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Continuing Medical Education

CME FOR MDs, DOs, PAs AND OTHER HEALTH CARE PROVIDERS

2020 TENNESSEE MEDICAL LICENSURE PROGRAM

TARGETED SERIES OF CME FOR LICENSE RENEWAL

PROGRAM INCLUDES:

3

HOURS

*Prescribing Controlled Substances**

***MANDATORY CME REQUIREMENT**

Tennessee Physicians must complete 2 hours of CME in controlled substance prescribing in accordance with board rules

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2020 TENNESSEE

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REQUIRED TO RECEIVE CREDIT

*Completion of this course satisfies the mandatory 2 credits in controlled substance prescribing which must include instruction in the Department's Chronic Pain Guidelines.

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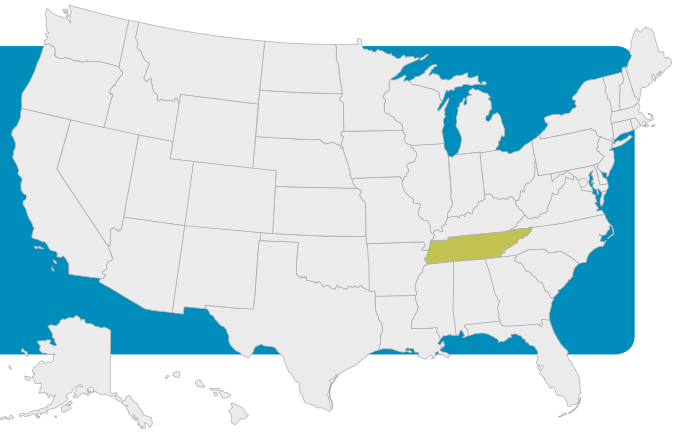

Tennessee Professional License Requirements

MANDATORY CONTINUING MEDICAL EDUCATION REQUIREMENT FOR LICENSE RENEWAL

A medical license expires on the last day of licensee's birth month and must be renewed prior to this date.

PHYSICIAN CME REQUIREMENTS

By Board Rule, all licensees are required to complete forty (40) hours of continuing medical education courses during the two (2) calendar years (January 1 – December 31) preceding their licensure renewal year. All licensees (unless exempt under TENN. CODE ANN. § 63-1-402(c)) shall complete at least two (2) of the forty (40) required hours of continuing education on controlled substance prescribing, which must include instruction in the Department's Chronic Pain Guidelines on opioids, benzodiazepines, barbiturates and carisoprodol and may include topics such as medicine addiction, risk management tools and other topics approved by the Board.

EXEMPTION

The following licensees are exempt from these new requirements:

1) Veterinarians.

2) Providers practicing at a registered pain management clinic.

3) Medical doctors who are board certified by the American Board of Medical Specialties (ABMS) or the American Board of Physician Specialties (ABPS) in one or more of the following specialties or subspecialties: pain management, anesthesiology, physical medicine and revhabilitation, neurology or rheumatology.

OSTEOPATHIC PHYSICIANS

If you are a licensed osteopathic physician in the state of Tennessee with a DEA registration, as a condition of renewal, you will be required to complete two (2) hours of continuing education related to controlled substance prescribing which must include instruction in the Department's Chronic Pain Guidelines.

PHYSICIAN ASSISTANT CME REQUIREMENTS

Continuing Education - Hours Required (a) All physician assistants must, within a two (2) year period prior to the application for license renewal, complete one hundred (100) hours of continuing medical education satisfactory to the Committee.

1. At least fifty (50) hours shall be obtained in certified medical education Category I.

2. If you're a licensee with a DEA Registration at least two (2) Category I hours of the required continuing education hours shall address controlled substance prescribing, which must include instruction in the Department's treatment guidelines. Licensees without a DEA registration must complete one (1) hour in prescribing practices.

3. The division of hours between Category I & Category II continuing medical education must be consistent with the requirements of the N.C.C.P.A. as described on the most current N.C.C.P.A. "Continuing Medical Education Logging Form."

Tennessee Board of Medical Examiners
665 Mainstream Drive, 2nd Floor
Nashville, TN 37243
615-532-3202 local or
1-800-778-4123 nationwide

MD/DO CME DEADLINES:

Licensees renewing in 2020:
CME must be earned by 12/31/2019
Licensees renewing in 2021:
CME must be earned by 12/31/2020

LICENSE TYPES:

Physcians and Physician Assistants

ABOUT US

For more than 45 years InforMed has been providing high level education activities to physicians and other healthcare professionals. Through our level of engagement with a wide variety of stakeholders, including our physician association, we have become the foremost public health policy continuing medical education organization in the United States. We are recognized as the leading provider of mandatory CME activities to physicians as a means of updating knowledge, improving competencies and fulfilling requirements for federal, state, regulatory and license renewal

Dear Tennessee Medical Professionals,

InforMed is pleased to offer this collection of CME activities for health care professionals in the state of Tennessee. The uniquely tailored curriculum is designed to promote a learning experience customized to the educational needs of the Tennessee medical professional. Participants earn *AMA PRA Category 1 Credit™* through these self-directed, on-demand courses.

The CME series is designed to streamline the education requirements of the Tennessee Board of Medical Examiners. Licensees who complete this program optimize their learning path while satisfying professional credentialing requirements in controlled substance prescribing. All activities are independently sponsored by InforMed Continuing Medical Education without commercial support.

Thank you for choosing InforMed as your CME provider. Please do not hesitate to contact us with any questions, concerns or suggestions.

-InforMed CME Team

COMPLETION INSTRUCTIONS

- **ONLINE:** Visit TN.CME.EDU, select NETPASS to begin. After receiving a passing score on the test(s), claim your credit and print your verified certificate.

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- **MAIL:** Use the enclosed envelope to mail self-assessment answer sheet, course evaluations and payment information to InforMed. If the envelope has been misplaced, please mail to the following address:

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- **FAX:** Fax self-assessment answers, course evaluation and payment information. Scores of 70% or higher will receive a verified certificate. For answers submitted via fax, please allow us 24 hours to process your request.

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TENNESSEE CLINICAL PRACTICE GUIDELINES FOR MANAGING CHRONIC PAIN

COURSE DATES:	MAXIMUM CREDITS:	FORMAT:
Release Date: 09/2019 Exp. Date: 08/2022	*3 AMA PRA Category 1 Credits™*	Enduring Material (Self Study)

TARGET AUDIENCE

This course is designed for all physicians and health care providers involved in the treatment and monitoring of patients with pain.

COURSE OBJECTIVE

This course is designed to increase physician knowledge and skills regarding Tennessee guideline-recommended principles of pain management, the range of opioid and non-opioid analgesic treatment options, and specific strategies for minimizing opioid analgesic prescription, diversion, and abuse.

HOW TO RECEIVE CREDIT:

- Read the course materials
- Complete the self-assessment questions at the end. A score of 70% is required.
- Return your customer information/ answer sheet, evaluation, and payment to InforMed by mail, phone, fax or complete online at course website under NETPASS.

