioid abuse include a history of use of controlled medications, alcohol, and tobacco; a history of sexual abuse; and a family history of substance abuse and psychiatric disorders. A personal or family history of alcohol or drug abuse appears to be the best predictor of drug abuse, misuse, or other aberrant drug-related behaviors in patients being treated with opioids.[16] Preadolescent sexual abuse is associated with an increased risk of opioid misuse in women. People who are 16 to 45 years of age are also at increased risk for opioid abuse.[17]

Social history is relevant to risk assessment and includes employment, cultural background, social network, marital history, legal history, and other behavioral patterns. Patients with an unstable or dysfunctional social environment require additional monitoring during treatment.[2]

A substance abuse history does not necessarily prohibit opioid therapy, but it does warrant additional monitoring and assistance from persons with expertise in managing pain, addiction, or other mental health concerns.[3] If the patient has a history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors, the prescriber must be experienced in the management of such patients and able to implement more frequent and stringent monitoring.[2] In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist.[2,18] Patients who meet the criteria for a substance abuse disorder should be referred for appropriate treatment.

A variety of self-administered and provider-administered screening tools are helpful for risk stratification.[2,17,19] Tools available to assess abuse potential include the Screener and Opioid Assessment for Patients with Pain (SOAPP); the Diagnosis, Intractability, Risk, Efficacy (DIRE) instrument; and the Opioid Risk Tool (ORT) (Table 3).[2,19,20] Many practices have a risk assessment tool in their electronic health record (EHR) system. If you are not already using one of these tools, check your EHR system to see if it has one in place.

Table 3. Examples of Risk Assessment Tools

Tool	Features
To evaluate risk in patients considered for opioid therapy	
Opioid Risk Tool (ORT)	Administered by patient Includes 5 items Assesses risk of aberrant drug-related behaviors May be better suited for primary care settings that have a predominantly low-risk population
Screener and Opioid Assessment for Patients with Pain (SOAPP)	Usually self-administered in waiting room or examination room or before an office visit; may be completed as part of an interview with a nurse, physician, or psychologist Includes 24, 14, and 5 items; 4 different formats available Assesses risk of aberrant drug-related behaviors May be particularly useful in high-risk settings
Diagnosis, Intractability, Risk, and Efficacy Score (DIRE)	Administered by clinician Includes 7 items Assesses potential efficacy as well as harms
To identify misuse once treatment begins	
Pain Medication Questionnaire (PMQ)	Administered by patient Includes 26 items Intended to identify the degree of medication

	misuse or the aberrant behavior that characterizes the patient's opioid use once he or she has been taking opioids for some time
Current Opioid Misuse Measure (COMM)	Administered by patient Includes 17 items Intended to identify the degree of medication misuse or the aberrant behavior that characterizes the patient's opioid use once he or she has been taking opioids for some time
Prescription Drug Use Questionnaire (PDUQ)	Administered by clinician Includes 40 items Intended to identify the degree of medication misuse or the aberrant behavior that characterizes the patient's opioid use once he or she has been taking opioids for some time

*From Substance Abuse and Mental Health Services Administration.[21]

Table 4. CDC Recommendations for Assessing and Addressing Risks of Opioid Use

- Before starting opioid therapy and periodically during treatment, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone in the presence of factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use.
- Clinicians should review the patient's history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy, ranging from every prescription to every 3 months.
- Clinicians should use UDT before prescribing opioid therapy and consider UDT at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
- Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
- Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for

patients with opioid use disorder.

CDC = Centers for Disease Control and Prevention; MME = morphine milligram equivalents; PDMP = prescription drug monitoring program; UDT = urine drug testing.
From the CDC.[1]

For practical guidance on risk assessment, tune in to this discussion by Drs Kate Galluzzi and Randy Hudspeth.

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It is important that prescribers of opioid analgesics understand what is meant by the terms "abuse," "misuse," and "aberrant behavior" and that they understand the distinction between "addiction" and "physical dependence."[12,13] Addiction is a chronic, relapsing disease characterized by chronic drug-seeking and use despite negative consequences and by long-lasting changes in the brain.[10] In contrast, physical dependence is a physiologic state that can occur with regular drug use (use to maintain normal activity levels) and results in withdrawal symptoms when drug use is abruptly discontinued.

Abuse is any intentional, nontherapeutic use of a drug product or substance for the purpose of achieving a desirable psychological or physiologic effect.[16] Misuse is the inappropriate use of a prescribed medication (use other than as directed); the definition of "misuse" excludes uses that meet the definition of "abuse."

Aberrant behaviors consist of a range of behaviors that suggest misuse by the patient and may indicate a substance use disorder.[3] Examples of aberrant behaviors include obtaining prescription drugs from nonmedical sources and prescription forgery.[3] Diversion is any intentional act that results in transferring a drug product from lawful to unlawful distribution or possession.

Special Patient Populations

Older Adults

When considering opioid therapy to manage pain in older patients, keep in mind that older persons may have medical problems that increase the risk of opioid-related adverse events (AEs), such as respiratory depression.[22] The risk of respiratory depression may be increased because of age-related changes in distribution, metabolism, and excretion. More cautious initiation and titration of opioid therapy are warranted in older persons, particularly those who are frail or have comorbidities. Patients should be monitored closely, especially when initiating and titrating therapy and when patients are taking other drugs that depress respiration, such as sedative/hypnotics or benzodiazepines.[2,22] The starting dosage should be reduced to one-third to one-half of the usual dosage in debilitated, non-opioid-tolerant (opioid-naive) patients, and the dose should be titrated cautiously ("start low and go slow").

Because of the potential for opioid-induced constipation, a bowel regimen should be routinely initiated in older patients treated with opioids.

Assess whether the patient or caregiver will be able to manage the opioid therapy responsibly. Emphasize that these medications have to be safeguarded from theft by and accidental exposure to others (eg, children, grandchildren, and pets).

Women With Childbearing Potential

It is important to know the reproductive plans and pregnancy status of your patients. Opioid exposure during pregnancy causes increased risk for the fetus.[2,10] The potential risks to the newborn include:

- Low birth weight
- Premature birth
- Hypoxic-ischemic brain injury
- Neonatal death
- Prolonged QT syndrome
- Neonatal opioid withdrawal syndrome

Because most women who become pregnant do not know they are pregnant in the first few weeks, all women of childbearing age should be considered at risk.[23] Counsel women of childbearing potential about the risks and benefits of opioid therapy during pregnancy and after delivery.[2,10] (At present, there are no adequate or well-controlled studies of opioids for pain in pregnancy.) Encourage minimal or no opioid use during pregnancy, unless potential benefits outweigh risks to the fetus. Refer pregnant women who are receiving opioid therapy to an obstetrician-gynecologist who is experienced in treating high-risk patients.

