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SCOPE of Pain

Safe and Competent Opioid Prescribing Education

Provided by

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Boston University School of Medicine

Supported by an independent educational grant from the ER/LA Opioid Analgesic REMS Program Companies.

SCOPE of Pain: Safe and Competent Opioid Prescribing Education

PROGRAM DESCRIPTION

Designed for physicians, nurse practitioners, nurses, physician assistants, dentists, and pharmacists, SCOPE of Pain will help you safely and competently manage your patients with chronic pain. You'll meet Mary Williams, a 42-year-old woman with painful diabetic neuropathy and chronic low back pain. Through her case, you'll learn how to: 1) determine the appropriateness of opioid analgesics; 2) assess for opioid misuse risk; 3) counsel patients about opioid safety, risks and benefits; 4) competently monitor patients prescribed opioids for benefit and harm; 5) decide on continuing, modifying, or discontinuing opioid analgesics; 6) safely discontinue opioids when there is too little benefit or too much risk and harm.

NEEDS ASSESSMENT

Healthcare practitioners (HCPs) who prescribe opioid analgesics to treat chronic pain are in a key position to balance the benefits and risks of chronic opioid treatment. The importance of education for HCPs cannot be overstated as, according to a 2011 report by the Institute of Medicine (IOM), the social and economic burden of pain nationwide is staggering. The IOM report found that the annual health economic impact of pain represents a $560 billion to $635 billion burden to the United States (US).[1] The escalation of opioid prescribing and the corresponding increase in opioid misuse (including, addiction, overdose, and diversion) have been well documented by both regulatory agencies and the lay press.[2]

According to SAMHSA's 2010 National Survey of Drug Use and Health report, among the US population aged 12 or older, nonmedical use of prescription pain relievers was the second most prevalent type of illicit drug use after marijuana use.[3] In addition, mortality rates from unintentional overdose of opioids have increased dramatically. Despite these concerns, according to the National Institute on Drug Abuse, opioid pain medicines are safe and usually do not cause addiction when managed well medically and taken as prescribed.[4] However, HCPs struggle with the need to assist their patients with adequate management of chronic pain while confronting the risks associated with opioid prescribing.

REFERENCES

1. Institute of Medicine. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington DC: The National Academies Press; 2011.
2. Jamison RN, Clark D. Opioid medication management: clinician beware! *Anesthesiology.* 2010;112:777-778.
3. Substance Abuse and Mental Health Services Administration. *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings*. Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4856Findings: Rockville, MD; 2010.
4. National Institute on Drug Abuse. Research Report Series - Prescription Drugs: Abuse and Addiction. http://www.drugabuse.gov/ResearchReports/Prescription/prescription2.html. Accessed February 10, 2016.

EDUCATIONAL OBJECTIVES

After taking part in this educational activity, clinicians should be better able to:

- Employ a systematic approach to the assessment of chronic pain and prescription opioid misuse risk, including screening for unhealthy substance use
- Describe the role of opioids in the management of chronic pain, including a discussion of opioid pharmacology, formulations, efficacy, and risks
- Identify and select individualized opioid regimens based on patients' pain assessments and a balance of benefits and potential risks for a given patient
- Implement office systems incorporating Universal Precautions including the use of Patient Provider Agreements with informed consent and plan of care to meet best practice standards and medicolegal requirements when treating patients with chronic opioid therapy

INTENDED AUDIENCE

Physicians, nurse practitioners, nurses, physician assistants, dentists, and pharmacists

ACCREDITATION STATEMENT

Boston University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Boston University School of Medicine designates this enduring material CME activity for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Continuing Nursing Education Provider Unit, Boston University School of Medicine is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CNE Contact Hours: 2, all of which is pharmacology credit worthy.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC points and patient safety MOC credit in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn

MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Estimated time to complete activity: 2 hours

Release Date: March 1, 2016

Expiration Date: February 28, 2017

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FACULTY

Course Director

Daniel P. Alford, MD, MPH, FACP, FASAM

Associate Professor of Medicine and Assistant Dean of Continuing Medical Education
Boston University School of Medicine
Director of the Clinical Addiction Research and Education Unit
Boston Medical Center
Boston, Massachusetts

Dr. Alford has nothing to disclose with regard to commercial support.

This activity does include discussion of the off-label use of sublingual buprenorphine to treat pain. Sublingual buprenorphine has been FDA-approved for addiction treatment but not pain treatment. This presentation does include discussion of the off-label use of clonidine and tizanidine to treat opioid withdrawal symptoms. Clonidine and tizanidine are not FDA-approved for this use.

PLANNING COMMITTEE

Patti-Ann Collins, DNP, MSN/MBA, RN, Lead Nurse Planner, BUSM

Ilana Hardesty, Program Operations Manager, BUSM

Colleen Labelle, RN, Nursing Course Advisor, BUSM

Stephen A. Wyatt, DO, independent reviewer

Jason Worcester, MD, independent reviewer

Publisher – Haymarket Medical Education: Priya Wanchoo, MD, Medical Director; Margot Fisher, Clinical Editor; Kenny Cox, CHCP; and Lynne Callea, CHCP, Program and Production Managers

Planning committee members have nothing to disclose with regard to commercial support.

ORIGINAL CONTENT DEVELOPMENT

Seddon Savage, MD, MS, FASAM; Dartmouth Medical School:
Dr. Savage has nothing to disclose with regard to commercial support.

Lynn Webster, MD, FACPM, FASAM; CRI-Lifetree:
Dr. Webster is a consultant for Covidien Mallinckrodt, Medtronic, Nektar Therapeutics, and Salix Pharmaceuticals.

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This educational activity is supported by an independent educational grant from the ER/LA Opioid Analgesic REMS Program Companies. Please see **http://ce.er-laopioidrems.com/IwgCEUI/rems/pdf/List_of_RPC_Companies.pdf** for a listing of the member companies. This activity is intended to be fully compliant with the ER/LA Opioid Analgesic REMS education requirements issued by the US Food & Drug Administration.

WEB POSTING

This issue will be posted on March 1, 2016. To take the test and process your CME certificate, please log in to: **www.scopeofpain.com/folio/create-an-account.php.** For your convenience, the test is printed at the end of this monograph. You can mark your answers and proceed to the CME test when you log in.

Dear Colleague:

Welcome to ***SCOPE of Pain: Safe and Competent Opioid Prescribing Education****. This monograph is part of a national initiative to educate clinicians in the safe use of opioid analgesics when managing patients with severe chronic pain.*

In 2011, the US Food and Drug Administration (FDA) mandated that manufacturers of extended-release/long-acting (ER/LA) opioid analgesics make available comprehensive prescriber education in the safe use of these medications as part of a Risk Evaluation and Mitigation Strategy (REMS). This REMS education is based on the FDA curriculum known as the Blueprint for Prescriber Education. Boston University School of Medicine was awarded the first unrestricted educational grant to provide this education and has trained more than 25,000 clinicians since.

The following activity will take you through the case of Mary Williams, a 42-year-old woman with painful diabetic neuropathy and chronic low back pain, which is designed to enhance the way you:

- *Determine the appropriateness of opioid analgesics*
- *Assess patients for opioid misuse risk*
- *Counsel patients on opioid safety, risks, and realistic benefits*
- *Better monitor patients who have been prescribed opioids*
- *Make decisions on continuing, modifying, or discontinuing opioid analgesics*
- *Safely discontinue opioids when there is too little benefit or too much risk*

The evaluation of this SCOPE of Pain program has shown that it significantly improves clinician knowledge, attitudes, confidence, and clinical practice in safe opioid prescribing.[1]

It is important to keep in mind, however, that the FDA is continually assessing for optimal approaches to the complex challenge of chronic pain management and safe opioid prescribing[2] *and providers should keep abreast of new regulations and recommendations as they evolve. Educating ourselves about opioid analgesics is the best way to maximize benefits and minimize harms for our patients.*[3]

Sincerely,

Daniel P. Alford, MD, MPH, FACP, FASAM
Associate Professor of Medicine and Assistant Dean of Continuing Medical Education
Boston University School of Medicine
Director of the Clinical Addiction Research and Education Unit
Boston Medical Center
Boston, Massachusetts

REFERENCES

1. Alford DP, Zisblatt L, Ng P, Hayes SM, Peloquin S, Hardesty I, White JL. SCOPE of pain: an evaluation of an opioid Risk Evaluation and Mitigation Strategy continuing education program. *Pain Med.* 2016;17:52-63.
2. Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse [published online February 4, 2016]. *N Engl J Med.* DOI:10.1056/NEJMsr1601307.
3. Alford DP. Opioid prescribing for chronic pain – achieving the right balance through education. *N Engl J Med.* 2016;374(4):301-303.

TABLE OF CONTENTS

SCOPE of Pain:

Safe and Competent Opioid Prescribing Education

INTRODUCTION: THE SCOPE OF THE CHALLENGE

Chronic pain is a common, costly, and complex condition. As opposed to acute pain, which is a life-sustaining symptom that can often be adequately managed with medication alone, chronic pain is multidimensional and very much like a chronic disease requiring a multimodal therapeutic approach. Chronic pain is a disorder of the somatosensory and pain signaling system that results in maladaptive sensitization that persists well after the acute tissue injury.[1] Therefore, management approaches designed for acute, self-limited pain are inadequate for treating chronic pain.

Chronic pain affects approximately 100 million adults in the United States (US), with an estimated annual cost of medical treatments, lost income, and lost productivity totaling approximately $600 billion.[2] A survey conducted in over 1000 adults found that 57% had experienced chronic pain in the previous year: 42% reported pain lasting more than a year, 33% reported pain as disabling, and 63% reported that they had seen a primary care physician for treatment of their pain.[3]

The use of opioids has become increasingly common in the treatment of chronic pain. Although opioids have established efficacy for acute pain management, they also have a potential for misuse (eg, overdose, addiction, diversion). While more data are needed regarding the effectiveness of opioid therapy for chronic pain, worrisome trends have been identified (***Figure 1***).[4-7]

Data collected through the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System (http://www.radars.org/) indicate that there has been a parallel relationship between the availability of prescription opioid analgesics and the diversion and misuse of these agents, with a concomitant increase in adverse outcomes.[8] The number of prescriptions dispensed for opioid analgesics increased from 47 million per quarter at the beginning of 2006, to a peak of 62 million during the fourth quarter of 2012, and 60 million in the last quarter of 2013.[8] Results from the 2014 National Survey on Drug Use and Health indicate that about 15 million people aged 12 years or older used prescription drugs nonmedically in the past year.[9] Between 2001 and 2011, the latest year for which data are available, there was a 5-fold increase in the number of admissions to addiction treatment centers for problems related to prescription opioids in patients 12 years of age and older.[10] Opioid-related emergency department visits more than doubled from 2004 to 2011, with an estimated 488,000 visits in 2011.[11]

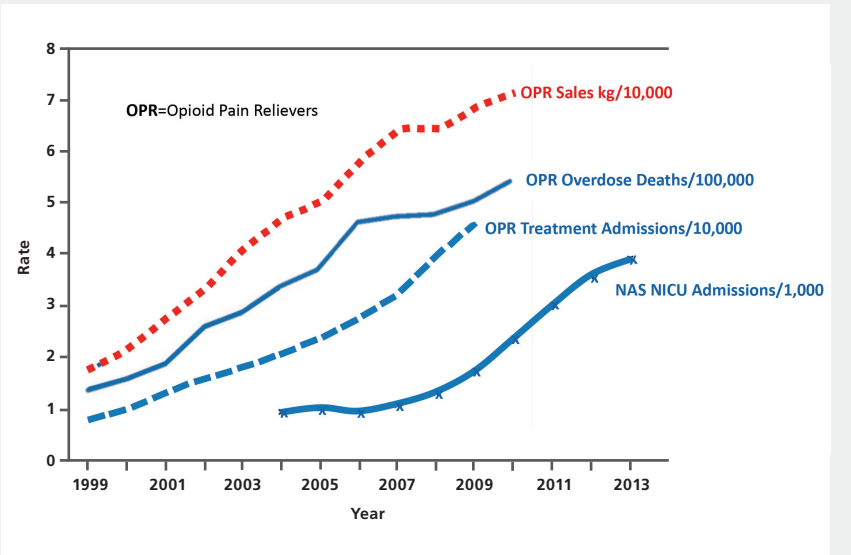
A systematic review of 38 studies documented the extent of problematic prescription opioid use in patients with chronic pain: 26% of the studies were conducted in primary care settings; 53% were in pain clinics.[12] Rates of opioid misuse, which was defined as use contrary to the directed or prescribed pattern of use (regardless of the presence or absence of harmful effects), ranged

from 21% to 29% (95% CI, 13%–38%). Addiction rates ranged from 8% to 12% (95% CI, 3%–17%): addiction was defined as a pattern of continued use with experience of, or demonstrated potential for, harm (eg, impaired control over drug use, compulsive use, continued use despite harm, and craving).

In addition to their misuse potential, opioids are high-risk medications related to fatalities. In 2010, opioids accounted for over 75% of overdose deaths in the US.[13] Deaths have more than tripled since 1999, with an estimated 16,235 deaths attributable to prescription opioids in 2013.[4] In addition, the incidence of Neonatal Abstinence Syndrome (NAS), which is most commonly associated with opioid withdrawal following in utero exposure to opioids, tripled from 2000 to 2009.[6] Although initially associated with maternal illicit opioid use, recent data indicate that NAS is now most often associated with use of prescription opioids.[6]

Despite these challenges, opioids have a role in chronic pain management. The American Academy of Pain Medicine recommends chronic opioid therapy, not as a first-line treatment, but for moderate to severe pain that is not sufficiently managed with more conservative methods.[14] This monograph addresses the appropriate use of opioid analgesics to manage chronic pain in the context of a hypothetical patient case.

FIGURE 1. Worrisome trends and associations in opioid-related morbidity and mortality, 1999-2009[4-7]



NAS, Neonatal Abstinence Syndrome; NICU, neonatal intensive care unit.

CASE STUDY

Mary Williams: Presentation

Mary Williams, a 42-year-old woman, presents to a new practice for the first time to obtain a new prescription, at a higher dose, of her opioid analgesic medication. She has brought in her previous medical records for review and explains that her previous primary care provider moved out of state, leaving her with barely enough medication to last her 1 more week.

Her past medical history includes type 2 diabetes mellitus for 8 years (hemoglobin A1C 7.4%), painful diabetic neuropathy for 2 years, spinal stenosis with chronic low back pain, hypertension, obesity, tobacco use disorder, and a remote history of alcohol use disorder. Her current medications are metformin 1000 mg twice daily, lisinopril 10 mg once daily, hydrochlorothiazide 12.5 mg once daily, and aspirin 81 mg once daily.

For pain, Mary is currently taking oxycodone 5 mg/acetaminophen (APAP) 325 mg 1 to 2 tablets every 4 to 6 hours and gabapentin 300 mg 3 times daily. In the past, her pain has been treated with nonsteroidal anti-inflammatory drugs (NSAIDs), APAP, tricyclic antidepressants (TCAs), tramadol, and APAP with codeine. However, none of these medications provided adequate pain relief and some had intolerable side effects (eg, upset stomach with NSAIDs; dry mouth with TCAs).