LEARNING OBJECTIVES

Completion of this course will better enable the course participant to:

1. Discuss the fundamental concepts of pain management, including pain types and mechanisms of action of major analgesics.
2. Identify the range of therapeutic options for managing acute and chronic pain, including non-pharmacologic approaches and pharmacologic (non-opioid and opioid analgesics) therapies.
3. Explain how to integrate opioid analgesics into a pain treatment plan individualized to the needs of the patient, including counseling patients and caregivers about the safe use of opioid analgesics.
4. Discuss recommendations for incorporating emergency opioid antagonists into prescribing practice, and for training patients and family members on the use of naloxone.
5. Recognize the risks of addiction inherent in the use of opioids for both acute and chronic pain and identify strategies to mitigate risks of diversion and misuse.
6. Identify medications currently approved for the treatment of opioid use disorder and the ways these medications differ in terms of mechanisms of action, regulatory requirements, and modes of administration.

ACCREDITATION STATEMENT

InforMed is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

DESIGNATION STATEMENT

InforMed designates this enduring material for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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DISCLOSURE OF INTEREST

In accordance with the ACCME Standards for Commercial Support of CME, InforMed implemented mechanisms, prior to the planning and implementation of this CME activity, to identify and resolve conflicts of interest for all individuals in a position to control content of this CME activity.

COURSE SATISFIES

SPECIAL DESIGNATION

Completion of this course satisifies the Tennessee Board of Medical Examiner's requirement in controlled substance prescribing which must include instruction in the Department's Chronic Pain Guidelines on opioids, benzodiazepines, barbiturates and carisoprodol.

Tennessee Licensees must complete two hours of controlled substance prescribing CME as a condition of renewal (unless they are exempt under TENN.CODE ANN. § 63-1-402(c)).

FACULTY/PLANNING COMMITTEE DISCLOSURE

The following faculty and/or planning committee members have indicated they have no relationship(s) with industry to disclose relative to the content of this CME activity:

- Stephen Braun
- Michael Brooks

The following faculty and/or planning committee members have indicated that they have relationship(s) with industry to disclose:

- Paul J. Christo, MD, MBA has received honoraria from GlaxoSmithKline, Daiichi Sankyo, and BTG International.
- Melissa B. Weimer, DO, MCR, FASAM has recieved honoraria from Alkermes

STAFF AND CONTENT REVIEWERS

InforMed staff, input committee and all content validation reviewers involved with this activity have reported no relevant financial relationships with commercial interests.

DISCLAIMER

The challenge of pain management

The experience of pain has been long-recognized as a national public health problem with profound physical, emotional, and societal costs.[1] Although estimates vary depending on the methodology used to assess pain, chronic pain is estimated to affect 50 million U.S. adults, and 19.6 million of those adults experience high-impact chronic pain that interferes with daily life or work activities.[2] The cost of pain in the United States is estimated at between $560 billion and $635 billion annually.[3] Primary care physicians, pain specialists, and other healthcare providers in Tennessee and across the country have been working to improve care for those suffering from acute and chronic pain in an era challenged by the opioid crisis.

The United States has seen three successive waves of opioid overdose deaths related to both legal and illegal opioids (Figure 1).[4] The first began in the 1990s and was associated with steadily rising rates of prescription opioids. In 2010, deaths from heroin increased sharply, and by 2011 opioid overdose deaths reached "epidemic" levels as described by the Centers for Disease Control and Prevention (CDC).[5] The third wave began in 2013 with a sharp rise in overdose deaths attributed to synthetic opioids, particularly those involving illicitly-manufactured fentanyl. By 2017 (the latest year for which data are available) an average of 130 people were dying every day from opioid-related overdoses.[6] Between 1999 and 2017, the CDC estimates that nearly 400,000 people in the United States died from such overdoses.[7]

Coupled with rising rates of overdose death are equally dramatic increases in the number of people misusing or abusing opioids. As many as 1 in 4 patients on long-term opioid therapy in a primary care setting are estimated to be struggling with opioid use disorder (OUD), also called opioid addiction.[8-10] In 2016 approximately 11.5 million Americans reported misusing prescription opioids in the previous year.[11]

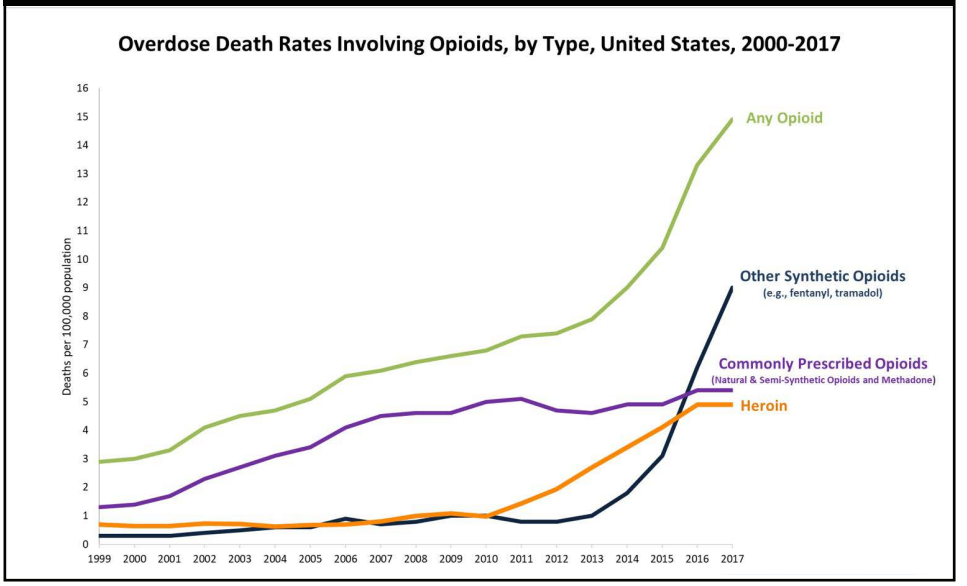
The situation in Tennessee remains dire, despite some recent progress on several fronts as illustrated by the following statistics from 2017, the latest year for which data are available:

- 1,269 Tennesseans died from an opioid-related overdose, and average of more than 3 deaths every day, although the rate declined somewhat compared to the previous year.[12]
- Tennessee had the nation's third-highest rate of opioid prescriptions (94.4 for every 100 persons), which was one-and-a-half times higher than the national average of 58.7 prescriptions per 100 persons.[12] Nonetheless, this rate represents a 25% decline in the state's opioid prescribing rate since 2013.
- 1,090 cases of Neonatal Abstinence Syndrome were reported, a 16% increase from 2013 and the highest rate yet recorded in the state.[12]

It is against this background that providers in Tennessee must make daily decisions about how best to treat their patients in pain. Unfortunately, many providers are unfamiliar with the growing evidence base suggesting that opioids are actually not very effective for relieving chronic non-cancer pain in the long-term and, in fact, may be associated with harms such as increased pain, reduced functioning, and physical opioid dependence.[13,14] Providers may also not be aware of the expanding range of both non-opioid medications and non-pharmacological therapies shown to be effective in reducing many common chronic pain conditions.