If chronic opioid therapy is used during pregnancy, anticipate and manage risks to the patient and newborn. If the patient is using opioids on a daily basis, consider prescribing methadone or buprenorphine.

Adolescents and Children

Immediate-release (IR) opioids should be used judiciously in pediatric patients. The safety and effectiveness of most ER/LA opioids in children younger than 18 years have not been established, and most of these agents are not indicated for children. An exception is transdermal fentanyl, which is approved in opioid-tolerant children aged 2 years and older. Also, note that dosing changes have been made for oxycodone ER for children 11 years and older.[24-27] Extrapolation of adult doses based on an "mg/kg" approach leads to overdosing in some pediatric populations and underdosing in others, due to age-related and developmental changes in pharmacokinetics.[24]

ER/LA opioids are primarily used in life-limiting conditions for pediatric patients. When prescribing ER/LA opioids to adolescents or children, consult a pediatric palliative care team or pediatric pain specialist or refer the patient to a specialized multidisciplinary pain clinic.

Initiating Therapy

When Should You Consider a Trial of an Opioid?

The decision to give the patient a trial of an opioid is based on many considerations, but the basic principles are to consider a trial when:

- The potential benefits are likely to outweigh the risks
- The patient has not adequately responded to nonopioid and nonpharmacologic interventions
- The patient's pain is moderate to severe

According to the CDC guidelines, nonpharmacologic therapy and nonopioid therapy (including complementary and alternative medicine) are preferred options for managing chronic pain. Clinicians should consider opioid therapy only if the benefits for pain and function are anticipated to outweigh the risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy as appropriate.[1] When opioids are being prescribed, the CDC recommends[1]:

- Begin with an IR opioid analgesic
- Prescribe the lowest effective dosage
- Use caution at any dosage, but particularly when increasing dosages to ≥50 MME/d, and carefully justify a decision to titrate dosages to ≥90 MME/d
- For acute pain, prescribe the lowest effective dose of IRs; prescribe no more than is needed
- Reevaluate risks and benefits within 1 to 4 weeks of initiation or dose escalation
- Reevaluate risks and benefits every 3 months; if benefits do not outweigh harms, optimize other therapies, work to taper, and discontinue

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Managing and Monitoring Therapy

Managing and Monitoring Therapy

Before starting a trial of opioid analgesic therapy, clinicians must inform patients about the potential risks and benefits of therapy and obtain informed consent to treat.[1,2] Clinicians also must discuss the goals of therapy, how opioids will be prescribed and taken, expectations for monitoring, alternative therapies, and indications for tapering or discontinuing therapy. Opioid

therapy should be continued only if there is a clinically meaningful improvement in pain and function that outweighs the risks to patient safety.[1,3]

The treatment goals should include realistic goals for pain and function. To avoid unrealistic patient expectations, explain to patients that total pain relief with opioid therapy is rare. Patients who do not understand this may accidentally overdose in an attempt to obtain an unrealistic degree of pain relief. Also explain to patients that an opioid analgesic is only one component of their management plan to reduce pain and improve functional capacity. Other components may include physical therapy, relaxation training, or behavioral health treatment. Multimodal management of persistent pain is an interdisciplinary approach that requires the patient's active participation and may require lifestyle changes.

Informed Consent

When initiating a trial of opioid analgesic therapy, the clinician must confirm the patient's understanding of informed consent, which includes the analgesic and functional goals of therapy, expectations, potential risks (abuse, addiction, respiratory depression, and overdose), and alternatives to opioid therapy. Informed consent should also cover the common AEs, such as constipation, nausea, and sedation, and the AEs associated with long-term therapy, such as hyperalgesia, low testosterone level, irregular menses, and sexual dysfunction.

The Patient-Prescriber Agreement

The patient-prescriber agreement (PPA) is a document that serves a number of purposes, such as clarifying the treatment plan and goals with the patient, the patient's family, and other clinicians involved in the patient's care. The PPA documents patient and prescriber responsibilities and supports patient education by, for example, reinforcing safe and appropriate opioid use. Examples of safe use practices include:

- There should be only 1 opioid prescriber
- The patient should consider using only 1 pharmacy
- The opioids should be kept in a locked place and should not be stored in a medicine cabinet
- The opioids should not be shared with others or sold
- The patient should be given instructions for disposal of the drug when it is no longer needed
- The prescriber should be notified of any event resulting in a pain medication prescription

The PPA also includes specifics about how the patient will be monitored, including the use of a UDT (urine drug test) and pill counts, prescription refills, behaviors that warrant discontinuing the drug, and the exit strategy. The PPA also clearly delineates the expected behaviors of both the patient and the prescriber. The PPA should be signed by both the patient and the prescriber when the opioid is prescribed.

Monitoring Patients During Therapy

Patients being treated with opioid analgesics must be routinely monitored for adherence to the treatment plan and for aberrant behaviors. Because patient self-report may be unreliable, consider using other strategies to supplement self-report, such as[2]:

- Querying state PDMPs
- Ordering a UDT to identify the presence of a nonprescribed drug or an illicit substance and to confirm the presence of the prescribed opioid
- Interviewing family members or caregivers
- Using monitoring tools, such as the COMM, Pain Assessment and Documentation Tool (PADT), Pain Medication Questionnaire, or PDUQ
- Using medication reconciliation (eg, pill counts)

The COMM is a monitoring tool that can help identify aberrant behaviors associated with the misuse of opioid medications.[28-31] The COMM is useful for documenting decisions about the level of monitoring needed for a particular patient because it can provide a basis on which to decide whether to request more frequent office visits, pill counts, UDT, or discontinuation of therapy; it also can be used to justify referrals to a specialty pain clinic.[29] The COMM results should be considered in combination with other clinical information when deciding whether a patient's treatment plan needs to be modified.

Aberrant drug-related behaviors that are particularly important to watch for include:

- Unsanctioned dose escalations or other nonadherence to therapy on 1 or 2 occasions
- Unapproved use of the drug to treat another symptom
- Openly acquiring similar drugs from other medical sources
- Multiple dose escalations or other nonadherence to therapy despite warnings
- Prescription forgery
- Obtaining prescription drugs from nonmedical sources

The presence of any of these behaviors should be taken seriously and may be a sign that opioid therapy should be discontinued.