The social history reveals that Mary, who is a part-time (20 hours/week) receptionist in a law office, is married to the manager of a hardware store and has 3 children aged 6, 12, and 15 years. She reports that she was an "alcoholic" but has been in recovery for the past 10 years. Although she tried marijuana in high school, she denies any recent history of illicit drug use. She continues to smoke, about 1 pack/day for the past 25 years. Her family history is unremarkable, other than that her mother died from complications of alcoholic cirrhosis.

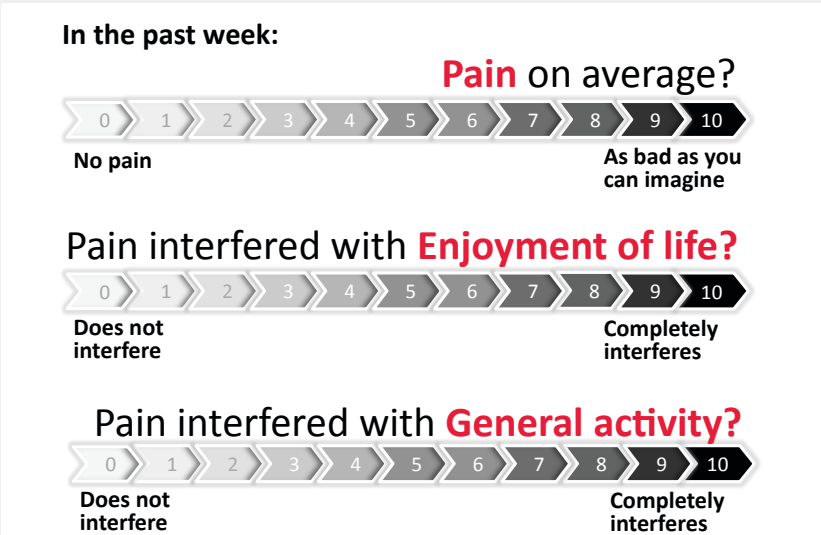
Mary reports that she usually takes 4 to 8 oxycodone/APAP tablets per day, but 8 tablets provide the best pain relief, making it possible for her to go to work. Her previous prescription was limited to 150 tablets/month (up to 5 tablets/day) because her previous primary care provider feared that dose escalation would cause Mary to become addicted: she is careful not to run out of her medication because, when she does, she experiences nausea, vomiting, and diarrhea due to physical dependence.

ASSESSMENT OF CHRONIC PAIN AND COMORBIDITIES

Further assessments are needed before deciding on continuing or changing opioid therapy. A key factor in obtaining an adequate assessment of pain is establishing trust between the provider and the patient. Patients may assume that pain complaints will not be taken seriously, and so may exaggerate their level of pain (eg, "20" on a 10-point scale) and functional limitations (eg, "I can't do anything because of my pain!"). Furthermore, patients who are getting adequate pain relief may not believe it is in their best interests to report that fact.[15] Such beliefs may be fueled by the fear that the provider might reduce the dosage of the opioid analgesic, or that the provider may decrease efforts to identify the source of pain despite a previously thorough workup.

Providers can employ a variety of strategies to build trust. The first step is to take a thorough pain history. It is important to educate the patient about the need for accurate pain scores to assess therapy and to discuss factors that can worsen pain and limit treatment options (eg, substance use, mental health illness). It is also important to show empathy for the patient's experience of pain. Finally, it is important to validate that you believe the patient's pain is real—but believing a patient's pain complaint does not mean opioids are indicated. The decision to prescribe opioids for chronic pain should be based on a careful risk and benefit assessment, as discussed later.

FIGURE 2. Pain, Enjoyment, General Activity (PEG) scale assessment



Chronic Pain Assessment

Pain scales provide a simple way to assess pain. Unidimensional pain scales, which may use numeric ratings, visual analogs, or a "faces" scale, can be useful in the assessment of acute pain[16] but do not provide enough information about chronic pain and about whether treatment is helping with function and quality of life. Multidimensional instruments, such as the McGill Pain Questionnaire, Graded Chronic Pain Scale, and Brief Pain Inventory (BPI), can provide this kind of information but are generally impractical for use in primary care settings and are reserved for use in specialty pain management practices. However, the 3-question Pain, Enjoyment, General activity (PEG) scale is a multidimensional instrument that was derived from the BPI, has been validated, and is well suited for use in primary care settings (***Figure 2***).[17] The PEG will not prove or disprove a patient's pain complaint and it cannot be used to compare PEG scores among patients, as one patient's 8 is another patient's 6. The PEG is particularly useful because it can be followed over time to assess the patient's response to new medications or adjustments to the therapeutic regimen, including the impact of nonpharmaceutical interventions.

Screening for Depression and Unhealthy Substance Use

Simple, single-item screening questions have been validated to identify unhealthy alcohol and/or drug use in the primary care setting (***Figure 3***).[18,19]

FIGURE 3. Screening for unhealthy substance abuse[18,19]

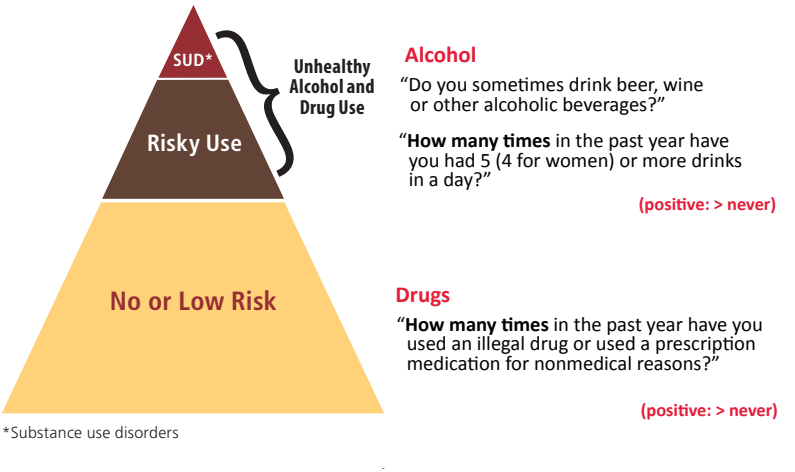


Image source: SBIRT Clinician's Toolkit, www.MASBIRT.org.

For alcohol, the first question is "Do you sometimes drink beer, wine, or other alcoholic beverages?" If yes, the follow-up question is: "**How many times** in the past year have you had 5 (4 for women) or more drinks in a day?" Any number more than zero or "never" is considered a positive screen for unhealthy use of alcohol: further questions (eg, AUDIT: Alcohol Use Disorders Identification Test) are needed to determine how severe their unhealthy alcohol use is (ie, is the patient an at-risk drinker or does the patient have an alcohol use disorder).[18] A similar single-question screening test can be used for illicit drug use or inappropriate use of prescription medications.[19] In this case, the screening question is: "**How many times** in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" Again, a response of 1 or more times is considered a positive screen and requires further questions (eg, DAST: Drug Abuse Screening Test) to determine if the patient has a drug use disorder. Useful information is more likely to be obtained if questions are asked in a normative manner, exactly as they were studied. That is, it is important to ask: "**How many times** in the past year have you ...?" rather than to paraphrase it as, for example, "In the past year, did you…?".

The assessment must also consider physical and psychosocial factors. While 2 patients may have the same pain score, there may be complex differences, not only in the sources of pain, but also in its impact on their functioning and quality of life. Chronic pain is more difficult to assess than acute pain due to its far-reaching effects[16] and psychiatric and medical comorbidities.[20] Patients often report experiencing depression and other psychiatric disorders, marital stress, social withdrawal, sleep disorders, impaired cognitive function, lack of ability to work, and fatigue.[16,21] **Table 1** outlines the prevalence of psychiatric comorbidities commonly seen in patients with chronic pain.[22-27] These comorbidities make pain worse and pain makes these psychiatric conditions worse. It is therefore important to screen for and comanage these conditions when they are identified.

Screening for depression can be done using the Patient Health Questionnaire (PHQ).[28] The PHQ-2 is a simple, 2-item screening-tool questionnaire that is more suitable for busy primary care practices

TABLE 1. Psychiatric comorbidities[22-27]

Condition	Prevalence Chronic Pain Patients
Depression	33% - 54%[22,23]
Anxiety Disorders	16.5% - 50%[22,24]
Personality Disorders	31% - 81%[25,26]
PTSD	49% veterans[27]; 2% civilians[24]
Substance Use Disorders	15% - 28%[22,25]

PTSD, posttraumatic stress disorder.

than the longer PHQ-9.[28] The PHQ-2 simply asks: "Over the last 2 weeks, how often have you been bothered by any of the following problems?" Item 1: assesses the degree of interest or pleasure in doing things; item 2: assesses the extent to which they feel down, depressed, or hopeless.

For each of these 2 items, patients can respond with: not at all, several days, more than half the days, and nearly every day, scored as 0, 1, 2, and 3, respectively.[28] A score of greater than or equal to 3 (or less if there are other signs of depression) may indicate the full PHQ-9 is needed. The PHQ-2 is not meant to monitor depression severity, assess depression outcomes in response to treatment, or establish a final diagnosis, and unlike the PHQ-9, it does not include all 9 symptom criteria to make a DSM-5 depressive disorder diagnosis. Nevertheless, the PHQ-2 has 83% sensitivity and 92% specificity for a diagnosis of depression.

Case Study

Physical Assessment and Screening Results

When asked to describe her pain, Mary reports mild lower back pain that is constant, nagging, like a "dull toothache" without radiation or weakness. It is exacerbated with walking and standing and relieved with sitting or lying. Her severe bilateral foot pain (stocking distribution) is burning with numbness and tingling and worse at night, making it difficult to sleep.

She states that her pain now is a "20" on a scale of zero to 10 because it's the end of the month and she's only able to take 3 to 4 tablets per day. However, after being reassured that the severity of her pain and suffering is believed and that the primary goal on this first visit is not necessarily to decrease her pain medication regimen, Mary states that her pain is 8 out of 10 (moderate to severe) for each of the 3 PEG Scale questions: Pain, Enjoyment of life, and General activity. Other than a nicotine use disorder, Mary screened negative for other unhealthy substance use. She also screened negative for depression.

The visit continues with a physical examination. Mary is obese, weighing 220 lb (body mass index [BMI] 32 kg/m^2). There are no signs of acute distress, and her vital signs and cardiopulmonary examination are normal. Spine alignment is normal, with no point tenderness and a negative straight leg test. Her neurologic exam is consistent with her diabetic neuropathy. There is no Achilles tendon reflex bilaterally, and although the diabetic foot exam reveals no lesions or ulcerations and normal pulses, there is loss of protective sensation (LOPS) by vibration (tuning fork) and pressure (monofilament) tests.

THE PLACE OF OPIOIDS IN CHRONIC PAIN MANAGEMENT

The criteria for when opioids may be indicated include: pain is severe, has a significant impact on function and quality of life, pain type is potentially opioid responsive (eg, musculoskeletal and neuropathic pain but NOT fibromyalgia or migraines), nonopioid therapies have been tried and found inadequate, and if the patient is already on opioids (as in the case presented here), there is documented benefit. Upon reviewing Mary's past history and current

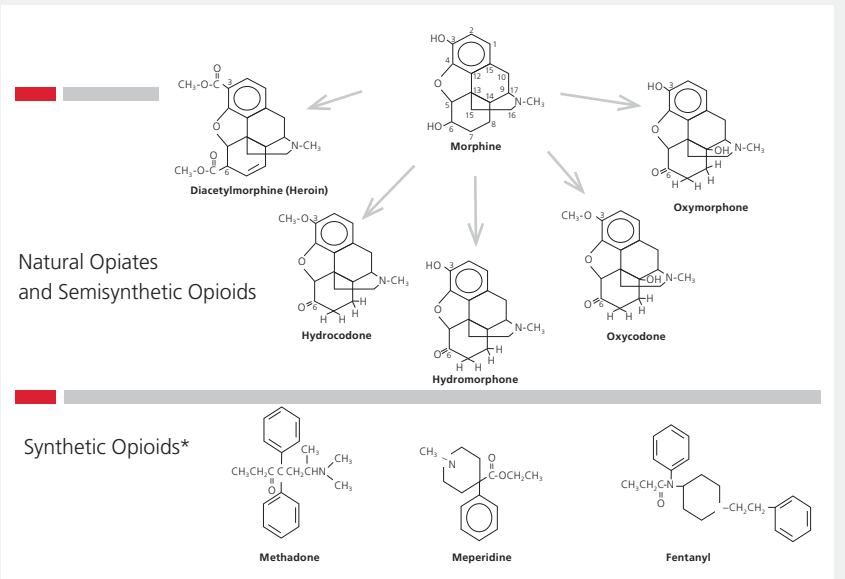
pain assessment, it appears that opioids may be indicated. Her pain is likely both musculoskeletal and neuropathic; her PEG score of 8/10 demonstrates that her pain is severe and significantly impacting her function and quality of life; and she has been tried on nonopioid pharmacotherapy, which has provided inadequate benefit. However, her previous medical records will need to be reviewed, and her previous primary care provider contacted, to assess for documented functional benefit from opioid therapy. Nonetheless, Mary believes that she is gaining an analgesic benefit from the medication (ie, it enables her to work and care for her children), despite feeling that she needs more. The questions, then, may be whether she is receiving the optimal medical regimen for her individual needs, whether her pain might be better managed with other treatment modalities or other medications, or whether a different opioid class or formulation should be considered.

Opioid Pharmacology

In addition to the naturally occurring opiate compounds (morphine, codeine, and thebaine), there are semisynthetic and synthetic opioids (***Figure 4***).[29] Semisynthetic opioids include diacetylmorphine (heroin), hydromorphone, hydrocodone, oxymorphone, oxycodone, and buprenorphine; synthetic opioids include fentanyl and methadone.

It is important to understand the pharmacology of opioids to properly interpret urine drug testing (UDT) results (see full

FIGURE 4. Natural opiates and semisynthetic and synthetic opioids



*Note: Synthetic opioids do not revert back to codeine or morphine and so will not result in a positive urine test for opiates.

discussion of UDT below). Semisynthetic opioids like hydrocodone, hydromorphone, oxycodone, oxymorphone, and diacetylmorphine (heroin) are created by molecular alterations to naturally occurring opiates (morphine and/or codeine). Urine opiate drug testing detects morphine and codeine, as well as their semisynthetic derivatives, to differing degrees, which revert back to morphine and/or codeine (heroin reliably, oxycodone not reliably) and thus yield a positive test for opiates in the urine. By contrast, the synthetic opioids (eg, methadone, fentanyl) do not convert back to opiates (morphine and/or codeine), and so do not test positive for opiates (morphine and/or codeine) on UDT. All opioids, however, whether semisynthetic or synthetic, can be specifically tested for with immunoassays.

Opioid Receptor Pharmacodynamics

Opioids also can be grouped according to their actions at opioid receptors. Full opioid agonists (eg, morphine, oxycodone) interact at receptors to produce a response, while full opioid antagonists (eg, naloxone, naltrexone) bind to receptors but produce no functional response and prevent an agonist from binding to and activating the receptor. Partial opioid agonists (eg, buprenorphine) bind to receptors but produce only a partial functional response, resulting in a "ceiling effect."[29]

Opioids produce analgesia by activating opioid receptors at 4 principal sites: the midbrain, where they turn on descending inhibitory systems; the second order pain transmission cells, where they prevent ascending transmission of pain signals; the dorsal horn of the spinal cord, where they inhibit terminals of C-fibers; and in the periphery, where they inhibit the activation of nociceptors and cells that release inflammatory mediators.[30] Opioids also activate the "reward pathway" in the midbrain, a dopaminergic system that produces euphoria.