In 2019 the Tennessee Department of Health issued the 3rd edition of its clinical practice guidelines for the outpatient management of chronic non-malignant pain.[15] The purpose of this CME course is to provide a detailed review of these updated guidelines and the evidence on which they are based to inform and improve the prescribing of opioid analgesics and other controlled substances for the treatment of pain.

Figure 1. Opioid-related overdose deaths by type in the United States[7]



Key opioid-related terms

Opioid: any psychoactive chemical resembling morphine, including opiates, and binding to opioid receptors in the brain. This term describes opioid and opiates.

Opiate: "natural" opioids derived from the opium poppy (e.g., opium, morphine, heroin).

Semi-synthetic opioids: analgesics containing both natural and manufactured compounds (e.g., oxycodone, hydrocodone, hydromorphone, oxy-morphone).

Synthetic opioids: fully-human-made compounds (e.g., methadone, tramadol, and fen-tanyl).

The nature of pain

As unpleasant as it is, acute pain serves an important adaptive biological purpose: it alerts people to internal or external bodily damage or dysfunction. Acute pain can provoke a range of protective reflexes (e.g., withdrawal of a damaged limb, muscle spasm, autonomic responses) that can prevent further damage and help the body heal. Even brief episodes of acute pain, however, can induce suffering, neuronal remodeling, and can set the stage for chronic pain.[16]

Pain can be classified on the basis of its pathophysiology. Nociceptive pain is caused by the activation of nociceptors (pain receptors), and is generally, though not always, short-lived, and associated with the presence of an underlying medical condition. This is "normal" acute pain: a physiological response to an injurious stimulus. Neuropathic pain, on the other hand, results from an injury to the peripheral or central nervous system. It is an abnormal response to a stimulus caused by dysfunctional neuronal firing in the absence of active tissue damage. It may be continuous or episodic and varies widely in how it is perceived. Neuropathic pain is complex and can be difficult to diagnose.

Related to both nociceptive and neuropathic pain is the phenomenon of sensitization, which is a state of hyperexcitability in either peripheral nociceptors or neurons in the central nervous system (i.e., central sensitization). Sensitization may lead to either hyperalgesia (heightened pain from a stimulus that normally provokes pain) or allodynia (pain from a stimulus that is not normally painful).[17] Sensitization may arise from intense, repeated, or prolonged stimulation and subsequent upregulation of nociceptors, from the influence

of compounds released by the body in response to tissue damage or inflammation, or sometimes as an adaptation to prolonged exposure to opioid analgesics.[18] Many patients—particularly those with chronic pain—experience pain with both nociceptive and neuropathic components, which complicates assessment and treatment.

Differentiating between nociceptive and neuropathic pain is critical because the two respond differently to pain treatments. Neuropathic pain, for example, may respond poorly to both opioid analgesics and non-steroidal anti-inflammatory (NSAID) agents.[19] Other classes of medications, such as anti-epileptics, antidepressants, or local anesthetics, may provide more effective relief for neuropathic pain.[20]

Another important dimension of pain is its effects beyond strictly physiological functioning. Pain is currently viewed as a multi-dimensional, multi-level process similar in many ways to other disease processes which may start with a specific injury but which can lead to a cascade of events that can include physical deconditioning, psychological and emotional burdens, and dysfunctional behavior patterns that affect not just the sufferer, but their entire social milieu (illustrated in Figure 2).[1] The pain community is currently discussing an expansion of the current definition of pain to include a biopsychosocial perspective: "pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components."[21]

Acute pain is defined as having an abrupt onset and is typically due to an obvious cause, such as an injury or surgical procedure. It has a generally short duration, and usually lasts less than four weeks, improving with time.[16] Acute pain is one of the most common presenting complaints in ambulatory care.[22] In contrast, chronic pain is defined as lasting more than three months or past the time of normal tissue healing. It can result from an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause.[23]

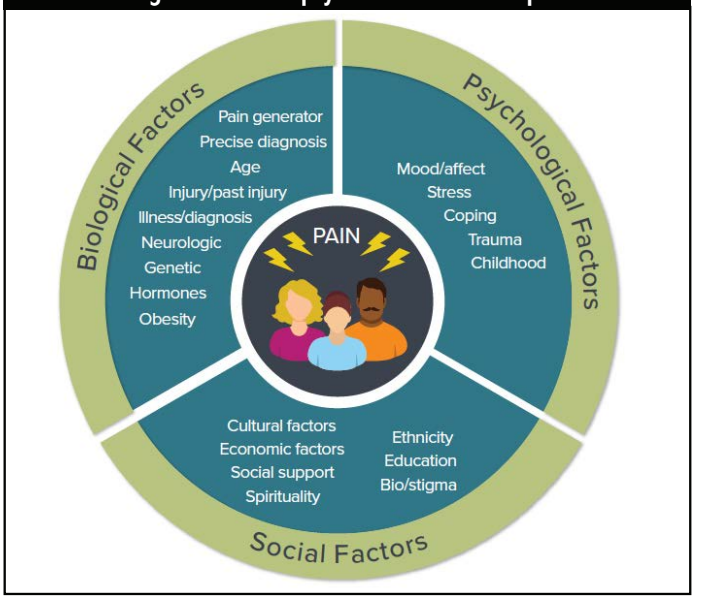
Although pain is expected after injury or surgery, the patient pain experience can vary markedly. The intensity of pain can be influenced by psychological distress (e.g., depression or anxiety), heightened illness concern, or ineffective coping strategies regarding the ability to control pain and function despite it.[24] It may also be shaped by personality, culture, attitudes, and beliefs. For example, injured soldiers who had positive expectations of pain (e.g., evacuation and safe recuperation) requested less analgesic medication than civilians with comparable injuries who had more negative associations with pain (e.g., loss of wages and social hardship).[16]

General principles

Non-pharmacological therapy and non-opioid pharmacological therapy are preferred for treating chronic pain. Providers should only consider adding opioid therapy if the expected benefits for both pain and function are anticipated to outweigh risks. In addition, keep the following principles in mind:

1. If a patient has been prescribed opioids by a previous provider, that is not, in and of itself, a reason to continue opioids.
2. All reasonable non-drug, and non-opioid treatments should be tried, or at least considered, before opioids are initiated.
3. All newly pregnant women should have a urine drug test administered by the appropriate women's health provider.
4. The provider should discuss a birth control plan to prevent unintended pregnancy with every woman of child-bearing age who has reproductive capacity when opioids are initiated.
5. The patient's medical history, physical examination, laboratory tests, imaging results, electro-physiologic testing, and other elements supporting the plan of care, should be documented in the medical record prior to initiating opioid therapy.
6. Chronic pain should not be treated by the use of opioids or other controlled substances through telemedicine.