It is also important to periodically reassess patients during therapy to evaluate their progress toward the goal of stable relief of pain and effective management of AEs.[1,2] Regular monitoring is critical because the risks and benefits can be affected by changes in the patient's underlying pain condition, coexisting disease, or psychological or social circumstances.[1,2] Monitoring can help identify patients who are benefiting from therapy; patients who might benefit more with restructuring of treatment or by receiving additional services, such as treatment for addiction; and patients in whom the benefits of treatment are outweighed by the harms.

The periodic assessment of the patient's continued need for opioid therapy includes reevaluating the underlying condition if the clinical presentation changes, such as when pain level decreases in stable patients. Documentation is essential, and the medical record for each encounter should specifically address comfort, function, AEs, and treatment adherence. Table 5 summarizes what should be assessed at every visit.

Table 5. What to Assess and Document at Every Visit

- Degree of pain control (including patient self-reported pain intensity, pattern, and effects)
- Functional status (level of functioning and progress toward achieving functional therapeutic goals)
- Health-related quality of life
- Opioid-related AEs (frequency and intensity, and response to any treatment)
- Adherence to the PPA and other aspects of treatment plan; may include UDT or querying state PDMPs
- Possible changes in the underlying medical condition

AE = adverse event; PDMP = prescription drug monitoring program; PPA = patient-prescriber agreement; UDT = urine drug testing.

Click here to listen to Drs Galluzzi and Hudspeth continue their discussion of patient-provider communication.

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Opioid-Associated AEs

Anticipating and promptly treating opioid-associated AEs will decrease the likelihood that patients will discontinue therapy because of intolerable AEs and may allow the use of higher doses, if needed, for uncontrolled pain (Table 6).[2]

Table 6. Possible Opioid AEs

- Respiratory depression -- most serious
- OIC -- most common
- Sedation, cognitive impairment
- Falls and fractures
- Sweating, miosis, urinary retention
- Hypogonadism
- Tolerance, physical dependence, hyperalgesia
- Addiction in vulnerable patients

OIC = opioid-induced constipation.

Respiratory depression is the most serious AE of opioid therapy.[3] If respiratory depression is not immediately recognized and treated, it may lead to respiratory arrest and death. Instruct patients and their families to call 911 if they see any of the signs of respiratory depression (reduced respiratory rate, shallow breathing). The risk of respiratory depression is greatest when opioid therapy is being initiated or the dosage has been increased. It is more likely to occur in patients who are elderly, cachectic, or debilitated and in patients who are taking other drugs that

can cause respiratory depression.[2,3] Strategies for reducing the risk of respiratory depression include:

- Proper dosing and titration; do not overestimate the dose when converting from another opioid product (that can result in fatal overdose with the first dose)
- Instruct patients to swallow tablets/capsules whole; taking cut, crushed, dissolved, or chewed tablets/capsules may be fatal, particularly in opioid-naive individuals

Constipation is the most common AE associated with opioids.[2,3] Most patients have some degree of constipation after the initiation of therapy or an increase in dosage, and it is not likely to resolve during therapy. In older adults or other patients at risk for constipation, consider initiation of a bowel regimen before the development of constipation. Bowel regimens, including increased fluid and fiber intake, stool softeners, and laxatives, are often effective. Peripherally acting μ-opioid receptor antagonists may be needed to help prevent or treat opioid-induced bowel dysfunction.

Nausea and vomiting are common AEs that tend to diminish over days or weeks of continued opioid exposure.[2] Oral and rectal antiemetic therapies are available for treatment.

Somnolence, clouded mentation, decreased concentration, and slower reflexes or incoordination are common and are especially likely to occur when therapy is initiated or the dosage is increased.[2] Patients should be counseled about driving and about work and home safety when initiating opioid therapy or changing doses. Patients should not drive or engage in potentially dangerous activities if they show signs of impairment.[2] Patients may be at risk for falls and fractures. In addition, patients should be counseled on the effects and risks of concomitant exposure to other drugs and substances with sedating effects, including alcohol.

Long-term use of opioids has been associated with hypogonadism and decreased levels of dehydroepiandrosterone sulfate.[2] Patients should be tested for such hormonal deficiencies if they report symptoms consistent with these effects, such as decreased libido, sexual dysfunction, or fatigue. Other common AEs include pruritus and myoclonus.[2] Patients also may experience headache, dry mouth, asthenia, and sweating. Pruritus, erythema, and rash at the application site have been reported with transdermal buprenorphine and fentanyl products.[3] As already noted, tolerance, physical dependence, hyperalgesia, and addiction are potential opioid-related AEs.

Prescribers should report serious AEs to the FDA.

When to Consider Switching From an IR to an ER/LA Opioid

ER/LA opioids are a therapeutic option for patients with persistent pain that is severe and is adversely affecting the patient's functioning or quality of life and has failed to adequately respond to appropriate nonopioid therapies.[2,3] Prescribers may consider a therapeutic trial when potential benefits are likely to outweigh risks and when no alternative therapy is likely to pose as favorable a balance of benefits to harms. Although there are significant risks with opioids in general, the risks are magnified with the use of ER/LA opioids.[3] The main reasons for considering an ER/LA opioid are:

- To maintain stable blood levels (steady state plasma)
- To provide a longer duration of action
- When multiple IR doses are needed to achieve effective analgesia
- When there is poor analgesic efficacy despite dose titration
- To achieve less sleep disruption

Other potential reasons for switching from an IR to an ER/LA opioid include:

- Patient desire or need to try a new formulation
- Cost or insurance issues
- Adherence issues
- Change in clinical status that requires an opioid with different pharmacokinetics
- Problematic drug-drug interactions

Contraindications to ER/LA opioid therapy include:

- Significant respiratory depression
- Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (eg, anaphylaxis)

See the individual product information for additional contraindications.

When considering prescribing an ER/LA opioid, remember that specific drug selection and dosage are critical. Some ER/LA opioids or dosage forms are recommended only for opioid-tolerant patients; this includes any strength of transdermal fentanyl or hydromorphone ER and certain strengths or doses of other ER/LA products. It is vital that prescribers check the prescribing information (PI) for the specific drug they are considering. In patients who have modest previous opioid exposure but are not opioid tolerant, individualize the dosing based on the patient's previous treatment experience, and titrate as needed to provide adequate analgesia and minimize AEs. The goal of optimal opioid titration for a stable chronic pain condition is to find, incrementally, the lowest effective dose that achieves a satisfactory balance between benefits and harm.

Carefully monitor the patient for respiratory depression, especially within 24 to 72 hours of initiating therapy and increasing dosage. Keep in mind that respiratory depression can occur even when an ER/LA opioid is used as recommended.