Physical Dependence and Tolerance

Opioid treatment for chronic pain will often result in physical dependence and tolerance.[31] These biologic adaptations to being exposed to an opioid are not the same as addiction (a behavioral maladaptation—discussed below). **Physical dependence** refers to the withdrawal symptoms, such as anxiety, nausea, vomiting, diarrhea, sweating, muscle aches, and abdominal cramping, that can follow abrupt discontinuation, rapid dose reduction, or administration of an opioid antagonist (eg naloxone, naltrexone). Although physical dependence is expected after long-term use, it can develop after as few as 48 hours of use. **Tolerance** is characterized by the need for increased amounts of opioid for the desired level of pain relief due to the diminished effect of the same opioid over time. Tolerance develops reliably for sedation and respiratory depression but less so for constipation; the development of tolerance to the analgesic effects of opioids is not well defined.

Opioid Formulations

Opioids can be divided into 2 categories: immediate-release/short-acting (IR/SA) and extended-release/long-acting (ER/LA) formulations (***Table 2***). ER/LA opioids, which are typically administered twice a day or less, may be transdermal or oral preparations.[32]

The distinction between IR/SA and ER/LA opioids is based on their onset and duration of action, which is depen-

dent on their formulation rather than any difference in their molecular structure. IR/SA opioids have a more rapid increase and decrease in serum levels, whereas ER/LA opioids are formulated to release drug gradually and have a long half-life.[33]

While ER/LA opioid formulations are designed to release drug gradually, physical tampering with the agent can convert it to an IR, high-dose preparation. This can result in opioid overdose. For this reason, ER/LA opioid formulations with such release systems may be dangerous for patients at risk for substance misuse, and patients should be informed not to crush, split, or alter the tablet or patch in any way.[33]

Which formulation is more effective and which is safer? A meta-analysis revealed that there was not enough evidence to determine that ER/LA opioids, when compared to each other or to IR/SA opioid formulations, have different efficacy or adverse event rates when used to treat chronic pain.[14,32] IR/SA opioids, since they have a shorter half-life, are safer for initial therapy in opioid-naïve patients.[14] Some experts advise that the use of ER/LA opioids with around-the-clock dosing may provide more consistent pain control and better medication adherence. However, there is insufficient evidence to determine whether ER/LA opioids are more effective or more likely to result in tolerance, hyperalgesia, or addiction than IR/SA opioids.[32,33]

TABLE 2. Opioid formulations*

Immediate-Release/Short-Acting (IR/SA)	Extended-Release/Long-Acting (ER/LA)*
Morphine	Morphine
Hydrocodone	Hydrocodone
Hydromorphone	Hydromorphone
Oxycodone	Oxycodone
Oxymorphone	Oxymorphone
Tramadol	Tramadol
Tapentadol	Tapentadol
Codeine	Methadone
	Fentanyl transdermal
	Buprenorphine transdermal

*Detailed product-specific information available at http://dailymed.nlm.nih.gov/dailymed.

Alcohol-induced dose dumping may result in respiratory depression.

Therefore, treatment should be individualized according to patient needs. In general, if an opioid is deemed appropriate for pain management, opioid-naïve patients should be started on a low dose of an IR/SA opioid. For patients with incidental and intermittent pain, the chronic use of low-dose IR/SA opioids may be appropriate. For patients with opioid tolerance with constant, around-the-clock pain, the amount of IR/SA opioid needed in a 24-hour period can be converted, with a decrease in total dose due to incomplete cross-tolerance, to dosing in a more convenient ER/LA opioid following a trial period of IR/SA opioid.

Some ER/LA opioids may rapidly release drug when taken with alcohol, posing a serious safety concern.[34] This is known as "alcohol-induced dose dumping." Respiratory depression, which is the most serious adverse effect of opioids, may result when alcohol is combined with ER/LA opioid dosage forms, leading to hypoxia and death.

No adequate and well-controlled studies of ER/LA opioid analgesics have been conducted in pregnant women. Therefore, ER/LA opioid analgesics should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Selected Opioids With Unique Properties

Transdermal Preparations. Fentanyl and buprenorphine are available as transdermal patches; fentanyl patches provide pain relief for 72 hours and buprenorphine patches provide pain relief for 7 days. Transdermal patches are convenient for patients. However, their onset of action is slow, and adequate subcutaneous fat, intact skin, and predictable blood flow are required. The absorption of the medication from the transdermal patch into the bloodstream is affected by body temperature, the presence of broken skin, or edema. Fever increases absorption and edema decreases absorption. Some patches have metal foil backings and cannot be left on during MRI studies. Even patches that are no longer usable by the patient have residual drug in them and need to be carefully disposed of to avoid poisoning pets or children. The use of a transdermal fentanyl patch in young children warrants caregiver education to avoid an exploratory ingestion of the patch by a young child.

Methadone. Methadone is a mu opioid agonist and an N-methyl-D-aspartate (NMDA) receptor antagonist considered to be a second- or third-line opioid in the treatment of chronic pain.[35] It potentially causes less analgesic tolerance and has better efficacy in the treatment of neuropathic pain. However, methadone is a complex drug for providers to manage due to its long, variable, and unpredictable serum half-life (up to 120 hours) in relation to the duration of its analgesic effect (6 to 8 hours), its role in many drug interactions, and the risk of QTc prolongation leading to torsade de pointes. For this reason, opioid switching to methadone should only be done by providers who are familiar with methadone's pharmacology and are experienced with using the medication.

Dual-Mechanism Opioids: Tramadol and tapentadol. Tramadol is a centrally acting opioid agonist, structurally related to morphine and codeine, with 2 enantiomers.[36] The combined actions of the 2 enantiomers (ie, agonism of the mu opioid receptor and inhibition of norepinephrine and serotonin uptake) results in improved analgesic efficacy and tolerability. Tramadol has minimal effects on respiratory function as compared to morphine and other opioids and has relatively low gastrointestinal inhibition. Tramadol is a schedule IV medication under the Controlled Substances Act (***Table 3***).[37] Tapentadol is also a dual-mechanism, centrally acting opioid agonist, via agonism of the mu opioid receptor and inhibition of norepinephrine reuptake.[38] This medication is a schedule II substance with efficacy and adverse effects similar to morphine and oxycodone.[39]

Opioid Efficacy in Chronic Pain

Despite the widespread use of opioids for chronic pain, most of the literature regarding their efficacy in this setting is based on surveys and uncontrolled case series.[40-44] There are some data from randomized clinical trials, but these studies tend to be of short duration (<8 months), with small sample sizes (<300 patients), and most are pharmaceutical company–

sponsored. These randomized clinical trials do show analgesia with opioids for chronic pain as statistically significantly better than with placebo. However, the degree of pain relief, as with any medication or other treatments for chronic pain, is modest. For example, a Cochrane review of 2 controlled studies with longer follow-up reported that 44.3% of participants (total N=442) had at least 50% pain relief.[45] Furthermore, outcomes in terms of function and quality of life are mixed, and none of these studies have provided clinically useful information about addiction potential.

Taking into account the risks that opioids pose for substance misuse, adverse effects, and increased risk for overdose-related fatalities, opioids should not be used as first-line therapy for chronic pain. Instead, they should be second- or third-line treatment. It is important to remember that for chronic pain, chronic opioid therapy has been inadequately studied.[41,46,47]

OPIOID SAFETY AND RISKS

Although opioid allergies are rare, and organ toxicities are less common than with other analgesics such as NSAIDs and APAP, opioid adverse effects are an important concern.[48] Suppression of the hypothalamic-pituitary-gonadal axis is possible, and some patients develop hypogonadism on chronic opioids, resulting in poor bone health.[49] Common adverse effects include: nausea, sedation, constipation, urinary retention, sweating, pruritus (due to histamine release), and respiratory depression.[43,48]

Respiratory depression is of particular concern in patients with underlying pulmonary disease or sleep apnea. Opioid analgesics interfere with ventilatory control via depression of the medullary respiratory center, resulting in hypercapnea, hypoxia, and decreased oxygen saturation.[50] Sedation and bradypnea can be warning signs of pending respiratory depression. Because the risk is greatest

TABLE 3. Schedule classifications of medically approved opioids in the US[37]

Schedule II*	Schedule III†	Schedule IV‡
Hydrocodone	Tylenol with codeine	Tramadol
Methadone	Buprenorphine	Butorphanol
Hydromorphone	Buprenorphine/naloxone	
Oxycodone		
Meperidine		
Fentanyl		
Codeine		
Oxymorphone		
Morphine		
Tapentadol		

*High potential for abuse, which may lead to severe psychological or physical dependence. Verbal/oral order is permitted in an emergency situation. No refills allowed.
†Moderate to low potential for psychological or physical dependence. Verbal/oral order is permitted. Up to 5 refills allowed within 6 months from the date issued.
‡Low potential for abuse and low risk for dependence. Verbal/oral order is permitted. Up to 5 refills allowed within 6 months from the date issued.

during sleep, when respiration is already depressed, it is prudent for patients to avoid dose increases at night until they become tolerant of the respiratory depression effect.

The Risk of High-Dose Opioids

Higher opioid doses may be indicated in some patients, but these patients should be managed as higher risk, with a corresponding increase in monitoring and support. High dose is generally considered to be more than 100 mg morphine equivalents (eg, >67 mg oxycodone, >25 mg hydromorphone, >100 mg hydrocodone).[14,40,51] There is evidence that these doses may be associated with a range of consequences, in terms of both individual clinical outcomes and public health.

Higher doses of opioids have been associated with higher levels of analgesic tolerance[52]; conversely, higher doses of opioids have been associated with an increased incidence of opioid-induced hyperalgesia (ie, increased pain).[53,54] In addition, there is population data suggesting that function is reduced with higher doses of opioids.[55,56] Finally, there is evidence of a higher incidence of overdose deaths associated with higher doses of opioids.[57-61]

Management of Adverse Effects

Strategies for reducing adverse effects associated with opioid use include more conservative opioid prescribing practices and the "start low and go slow" approach.[62] Addressing specific adverse effects of opioid therapy, despite selective prescribing and careful dosing, is also needed. Constipation can be addressed with stool softeners and/or laxatives. Bulk laxatives, however, are not recommended for the treatment of opioid-induced constipation, as they may increase the likelihood of bowel obstruction in patients with already impaired gastrointestinal motility.[63]

Peripheral opioid receptor antagonists (eg, methylnaltrexone and naloxegol) reverse the impaired gut motility induced by opioids. These agents do not reverse central analgesia due to their limited ability to cross the blood-brain barrier: in the case of methylnaltrexone, this is due to its structure (a quaternary derivative of naltrexone); in the case of naloxegol, this is due to its composition of naloxone conjugated with a polyethylene glycol polymer.[64,65]

Nausea and vomiting will usually resolve within days. Although antiemetics can be used, the downside of adding such pharmacologic agents to opioid therapy is that some antiemetics, such as chlorpromazine, may cause additional sedation and cognitive impairment. Antiemetics, such as the 5-HT3 receptor antagonists, may be preferred based on their adverse effect profile.[66] **Figure 5** depicts strategies for managing some of the more common opioid adverse effects.[48]

Drug-Drug Interactions

A study of drug-drug interactions involving opioids used for treating chronic pain revealed there are 3 major categories of drug-drug interactions in this setting: increased opioid adverse events (eg, sedation, respiratory depression), central nervous system (CNS) toxicities, and decreased opioid effects (resulting in withdrawal or loss of pain control).[67]

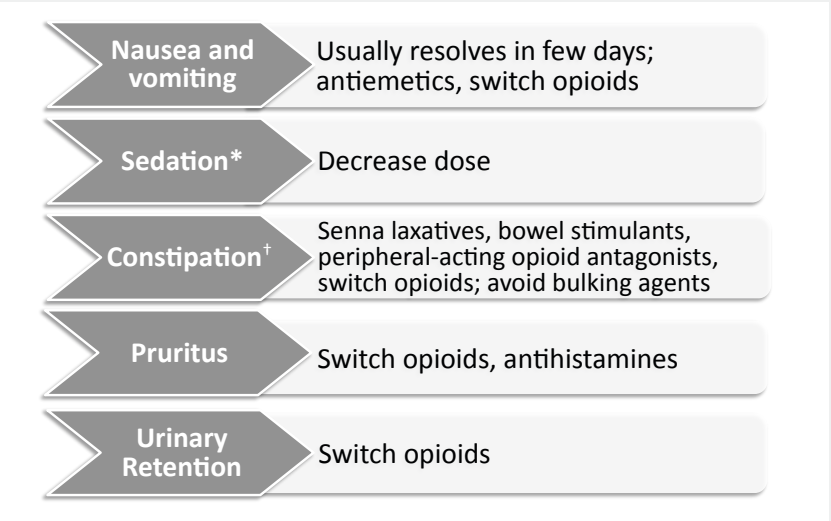
In core messages regarding safer opioid prescribing developed by the FDA to be communicated to providers in its Blueprint for Prescriber Education,[68] the

FDA highlights the following opioid drug interactions:

- **Other CNS depressants:** The combination of an opioid with another drug that causes CNS depression (eg, TCAs, alcohol, sedatives, hypnotics, tranquilizers) can increase the risk of acute opioid toxicity including respiratory depression and sedation
- **Alcohol:** When exposed to alcohol, some ER opioid formulations may rapidly release opioid ("dose dump"); alcohol can increase drug levels of some opioid formulations without dose dumping (consult individual product labeling)
- **MAOIs:** The use of opioids with monoamine oxidase inhibitors (MAOIs) may cause increased respiratory depression. In addition, the combination of certain opioids with MAOIs may result in serotonin syndrome
- **Diuretics:** Opioids may reduce the efficacy of diuretics via release of antidiuretic hormone
- **QTc prolongation:** Some opioids (eg, methadone, buprenorphine) can prolong the QTc interval
- **Cytochrome P450 metabolism:** The use of inhibitors or inducers of certain cytochrome P450 enzymes can increase or decrease blood levels of some opioids

Detailed information regarding potential interactions for specific medications can be found at the DailyMed website (**http://dailymed.nlm.nih.gov/dailymed/**). This site is provided as a public service by the National Library of Medicine, as the official provider of FDA label information (package inserts).

FIGURE 5. Managing opioid adverse effects[48]



*Occurs mostly during initiation or change in dose.
†Most common adverse effect; should be anticipated.

DailyMed provides a comprehensive, up-to-date look-up and download resource of the most recent drug labeling information submitted to the FDA; it may include, for example, strengthened warnings undergoing FDA review.

Age-Related Considerations

Elderly Patients. Chronic pain is a prevalent condition in the older adult population, with 45% to 85% experiencing moderate to severe chronic pain.[69] There are a number of barriers to safe opioid use in the elderly. A less predictable response to opioids is expected in this population due to age-related changes, including increased drug sensitivity and adverse drug effects. Other concerns include the presence of comorbidities (eg, cognitive impairment, gait disturbance), polypharmacy use, and adverse effects such as dizziness and sedation posing an increased risk of falls.

The choice of an opioid analgesic in an older adult can be made based on the drug's adverse event profile. Opioids should be used with caution in frail older adults with respiratory conditions (eg, chronic obstructive pulmonary disease) and risk factors for QT prolongation.[69] The overall message for opioid use in the elderly is to use the lowest effective dose and be aware of the potential for drug-drug and drug-disease interactions.