Figure 2. The biopsychosocial model of pain[1]



Overview of treatment approach

The recommended approach to treating patients with chronic non-malignant pain is summarized in Figure 3. This algorithm details a cautious approach: non-opioid and non-drug therapies are tried first, patients are thoroughly evaluated, informed consent is obtained, and, if opioids are eventually prescribed, patients are closely monitored. Patients on opioid doses of 120 Morphine equivalent dose/day (MED) require even closer attention.

Assessing pain

Goals and Elements of the Initial Assessment

Important goals of the initial assessment of pain include establishing rapport with the patient and providing an overview of the assessment process.[25] These processes help to engage the patient, foster appropriate treatment expectations, and promote a coordinated approach to management. The clinician's primary objective is to obtain information that will help identify the cause of the pain and guide management. A patient history, physical examination, and appropriate diagnostic studies are typically conducted for this purpose. A current diagnosis should be established that justified a need for any opioid medications.

The primary goal of treatment should be clinically significant improvements in function. Framing goals this way allows prescribing decisions (or decisions to terminate treatment) to be based on objective data such as walking a designated distance or number of steps. Function-based opioid management plans may also help a clinician differentiate patients who are addicted from patients who are not addicted but are nonetheless seeking an increased dose: addiction typically leads to decreased functioning, while effective pain relief typically improves functioning.[26]

To be effective, functional treatment goals should be realistic and tailored to each patient. A helpful strategy is to help the patient define SMART goals (specific, measurable, action-oriented, realistic, and time-sensitive).[27] Because patients with long-standing chronic pain are often physically deconditioned, progress in achieving functional goals can be slow or interrupted with "setbacks." It is better, therefore, to set goals slightly too low than slightly too high. Raising goals after a

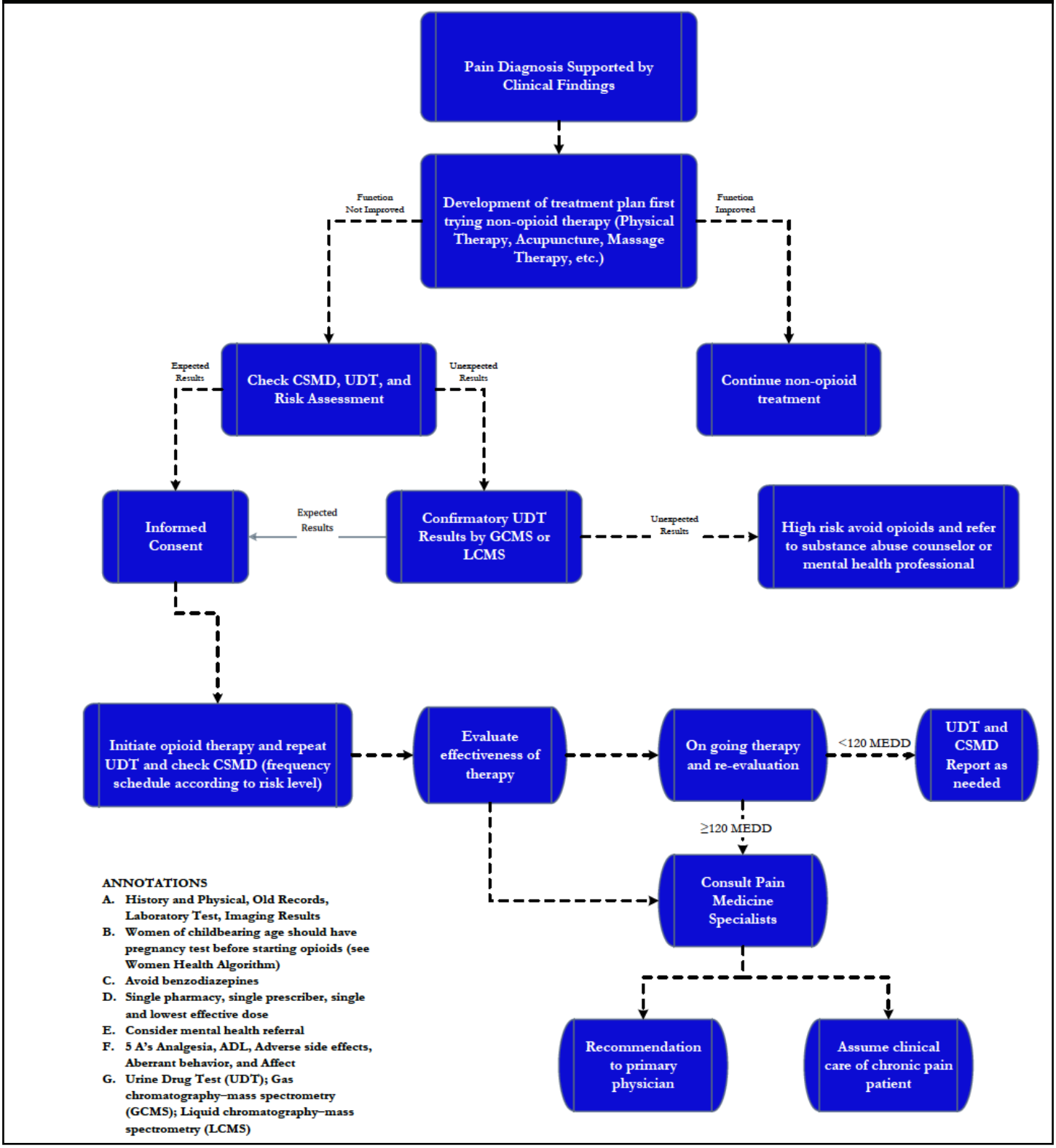
patient has "succeeded" is preferable—and more motivational—than lowering goals after a patient has "failed." One widely-used assessment is the 3-item PEG Assessment Scale:

- Pain average
- Interference with Enjoyment of life
- Interference with General Activity

A treatment plan is expected to include other treatments or modalities beyond opioids, both non-pharmacological and pharmacological. The provider should make reasonable attempts to implement this treatment plan, allowing for barriers such as finances, accessibility, and the availability of local treatment resources.

The patient should be counseled that the goal of chronic opioid therapy is to increase function and reduce pain, not to eliminate pain. Most randomized controlled trials have shown modest reductions in pain with opioids averaging 30%. A recent systematic review found that only 44.3% of patients had 50% pain relief with opioids in the short term.[28] Documentation of this discussion should be included in the medical record.

Figure 3: Algorithm for treating patients with chronic non-malignant pain[15]



Patient evaluation

A specific evaluation and a history of the patient's pain condition should be obtained in order to establish a current diagnosis that would justify the need for an opioid analgesic. The history should include the nature, location, duration, and intensity of the pain, aggravating and alleviating pain factors, past and current treatments for pain, any co-occurring disorders, the effect of the pain on the patient's life functioning (e.g., work, activities of daily living, exercise, relationships, recreation, and sleep), and the patient's expectations from pain treatment.[29] The presence of important co-morbid medical conditions should be assessed and considered when deciding whether to initiate opioids (e.g., chronic obstructive pulmonary disease, sleep apnea, diabetes, congestive heart failure). The McGill Pain Questionnaire, Brief Pain Inventory[30], or Pain, Enjoyment, and General activity (PEG) scale[31] are multidimensional instruments that can be used to aid in the pain history. A review of prior records directly related to the patient's chronic pain condition is encouraged before opioids are prescribed.