Individualize the dosage by titration based on efficacy, tolerability, and the presence of AEs. Therapy is considered effective when the patient reports improvement in pain relief and function, with minimal or acceptable AEs. Careful upward dosage titration is necessary to minimize toxicity, to allow sufficient time for the patient to develop tolerance to opioid AEs, and to find the optimal dose. A too-rapid upward titration may exceed the patient's level of opioid tolerance and lead to serious complications, such as respiratory depression.

Check the ER/LA opioid's PI for minimum titration intervals. If pain is not controlled while titrating the ER/LA opioid dose, pain management can be supplemented with IR analgesics (opioid and/or nonopioid).[2,3]

When considering prescribing an ER/LA opioid, keep in mind the following points:

- ER/LA opioid analgesics should not be given to opioid-naive patients or patients who have not been given an adequate trial of nonopioid and nonpharmacologic therapies. ER/LA opioid analgesics should be prescribed only to selected patients who have been taking an IR opioid for pain management
- It is essential that prescribers understand the difference between IR and ER/LA opioids. ER opioids provide a longer period of drug release, so they can be taken less frequently than IR opioids, which work for a shorter period. ER opioids are designed to allow a controlled release of active agent to provide relatively consistent and prolonged plasma drug levels with lower maximal concentration and fewer peak-to-trough fluctuations.[32] The time to peak blood concentration level is longer with ER opioids than with IR opioids. LA opioids have a longer duration of action because of unique characteristics of the drug substance, which stays in the body longer. Because the ER products are designed to release the drug over a longer period, they tend to contain a much larger amount of the opioid analgesic than do the IR opioids. This is one of the reasons that ER/LA opioids are potentially more dangerous[2,3,32]
- ER/LA prescription opioid analgesics are μ-opioid agonists and schedule II or schedule III drugs (in the case of transdermal buprenorphine) and controlled substances with abuse liabilities similar to other opioid agonists.[3] Before starting a trial of ER/LA opioid analgesic therapy, clinicians must inform patients about the potential risks and benefits of therapy and obtain informed consent to treat[2]
- The initial therapeutic trial of an ER/LA opioid may last from several weeks to several months.[2,3] The decision to proceed with long-term therapy should be based on careful consideration of outcomes during the trial. Outcomes to consider include progress toward meeting therapeutic goals (reduced pain severity and improved functional ability), presence of AEs, changes in the underlying pain condition, changes in psychiatric or medical comorbidities, and the identification of aberrant drug-related behaviors
- For patients at low risk for adverse outcomes who are stable while taking doses of ER/LA opioids, monitoring at least once every 3 to 6 months may be sufficient. Schedule follow-up visits at least every 2 to 4 weeks after any change in medication regimen. Patients who require relatively high doses of ER/LA opioids may need more frequent follow-up visits.[2] They should be regularly evaluated for unique opioid-related AEs, changes in health status, and treatment adherence. Also evaluate potential causes of the need for higher dosages and reassess the relative benefits and harms. Other patients who may need more frequent or intense monitoring include patients with a history of addiction, those with comorbid psychiatric or medical conditions, and older adults. For patients at very high risk for adverse outcomes, monitoring on a weekly basis may be appropriate

Opioid Tolerance

Tolerance to the sedating and respiratory-depressant effects is critical to the safe use of certain products and dosage unit strengths. Patients considered to be opioid tolerant are patients who are taking at least 1 of the following products and doses for 1 week or longer[1-3]:

- 60 mg oral morphine per day
- 25 µg transdermal fentanyl per hour
- 30 mg oral oxycodone per day
- 8 mg oral hydromorphone per day
- 25 mg oral oxymorphone per day
- An equianalgesic dose of another opioid

Opioid Rotation

Some patients may have poor opioid responsiveness characterized by inadequate analgesic efficacy despite aggressive dose titration or may have intolerable AEs during dose titration. In this setting, opioid rotation (changing the specific opioid or the route of administration) may help improve analgesic efficacy and reduce AEs.[33-35] In some cases, a change in the patient's clinical status or clinical setting suggests that the patient may benefit from an opioid with different pharmacokinetic properties.

Opioid rotation involves the principle of incomplete cross-tolerance to the effects of one opioid versus another. Patients may respond differently to one opioid than to another with respect to analgesic effect and AEs, partly because of the presence of multiple different µ-opioid peptide receptors (polymorphism).[2,35] A patient who has developed tolerance to one opioid may experience enhanced analgesia with an opioid that binds to different µ-receptors and may have improved analgesia at a dose lower than that calculated by using an equianalgesic dosing table.

One of the challenges in safely and effectively rotating from one opioid to another is that the new opioid must be started at a dosage that will not cause toxicity or withdrawal symptoms but will provide sufficient analgesia.[34] Opioid rotation requires the calculation of an approximate equianalgesic dose between the current and the new opioids. When switching opioids in an opioid-tolerant patient, the dosage of the second drug is often calculated by using an equianalgesic dosing table and decreasing that dose by 25% to 50% to allow for the possible enhanced analgesia and to avoid AEs due to incomplete cross-tolerance. An example of one of these tables is shown in Table 7.

Table 7. Example of an Equianalgesic Dosing Table

	Equianalgesic Dose		Usual Starting Dosage	
Drug	**SC/IV**	**PO**	**Parenteral**	**PO**
Morphine	10 mg	30 mg	2.5-5 mg SC/IV q3-4h (1.25-2.5 mg)	5-15 mg q3-4h (IR or oral solution) (2.5-7.5 mg)
Oxycodone	N/A	20 mg	NA	5-10 mg q3-4h

				(2.5 mg)
Hydrocodone	N/A	30 mg	N/A	5 mg q3-4h (2.5 mg)
Hydromorphone	1.5 mg	7.5 mg	0.2-0.6 mg SC/IV q2-3h (0.2 mg)	1-2 mg q3-4h (0.5-1 mg)

IV = intravenous; N/A = not applicable; PO = oral; SC = subcutaneous; q2-3h = every 2 to 3 hours; q3-4h = every 3 to 4 hours.