Pediatric Patients. Although some IR/SA opioid formulations have been approved by the FDA for use in pediatric patients, few ER/LA opioids are approved for use in children. The only ER/LA opioid products approved by the FDA for pediatric use are transdermal fentanyl (2 years and older) and ER/LA oxycodone (ages 11 to 16 years). Despite the FDA approval for ER/LA oxycodone for children ages 11 to 16 years of age, opioids are rarely used in multimodal approaches to pediatric chronic pain.[70,71]

OPIOID MISUSE AND ADDICTION RISK

In addition to managing pain, opioid misuse risk is another factor that needs to be examined prior to initiating or continuing opioid therapy. Problematic use of opioids can be characterized as misuse (intentional use of a drug in a way other than prescribed), or addiction (opioid use disorder: behavioral, cognitive, and psychological experiences after repeated use of a drug resulting in persistent drug use, craving, and making the drug a priority in life).[72]

As previously discussed, rates of prescription opioid **misuse** and **addiction** are 22% to 29% and 8% to 12%, respectively.[12] **Misuse** was defined as opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects. **Addiction** was defined as a pattern of continued use with experience of, or demonstrated potential for, harm (eg, impaired control over drug use, compulsive use, continued use despite harm, and craving, or the "Four C's of Addiction").[12,73] These data highlight that there is a need for a standardized approach to assessing misuse and addiction.

Addiction (opioid use disorder) is characterized by compulsive drug-seeking behavior and related adverse conse-

The Four C's of Addiction

- Loss of Control
- Compulsive use
- Continued use despite harm
- Craving

quences.[74] There are several factors that contribute to patients becoming addicted to opioids. Opioids produce alterations in brain function via activation of midbrain mu receptors, resulting in euphoria. The dopaminergic system provides the "reward system" reinforcing the need for continued opioids. IR/SA opioids may have more addictive potential than ER/LA opioids due to a more rapid increase of opioid concentrations in the brain.[31] ER/LA opioid formulations are expected to be less rewarding due to their slow onset of action, provided the ER/LA release mechanism is not altered by chewing or crushing.[74]

There are several risk factors for prescription opioid misuse, as shown in **Table 4**.[75-79] A variety of opioid formulations that are designed to be abuse-resistant or -deterrent are in development.[80,81] These approaches include: novel formulations and routes of administration that aim to reduce drug rewards, as well as aversive components that cause side effects if taken in higher-than-prescribed doses; prodrugs that do not release the active opioid unless ingested orally; and agonist-antagonist combinations in which the antagonist is released if the tablet is altered. However, while abuse-deterrent or -resistant formulations have been shown to decrease misuse,[82] there is currently no opioid or opioid formulation that is 100% resistant to misuse.

TABLE 4. Known risk factors for opioid misuse[75-79]

■ Young age (<45 years)
■ Personal history of substance use disorder (illicit, prescription, alcohol, nicotine)
■ Family history of substance use disorder
■ Legal history (driving while impaired, incarceration)
■ Mental health problems
■ History of sexual abuse

Opioid Misuse Risk Stratification

Assessment of an individual patient's risk for misuse of opioids should include UDT as well as a check of state Prescription Drug Monitoring Program (PDMP) data, if available, to see where the patient has been getting prescriptions (see more detail below). It is also helpful to review the patient's medical records and, if possible, talk to the previous provider.[83]

There are a number of validated questionnaires that can be used to help assess opioid misuse risk, although no particular one is considered the "gold standard." The Opioid Risk Tool (ORT) is shown in **Figure 6**[84]; others include the Screener and Opioid Assessment for Patients With Pain (SOAPP) Version 1, the revised SOAPP (SOAPP-R), and the Diagnosis, Intractability, Risk, Efficacy (DIRE) instrument. The SOAPP Version 1, SOAPP-R, and ORT are patient self-reported questionnaires assessing the risk of aberrant drug-related behaviors, whereas the DIRE is clinician-administered to assess potential efficacy and risks.[14]

When the ORT is applied to risk-stratify Mary Williams, she gets a total of 5 points, indicating a moderate risk for opioid misuse. This score should be used to discuss the level of concern with the patient: in this case, the provider might say, "Despite being in recovery

from alcoholism, which is commendable, you're still at higher risk for developing problems with this opioid pain medication. Therefore, I'm going to be really careful when I prescribe it to you, and I'm sure that's what you want me to do, to keep you safe."

Opioid risk stratification also indicates what level of monitoring should be implemented when opioid therapy is initiated. For example, how often should the patient be seen, and how often should UDTs and/or pill counts be conducted? High-risk patients may need to agree that they're willing to comply with random callbacks, where they are required to come in within 24 hours for UDT and a pill count. This is probably the highest level of monitoring that is practical in a primary care setting.

In some cases, the risk stratification will suggest the need for a pain or addiction

FIGURE 6. Opioid Risk Tool[84]

		Female	Male
Family history of substance abuse			
	Alcohol	❑1	❑3
	Illegal drugs	❑2	❑3
	Prescription drugs	❑4	❑4
Personal history of substance abuse			
	Alcohol	❑3	❑3
	Illegal drugs	❑4	❑4
	Prescription drugs	❑5	❑5
Age between 16 and 45 years		❑1	❑1
History of preadolescent sexual abuse		❑3	❑0
Psychological disease			
	ADHD, OCD, bipolar, schizophrenia	❑2	❑2
	Depression	❑1	❑1

Scoring: 0-3, low risk; 4-7 moderate risk; ≥8 high risk.

ADHD, attention-deficit hyperactivity disorder; OCD, obsessive-compulsive disorder.

medicine consult, if available. In other patients, however, opioid analgesics may simply be too risky. A case in point would be someone with an active or recent opioid use disorder: even though the patient has severe pain that may be opioid responsive, it might just be too early in their recovery to prescribe an opioid analgesic safely.

Diagnosing Addiction (Opioid Use Disorder)

As noted earlier, the diagnosis of addiction is based upon the 4 "C's": control (loss of), compulsive use, continued use despite harm, and craving).[73,85] It is important to distinguish between addiction and physical dependence. **Physical dependence** is a ***biologic adaptation*** when patients are on chronic opioid therapy resulting in withdrawal symptoms when the opioid is stopped, whereas **addiction** is a ***behavioral maladaptation*** resulting in compulsive drug-seeking behavior and related adverse consequences. The use of the *American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5)* criteria[85] to diagnose opioid use disorder can be complicated in patients prescribed opioids for chronic pain. Despite the exclusion of the first 2 symptoms of tolerance and withdrawal in this population, some patients on opioids for chronic pain may still meet some of the other 9 criteria due to poorly controlled pain rather than negative consequences of the opioid (***Table 5***).

Opioids and Overdose

As discussed in the introduction, unintentional opioid overdose deaths have increased 4-fold in a decade.[13] The vast majority of prescription opioids that are misused are not obtained by prescription from a single doctor. Data from the 2013 and 2014 National Survey on Drug Use and Health indicate that over 50% of people who misuse prescription pain relievers obtained them from family or friends for free; only 22% obtained them from a doctor (see ***Sidebar, Collateral Opioid Risk***).[86] The ready availability of opioids without a prescription highlights the need to continue efforts to educate both patients and providers about safe storage and disposal of opioids; in addition, patients with acute (vs chronic) pain should be given only limited opioid supplies (eg, 2-3 days).

TABLE 5. Criteria for opioid use disorder (OUD)[85]

- Tolerance*
- Withdrawal*
- Use in larger amounts or duration than intended
- Persistent desire to cut down
- Giving up interests to use opioids
- Great deal of time spent obtaining, using, or recovering from opioids
- Craving or strong desire to use opioids
- Recurrent use resulting in failure to fulfill major role obligations
- Recurrent use in hazardous situations
- Continued use despite social or interpersonal problems caused or exacerbated by opioids
- Continued use despite physical or psychological problems

Mild OUD: 2-3 Criteria
Moderate OUD: 4-5 Criteria
Severe OUD: ≥6 Criteria

*This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.

Collateral Opioid Risk

The presence of opioid analgesics in the home presents 2 risks: the risk for an exploratory ingestion by a young child resulting in poisoning, and the intentional ingestion by an adolescent leading to addiction or overdose.[87] Patients and caregivers need education to take some simple steps to prevent these potentially fatal ingestions from occurring. Storage of opioid analgesics, as with all medication, should be in a high location, out of young children's reach. As an added measure, for both the young child and the adolescent, the medication should be stored in a locked box, such as a fishing tackle box or another container that can be secured with a padlock.

The number for the National Poison Control Center National Hotline should be on all phones (800-222-1222), and where available, naloxone should be provided to families with opioids in the house. This opioid antagonist reverses the toxic effects of opioid overdose and may be available through community-distribution programs. Many states have adjusted their laws in order to increase access to naloxone. Updated information regarding the use of and state regulations around naloxone prescribing can be found at **www.prescribetoprevent.org.**

Case Study

Second Office Visit

Mary Williams' history indicates that she has some prescription opioid misuse risk factors (personal and family history of a substance use disorder and being less than 45 years old), with an Opioid Risk Tool Score of 5 (moderate risk). As part of the comprehensive opioid misuse risk assessment, a UDT is ordered and she is scheduled to return in 1 week when her current opioid prescription will be completed.

During the week between visits, the new provider is unable to contact Mary's previous primary provider who moved out of state. Mary's UDT is positive only for oxycodone, as expected. In addition, the state prescription drug monitoring program (PDMP) shows that she has used only 1 provider and 1 pharmacy for her opioid pain medication. Her medical records are reviewed and her problem and medication lists are reconciled. The radiology reports indicate lumbar degenerative joint disease and mild spinal stenosis. There is a lack of adequate documentation in the notes about any analgesic or functional benefits of opioid treatment but there is also no evidence of aberrant medication-taking behavior suggestive of prescription opioid misuse.

When she comes in for her second office visit, Mary's PEG Scale scores are unchanged (8/10 for each PEG question: Pain, Enjoyment of life, and General activity). She reports that she has completed the remainder of her previous prescription for IR/SA oxycodone/APAP on schedule and is clearly worried about the recurrence of pain symptoms.

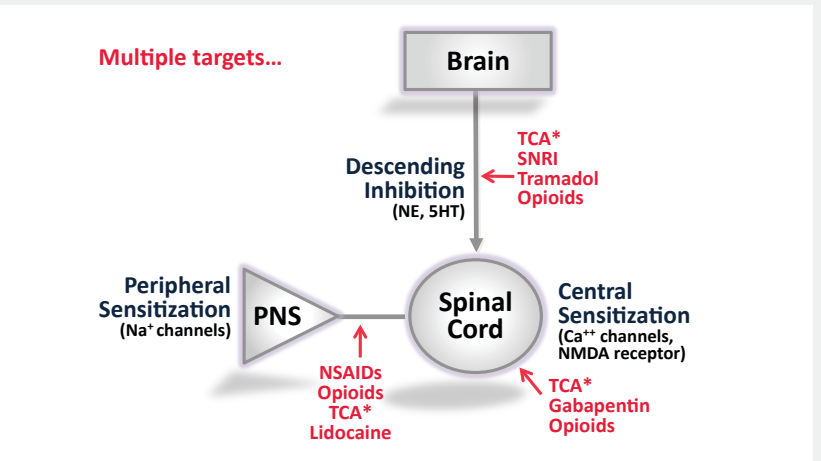
OPIOID CHOICE AND DOSING

It would be appropriate in this case to consider switching the patient to an ER/LA opioid since she has continual round-the-clock pain, is not opioid-naïve (ie, has opioid tolerance), and is taking multiple IR/SA opioid doses per day. However, it is important to carefully consider and discuss with the patient the risks and benefits of treatment whenever opioid therapy is initiated, continued, or modified. In all circumstances, it is important to always start with low doses and make changes slowly.

The choice of agent and dose should be guided by a variety of considerations. The duration and onset of action should match the patient's pattern of pain (ie, incident/intermittent or constant). Factors related to receptor-binding profiles of opioids, pharmacokinetics, and pharmacodynamics affect how individual patients will respond to a specific opioid.[88] Opioid metabolism is affected by factors such as age, genetics, comorbid conditions, and concomitant medications.[88] There are more than 100 polymorphisms in the human mu opioid receptor gene and different mu receptor subtypes.[89] Identifying specific opioids that will be efficacious and tolerable for the individual patient can be an imperfect science, leading to trials of several opioids before finding one that balances analgesia and adverse effects.[88] That is, if a patient does not respond to one opioid, it is reasonable to try another before concluding that the patient has pain that is poorly opioid responsive.

The individual's prior experience with different opioids should also be considered. Biogenetic variations affect individual sensitivities to different opioids in terms of both analgesic effects and side

FIGURE 7. Schema for rational polypharmacy[90,91]



*Tricyclic antidepressants (TCAs) remain first-line medication for neuropathic pain, followed by anticonvulsants, opioids, and serotonin-norepinephrine reuptake inhibitors (SNRIs).

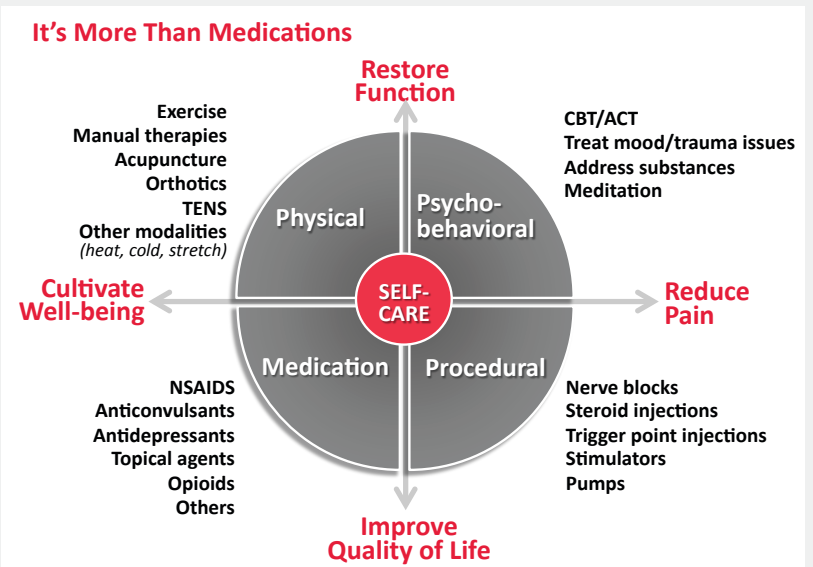
effects. In addition, the patient's level of opioid tolerance should be considered, and opioid-naïve patients should not be started on ER/LA opioid formulations. The route of administration (oral vs transdermal) is an additional consideration. The euphorigenic potential of IR/SA opioids should be considered especially carefully in patients who have a history of substance use disorders or addiction: the faster the onset of the action, the greater the reward potential. Finally, we need to consider the cost of the medications, whether there is full insurance coverage, or whether it is self-pay.

Rational Polypharmacy

There is a role for rational polypharmacy in chronic pain management—that is, the combination of medications from different drug classes following a well-thought-out plan. Nevertheless, drug interactions and dosing adjustments must be taken into consideration when using combination regimens.[72] Different medications act at different points in the pain pathway (***Figure 7***), so combining them may exploit their synergism and allow for better analgesia at lower doses.[90,91] For example, an opioid analgesic may be given with an antidepressant or antiepileptic agent, or a topical agent may be given along with an oral medication.