Other Drugs of Concern in Tennessee

In addition to opioids, three other drug classes are of concern to public health officials in Tennessee: benzodiazepines; barbiturates; and the muscle relaxant carisoprodol.

- Benzodiazepines and barbiturates are generally used as anti-anxiety medications and share with opioids the potential for abuse, addiction, and respiratory depression. For this reason they should not be prescribed concurrently with any opioid analgesic, and patients should be educated about the hazards of combined use.
- Carisoprodol is a centrally-acting skeletal muscle relaxant. It's primary active metabolite is meprobamate, which is a controlled substance (carisoprodol itself is classified in Schedule IV). Meprobamate has an addictive potential similar to benzodiazepines and is pharmacologically similar to barbiturates. Its clinical effectiveness is low and its side effect profile is high.
- Patients have been reported to substitute the easily-obtained carisoprodol for the more strictly controlled opioids and benzodiazepines.

An initial, condition-appropriate physical examination (including systems review) should be conducted. This should include a cardiopulmonary, neurologic, musculoskeletal, and psychiatric examination. At the end of the examination, the provider should be able to define the pain as nociceptive (visceral or somatic pain), neuropathic, or a combination of nociceptive and neuropathic in origin.

The possible presence of co-occurring mental health disorders should be considered, and screening tests should be used if depression, anxiety, PTSD, current or past substance use disorder, or any other mental health conditions are suspected. The PHQ2, PHQ9, or Beck Depression Inventory are effective screening tools for depression[32] The Primary Care PTSD screen is effective for PTSD screening.[33] Screening for unhealthy substance use can be done by asking the following questions for alcohol and drugs, respectively: "How many times in the past year have you had 5 (4 for women) or more drinks in a day?" and "How many times in the past year have you used an illegal drug or used a prescription medication for non-medical reasons?"[34] If the patient answers "one or more" to either of these questions, it is considered a positive screening test and further evaluation should be done. Prescribers should obtain a Urine Drug Test (UDT) (or a comparable test on oral fluids) prior to initiating opioid therapy and they should access the Tennessee Controlled Substances Monitoring Database (CSMD) to obtain data about a patient's risk of misuse, abuse or diversion of medications.

As part of an evaluation for pain management, women of child-bearing age who have reproductive capacity should be asked about the possibility of pregnancy. For women who wish to avoid unintended pregnancy, use of long-acting reversible contraceptives should be discussed, or referral to appropriate high-risk obstetrician made.

Assessment tools

Many tools have been developed to document and assess pain. Initial approaches to assessing pain severity use a visual analog scale (VAS) rating pain from 0 (no pain) to 10 (worst pain you can imagine) (some scales use a 0 to 100 scale). Such scales are often used in clinical trials of pain therapies, and the minimal clinically important difference using these scales is generally considered a 20%-30% change from baseline (i.e., 2-3 points on a 0-10 scale or 20-30 points on a 0-100 scale).[35]

Multidimensional tools, such as those described below, include questions relating to quality of life and participation in daily activities. Such tools can provide a more comprehensive approach to assessing pain and response to treatment. The selection of a pain assessment tool must balance the comprehensiveness of the assessment obtained with the time and energy required to use the tool in a real-world practice setting.

Brief pain inventory

The Brief Pain Inventory (BPI) is used frequently in clinical trials to assess pain. Specifically developed for patients with chronic pain, the BPI more fully captures the impact of pain on patient function and quality of life than simple VAS scales.[36] By including a pain map, the BPI allows tracking of the location of pain through the course of management. The BPI is self-administered but somewhat time-consuming, which may limit its role in a busy clinical practice.

PEG scale

The PEG scale (Pain average, interference with Enjoyment of life, and interference with General activity) is a three-item tool based on the BPI and is practical for clinical practice (Figure 4). Zero-to-10 scales are used to assess pain, enjoyment of life, and general activity. PEG can be self-administered or done by the clinician and is relatively brief. [31]

Figure 4: PEG scale[31]

1. What number best describes your pain on average in the past week?

0 1 2 3 4 5 6 7 8 9 10

Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0 1 2 3 4 5 6 7 8 9 10

Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0 1 2 3 4 5 6 7 8 9 10

Completely interferes

Assessing acute pain

Acute pain intensity can be assessed with unidimensional tools such as the VAS and the Wong-Baker FACES Pain Rating Scale (faces depicting increasing levels of pain). While useful for a quick assessment, these scales alone may not appropriately identify patients with pain-related suffering driven by functional limitations, worry, or other factors, and may not detect some patients with clinically significant pain.[37]

Although developed for patients with chronic pain, the BPI is also applicable to patients with acute pain. Completed by the patient, the BPI captures ways that pain impacts function and quality of life, although, like most multidimensional questionnaires, it requires more time (about 10 minutes) and concentration to complete, which may limit its utility in some elderly patients.[36]

Assessing pain in the cognitively impaired

Although patients with mild-to-moderate dementia can report their pain and its location, those with severe dementia are often unable to communicate their pain experience or request medication. In these patients, physicians need to observe pain behaviors, including facial expressions, verbal cues, body movements, changes in interpersonal interactions, activity patterns, and mental status. Caregiver observations and reports are critical to appropriate assessment and management of chronic pain conditions.[38]

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 1.

Screening for risk of chronic pain after acute pain

A number of factors have been associated with an increased risk for chronic pain following acute pain or surgery including older age, psychological problems, higher levels of pre-procedural pain or pain sensitivity, type and duration of surgery, severity and number of comorbidities, and use of post-procedural radiation or chemotherapy.[39]

Some tools have been developed to help clinicians predict the likelihood that a patient will experience chronic pain following acute injury or procedures. The 5-item PICKUP model, for example, showed moderate prognostic performance in a derivation study using data from 2,758 patients with acute low back pain.[40] And Sipila and colleagues developed a 6-item screening instrument for risk factors of persistent pain after breast cancer surgery based on a cohort of 489 women.[41]

Screening for opioid abuse risk factors

Screening and monitoring in pain management seeks to identify patients at risk of substance misuse and overdose as well as improve overall patient care. Evaluations of patient physical and psychological history can screen for risk factors and help characterize pain to inform treatment decisions. Screening approaches include efforts to assess for concurrent substance use and mental health disorders that may place patients at higher risk for OUD and overdose. This includes screening for drug and alcohol use and the use of urine drug testing, when clinically indicated. These approaches enable providers to identify high-risk patients so that they can consider substance misuse and mental health interventions, and education materials to mitigate opioid misuse.[1]

Case Study 1

Harold, a 62-year-old African American man, uses a walker to slowly make his way down your clinic hallway. In the exam room, he says he has always been physically active, playing golf and enjoying long walks, but now feels exhausted all the time and has lost his desire for previous activities. He was diagnosed with metastatic prostate cancer 17 years ago, and the cancer has been held in check by a novel chemotherapeutic agent. Now, however, he has severe (8 out of 10) axial lumbar pain due to disc herniation at the L4 – L5 region. For the past four months he says he's been unable to play golf or do any of his former activities, in addition to being tired from disrupted sleep. He describes breakthrough pain occurring despite the Tylenol #3 he was prescribed. "I just can't go on like this," he says. "You've got to help me out. I'm at the end of my rope."