Many different versions of equianalgesic dosing tables are available to help calculate the new starting dosage.[36-39] Keep in mind that these different versions vary with respect to equianalgesic values, whether ranges are used, and which opioids are included (they may or may not include transdermal opioids, rapid-onset fentanyl, ER/LA opioids, or opioid agonist-antagonists). It is also important to be aware that there are limitations with the use of equianalgesic dosing tables.[34]

When using an equianalgesic dosing table, remember that:

- Incomplete cross-tolerance and interpatient variability require the use of conservative dosing when converting from one opioid to another
- The equianalgesic dose is a starting point for opioid rotation and is meant to be a general guide
- The calculated dosage of the new drug from the table must be reduced, then titrated as needed
- The patient should be closely followed during periods of dose adjustment
- The conversion instructions in the individual ER/LA opioid PI (when available) should be followed

Here are the basic steps: calculate the equianalgesic dosage of the new opioid based on the equianalgesic table.[33] Reduce the calculated equianalgesic dosage by 25% to 50% (75% to 90% reduction for methadone). Select the dose reduction based on clinical judgment after assessing the patient. The reduction should be closer to 50% if the patient is receiving a relatively high dose of the current opioid or if the patient is elderly or frail. Otherwise, the reduction should be closer to 25%. The dose reduction also should be closer to 25% if the patient is switching to a different route of administration of the same drug.

Standard equianalgesic dosing tables are less helpful in opioid rotation to methadone. If switching to methadone, the automatic dose reduction window should be 75% to 90% lower than the calculated equianalgesic dosage, because of evidence of higher-than-anticipated potency when switching to methadone. In opioid-tolerant patients, methadone dosages should not exceed 30 to 40 mg/d on rotation. Consider inpatient monitoring, including serial electrocardiography. In opioid-naive patients, methadone should not be given as initial drug therapy.

- **Fentanyl:** calculate dose conversion based on equianalgesic dose ratios included in the PI
- **Buprenorphine:** follow instructions in the PI

If switching to transdermal fentanyl, calculate dose conversions based on the equianalgesic dose ratios in the PI. If switching to buprenorphine, follow the instructions in the PI for conversion from other opioids.

To decide whether an additional reduction is necessary, prescribers should still take into account the daily dose, potency, and characteristics of the opioid the patient has been taking; the degree of opioid tolerance; and the medical status of the patient. After the initial conversion, prescribers should have a strategy in place to frequently assess initial response, including analgesia, AEs, and withdrawal symptoms, and titrate the dosage of the new opioid to optimize outcomes and safety. The times required to reach steady-state plasma concentrations are product specific. Refer to the ER/LA opioid PI for minimal titration intervals.

The following case scenario illustrates rotation from an IR opioid to an ER/LA opioid.

Michael is a 72-year-old man with severe chronic shoulder pain resulting from trauma related to a car accident. His pain often disrupts his sleep. He is currently receiving IR oxycodone 5 mg every 6 hours and 1 extra dose at bedtime. Because his pain is not well controlled and disrupts his sleep and because he complains about having to take so many pills, his clinician considers rotating to an ER/LA opioid.

Michael is reluctant to take morphine or methadone. He cannot take hydromorphone ER or transdermal fentanyl because his current regimen of oxycodone 25 mg/d does not meet the criteria for opioid tolerance. His clinician decides to rotate treatment to oxymorphone ER. The equianalgesic table that the clinician uses indicates that the equianalgesic dose for oral oxycodone is 20 mg and the equianalgesic dose for oral oxymorphone is 10 mg. Knowing that the patient's current regimen is 25 mg/d, the clinician calculates the equianalgesic 24-hour dose for the new opioid to be 12.5 mg.

For safety, the calculated dose should be reduced by 25% to 50%. Because Michael was taking a low dose of oxycodone, a 25% reduction is reasonable. The calculated dose of 12.5 mg is reduced by 25%, which equals 9.4 mg. This can be rounded up to 10 mg, given as 5 mg every 12 hours.

Michael's clinician initiates oxymorphone ER at 5 mg every 12 hours, with IR oxycodone 5 mg as needed for breakthrough pain.

Managing Breakthrough Pain

If a patient taking an around-the-clock opioid experiences breakthrough pain, this can be managed with an IR opioid. The dose for the IR opioid is 5% to 15% of the total daily opioid dose, administered at an appropriate interval. It is never appropriate to use an ER/LA opioid to manage breakthrough pain.

Consider a trial of an IR opioid taken as needed based on assessment of the benefits versus risks. For patients at high risk of aberrant drug-related behaviors, a trial must be in conjunction with frequent monitoring and follow-up. For patients at low risk, routine monitoring and follow-up

are appropriate. Also consider nonopioid therapies and nonpharmacologic treatments to manage breakthrough pain.

The management of treatment-refractory pain in patients taking high doses of ER/LA opioids is challenging. Although progressively higher doses may improve symptom control in some patients, repeated dose escalations can be a marker for a substance use disorder or diversion. Many experts agree that a reasonable definition of high-dose therapy is more than 200 mg of oral morphine (or equivalent) per day.[2] When doses reach 200 mg of morphine (or equivalent) per day, more frequent and intense monitoring is often needed. Treatment may require restructuring, such as including tapering or discontinuation, if assessment indicates a reduction in analgesia, function, or quality of life; the presence of aberrant drug-related behaviors; or intolerable AEs.

Urine Drug Testing

UDT can help identify drug misuse or addiction before starting treatment with controlled substances. UDT is commonly included in a written PPA as a requirement of opioid therapy to help monitor adherence to the treatment plan, as well as to identify misuse and diversion.[2,40-43] UDT should be completed and discussed with the patient before the first opioid prescription is given. The frequency of testing should be based on clinical judgment of the patient's risk.[42] UDT can be performed randomly to monitor treatment, before renewing prescriptions, or more frequently if the patient exhibits aberrant behavior or if diversion of prescribed medications is suspected.[44]

Because some patients are offended by the suggestion that they undergo UDT, it may be helpful when discussing UDT with patients to emphasize that this testing is done “for” and not “to” the patient.