The principle of rational polypharmacy was demonstrated in a study of patients with neuropathic pain who were given placebo, gabapentin, morphine, and a combination of gabapentin and

FIGURE 8. Elements of multidimensional care



TENS, transcutaneous electrical nerve stimulation; CBT, cognitive behavioral therapy; ACT, acceptance and commitment therapy.

morphine. Although each treatment showed incremental decreases in intensity of pain from baseline, the greatest decrease in pain intensity was seen with combination treatment. Furthermore, the dose requirement for both gabapentin and morphine was lower when the medications were combined.[92]

Multimodal Care

One of the complexities in management of chronic pain is that it does not typically respond to single therapeutic measures (eg, medications) that effectively treat acute pain.[21] Chronic pain management should be multimodal and go beyond pharmacologic treatments alone (***Figure 8***). It should start with self-care and be accompanied by psychobehavioral (eg, cognitive behavioral therapy), physical (eg, physical therapy), and/or procedural interventions (eg, steroid injections).

Self-care measures may include exercise, stress reduction, pacing activities, cold/heat packs, and stretching, among other activities.[93] Patients also should be encouraged to seek treatment to address any coexisting conditions such as depression or anxiety that may contribute to pain. The response to medication may be improved when other nonpharmacologic therapies are integrated into the patient's care.[94]

It is, of course, important to educate patients about which complementary therapies are evidence-based and to warn them that even apparently benign herbal supplements promoted for pain relief may cause harm from the standpoint of both toxicity and drug-herbal interactions.[95,96] Patients also can be directed to the American Chronic Pain Association website (**www.theacpa.org**) for guidance about pain-management tools and self-care skills that can help cultivate well-being, contribute to reduced pain and restored function, and help improve quality of life.

SAFE OPIOID PRESCRIBING

A variety of strategies can be employed to prescribe opioids safely. These include the use of universal precautions, including patient prescriber agreements with informed consent and plan of care, PDMP, UDT, pill counts, and evaluation for drug-drug interactions, as well as the use of formulations that make snorting, injecting, or smoking oral opioid formulations more difficult.

Universal Precautions in Pain Medicine

Although appropriate opioid treatment should be individualized, universal precautions should be employed whenever opioid therapy is initiated, continued, or modified. The prediction of opioid misuse risk is imprecise. Therefore, applying a consistent controlled substance policy reduces stigma for individual patients while it helps protect the patient, public, and community health.[97,98]

The application of universal precautions should begin with a comprehensive pain assessment, including an assessment of the risk for misuse of prescription opioids, along with a diagnostic formulation of the source of pain and any contributing factors.[97] Regular face-to-face visits should be planned and the use of opioids should be conceptualized as a trial or test of care that can be continued depending on how the patient progresses toward the goals of treatment or if the patient encounters challenges related to opioid therapy.[99] Framing the opioid therapy as a **trial** or **test**, where decisions to continue opioid therapy are made every 1 to

3 months, allows the patient to gain an understanding of why or when a modification in therapy may be warranted.[97] Regular in-office visits and clear, well-documented communications are necessary to ensure a thorough assessment of the risks and benefits of opioid therapy.

Patient Prescriber Agreements

A Patient Prescriber Agreement (PPA) with informed consent and a plan of care (***Table 6***)[100,101] should be signed by the both the patient and the provider. This document should be written at a level that patients can easily understand. A copy should be given to the patient to serve as a **"Patient Counseling Document."**

TABLE 6: Elements of PPA plan of care documents[100,101]

- Engagement in other recommended treatments
- Policies – monitoring, refills
- Permission to communicate with key others
- No illegal drug use, avoid sedative use
- Notifying provider of all other medications and drugs
- Discuss birth control, periodic monitoring for pregnancy
- Medication management:
  - Use exactly as directed (no adulteration of pills or patches, guidance on missed doses)
  - Protect from theft, safe storage (away from family, visitors, pets)
  - Safe disposal (read product-specific information for guidance)
  - No diversion, sharing, or selling

Elements of informed consent include the diagnosis, purpose of the proposed treatment, and risks and benefits.[102] The patient should be advised that monitoring for adherence, misuse, and diversion includes UDT, pill counts, and data from the PDMP. Patients should also be counseled to read and follow all directions regarding their medication, including directions for storage and disposal, in the medication guide for any products obtained from the pharmacist.

Informed consent goes beyond the simple formality of signing a paper outlining risks and treatment plans. The provider must discuss all aspects of proper opioid use and treatment adherence

Neonatal Abstinence Syndrome

Infants being born to mothers who use prescription opioids or illegal opioids can put the infant at risk for Neonatal Abstinence Syndrome (NAS). NAS can present in different ways ranging from problems with feeding, sleeping, and temperature regulation to seizures, failure to thrive, respiratory distress, and general central nervous system hyperirritability.[105,106] Long-term use (>30 days) and late use (ie, extending into third trimester) are associated with a greater risk for NAS.[106] When clinicians consider the use of opioids in pregnant women, the duration and timing of opioid therapy should be minimized if clinically indicated and risk factors should be explored.[103,106]

with the patient, including the proposed treatment plan, risks of addiction, and physical dependence; they also must verify the patient's understanding of the plan of care and address any questions that may arise.[97,100,101]

Included in the informed consent is the setting of realistic goals such as reducing (rather than eliminating) pain and increasing function. Goals should be SMART: that is **S**pecific, **M**easurable, **A**ction-oriented, **R**ealistic, and **T**ime-sensitive. Potential risks should be discussed, including: side effects and physical dependence; drug interactions/oversedation; possible impairment (eg, driving) when dose changes are being made; addiction and/or overdose; possible hyperalgesia (increased pain); and victimization by others seeking opioids. In women of childbearing potential, it is also important to discuss the significant risk of neonatal abstinence syndrome (see ***Sidebar, Neonatal Abstinence Syndrome***).[6,102-104]

When discussing universal precautions with the patient, the provider should use a health-oriented risk-benefit framework that judges the effectiveness of the opioid treatment, not the patient. The emphasis should be patient-centered, recognizing that each patient is unique and should be involved in safe decision-making. The provider's focus should be on whether the benefits of opioid therapy outweigh the risks for the specific patient (or for society).[103] This is in contrast to a judgmental approach in which the provider's framework for deciding to treat with opioids rests on whether the patient is good or bad, if the patient deserves opioids, if the patient should be rewarded or punished, and if the patient can be trusted.

Case Study

Plan of Care

When discussing the PPA's plan of care, the new provider explains that there are various opioid regimens that might be considered. Mary is able to tolerate her oral IR/SA oxycodone formulation, with good analgesia and no sedation at a dose of about 40 mg/day in divided doses. However, she is experiencing periodicity of effects (on-off response) that may be causing a withdrawal-mediated increase in pain. Her provider suggests that analgesia might be improved by achieving more stable blood levels of oxycodone using an ER/LA formulation at a lower dose (eg, 15 mg twice daily); the provider also recommends increasing the dose of gabapentin to 400 mg/day for synergy.

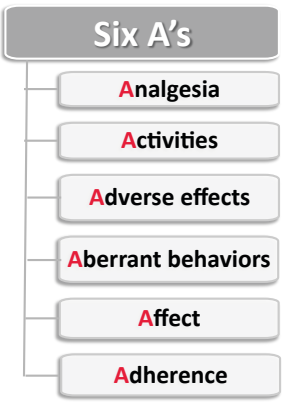
Mary agrees to this change in regimen, with the understanding that this is a test and that the treatment plan can be changed based on her response.

MONITORING STRATEGIES

Whether initiating or continuing opioid therapy, multifaceted monitoring, with regular face-to-face interactions, is essential not only to assess pain relief and functional improvement but also to identify adverse effects and to know when dosage adjustments or changes in regimen are needed. It may be helpful to frame the discussion of monitoring as a way to help protect the patient from getting harmed by opioid medications analogous to monitoring done for other medications that carry risk (eg, measuring renal function in patients on an ACE inhibitor for hypertension).

Although monitoring should be individualized to match patient risk, it is important to use a consistent approach employing Universal Precautions (see above). **Figure 9** outlines an approach to monitoring during office visits that is based on assessment of the **Six A's**. Assessment of analgesia and activities ensures that the patient is making progress toward pain relief and functional activity goals without experiencing intolerable adverse effects.[107] It is also important to assess any aberrant medication-taking behavior, carefully review adherence to the treatment regimen, and evaluate the patient's affect (eg, depression, anxiety).

FIGURE 9. Regular monitoring during office visits[107]



In addition, patients should be asked for a 24-hour inventory of their opioid use.[41,108,109] There is evidence that such behavioral observations may improve adherence and decrease illicit drug use.[110-112] It is important to keep in mind, however, that no monitoring strategy can prevent a dedicated deceiver from diverting their medication. For example, they may save the right number of medications and bring them to every appointment, falsify urine given for a UDT, or fill their prescriptions across state lines to avoid prescription data showing up on their state PDMP. Nevertheless, consistently applied monitoring strategies can reduce the risk of diversion and misuse.

Urine Drug Tests

Urine drug testing (UDT) provides objective evidence of medication adherence or absence of other substance use (***Figure 10***).[41,107-117] It is recommended that initial testing be done by immunoassays, as they are inexpensive and adequate for monitoring patients over time. However, immunoassay testing has important limitations. Labs and point of care drug testing kits vary as to the detectable drugs, the list of cutoff values for the detectable drugs and their metabolites (which may lead to false negative results), and the risk of false positives due to cross-reactivity between medications. In addition, UDT does not provide valid drug levels to determine the amount of opioid ingested. Due to these variables, unexpected results found with immunoassay screening tests should be confirmed with gas chromatography/mass spectroscopy (GC/MS).[118]

GC/MS, while more expensive, is more sensitive and specific than immunoassay tests: as shown in **Figure 11**, it

FIGURE 10. Rationale for urine drug testing[41,107-117]

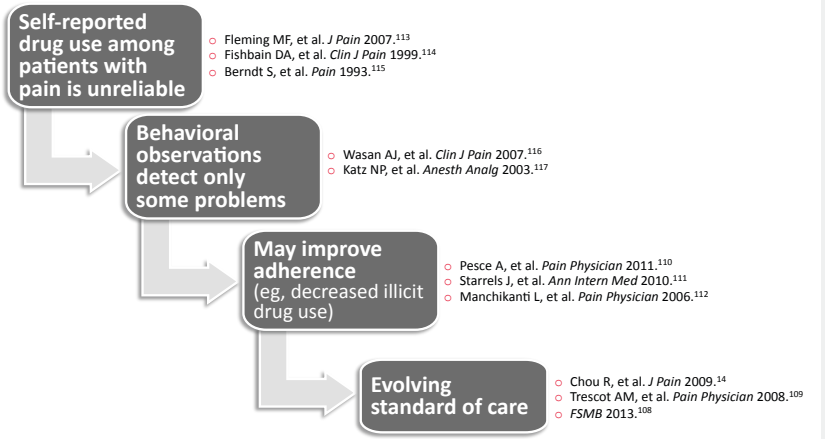
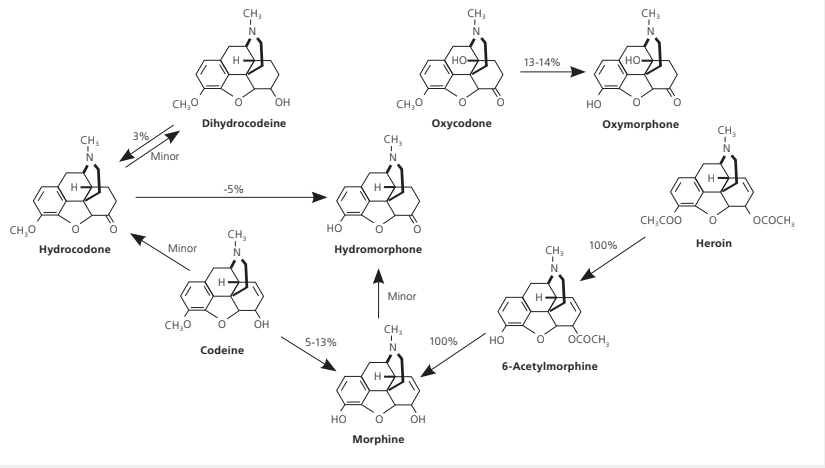


FIGURE 11. Molecules identified by urine drug testing[118]



can identify specific opioid molecules.[118-121] It is critical to have a toxicologist or a clinical pathologist who can be consulted to help interpret UDT and to help decide on the need for appropriate confirmatory testing. Useful references for UDT can be found at **www.pharmacomgroup.com/udt/udt5.pdf**.

Conducting Pill Counts

Pill counts are a helpful strategy to confirm the patient's adherence to the prescribed dosing schedule and to minimize the potential for diversion (***Table 7***). Using a 28-day rather than a 30-day prescription prevents patients from running out of medication on the weekends as well as from accumulating extra medication between refills. For example, using a 28-day process means that when a prescription is written on a Wednesday, it will be due for a refill in exactly 4 weeks on a Wednesday. If concerns arise in the course of treatment—for example, if it appears that a patient is diverting their medications or running out early—the patient can be asked to come in within a specified period of time for an immediate count of their medications. Another approach is to conduct random callbacks in which the patient knows that they will be called and asked to come in within 24 hours for a pill count.

TABLE 7: Strategy for conducting pill counts

To confirm medication adherence and minimize diversion:
■ Prescribe 28-day supply, rather than 30-day supply
■ Prescribe so that patient should have residual medication at appointments
■ Ask patient to bring in medications at each visit
■ For identified risks or concerns, request random callbacks for immediate counts

Prescription Drug Monitoring Program Data

Prescription drug monitoring programs (PDMPs) are statewide electronic databases with controlled substances prescription data that allow providers to monitor for patients who are going to multiple providers and pharmacies to obtain controlled substances.[122] These data are available to providers and pharmacists and include 12 months of data: date dispensed, patient name, provider name, pharmacy name, medication, and dose. Each state varies in terms of how quickly reports are generated (some are in real time; others may take days to weeks). Updated information on state PDMP programs can be obtained at **http://pdmpassist.org/content/stateterritorydistrict-contacts**. Several studies suggest an association between PDMP use and positive outcomes related to improving prescribing and reducing prescription drug abuse.[123]

Office Systems and Documentation

In order to optimize the office visit, systems need to be in place that support appropriate, safe opioid prescribing and that are consistent with federal and state guidelines and regulations regarding opioid prescribing, which are available at **http://www.deadiversion.usdoj.gov/index.html**. These tools, including controlled substance policies, PPA (informed consent and plan of care), management flow sheets, patient registries, and a list of referral and support sources, can be challenging to set up initially. However,

Safe opioid prescribing is a lot of work.