Instructions: Review the mental health assessment tools below and consider the questions that follow.

Mental Health Assessment Tools:

- Patient Health Questionnaire –2 (PHQ-2). This is a simple two-item screening tool. If it is positive on either item, the clinician should offer another more detailed questionnaire to better assess the presence or absence of a depressive disorder. Available at: https://www.hiv.uw.edu/page/mental-health-screening/phq-2
- Patient Health Questionnaire–9 (PHQ-9). This nine-item tool screens for a depressive disorder, and often is used as a follow-up to the PHQ-2. It's easy to score and use. Available at: https://www.hiv.uw.edu/page/mental-health-screening/phq-9
- Zung Self-Rating Depression Scale (Zung). This is a 20-item written questionnaire. Available at: https://psychology-tools.com/test/zung-depression-scale
- Hamilton Depression Rating Scale (Ham-D). This is 21-item screening questionnaire. Cutoff scores is <7 is normal. Available at: https://www.psychcongress.com/hamilton-depression-rating-scale-ham-d
- Generalized Anxiety Disorder 7-item Scale (GAD). This is a 7-item scale to screen for generalized anxiety. Available at: https://psychology-tools.com/test/gad-7
- Primary Care PTSD (PC-PTSD). This is a four item screening test for Post-Traumatic Stress Disorder. Available at: https://www.ptsd.va.gov/professional/assessment/screens/pc-ptsd.asp

1. **Which of these tools might be appropriate to use with Harold?**

2. **How might Harold's mental health issues interact with the management of his pain?**

3. **What other tools or techniques might be used to better characterize Harold's overall mental and physical functioning? (e.g., taking a psychosocial history; using the mini mental status exam; or asking questions aimed at assessing his level of physical and social functioning.)**

Many tools have been developed for the formal assessment of a patient's risk of having a substance misuse problem, some of which are appropriate for routine clinical use because they are relatively brief and easily implemented. Table 1 lists the tools that appear to have good content, and face and construct validity for assessing patient risks related to chronic opioid therapy, although to date, no single tool has been widely endorsed or thoroughly validated.[42]

The Screening, Brief Intervention and Referral to Treatment (SBIRT) is an evidence-based tool used to facilitate screening patients for OUD, which typically takes 5-10 minutes to administer.[43] SBIRT has been endorsed by the Substance Abuse and Mental Health Services Administration (SAMHSA), but should always be paired with referral to treatment.[44] SAMHSA recommends universal screening with oral or writing-based tools because of the high prevalence of substance use disorders in patients visiting primary care settings. In contrast, universal screening with urine, blood, or oral fluid tests are not recommended.[44]

Other tools for universal substance abuse screening include:

- Single screening question screening tool for drug use
- Drug Abuse Screening Test (DAST) 10
- Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)
- Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)
- the CAGE questionnaire adapted to include drugs (CAGE-AID)

If results from an assessment tool indicate that a patient has misused opioids, probe further using the "5 A's" approach:

- *Ask* specifically about opioid use
- *Advise* patients to use medication-assisted treatment for opioid use disorder with, or without, psychotherapeutic or cognitive-behavioral treatments
- *Assess* the patient's willingness to enter treatment and diagnose OUD using DSM-5 criteria
- *Assist* patients by connecting them with treatment (provide a referral if no available in-office)
- *Arrange* follow-up appointments, either in person or by telephone

Using the Tennessee Controlled Substances Monitoring Database

The CSMD contains prescription information from all dispensers of controlled substances in Tennessee and also those dispensers who ship to a patient residing in Tennessee. This includes mail-order pharmacies and some Veteran's Affairs pharmacies as well. The CSMD collects and maintains dispensing data regarding all Schedule II, III and IV, and Schedule V controlled substances. Data are to be submitted at least once every seven days for all the controlled substances dispensed during the preceding seven-day period. The following information is required to be submitted:

- Prescriber DEA number
- Dispensing date
- Patient identifier
- Controlled substance NDC number
- Quantity dispensed
- Strength of controlled substance
- Estimated day supply
- Dispenser DEA number
- Date the prescription was written
- Whether the prescription was new or a refill
- Source of payment

All data in the CSMD are reported as submitted to the data collection website by the dispenser. Therefore, if there are any questions about the data a practitioner should contact the dispenser identified within the report. The dispenser can, in turn, correct any errant information by coordinating with the state's data collection vendor. Neither the data collection vendor nor the Department of Health can edit prescription information found in the CSMD.

Registration

All prescribers and dispensers of controlled substances in Tennessee must register for access to the CSMD. Healthcare practitioners wishing to register with the CSMD to access prescription information are required to navigate to www.TNCSMD.com and choose the "register" link. A registration form will appear requesting information used to validate a healthcare provider's statutory authority to access CSMD data. A username and password will be sent to the approved registrant after validation and processing by CSMD administration. All passwords are case-sensitive, must be at least eight characters long and must contain an upper and lowercase letter, at least one number and one special character.

A healthcare provider may also choose to allow licensed and up to two unlicensed physician extenders per practice location to register with the CSMD in order to retrieve prescription information on the prescriber or dispenser's behalf. The extender should navigate to www.TNCSMD.com and register for a separate account. In addition to supplying self-identifying information, the extender must provide information which identifies the supervisor permitting access to the CSMD. After validation by CSMD administrative staff, the supervisor must log in to his/her account to approve the registrant as their extender. Once this process is complete, the extender may access CSMD information. All access by any user leaves an audit trail that can be monitored and accessed as needed. A supervisor may revoke CSMD access of their extender at any time if necessary.

Law enforcement personnel engaged in an official investigation or enforcement of state or federal laws involving controlled substances wishing to request information must follow a distinct process outlined in T.C.A. § 53-10-306 (a) (6) in order to request information from CSMD administration.

Patient Report

A patient's CSMD report contains a variety of information related to the prescriber or dispenser of controlled substances. After entering the search criteria, a box of potential patient matches appears to consider incorporating into the report. Please note that many patients may have a similar name or date of birth as another patient in the CSMD and it is possible for erroneous information to be incorporated into the patient report if inappropriate patients are selected during this process.

Once the report is generated, a CSMD user will see a list of all patients incorporated into the report along with address information. The user will also see a list of all prescriptions attributed to the selected patient(s) in reverse chronologic order. On the right side of the first page is an estimated morphine equivalent dose that the patient is currently taking. For further explanation of the MEDD. At the end of the report there is a listing of all prescribers and dispensers associated with the patient's selected prescription history, as well as additional information used to calculate the morphine equivalent dose.