UDT can be done via immunoassay drug panels, gas chromatography-mass spectrometry, or liquid chromatography-mass spectrometry. Immunoassay drug panels, which can be either laboratory based or point of care, identify substances as present or absent according to cutoff values. Many test methods do not identify individual drugs within a class and are subject to cross-reactivity and variability. Gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry identify the presence and quantity of substance(s) and identify drugs not included in immunoassays. These test methods can be used when UDT results are contested.[45]

Interpretation of UDT results is challenging and requires an understanding of opioid drug metabolism and pharmacokinetics and limitations of testing methods.[2,42] UDT results usually do not suggest a definitive course of action but should be interpreted in the context of individual patient circumstances (Table 8). If the results are abnormal, consider the other possible causes of abnormal UDT results, including drug abuse or addiction, self-treatment of poorly controlled pain, psychological issues, and diversion.[2,42]

Table 8. What UDT Results Can and Cannot Demonstrate

	Positive Result

- Demonstrates recent use:
    - Most drugs in the urine have detection times of 1 to 3 days
    - Long-term use of lipid-soluble drugs: test positive for ≥1 week
- Does not diagnose addiction, physical dependence, or impairment
- Does not provide sufficient information to determine exposure time, dose, or frequency of use

Negative Result

- Does not prove diversion (more complex than just the presence or absence of drug in the urine)
- May be the result of
    - Maladaptive drug-taking behavior, eg, bingeing, running out of a prescription early
    - Other factors, such as cessation of insurance or financial problems

UDT results that are not consistent with the history gathered from the patient are useful to support a decision to refer a patient to a specialist, such as a pain management specialist who is knowledgeable in addiction medicine or an addiction specialist.[43,44] Unexpected positive results for misused or nonprescribed drugs warrant further evaluation, but a positive result is not diagnostic of addiction, a substance use disorder, or current impairment.[41,42,46,47] The positive result should not be ignored and may indicate a need for closer monitoring and/or possible referral to a specialist in substance misuse.[47] Positive results do not usually provide sufficient information to determine the exposure time, dose, or frequency of use.[44,49-50]

An inappropriately negative UDT result may indicate drug diversion but also may occur secondary to maladaptive drug-taking behavior, such as bingeing, running out of the prescribed controlled substance early, and multiple other factors (eg, cessation of insurance coverage, monetary difficulties).[44,50] Clinicians should discuss unexpected results with the patient to determine the "motive" behind the behavior.

Clinicians should be aware of the time taken for drugs to be absorbed and eliminated from the body. Knowing the time of last use and the quantity of drug(s) taken can be helpful in interpreting UDT results. Opioid metabolism may explain the presence of apparently nonprescribed drugs; therefore, clinicians ordering UDT should be aware of metabolites for the drugs they prescribed. Opioid metabolism is an additional consideration in UDT (Table 9).

Table 9. Noteworthy Points About Opioid Metabolism

- Codeine is metabolized to morphine, so both substances can occur in urine after codeine use:
    - A prescription for codeine may explain the presence of both drugs in the urine
    - A prescription for codeine does not normally explain the presence of only morphine; this is most consistent with the use of morphine or heroin
    - Prescribed morphine cannot account for the presence of codeine

    - Codeine metabolizes to morphine, but the reverse does not occur
    - Codeine alone is possible because a small proportion of patients lack the necessary activity of the CYP2D6 enzymatic pathway to convert codeine to morphine[51]
- Morphine may be metabolized to produce small amounts (generally less than 10%) of hydromorphone[52-58]
- Hydrocodone may be metabolized to small quantities of hydromorphone[59]
- Metabolism of codeine may produce small quantities of hydrocodone[60]
- Oxycodone is metabolized by CYP3A4 to noroxycodone and by CYP2D6 to oxymorphone[61,62]
    - If the urine of a patient prescribed oxycodone tests positive for oxymorphone, a quantitative analysis should confirm -- in most cases -- that the relative concentration of oxycodone is greater than that of oxymorphone[61]
    - Test results for patients prescribed oxymorphone are easier to interpret because oxymorphone does not produce any metabolites that can be mistaken for another opioid (although oxymorphone tablets may contain up to 1% oxycodone as a manufacturing byproduct, which should generally not be detectable with UDT)[61]

CYP = cytochrome P450.

Discontinuing Opioid Therapy

There are several situations in which opioid therapy should be discontinued, for example[2,3]:

- The problem requiring opioid therapy is resolving and the patient no longer requires opioids
- No progress has been made in reaching the therapeutic goals despite adequate titration and opioid rotation (if indicated); in this situation, further investigation is warranted to attempt to identify the reason for the lack of progress
- The patient has intolerable AEs that cannot be resolved despite maximal attempts to mitigate them or rotation to another opioid (if indicated)
- The patient is exhibiting repeated aberrant drug-related behaviors suggestive of drug abuse/addiction or diversion, such as[62-65]:
    - Use of illicit drugs or use of nonprescribed opioids
    - Repeatedly obtaining opioids from multiple outside sources
    - Prescription forgery
    - Multiple episodes of prescription loss
    - Diversion
- The patient demonstrates serious nonadherence to the treatment plan or unsafe behaviors, such as:
    - One or more episodes of unauthorized dose increase without the prescriber's knowledge
    - Unapproved opioid use to treat another symptom (eg, insomnia)
    - Sharing medications

If you detect any signs of nonadherence or aberrant drug-related behavior, a reevaluation of the patient's treatment is clearly warranted, and it may be necessary to change therapy. How to respond to aberrant drug-related behavior is based on clinical judgment about the seriousness of the behavior, its cause(s), the likelihood that it will recur, and the clinical context. Patient education and enhanced monitoring may be sufficient if the patient is not considered to be at high risk and his or her behavior is not serious -- for example, 1 or 2 episodes of unauthorized opioid escalation. Summarily discharging a patient because of a single behavior is not recommended.[61]

Patients who are repeatedly nonadherent or engage in more serious aberrant behaviors (eg, obtaining opioids from outside sources) probably require consultation or referral, major restructuring of therapy, or, in many cases, discontinuation of opioid therapy. Restructuring of therapy may include more frequent or intense monitoring, tapering of opioid doses, or the addition of psychological therapies or other nonopioid treatments.[2]

In patients with opioid addiction who require ongoing pain treatment and do not respond to nonopioid analgesic interventions, structured opioid agonist treatment with methadone or buprenorphine through a licensed program may be appropriate. If illegal behaviors are clearly involved (eg, the patient is known to be diverting opioids) or the patient is engaging in seriously aberrant behaviors (eg, injecting an oral formulation), opioid prescribing should stop immediately and withdrawal should be addressed.[2]

Patients who demonstrate behaviors suggesting addiction or substance abuse should be referred for treatment.[2] Resources include:

- Substance Abuse and Mental Health Service Administration (SAMHSA) substance abuse treatment facility locator
- SAMSA Mental Health Facility Locator

High-risk patients and those with complex conditions and/or multiple comorbidities, including other psychiatric disorders, should be referred to an addiction specialist.[1-3] Check your state requirements for pain management referral.

Patients whose opioid therapy is to be discontinued may require referral or consultation for assistance with opioid detoxification and management of withdrawal. To minimize withdrawal symptoms in an opioid-dependent patient, consider medications to assist with withdrawal. The process of tapering the dose while discontinuing therapy may involve a range of approaches from a slow 10% dose reduction per week to a more rapid 25% to 50% reduction every few days. If the patient has an opioid use disorder or a failed taper, refer to an addiction specialist or consider opioid agonist therapy.