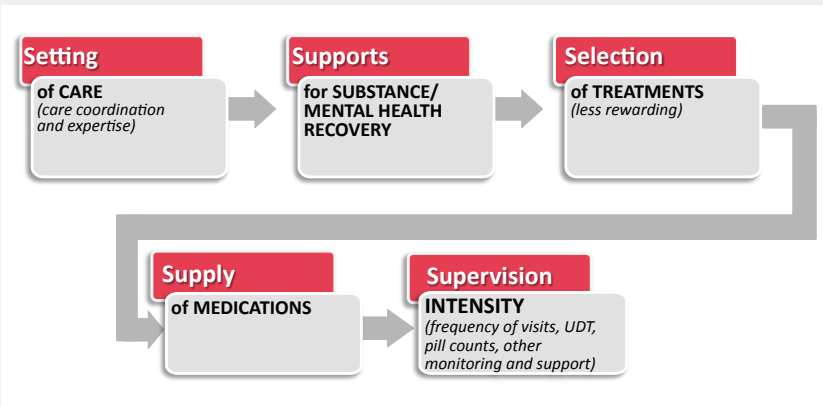
optimizing office systems can save time in the long-term. In addition, well-implemented office systems provide documentation that acts as a silent witness to address any future medicolegal issues. Documentation of clinical and diagnostic impressions and the rationale behind decisions protects the provider from a medicolegal standpoint and documents appropriate patient care.[107]

Office staff, including nurses, pharmacists, behavioral health specialists, and medical assistants, can provide valuable input into the development of these systems. Keep in mind, however, that having optimal office policies and procedures in place for opioid therapy is not helpful without a candid 2-way discussion with patients about their past medical and addiction histories and what their expectations are regarding therapy. Just as with informed consent, the process is not simply having the patient sign a paper outlining risks and treatment plans.

Patients With Past History of Addiction

Special consideration should be given to patients with history of a substance use disorder. First and foremost is careful selection of treatment with adequate trials of nonopioid therapy, using medications that are less rewarding and may be less risky for the patient; there should also be adequate trials of nonmedication treatments. If all other options have been tried and opioids are indicated, the intensity of supervision should be heightened.[124] Fundamental ways to increase the structure of care for patients on opioid therapy are outlined in **Figure 12**. These include the Five S's: the **S**etting of care, **S**upporting frameworks for recovery, **S**electing treatments with care, **S**upplying medications as appropriate, and **S**upervising at an appropriate intensity level.

FIGURE 12. Increased structure of care for patients with past history of addiction[124]



Setting and **Supports.** It is important to consider whether opioid therapy can be safely coordinated in the primary care setting, or whether a specialized setting may be more appropriate. In some cases, patient care may be enhanced by the care coordination and expertise available in psychiatric, mental health, or pain treatment settings. Whatever the setting, it is vital that the patient and provider both recognize that addiction is a challenging health issue.

In terms of supports, the provider should express admiration for the patient's recovery and acknowledge their desire to remain sober and ensure that they receive the supports they need for their recovery. In some cases, it may be appropriate to require that the patient be engaged in mutual-help groups (eg, Alcoholics Anonymous, Narcotics Anonymous), counseling, or other approaches while they are receiving opioids. Similar principles apply for individuals with mental health disorders, who may be at risk for misusing their opioids.

Opioid Selection, Supply, and **Supervision.** When selecting opioids for a patient with a history of addiction, one option is to prescribe them on a less rewarding schedule. IR/SA opioids, for example, should be carefully supervised. The supply of medications also may be very important. For many patients, it is prudent to require medication renewals on a weekly or every-2-week basis instead of monthly. It may also be beneficial to increase the intensity of supervision, including more frequent face-to-face visits, pill counts, and UDT. For many patients in recovery, it is a support to know that they are going to undergo objective testing of adherence.

Case Study

Response to New ER/LA Opioid Regimen

Mary initially responded well to the switch from IR/SA to ER/LA oxycodone, reporting somewhat more consistent pain relief without bothersome sedation. However, she continued to experience end-of-dose pain, which interfered with her concentration, about 9 hours after taking her medication.

Her provider increased the ER/LA oxycodone dose to 20 mg every 12 hours to reduce end-of-dose failure. The nurse contacted her 1 week later and confirmed that that this new regimen was providing effective pain relief without sedation. Mary reported that she was more active and better able to concentrate on her work.

Mary continued to do well on this regimen, which included gabapentin 400 mg 3 times daily, for nearly 1 year. She remained adherent with monitoring and did not exhibit any issues of concern such as aberrant medication-taking behavior.

However, after 11 months, she began to experience increased leg and back pain and started taking an extra oxycodone tablet in the afternoon. When her prescription ran out early, she presented at the emergency department (ED) of her local hospital, requesting an early ER/LA oxycodone refill. The ED physician noted that she was in moderate to severe opioid withdrawal and gave her a prescription for enough oxycodone to last until her scheduled appointment with her provider the next week.

At this scheduled visit, she explains why she ran out of oxycodone early (ie, she took extra tablets due to increase in her pain level)

and says she is concerned that her body has become "used" to her current dose. She is upset that her husband has called her "addicted." Her work has been affected, and she is having trouble sleeping. She wants to increase her dose of oxycodone.

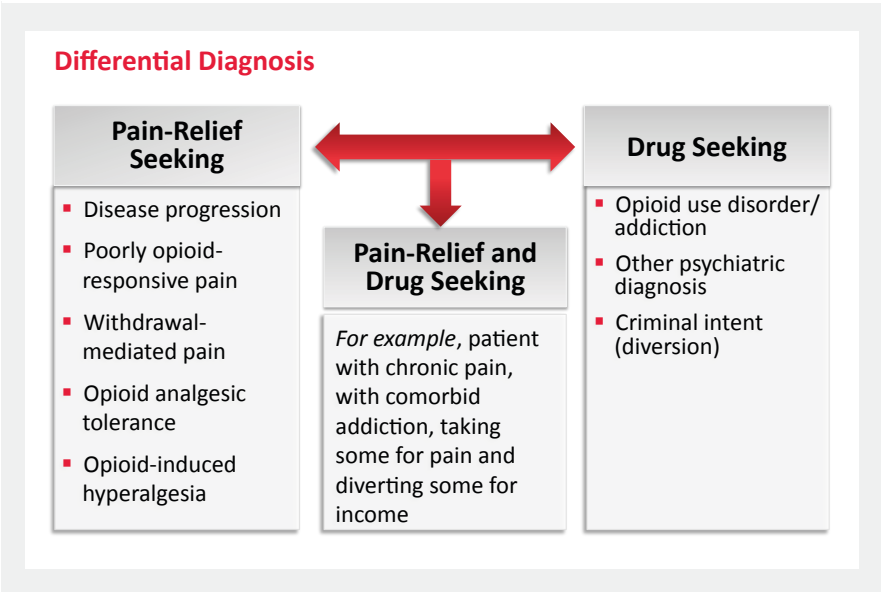
ASSESSING AND MANAGING ABERRANT MEDICATION-TAKING BEHAVIOR

The challenge here is to determine why the patient has requested an increase in her opioid dose. One issue may be that she has unrealistic expectations. If patients expect that opioids will eliminate their pain, they may think that more opioids will equal more pain relief. This can lead to unsanctioned dose escalation and/or continued requests for higher doses. In this situation, it is important to re-educate patients about realistic treatment goals and potential opioid risks.[125]

Monitoring for opioid misuse (eg, unsanctioned dose escalation) is necessary during opioid therapy, although the optimal monitoring intervals are unclear.[14] Various tools are available in addition to strategies such as pill counts, UDT, and monitoring PDMP data. In some instances, family members can provide honest, straightforward, objective information; however, there are instances in which family members provide inaccurate information for secondary gain.

Patient questionnaires, such as the Current Opioid Misuse Measure (COMM), can be useful in assessing the presence of aberrant drug-related behavior.[126] Unlike instruments such as the ORT, the COMM questionnaire, which contains 17 self-administered

FIGURE 13. Aberrant medication-taking behaviors[125]



items, was not designed to predict the risk of substance misuse; instead, it evaluates how patients are currently using their medication.[14]

Differential Diagnosis of Aberrant Medication-Taking Behaviors

The possibility of worsening pain, addiction, diversion, opioid-induced hyperalgesia, and analgesic tolerance are some of the concerns when a patient displays aberrant medication-taking behavior. The reasons for this behavior can be broken into 3 categories, as illustrated in **Figure 13**—the patient may be seeking pain relief, drugs, or both.[125]

Pain-Relief Seeking

The differential diagnosis of aberrant medication-taking behaviors needs to consider the issue of worsening pain. Pain may worsen due to disease progression, opioid analgesia tolerance, or opioid-induced hyperalgesia (OIH). Analgesic tolerance is a right shift in the dose-response curve, requiring an increasing dose to get the same level of analgesia. Analgesic tolerance has been demonstrated in animal models, but human studies find opioid doses can stabilize long-term. Therefore, it is reasonable to assume opioid analgesic tolerance is not common but may happen.[127] Increasing the opioid dose slightly should overcome the analgesic tolerance.

There are, however, cases in which increasing opioid doses improves analgesia but only temporarily. In such cases, one should consider OIH. OIH is a paradoxical enhanced pain sensitivity in patients on chronic opioid therapy.[128] The underlying pathophysiology is complex and not clearly understood, and the true incidence is unknown. There are also no official criteria or guidelines for diagnosing OIH. Clinically, OIH presents as generalized pain that is diffuse, ill-defined, and not necessarily located at the source of original pain; tapering off opioids should improve the pain symptoms.[54,129,130]

Drug Seeking

Drug seeking can be suggestive of addiction (opioid use disorder), self-medicating other conditions, and diversion. As previously noted, the diagnosis of addiction is based on the four C's (ie, loss of **C**ontrol; **C**ompulsive use; **C**ontinued use despite harm; and **C**raving), which manifest in aberrant medication-taking behaviors; again, it is important to keep in mind that addiction is not the same as physical dependence. Some patients will take opioids for nonpain-related symptom relief; for example, opioids can improve symptoms of depression and anxiety. It is important to assess this with the patient, as there are safer medications (selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs]) that should be used to treat these symptoms.

Diversion—that is, when a patient gives or sells their medications to others—can be hard to detect, but it should be considered with patients who refuse to comply with pill counts, have pill counts that are unexpected, or have UDTs that do not show presence of the opioid being prescribed. Unfortunately, patients of most concern may have a combination of both pain-relief seeking and drug seeking; for example, the patient with severe pain who has developed an opioid addiction and is selling part of their prescription to supplement their disability payments.

Aberrant Medication-Taking Behaviors Concerning for Addiction

Aberrant medication-taking behavior can present in many different ways: using opioids more than prescribed, forging prescriptions, selling prescriptions, unexpected UDT results, concurrent use of alcohol or illicit drugs, requests for early refills, visits to multiple doctors for opioid prescriptions, and reported lost/stolen prescriptions, just to name a few.[84] Particularly concerning behaviors for addiction—arranged on a scale of yellow to red alerts in order from worrisome to alarming—are listed in **Table 8**.[131]

MANAGING LACK OR LOSS OF BENEFIT

In this patient's case, it is possible that the aberrant medication-taking behavior was related to a lack or loss of benefit from the current opioid regimen. The factors that may be contributing to the pain should be reassessed to confirm opioid treatment is, indeed, appropriate or whether there may be alternate treatments that have not yet been given an adequate trial. Any comorbidities, including psychiatric disorders, should also be reassessed. A test of dose escalation or the addition of adjuvant medications also should be considered, as should the addition of breakthrough medication or possible opioid rotation. However, it should be remembered that not all chronic pain is opioid responsive and increasing the dose may simply increase the risk of adverse effects.

Breakthrough Pain

When starting ER/LA opioids, it should not be assumed that breakthrough medication is needed. However, when considering the use of breakthrough medication (rescue doses), the first choice should be nonopioids (eg, NSAIDs, APAP, adjuvant medications), followed by dual-mechanism opioids or IR/SA opioids. **Figure 14** depicts an algorithm for a stepwise approach to breakthrough pain.[132]

TABLE 8. Concerning behaviors for addiction[131]

Spectrum: Yellow to Red Flags	
O	Requests for increase opioid dose
O	Requests for specific opioid by name, "brand name only"
O	Nonadherence with other recommended therapies (eg, PT)
O	Running out early (ie, unsanctioned dose escalation)
O	Resistance to change therapy despite AE (eg, oversedation)
O	Deterioration in function at home and work
O	Nonadherence with monitoring (eg, pill counts, UDT)
O	Multiple "lost" or "stolen" opioid prescriptions
O	Illegal activities (eg, forging scripts, selling opioid prescription)

Modified from Portenoy RK. *J Pain Symptom Manage*. 1996;11(4):203-217.

Opioid Rotation

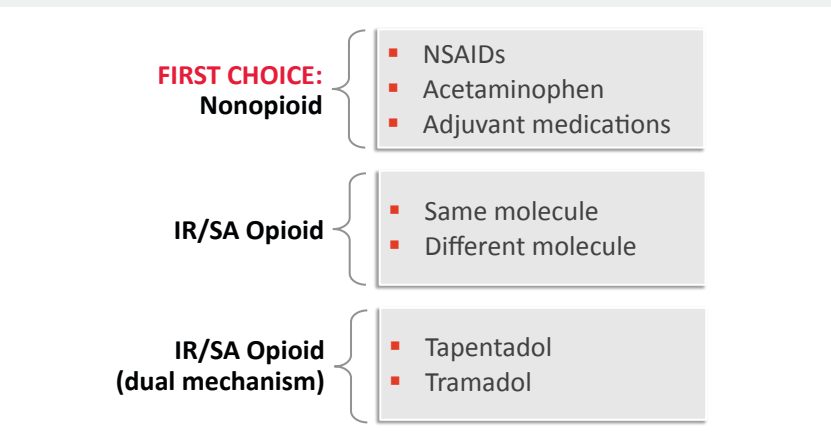
If a patient does not have adequate pain relief from an opioid or if there are adverse effects from a particular agent, switching to a different opioid may be warranted. Opioid rotation is based on the understanding that there is a large intraindividual variation in response to different opioids, presumably due to genetic variants of mu opioid receptors and pharmacokinetics (ie, opioid metabolism). This understanding is based largely on surveys and anecdotal evidence but it has yet to be validated in controlled studies.[133-135]

When converting from one opioid to another, it is customary to refer to an equianalgesic conversion table. Although many conversion tables and calculators (**www.globalrph.com/opioidconverter2.htm**) exist, there is no universally accepted method for converting between opioids. The so-called equianalgesic tables that exist are derived from relative potency ratios using single-dose analgesic studies in opioid-naïve rats. They do not reflect clinical realities of chronic opioid administration and are not reliable due to individual pharmacogenetic differences. In addition, most do not adjust for incomplete cross-tolerance. Consequently, patients can experience unmanaged pain, toxicity, and possibly overdose when dosing conversions are done.[136,137] While improved studies and resources emerge for opioid conversion, awareness of the risks associated with opioid conversions is necessary to prevent adverse outcomes associated with this practice. The safest approach is to decrease the "equianalgesic" dose of the new opioid by at least 50% to take into account incomplete cross-tolerance.

Continued Lack of Benefit

Unfortunately, not all chronic pain is responsive to opioids. More opioid does not always lead to better analgesia—and even if pain relief is improved, the risks associated with higher doses may outweigh the potential benefits. It is important to discuss continued lack of benefit

FIGURE 14. Considerations for breakthrough medication[132]



with the patient, empathizing with the severity and impact of their pain. This discussion should focus on the patient's strengths and encourage therapies that will help them cope with the pain; it is important to let patients know that you are abandoning opioids, not the patient, and that you remain concerned about them and their pain, even without opioids.