Table 1. Tools for patient risk assessment

Tool	Use	Who Administers?	Length
Current Opioid Misuse Measure (COMM)	Monitor for misuse by patients currently on long-term opioid therapy	Patient self-report	17 items
Diagnosis, Intractability, Risk, Efficacy (DIRE)	Screen for risk of opioid addiction	Clinician	7 items
Opioid Risk Tool (ORT)	Screen for risk of opioid addiction	Clinician or patient self-report	5 yes/no questions
Screener and Opioid Assessment for Patients with Pain, Version 1 and Revised (SOAPP, and SOAPP-R)	Screen for risk of opioid addiction	Patient self-report	24 items

Prescriber Self-Lookup

A prescriber can use the prescriber self-lookup report for multiple purposes. The report is useful for identifying potential prescription fraud, e.g., a stolen prescription pad or phoned-in prescriptions. It is also a useful snapshot of a prescriber's patient population and the prescriptions attributed to the prescriber.

Urine drug testing

Urine drug testing (UDT) is recommended before prescribing any opioid and at least annually thereafter.[45] The purpose of UDT is to identify the presence or absence of prescribed medication and the presence of illicit or non-prescribed substances. UDT is an important tool to identify aberrant behavior regarding opioid use. It is one of the only objective measures for adherence monitoring. When used appropriately, it can improve the safety of opioid therapy. Unexpected UDT results are seen frequently even in patient populations identified as low risk. According to the Tennessee guidelines, UDT with confirmation is required prior to the outset of chronic opioid therapy and at least twice per year for all patients on such therapy.

1. There are two broad categories of UDT: immunoassay and confirmation. Immunoassay tests are usually performed in the office (Point of Care Testing), while confirmation tests are usually completed in a laboratory. Immunoassay tests are qualitative in nature and detect the presence or absence of a drug class. They have the advantage of providing rapid results. Immunoassay tests have significant cross-reactivity with other substances. They have lower sensitivity and specificity compared to confirmation testing. Confirmation testing utilizes high performance chromatography/mass spectrometry technology and is necessary to confirm the absence or presence of a particular drug.
2. Typical office based testing for COT patients usually includes opiates, benzodiazepines, cannabinoids, cocaine, amphetamines, alcohol, barbiturates, oxycodone, methadone, and fentanyl. Synthetic and semisynthetic opiates, such as oxycodone, methadone, fentanyl, and meperidine, do not appear in opiate immunoassay tests. Points of care immunoassay tests are available for some of these drugs, but they have variable cut-off levels that affect sensitivity. Unexpected results on immunoassay tests should prompt confirmatory testing with gas chromatography/mass spectrometry.
3. Frequency of UDT is left to the prescriber's discretion, but general guidelines can be discussed, based on the relative risk for addiction or death of the patient.
4. Lower risk patients would typically be screened 1-2 times per year. Moderate risk patients would be screened 3-4 times per year. Higher risk patients and those over 100mg MEDD should be screened 4-5 times per year. Instances of aberrant behavior such as lost or stolen medication may also prompt additional screening. Unexpected or inappropriate immunoassay results should be sent for confirmatory testing.
5. Higher risk patients may also need routine confirmation because there are certain aberrant behaviors that will appear normal with immunoassay testing.
6. Interpreting UDT results can be complicated. It should be noted that certain parent drugs can be metabolized into other commonly prescribed drugs. If questions exist, a provider should contact the laboratory director, toxicologist, or local Medical Review Officer. A prescriber should inform the patient of the reason for testing and the potential consequences of the results. UDT should be performed in an unannounced fashion when possible. There are many ways a sample can be adulterated to provide a "clean" sample. Validity testing using temperature, pH, or creatinine is recommended. UDT cannot be used to determine the source of drugs detected or the dose of drug taken. It may be helpful to discuss UDT in terms of "Universal Precautions" to minimize any associated stigma or detract from the physician patient relationship

If the prescribed opioid is not detected, discuss the finding with the patient and, if diversion is confirmed or suspected, re-evaluate the pain management strategy or taper the opioid. If the patient tests positive for unprescribed drugs schedule more frequent follow-up visits, consider opioid discontinuation, offer naloxone, or refer for treatment for substance use disorder. Decision tools and help with interpreting urine drug testing results are available at: http://mytopcare.org/udt-calculator/interpret-opiates-test-result.

Overview of options for managing pain

Many pharmacologic and non-pharmacologic approaches to treating pain are available to primary care providers. These options should be employed using the following general principles:

- Identify and treat the source of the pain, if possible, although pain treatment can begin before the source of the pain is determined
- Select the simplest approach to pain management first. This generally means using non-pharmacologic approaches as much as possible and/or trying medications with the least severe potential side effects, and at the lowest effective doses
- Establish a function-based, individualized treatment plan if therapy is expected to be long-term

Non-drug approaches

Many nonpharmacologic and self management treatment options have been found to be effective alone or as part of a comprehensive pain management plan, particularly for musculoskeletal pain and chronic pain.[46] Examples include, but are not limited to, psychological, physical rehabilitative and surgical approaches, procedural therapies (e.g., injections, nerve blocks), complementary therapies, and use of approved/cleared medical devices for pain management.

Primary care providers should know about the range of treatment options available, the types of pain that may be responsive to those options, and when they should be used as part of a multidisciplinary approach to pain management.[46] Clinicians should also be aware that not all nonpharmacologic options have the same strength of evidence to support their utility in the management of pain, and some may be more applicable for some conditions than others.

Movement-based options

Movement therapies that may be helpful in patients with chronic pain include muscle-strengthening, stretching, and aerobic exercise (e.g., walking, aquatics). Recommended exercise programs typically occur one to three times a week for a total of 60-180 minutes per week, but any regimen must be carefully tailored to a patient's existing level of physical conditioning, comorbidities, and cognitive status.[47-49]

Additional movement-based options include:

- **Physical therapy** supervised by a licensed physical therapist, which can include resistance, aerobic, balance, and flexibility exercises as well as elements of massage, manipulation, or transcutaneous electrical nerve stimulation.
- **Tai chi**, a mind-body practice that combines controlled movements, meditation, and deep breathing. "Chair tai chi" can be an option for patients with limited mobility.
- **Yoga**, exercises or a series of postures designed to align muscle and bones, and increase strength and flexibility. It can also relax mind and body through breathing exercises and meditation. Gentler forms of yoga that may be more appropriate for older patients include Iyengar, Hatha, or Viniyoga.

Although these interventions may cause muscle soreness, increased back pain, or falls, movement-based options are generally considered safe.[49]

Weight loss

Some pain syndromes, such as knee osteoarthritis, are worsened by obesity. For some patients, pain due to this condition is improved by reducing body weight because of reduced loads and physical stresses on the affected joints. The goal of body weight reduction is a baseline weight loss of 7%-10% by calorie reduction and increased activity using a balanced diet with less than 30% of calories from fat, 15%-20% from protein, and 45%-60% from carbohydrates.[50]

Passive options

Acupuncture involves the stimulation of specific points on the body, most often involving skin penetration with fine metallic needles manipulated by hand but sometimes also including electrical stimulation or low intensity laser therapy. Potential adverse events include minor bruising and bleeding at needle insertion sites.[51]

Massage is the manual manipulation of the body to promote relaxation, reduce stress and improve well-being. Handheld devices may also provide relief for some patients. Some patients may report muscle soreness.[52]

Transcutaneous electrical nerve stimulation (TENS) is a machine that generates mild electrical pulses which are applied cutaneously. The electrical stimulation from TENS may block or disrupt pain signals to the brain, reducing pain perception. TENS machines can be used at home or in conjunction with other interventions like physical therapy.