For more information about tapering the ER/LA opioid dose when discontinuing therapy, see the Additional Resources section.

Know Your Federal and State Laws

Opioid prescribers must comply with federal and state laws and regulations that govern the use of opioid therapy for pain. Federal laws include:

- Code of Federal Regulations, Title 21 Section 1306: rules governing the issuance and filling of prescriptions pursuant to section 309 of the act (21 USC 829)
- United States Code (USC) -- Controlled Substances Act, Title 21, Section 829: prescriptions

Regarding state laws, consider consulting a database of state statutes, regulations, and policies for pain management.

Prescription Drug Monitoring Programs

PDMPs can provide a full accounting of prescriptions filled by a patient -- in particular, a record of the patient's controlled substance prescriptions. PDMPs can alert you to warning signs of potential misuse/abuse, such as:

- Existing prescriptions that are not reported by the patient
- Use of multiple prescribers and/or pharmacies
- Use of drugs that increase overdose risk when taken together
- The patient pays with cash (vs insurance) for controlled medications

Keep in mind that not all federally licensed facilities report to PDMPs. Individual state laws determine the following (http://www.namsdl.org/prescription-monitoring-programs.cfm):

- Who has access to PDMP information
- Which drug schedules are monitored
- Which agency administers the PDMP
- Whether prescribers are required to register with the PDMP
- Whether prescribers are required to access PDMP information in certain circumstances
- Whether unsolicited PDMP reports are sent to prescribers
- Bordering states may be available
- Designated surrogates may have access

Many states have moved to automated Web-based systems that make prescription history reports available at any time to authorized users, to readily alert them to signs of aberrant drug-procurement behavior.[44,66-68] Obtaining prescriptions from multiple prescribers is a red flag for the risk of overdose. A PDMP may also identify patients who are receiving multiple legitimate prescriptions for opioids or benzodiazepines and therefore are at increased risk for overdose or respiratory depression.[67] The method of payment, in particular cash transactions, can suggest questionable activity such as "doctor shopping."[68]

The information provided by a PDMP can provide an opportunity to discuss potential misuse or abuse with patients. The goal is patient safety and to get patients the treatment they need if they have a substance abuse problem.

Counseling Patients and Caregivers

The Patient Counseling Document

Counseling patients and caregivers is crucial to ensuring the safe use of opioids and is an ongoing responsibility that needs to be reinforced throughout treatment. A patient counseling document (PCD) on ER/LA opioids contains important safety information and is designed to facilitate discussions with your patients.[3] Be sure to review the PCD with the patient and/or the patient's caregiver at the time of prescribing. A copy of the PCD can be found in the Additional Resources section.

Counsel Patients About Proper Use

Clinicians should counsel patients and/or their caregivers every time an opioid analgesic is prescribed. Information that clinicians should explain to patients and their caregivers includes product-specific information about the IR or ER/LA opioid (especially when converting), how to take the opioid as prescribed, the importance of adherence to the dosing regimen, and how to handle missed doses.

In addition, clinicians should instruct patients and/or caregivers to read the specific opioid analgesic medication guide they receive from the pharmacy, contact their prescriber if the pain is not controlled, inform their prescriber about all medications being taken, call their prescriber for information about managing AEs and inform the prescriber about AEs, and store the opioid in a safe and secure place such as a locked container (away from children, family members, visitors, and pets and safe from theft). Clinicians should explain the risk of falls, working with heavy machinery, and driving; warn patients not to abruptly discontinue or reduce the opioid dose; explain that patients will be periodically assessed for benefits, AEs, and continued need for IR/ER/LA opioids; and explain that sharing or selling opioids can lead to the deaths of others and is against the law.

Because it is crucial to the safe use of opioids, patients must understand the importance of taking their medication only as directed. Be sure to warn patients of the following[1,3]:

- Under no circumstances should an oral ER/LA opioid analgesic be broken, chewed, crushed, or snorted and patches should not be cut or torn before use, because this may lead to rapid release of the ER/LA opioid, causing overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube
- Avoid hot tubs, hot baths and showers, and working or exercising in high temperatures because all of these situations can result in quicker absorption of a patch (transdermal) product
- The use of other central nervous system (CNS) depressants, such as sedative-hypnotics and anxiolytics, alcohol, or illegal drugs, with opioid analgesics can cause overdose and death

- Use other CNS depressants, including other opioids, only under the instruction of the prescriber

Warn patients and caregivers that opioids can cause death even when taken properly.[1,3] Patients and caregivers should be counseled regarding the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.

In case of possible opioid poisoning, caregivers should call 911 if:

- The patient cannot be aroused or awakened or is unable to talk
- The patient has any trouble with breathing; heavy snoring is a warning sign
- There are gurgling noises coming from the patient's mouth or throat
- The patient's body is limp, and he or she seems lifeless; the face is pale, clammy
- The patient's fingernails or lips turn blue/purple
- The patient has a slow or unusual heartbeat or no heartbeat

When to Consider Prescribing Naloxone

Naloxone is an opioid antagonist that reverses acute opioid-induced respiratory depression. It also reverses analgesia. Naloxone can be used as an antidote to acute opioid toxicity. Candidates for naloxone include patients who:

- Are taking high doses of opioids
- Are taking opioid preparations that may increase risk for overdose, such as ER/LA opioids
- Are undergoing opioid rotation
- Have been discharged from emergency medical care after opioid intoxication/poisoning
- Have a legitimate medical need for analgesia, coupled with suspected/confirmed substance abuse

Naloxone can be administered via injection, intranasally, or intravenously. Consider offering a naloxone prescription to all patients prescribed IR and ER/LA opioids. When prescribing naloxone, instruct patients to use it in the event of a known or suspected overdose and to also call an emergency medical services system. Discuss an “overdose plan,” and involve and train family, friends, partners, and/or caregivers. Patients should check expiration dates and keep a viable dose on hand.[69]

Prescription Drug Disposal

The FDA and the Drug Enforcement Administration (DEA) have provided guidance for consumers regarding the proper disposal of prescription drugs.[70,71] The new “disposal act” expands ways for patients to dispose of unwanted or expired opioids. The act is intended to decrease the amount of opioids introduced into the environment, particularly into the water supply. One option is to use collection receptacles. To find a local collection receptacle, call the DEA Registration Call Center at 1-800-882-9539. Mail-back packages can be obtained from authorized collectors. Authorized collectors include manufacturers, distributors, reverse

distributors, and retail or hospital/clinic pharmacies (including long-term care facilities). Another option may be local take-back events, which are conducted by federal, state, tribal, or local law enforcement agencies.