In some cases, it can be helpful to discuss difficult cases with a colleague, or to consider referral to a pain specialist, if available. Situations that may warrant a referral to a pain management specialist include uncertainty about a pain diagnosis or other treatment options, or for a second opinion about opioids in an individual patient. In some parts of the country, experts in the evaluation, diagnosis, and treatment of different types of pain offer a wide range of multimodal services, including counseling, physical therapy, and interventional treatments; patients should be advised about what services may be available. Pain management specialists can be found through state medical association websites and the American Academy of Pain Medicine website (**www.painmed.org**). In addition, free mentoring and education are available through the federally funded (Substance Abuse and Mental Health Services Administration) Providers' Clinical Support System for Opioid Therapies (PCSS-O) (**www.pcss-o.org**).

Concerns for Prescription Opioid Addiction

It is essential to give patients specific and timely feedback whenever a patient's behaviors raise concern for possible addiction; for example, loss of control, compulsive use, or continued use despite harm. Nevertheless, it is important to maintain a risk/benefit mindset, remembering that patients may suffer from both chronic pain and addiction. It may be necessary to "agree to disagree" with the patient if you perceive that the benefits of opioid therapy no longer outweigh the risks. You can make a statement such as, "I cannot responsibly continue prescribing opioids, as I feel it would cause you more harm than good."

Patients who are thought to have developed an addiction should always be offered referral to addiction treatment. Specific situations that should prompt referral to an addiction medicine specialist include when the patient is using illicit drugs, experiencing problems with other prescription medications (eg, benzodiazepines), or is addicted to alcohol. Referral to an addiction specialist is also indicated if a patient agrees they have an opioid addiction and wants help, such as referral to medication-assisted treatment (eg, methadone, buprenorphine, naltrexone), and/or has dual or trio diagnoses of pain, addiction, and psychiatric disease.

Resources to identify addiction treatment centers include the national Substance Abuse and Mental Health Services Administration (SAMHSA) website (**www.samhsa.gov/treatment**), along with various local resources. State medical societies and/or state departments of health should be able to provide listings of places where patients can be referred for acute detoxification and long-term residential treatment programs. They should also be able to give information about methadone maintenance treatment programs along with practices offering office-based treatment with buprenorphine or naltrexone. Finally, there are a host of free Alcoholics Anonymous and Narcotics Anonymous programs available in every community.

Tapering or Discontinuation of Opioids

There may be instances where tapering and discontinuation of opioid therapy are necessary: suspected addiction, diversion, toxicity, diminished efficacy, negative impact on quality of life, persistent nonadherence with agreed-upon treatment, resolution of the source of the pain, or reduced ability to function. Opioid withdrawal syndrome is a risk faced when patients on chronic opioid therapy have developed physical dependence and their therapy is discontinued. These symptoms start 2 to 3 half-lives after the last dose of an opioid and include anxiety, restlessness, tremor, diaphoresis, piloerection, cardiovascular effects (hypertension, tachycardia), gastrointestinal symptoms (nausea, abdominal cramping, diarrhea, anorexia), myalgias/arthralgias, rhinorrhea, sneezing, lacrimation, and yawning.[138]

Before considering tapering an opioid, identify if there is a definitive need for the tapering. If there is no physical dependence (eg, in patients who take intermittent IR/SA opioids), then tapering is not needed. In patients with physical dependence (eg, in patients taking around-the-clock opioids), opioid tapering is required. The speed of tapering contributes to the development of withdrawal symptoms. For example, despite the paucity of published literature on tapering long-term opioid treatment in cancer patients, one center published its practice of decreasing the original dose by 10% every 5 to 7 days until 30% of the dose is reached, followed by a weekly decrease of 10% of the remaining dose.[138] These providers found that their practice rarely precipitated withdrawal symptoms and promoted adherence.

Withdrawal symptoms may be treated with a centrally acting alpha-adrenergic agonist such as clonidine or tizanidine, although the use of these medications for treating withdrawal symptoms is off-label.[139] During the taper, alternative pain treatment modalities need to be instituted. Some patients may be reluctant to taper their opioids, despite explanation that the opioids are not offering enough benefit or are causing harm. These patients may make some of the following statements: "But I really, really need opioids," "Don't you trust me?," "I thought we had a good relationship/I thought you cared about me," "If you don't give them to me, I will drink/use drugs/hurt myself," or "Can you just give me enough to find a new doctor?" Your response to these statements should be: "I cannot continue to prescribe a medication that is not helping you (or is hurting you, or both)."

Case Study

Case Outcome After Next 12 Months

Following her presentation to the ED after running out of her oxycodone, Mary's regimen was adjusted. She was rotated off of ER/LA oxycodone 40 mg daily and converted to ER/LA morphine, with a 50% reduction in the equianalgesic dose to account for incomplete cross-tolerance to ER/LA morphine 15 mg twice daily. Gabapentin was titrated to 600 mg 3 times daily. Amitriptyline 10 mg at night and ibuprofen 400 mg every 8 hours for breakthrough pain were added to the regimen.

Mary joined a monthly chronic pain support group, which she says provides psychologic support and has helped her develop new pain-coping strategies. She has had good improvement in pain and function, with PEG scores remaining between 5 and 6 out of 10 at her regular assessments, and she has been able to stay employed. She has been adherent with the treatment plan and monitoring without aberrant medication-taking behaviors and has regularly scheduled follow-up visits.

SUMMARY AND CONCLUSIONS

As illustrated by this hypothetical case, safe opioid prescribing requires careful assessment, monitoring, reassessment with appropriate changes in the treatment plan, and documentation. Opioids should not be used as first-line therapy for chronic pain, but for patients with severe pain that is not improved with nonopioid therapies, opioids can provide pain relief and improve some patients' daily function and quality of life. They should be considered as just one tool in a multimodal approach that includes self-care and synergistic treatments, including nonpharmacologic therapies.

Although care must be individualized, it is essential to employ universal precautions due to the considerable misuse potential and risk of adverse events with opioid analgesics. Treatment should be initiated as a trial aimed at achieving defined functional goals—and it should be continued, modified, or discontinued depending on the patient's response and clinical indications.

Patients must be continually closely monitored to address the balance of benefit to risk, which can change over time. Regular office visits should be scheduled to determine whether to continue, modify, or discontinue therapy. The provider must remain vigilant for signs of aberrant medication-taking behavior that may signal drug misuse or inadequate benefit—or a combination of both.

In summary, opioids can be beneficial for some patients—but harmful for others. Side effects are common but usually manageable and typically diminish over time. Opioids do carry significant risks for overdose death and addiction—but many of these risks, including the misuse potential, can be addressed through a systematic approach to patient assessment and monitoring.

Additional Resources

Following is a list of links to selected tools that may be of particular value in establishing office systems and assessing patients who may be candidates for chronic opioid therapy.

- A wide range of tools and resources to facilitate safe opioid prescribing are available at the SCOPE of Pain website, **www.scopeofpain.com/tools-resources/**
- The FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics is available at **www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_opioids_2015-10-23_FDA_Blueprint.pdf**
- Detailed information regarding specific medications can be found at the National Library of Medicine's DailyMed website, **www.dailymed.nlm.nih.gov/dailymed/**

REFERENCES

1. Walk D, Poliak-Tunis M. Chronic pain management: an overview of taxonomy, conditions commonly encountered, and assessment. *Med Clin N Am.* 2016;100(1):1-16.
2. Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Report Brief. June 29, 2011. http://iom.nationalacademies.org/reports/2011/relieving-pain-in-america-a-blueprint-for-transforming-prevention-care-education-research.aspx. Accessed February 10, 216.
3. Peter D. Hart Research Associates. Americans Talk About Pain. A survey among adults nationwide conducted for Research!America. August 2003. http://www.researchamerica.org/sites/default/files/uploads/poll2003pain.pdf.
4. Rudd RA, Aleshire N, Zibbell JE, et al. Increases in drug and opioid overdose deaths — United States, 2000–2014. *MMWR.* 2016;64(50);1378-1382.
5. Centers for Disease Control Prevention. Vital signs: overdoses of prescription opioid pain relievers — United States, 1999–2008. *MMWR.* 2016;60(43);1487-1492.
6. Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med.* 2015;372:2118-2126.
7. Volkow ND, Frieden TR, Hyde PS, et al. Medication-assisted therapies-tackling the opioid-overdose epidemic. *N Engl J Med.* 2014;370:2063-2066.
8. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med.* 2015;372:241-248.
9. Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (HHS Publication No. SMA 15-4927, NSDUH Series H-50). http://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf.
10. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. *Treatment Episode Data Set (TEDS): 2001-2011. State Admissions to Substance Abuse Treatment Services.* BHSIS Series S-68, HHS Publication No. (SMA) 14-4832. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
11. Substance Abuse and Mental Health Services Administration. Emergency department data. Updated February 2, 2016. http://www.samhsa.gov/data/emergency-department-data-dawn/reports. Accessed January 6, 2016.
12. Vowles KE, McEntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain.* 2015;156(4):569-576.
13. King NB, Fraser V, Boikos C, et al. Determinants of increased opioid-related mortality in the United States and Canada, 1990–2013: a systematic review. *Am J Public Health.* 2014;104(8):e32-e42.
14. Chou R, Ballantyne JC, Fanciullo GJ, et al. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain.* 2009;10(2):147-159.
15. Evers GCM. Pseudo-opioid-resistant pain. *Support Care Cancer.* 1997;5:457-460.
16. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. *Br J Anaesth.* 2008;101(1):17-24.
17. Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *J Gen Intern Med.* 2009;24(6):733-738.
18. Smith PC, Schmidt SM, Allensworth-Davies D, Saltz R. Primary care validation of a single-question alcohol screening test. *J Gen Intern Med.* 2009;24(7):783-788.
19. Smith PC, Schmidt SM, Allensworth-Davies D, Saltz R. A single-question screening test for drug use in primary care. *Arch Intern Med.* 2010;170(13):1155-1160.
20. Gatchel RJ. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. *American Psychologist.* 2004;59(8):795-805.
21. Bennett RM. Emerging concept in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. *Mayo Clin Proc.* 1999;74:385-398.
22. Cheatle MD, Gallagher RM. Chronic pain and comorbid mood and substance use disorders: a biopsychosocial treatment approach. *Curr Psychiatry Rep.* 2006;8(5):371-376.
23. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. *Psychosom Med.* 2002;64(5):773-786.
24. Knaster P, Karlsson H, Estlander AM, et al. Psychiatric disorders as assessed with SCID in chronic pain patients: the anxiety disorders precede the onset of pain. *Gen Hosp Psychiatry.* 2012;34(1):46-52.
25. Polatin PB, Kinney RK, Gatchel RJ, et al. Psychiatric illness and chronic low-back pain. The mind and the spine—which goes first? *Spine* (Phila Pa 1976). 1993;18(1):66-71.

26. Fischer-Kern M, Kapusta ND, Doering S, et al. The relationship between personality organization and psychiatric classification in chronic pain patients. *Psychopathology.* 2011;44(1):21-26.

27. Otis JD, McGlinchey R, Vasterling J, Kerns RD. Complicating factors associated with mild traumatic brain injury: impact on pain and posttraumatic stress disorder treatment. *J Clin Psychol Med Settings.* 2011;18:145-154.

28. Kroenke K, Spitzer RL, Williams JBW. The patient health questionnaire-2 validity of a two-item depression screener. *Med Care.* 2003;41(11):1284-1292.

29. Pathan H, Williams J. Basic opioid pharmacology: an update. *Br J Pain.* 2012;6(1):11-16.

30. McCleane G, Smith HS. Opioid for persistent noncancer pain. *Med Clin North Am.* 2007;91(2):177-197.

31. Hojsted J, Sjogren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain.* 2007:490-518.

32. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. *J Pain Symptom Manage.* 2003;26(5):1026-1048.

33. Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc.* 2009;84(7):602-612.

34. Jedinger N, Khinast J, Roblegg E. The design of controlled-release formulations resistant to alcohol-induced dumping- a review. *Eur J Pharm Biopharm.* 2014;87(2):217-226.

35. Fredheim OMS, Moksnes K, Borchgrevink, et al. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand.* 2008;52:879-889.

36. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43(13):879-923.

37. Drug Enforcement Administration. Practitioner's manual. Updated 2006. http://www.deadiversion.usdoj.gov/pubs/manuals/pract/. Accessed January 27, 2016.

38. Wade WE, Spruill WJ. Tapentadol hydrochloride: a centrally acting oral analgesic. *Clin Ther.* 2009;31(12):2804-2818.

39. Wiffen PJ, Derry S, Naessens K, Bell RF. Oral tapentadol for cancer pain. *Cochrance Database Syst Rev.* 2015;9:CD011460.

40. Ballantyne JC, Mao Jianren. Opioid therapy for chronic pain. *N Engl J Med.* 2003;349(20):1943-1953.

41. Chou R, Turner JA, Devine EB, et.al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention workshop. *Ann Intern Med.* 2015;162(4):276-286.

42. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin. *JAMA.* 2005;293(24):3043-3052.

43. Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ.* 2006;174(11):1589-1594.

44. Kelso E, Edwards JE, Moore AR, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain.* 2004;112(3):372-380.

45. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain (review). *Cochrane Syst Rev.* 2010;20:CD006605.

46. Reuben DB, Alvanzo AAH, Ashikaga T, et al. National institutes of health pathways to prevention workshop: the role of opioids in the treatment of chronic pain. *Ann Intern Med.* 2015;162(4):295-300.

47. Manchikanti L, Singh V, Caraway AL, et al. Breakthrough pain chronic non-cancer pain: fact, fiction, or abuse. *Pain Physician.* 2011;14:E103-E117.

48. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician.* 2008;11(2 suppl):S105-S120.

49. Saunders KW, Dunn KM, Merrill JO, et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med.* 2010;25(4):310-315.

50. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology.* 2010;112:226-238.

51. Kobus AM, Smith DH, Morasco BJ, et al. Correlates of higher-dose opioid medication use for low back pain in primary care. *J Pain.* 2012;13(11):1131-1138.

52. Huxtable CA, Roberts LJ, Somogyi AA, et al. Acute pain management in opioid-tolerant patients: a growing challenge. *Anaesth Intensive Care.* 2011;39(5):804-823.

53. Brush DE. Complications of long-term opioid therapy for management of chronic pain: the paradox of opioid-induced hyperalgesia. *J Med Toxicol.* 2012;8(4):387-392.

54. Lee M, Silverman S, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician.* 2011;14:145-161.

55. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J Bone Joint Surg Am.* 2009;91(4):919-927.

56. Townsend CO, Kerkvliet JL, Bruce BK, et al. A longitudinal study of the efficacy of a comprehensive pain rehabilitation program with opioid withdrawal: comparison of treatment outcomes based on opioid use status at admission. *Pain.* 2008;140(1):177-189.

57. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med.* 2010;152(2):85-92.

58. Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med.* 2010;170(16):1425-1432.

59. Bohnert AS, Ilgen MA, Ignacio RV, et al. Risk of death from accidental overdose associated with psychiatric and substance use disorders. *Am J Psychiatry.* 2012;169(1):64-70.

60. Gomes T, Mamdani MM, Dhalla IA, et al. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011;171(7):686-691.

61. Paulozzi LJ, Kilbourne EM, Shah NG, et al. A history of being prescribed controlled substances and risk of drug overdose death. *Pain Med.* 2012;13(1):87-95.

62. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *BMJ.* 2015;350:g6380.

63. Fakata KL, Cole BE. Peripheral opioid antagonists: a therapeutic advance for optimizing opioid gastrointestinal tolerability. *J Fam Pract.* 2007; 56(6 suppl):S3-S12.

64. Webster L, Dhar S, Eldon M, et al. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. *Pain.* 2013;154(9): 1542-1550.

65. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med.* 2008;358(22):2332-2343.

66. Nicholson B. Responsible prescribing of opioids for the management of chronic pain. *Drugs.* 2003;63(1):17-32.

67. Kotlinska-Lemieszek A, Klepstad P, Haugen DF. Clinically significant drug-drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review. *Drug Des Devel Ther.* 2015;9:5255-5267.

68. US Food and Drug Administration. FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. http://www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_opioids_2015-10-23_FDA_Blueprint.pdf. Accessed February 8, 2016.

69. van Ojik AL, Jansen PA, Brouwers JR, et al. Treatment of chronic pain in older people: evidence-based choice of strong-acting opioids. *Drugs Aging.* 2012;29(8):615-625.

70. Baumbauer KM, Young EE, Starkweather AR, et al. Managing chronic pain in special populations with emphasis on pediatric, geriatric, and drug abuser populations. *Med Clin North Am.* 2016;100(1):183-197.

71. US Food and Drug Administration. CDER Conversation: Pediatric pain management options. http://www.fda.gov/Drugs/NewsEvents/ucm456973.htm. Accessed February 10, 2016.

72. Cheatle MD. Prescription opioid misuse, abuse, morbidity, and mortality: balancing effective pain management and safety. *Pain Med.* 2015;16 (1 suppl):S3-S8.

73. Savage SR, Joranson DE, Covington EC, et al. Definitions related to the medical use of opioids: evolution towards universal agreement. *J Pain Symptom Manage.* 2003;26(1):655-667.

74. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect.* 2002;1:13-20.

75. Akbik H, Butler SF, Budman SH, et al. Validation and clinical application of the screener and opioid assessment for patients with pain (SOAPP). *J Pain Symptom Manage.* 2006;32(3):287-293.

76. Ives TJ, Chelminski PR, Hammett-Stabler et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res.* 2006;6:46.

77. Liebschultz JM, Saitz R, Weiss RD, et al. Clinical factors associated with prescription drug use disorder in urban primary care patients with chronic pain. *J Pain.* 2010;11(11):1047-1055.

78. Michna E, Ross EL, Hynes WL, et al. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. *J Pain Symptom Manage.* 2004;28(3):250-258.

79. Reid CM, Engles-Horton LL, Weber MB, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med.* 2002;17:173-179.

80. Cassidy TA, DasMahapatra P, Black A, et al. Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. *Pain Med.* 2014;15(3):440-451.

81. Abuse-deterrent opioid formulations. *Med Lett Drugs Ther.* 2015;57(1476):119-120.

82. Sessler NE, Downing JM, Kale H, et al. Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. *Pharmacoepidemiol Drug Saf.* 2014;23:1238-1246.

83. Moore TM, Jones T, Browder JH, et al. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic management. *Pain Med.* 2009;10(8):1426-1433.

84. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. *Pain Med.* 2005;6(6):432-442.

85. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5.* Washington, DC: American Psychiatric Association; 2013.

86. Substance Abuse and Mental Health Services Administration. Emergency department data/DAWN. Updated September 12, 2014. http://www.samhsa.gov/data/emergency-department-data-dawn/reports. Accessed February 10, 2016.

87. Beletsky L, Rich JD, Walley AY. Prevention of fatal opioid overdose. *JAMA.* 2012;308(18):1863-1864.

88. Smith HS. Opioid metabolism. *Mayo Clin Proc.* 2009;84(7):613-624.

89. Smith HS. Variations in opioid responsiveness. *Pain Physician.* 2008;11(2):237-248.

90. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain.* 2010;150(3):573-581.

91. Woolf CJ; American College of Physicians; American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med.* 2004;140(6):441-451.

92. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, ot their combination for neuropathic pain. *N Engl J Med.* 2005;352(13):1324-1334.

93. Reid MC, Papaleontiou M, Ong A, et al. Self-management strategies to reduce pain and improve function among older adults in community settings: a review of the evidence. *Pain Medicine* (Malden, Mass). 2008;9(4):409-424.

94. Woodbury A, Soong SN, Fishman D, et al. Complementary and alternative medicine therapies for the anesthesiologist and pain practitioner: a narrative review. *Can J Anaesth.* 2016;63(1):69-85.

95. Wirth JH, Hudgins CJ, Paice JA. Use of herbal therapies to relieve pain: a review of efficacy and adverse effects. *Pain Management Nursing.* 2005;6(4):145-167.

96. Maroon JC, Bost JW, Maroon A. Natural anti-inflammatory agents for pain relief. *Surgical Neurology International.* 2010;1:80.

97. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med.* 2005; 6(2):107-112.

98. Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med.* 2014;160:38-47.

99. Franklin GM; American Academy of Neurology. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology.* 2014;83(14):1277-1284.

100. Fishman SM, Kreis PG. The opioid contract. *Clin J Pain.* 2002;18(4 suppl):S70-S75.

101. Arnold RM, Han PKJ, Seltzer D. Opioid contracts in chronic nonmalignant pain management: objectives and uncertainties. *Am J Med.* 2006;119(4):292-296.

102. Cheatle MD, Savage SR. Informed consent in opioid therapy: a potential obligation and opportunity. *J Pain Symptom Manage.* 2012;44(1):105-116.

103. Nicolaidis C. Police officer, deal-maker, or health care provider? Moving to a patient-centered framework for chronic opioid management. *Pain Med.* 2011; 12(6):890-897.

104. Paterick TJ, Carson GV, Allen MC, et al. Medical informed consent: general considerations for physicians. *Mayo Clin Proc.* 2008;83(3):313-319.

105. Stover MW, Davis JM. Opioids in pregnancy and neonatal abstinence síndrome. *Semin Perinatol.* 2015;39(7):561-565.

106. Desai RJ, Huybrechts KF, Hernandez-Diaz S, et al. Exposure to prescription opioid analgesics in utero and risk of neonatal abstinence syndrome: population based cohort study. *BMJ.* 2015;350:h2102.

107. Passik SD, Kirsh KL, Whitcomb L, et al. A new tool to assess and document pain outcomes in chronic pain patients receiving opioid therapy. *Clin Ther.* 2004;26(4):552-561.

108. Federation of State Medical Boards. Model policy for the use of opioid analgesics in the treatment of chronic pain. http://www.fsmb.org/policy-and-education/education-meetings/pain-policies. Accessed February 10, 2016.

109. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. *Pain Physician.* 2008;11(2 suppl):S5-S62.

110. Pesce A, West C, Rosenthal M, et al. Illicit drug use in the pain patient population decreases with continued drug testing. *Pain Physician.* 2011;14:189-193.

111. Starrels J, Becker WC, Alford DP, et al. Systematic review: treatment agreements and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med.* 2010;152(11):712-720.

112. Manchikanti L, Manchukonda R, Pampati V, et al. Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? *Pain Physician.* 2006;9:123-129.

113. Fleming MF, Balousek SL, Klessig CL, et al. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain.* 2007;8(7):573-582.

114. Fishbain DA, Cutler RB, Rosomoff HL, et al. Validity of self-reported drug use in chronic pain patients. *Clin J Pain.* 1999;15(3):184-191.

115. Berndt S, Maier C, Schütz HW. Polymedication and medication compliance in patients with chronic non-malignant pain. *Pain.* 1993;52(3):331-339.

116. Wasan AD, Butler SF, Budman SH, et al. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain.* 2007;23(4):307-315.

117. Katz NP, Sherburne S, Beach M, et al. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. *Anesth Analg.* 2003;97(4):1097-1102.

118. Reisfield GM, Chronister CW, Goldberger BA, et al. Unexpected urine drug testing results in a hospice patient on high-dose morphine therapy. *Clin Chem.* 2009;55(10):1765-1768.

119. Peppin JF, Passik SD, Couto JE, et al. Recommendations for urine drug monitoring as a component of opioid therapy in the treatment of chronic pain. *Pain Med.* 2012;13(7):886-896.

120. Heit HA, Gourlay DL. Urine drug testing in pain medicine. *J Pain Symptom Manage.* 2004;27(3):260-267.

121. Heit HA, Goulay DL. Tackling the difficult problem of prescription opioid misuse. *Ann Intern Med.* 2010;152(11):747-748.

122. Haffajee RL, Jena AB, Weiner SG. Mandatory use of prescription drug monitoring programs. *JAMA.* 2015;313(9):891-892.

123. Clark, T, Eadie J, Knue P, et al, for The Prescription Drug Monitoring Program Center of Excellence Heller School for Social Policy and Management, Brandeis University Prescription Drug Monitoring Programs: an assessment of the evidence for best practices. Prepared for The Pew Charitable Trusts, September 20, 2012. http://www.pdmpexcellence.org/sites/all/pdfs/Brandeis_PDMP_Report.pdf. Accessed February 10, 2016.

124. Savage SR, Kirsch KL, Passik SD. Challenges in using opioids to treat pain in persons with substance use disorders. *Addict Sci Clin Pract.* 2008;4(2):4-25.

125. Alford DP. Chronic back pain with possible prescription opioid misuse. *JAMA.* 2013;309(9):919-925.

126. Butler SF, Budman SH, Fernandez KC, et al. Development and validation of the current opioid misuse measure. *Pain.* 2007;130(1-2):144-156.

127. Joseph EK, Reichling DB, Levine JD. Shared mechanisms for opioid tolerance and a transition to chronic pain. *J Neurosci.* 2010;30(13):4660-4666.

128. Yi P, Pryzbylkowski P. Opioid induced hyperalgesia. *Pain Med.* 2015;16:S32-S36.

129. Chang G, Chen L, Mao J. Opioid tolerance and hyperalgesia. *Med Clin North Am.* 2007;91(2):199-211.

130. Eisenberg E, Suzan E, Pud D. Opioid-induced hyperalgesia (OIH): a real clinical problem or just an experiment phenomenon? *J Pain Symptom Manage.* 2014;49(3):632-636.

131. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. *J Pain Symptom Manage.* 1996;11(4):203-217.

132. Davies AN, Dickman A, Reid C, et al; Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain.* 2009;13(4):331-338.

133. Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain.* 2002;18:S3-S13.

134. Fine PG, Portenoy RK. Establishing "best practices" for opioid rotation: conclusions of an expert panel. *J Pain Symptom Manage.* 2009;28(3):418-425.

135. Smith HS, Peppin JF. Toward a systematic approach to opioid rotation. *J Pain Res.* 2014;7:589-608.

136. Rennick A, Atkinson T, Cimino NM, et al. Variability in opioid equivalence calculations [published online September 9, 2015]. *Pain Med.* doi:10.1111/pme.12920.

137. Webster LR, Fine PG. Review and critique of opioid rotation practices and associated risks of toxicity. *Pain Med.* 2012;13:562-570.

138. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: evidence and recommendations for everyday practice. *Mayo Clin Proc.* 2015;90(6):828-842.

139. Nicholls L, Bragaw L, Ruetsch C. Opioid dependence treatment and guidelines. *J Manag Care Pharm.* 2010;16(1 suppl B):S14-S21.

POSTTEST

Instructions: To receive CME credit, please register and complete the posttest online at ***www.scopeofpain.com/folio/create-an-account.php***

1. **Which of the following is NOT a risk factor for prescription opioid misuse?**
   A. Age less than 45 years
   B. Personal history of substance use disorder
   C. Family history of substance use disorder
   D. History of unemployment

2. **Some extended-release or long-acting (ER/LA) opioid formulations are rapidly released when the patient ingests alcohol, referred to as "dose dumping."**
   A. True
   B. False

3. **All of the following regarding methadone are true EXCEPT:**
   A. Serum half-life is long and highly variable (up to 120 hours)
   B. Analgesic effect of 6 to 8 hours
   C. It may shorten the QTc interval
   D. It is an NMDA receptor antagonist

4. **When starting transdermal fentanyl, inform patients:**
   A. To use on an "as-needed" basis when they have pain
   B. That they will get maximum effects within 10-15 minutes of applying patch
   C. That the patch should not be exposed to heat or put on broken skin
   D. When patch is removed, drug levels drop to zero within 4 hours

5. **One of ER/LA opioid analgesics' most severe adverse effects is:**
   A. Respiratory depression
   B. Diarrhea and dehydration
   C. Thromboembolism and stroke
   D. Myocardial infarction

6. **In which situation would ER/LA opioid prescribing be appropriate?**
   A. Acute pain
   B. Chronic constant pain in a patient with opioid tolerance
   C. Chronic intermittent/episodic pain
   D. All of the above correct

7. **Before prescribing ER/LA oxymorphone, one should first ensure that:**
   A. Patient is opioid-tolerant
   B. Patient has failed other ER/LA opioids
   C. Patient has acute pain
   D. Patient has intermittent, occasional chronic pain

8. **When prescribing ER/LA opioid analgesics, prescribers should:**
   A. Use a Patient-Prescriber Agreement only if the patient is at high risk for opioid addiction
   B. Use a legally binding contract with the patient that ensures that he/she will not resell the opioids
   C. Use a Patient-Prescriber Agreement as the basis for counseling the patient
   D. Use a legally binding contract to protect the prescriber from accusations of patient abandonment

9. **You get an anonymous call that your patient is selling the ER/LA opioid you have prescribed. You:**
   A. Fire the patient from your practice
   B. Report the patient to state police diversion unit
   C. Call the patient in for a random pill count and urine drug testing (UDT)
   D. Ignore the call

10. **When opioid therapy is initiated, both the patient and provider should expect:**
    A. A short-term trial/test of opioid therapy
    B. Long-term use of the opioid therapy
    C. Continued opioid therapy until adequate pain relief is achieved
    D. Continued opioid therapy until the patient shows signs of addiction

(posttest continued on next page)

POSTTEST

11. Match each tool to its use described below:

A. ORT scale
B. PEG scale
C. COMM scale
D. PHQ-2

1. Used as a quick assessment for assessing pain and measuring benefits from opioid therapy
2. Used to assess risk of prescription opioid misuse in a patient being considered for opioid therapy
3. Used to assess risk of prescription opioid misuse in a patient currently on opioid therapy
4. Used as a quick screen for depression

12. Match each effect to its correct description below:

A. Opioid-induced hyperalgesia only
B. Opioid tolerance only
C. Both opioid-induced hyperalgesia and opioid tolerance

1. Patient on chronic opioids presents with worsening pain
2. Should get sustained improvement with increase in opioid dose
3. May get worse with increase in opioid dose

13. Physical dependence:

A. Is equal to addiction
B. Results in withdrawal if the opioid is discontinued without a taper
C. Results in the need for increased opioid doses to achieve the same effect
D. Occurs when patients have inadequately treated pain

14. Your patient increases his opioid dose because his pain is "8 out of 10" and he appears oversedated. What would you do?

A. Increase dose of opioid because he still has severe pain
B. Continue current opioid dose until tolerance to sedation is reached
C. Decrease current opioid dose because of his oversedation
D. Stop the current opioid because the patient is likely addicted

15. All opioid equianalgesic tables adjust for incomplete cross-tolerance in opioid rotation.

A. True
B. False