If collection receptacles, mail-back programs, and take-back events are not available, opioids should be discarded in the household trash. This involves taking the drugs out of their original containers and removing any identifying information on the label, mixing with an undesirable substance, and placing in a sealable bag, can, or other container.

The FDA's prescription drug disposal recommendations are to flush medications down the sink or toilet as soon as they are no longer needed. This includes transdermal adhesive skin patches, which should be disposed of immediately after removal from the skin; used patches (after 3 days) still contain enough opioid to harm or kill a child. The patch should be folded in half so the sticky sides meet and then flushed down the toilet. Used or unneeded patches should not be placed in the household trash. Exceptions are the butrans (buprenorphine transdermal system), which can be sealed in the patch-disposal unit provided and disposed of in the trash.

Take-Home Points and General Drug Information

Key Take-Home Points

As described in parts 1 and 2 of this activity, the safe and effective use of opioid analgesics requires that prescribers follow several essential steps, including a thorough patient assessment, appropriate initiation and monitoring of therapy, and patient counseling that is specifically tailored to the use of these drugs. Before initiating the use of any opioid, clinicians should identify the cause of a patient's pain through careful history and physical examination to help select appropriate treatment. A validated screening tool for the risk of opioid abuse or addiction should be used to assist in patient selection. Before prescribing opioid therapy, clinicians must assure themselves that the potential benefits are likely to outweigh the risks and that no alternative therapy is likely to pose as favorable a balance of benefits to harms.

Although it is unrealistic to expect prescribers to retain in-depth knowledge about every available opioid product, they must be experts about the ones they do choose to prescribe. Necessary information to know includes:

- The drug substance and formulation
- Its relative strength or potency to morphine
- The recommended dosing interval
- Drug interactions
- Product-specific safety concerns

Prescribers should also understand the instructions for use and be knowledgeable about AEs and how to mitigate them and understand specific information on how to rotate to another opioid, when needed, by using equianalgesic dosing. Be sure to reinforce with patients the importance of safe storage and safe disposal of opioids.

Safe prescribing of opioids requires up-to-date understanding of drug interactions, pharmacokinetics, and pharmacodynamics. Key points to understand include the following[3]:

- CNS depressants can potentiate sedation and respiratory depression
- Use with monoamine oxidase inhibitors (MAOIs) may increase respiratory depression; certain opioids combined with MAOIs can cause serotonin syndrome
- Methadone and buprenorphine can prolong the QTc interval
- Some ER/LA products rapidly release opioid ("dose dump") when exposed to alcohol
- Some drug levels may increase without dose dumping
- Opioids can reduce the efficacy of diuretics, inducing release of antidiuretic hormone
- Drugs that inhibit or induce CYP enzymes can increase or lower blood levels of some opioids

Remember that is crucial to be aware of the red flags that point to possible opioid misuse, abuse, or addiction. ***For specific examples, tune in to Drs Galluzzi and Hudspeth's discussion of red flags.***

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Remember, ER/LA therapy should be reserved for patients whose pain:

- Is persistent and SEVERE
- Fails to respond to nonopioid and other interventions
- Requires around-the-clock therapy for an extended period

General Drug Information

Products Covered by the REMS For ER/LA Opioid Analgesics are listed next.

Brand Name Products

Arymo® ER	morphine sulfate ER tablets
Belbuca®	buprenorphine buccal film
Butrans®	buprenorphine transdermal system
Dolophine®	methadone hydrochloride tablets
Duragesic®	fentanyl transdermal system
Embeda®	morphine sulfate/naltrexone ER capsules
Exalgo®	hydromorphone hydrochloride ER tablets

Hysingla® ER	hydrocodone bitartrate ER tablets
Kadian®	morphine sulfate ER capsules
MorphaBond®	morphine sulfate ER tablets
MS Contin®	morphine sulfate CR tablets
Nucynta® ER	tapentadol ER tablets
Opana® ER	oxymorphone hydrochloride ER tablets
OxyContin®	oxycodone hydrochloride CR tablets
Targiniq™ ER	oxycodone hydrochloride/naloxone hydrochloride ER tablets
Troxyca® ER	oxycodone hydrochloride/naltrexone capsules
Vantrela™ ER	hydrocodone bitartrate ER tablets
Xtampza® ER	oxycodone ER capsules
Zohydro®	hydrocodone bitartrate ER capsules

Generic Products

Fentanyl ER transdermal systems
Methadone hydrochloride tablets
Methadone hydrochloride oral concentrate
Methadone hydrochloride oral solution
Morphine sulfate ER tablets
Morphine sulfate ER capsules
Oxycodone hydrochloride ER tablets

Key points to remember about transdermal/transmucosal dosage formulations are as follows[1,3]:

- Do not cut, damage, chew, or swallow the opioid product
- Exertion or exposure to external heat can lead to fatal overdose
- The location of application should be rotated
- Prepare the skin: clip (not shave) hair and wash area with water
- Monitor patients with fever for signs or symptoms of increased opioid exposure
- Metal foil backings are not safe for use in magnetic resonance imaging
- For buccal film products, the film should not be applied if it is cut, damaged, or changed in anyway -- use the entire film

Drug interactions common to ER/LA opioids include the following[3]:

- Concurrent use with other CNS depressants can increase the risk of respiratory depression, hypotension, profound sedation, or coma; reduce the initial dose of one or both agents
- Avoid concurrent use of partial agonists (buprenorphine) or mixed opioid agonist/antagonists (pentazocine, nalbuphine, butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist; in these patients, mixed

opioid agonists/antagonists and partial opioid antagonists may reduce the analgesic effect and/or precipitate withdrawal symptoms
- Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and increase respiratory depression
- Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus

Additional tips related to ER/LA opioids include:

- ER/LA opioid analgesics are scheduled under the Controlled Substances Act and can be misused/abused
- Remember that patients must be opioid tolerant to safely take most ER/LA opioid products
- Respiratory depression is the most serious AE; constipation is the most common long-term AE
- Be familiar with drug-drug interactions, pharmacokinetics, and pharmacodynamics of the opioids that you may prescribe; also remember that drug-drug interaction profiles vary among the opioids
- Caution patients and caregivers that CNS depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids

Specific drug information can be found in the Additional Resources section.

How will you improve your practice? Please click on the "Next" button to assess your planned changes in comparison with your peers by completing this brief survey. (Note: the following questions were developed by an independent consulting group with expertise in assessing the effectiveness of medical education.).

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