Cognitive and behavioral options

Cognitive behavioral therapy (CBT) is a structured, time-limited (typically 3-10 weeks) intervention focused on how thoughts, beliefs, attitudes, and emotions influence pain and can help patients use their minds to control and adapt to pain. This therapy includes setting goals, often with recommendations to increase activity to reduce feelings of helplessness.[53]

Meditation

Mindfulness meditation programs typically include a time-limited (8 weeks; range 3-12 weeks) trainings with group classes and home meditation. The objective is to inculcate a long-term practice that helps patients refocus their minds on the present, increase awareness of self and surroundings, and reframe experiences.[54,55]

Interventions

Several types of injection therapies can help to ease pain and provide durable relief. In the spine, multiple pain generators can be targeted: facet joints, discs, nerves, and muscles.[56] Parts of the sympathetic nervous system can be accessed with therapeutic injections for patients with visceral pain, and injections into specific joints with steroid or viscosupplements can reduce joint pain.[56] Epidural steroid injections, radiofrequency ablation, pulsed radiofrequency procedures, and neuromodulation treatments (spinal cord stimulation, peripheral nerve stimulation) all have an important role in reducing chronic pain.[57-59]

Non-opioid drug approaches

A wide range of medications can be used to treat pain, including:

- Acetaminophen
- NSAIDs (oral or topical)
- Antidepressants
  - serotonin and/or norepinephrine reuptake inhibitors
  - tricyclic antidepressants (TCAs)
  - selective serotonin reuptake inhibitors (SSRIs)
- Anticonvulsants
- Topical lidocaine or capsaicin
- Cannabinoid-based therapies
- Ketamine

Acetaminophen

Acetaminophen is available over the counter (OTC) in 325 mg, 500 mg, and 650 mg tablets. Lower doses are recommended to decrease risk of side effects. Patients should not exceed 1000 mg in a single dose. The maximum recommended dose for healthy adults is 4000 mg/day and 3000 mg/day for elderly patients.[60]

The most severe potential side effect of acetaminophen is liver toxicity. Acetaminophen is the most common cause of acute liver failure, accounting for 46% of all cases.[61] Patients should stay within recommended doses to help prevent side effects and should only be prescribed one acetaminophen-containing product at a time. Advise patients to read labels of all medications to determine if the product contains acetaminophen.

NSAIDs

NSAIDs reduce inflammation by inhibiting cycloxygenase (COX), either selectively (COX-2 predominantly) or non-selectively (COX-1 and COX-2 effects). Chronic use of NSAIDs may be limited by gastrointestinal (GI) toxicity, including GI bleeding, upper GI symptoms, ulcers, and related complications. For high-risk patients, including the elderly, patients on warfarin or aspirin, and those with coagulopathies, adding a proton pump inhibitor (PPI) may help reduce the risk.[62,63] In addition to GI side effects, NSAIDs have been associated with an increased risk of renal and cardiac complications.

Side effects with NSAIDs are typically lower with topical formulations. The effects on coagulation and renal function are unknown, but likely not clinically significant given limited systemic absorption.[64]

Some early trials suggested that COX-2 inhibitors, as a class, were associated with higher risks for myocardial infarction and stroke compared to other NSAIDs, and the COX-2 inhibitor rofecoxib (Vioxx) was removed from the market in 2004 because of such concerns.[65] More recent trials and meta-analyses, however, provide strong evidence that the risks of CV events with celcoxib are no greater than those of other NSAIDs, and in 2018 two FDA advisory panels recommended that the FDA change its advice to physicians regarding celecoxib's safety.[66]

Selective norepinephrine reuptake inhibitors

SNRIs such as duloxetine, venlafaxine, and milnacipran are characterized by a mixed action on norepinephrine and serotonin, though their exact mechanism of action for pain reduction is unknown. Side effects (e.g., nausea, dizziness, and somnolence) may limit treatment. Monitoring is required for blood pressure (duloxetine and venlafaxine), heart rate (venlafaxine), and drug interactions (duloxetine). SNRIs can be very helpful in patients who have central sensitization.

TCAs

TCAs inhibit reuptake of norepinephrine and serotonin, but their mechanism of action for pain relief is unknown. Examples of TCAs studied for the management of chronic pain include amitriptyline, desipramine, and nortriptyline. Side effects, such as anticholinergic effects (e.g., dry mouth, constipation, dizziness) and QTc prolongation limit the use of TCAs in elderly patients. The majority of side effects occur at the typically higher doses used to treat depression.

SSRIs

SSRIs, such as citalopram, fluoxetine, and paroxetine, block the reuptake of serotonin in the brain, making more serotonin available in the synapse. The mechanism of SSRIs for pain remains unknown. Compared to SNRIs and TCAs, there is relatively little evidence to support the use of SSRIs in treating chronic pain conditions.[42] Potential side effects of SSRIs include weight gain, sexual dysfunction, and QTc prolongation, especially with citalopram.

Anticonvulsants

Anticonvulsants, such as gabapentin, pregabalin, oxcarbazepine, and carbamazepine, are often prescribed for neuropathic pain and are thought to exert their analgesic effect by inhibiting neuronal calcium channels. Potential side effects include sedation, dizziness, and peripheral edema. Pregabalin and gabapentin have abuse potential in the general population, are currently classified as Schedule V by the DEA. Anticonvulsants can be very helpful in patients who have central sensitization.

Topical lidocaine and capsaicin

Topical lidocaine inhibits the conduction of nociceptive nerve impulses. Irritation at the application site is the most common side effect. The most common products for chronic pain management are lidocaine 5% patches, available by prescription, and lidocaine 4% patches available OTC. Capsaicin is an active component of chili peppers and has moderate analgesic properties at 8% concentrations for musculoskeletal and neuropathic pain.[67] The most common side effect is a mild-to-severe burning sensation at the application site.

Cannabinoid preparations

With medical cannabis now legal in 33 states and recreational use legal in 10 states and the District of Columbia (as of April, 2019)[68], there has been increased interest among patients for the use of cannabis or cannabis derivatives (e.g., cannabidiol [CBD]) for pain relief. The CB1 and CB2 receptors have been shown to mediate the analgesic effects of cannabinoids[69] and some evidence suggests a potential benefit for chronic pain. A 2017 National Academies of Science report, for example, concluded that "conclusive or substantial evidence" supports a beneficial role for cannabis or cannabinoids for treating chronic pain,[70] and a 2018 Cochrane review of the existing literature evaluating cannabinoids (cannabis, CBD, or combinations) suggests that these agents are moderately effective for neuropathic pain with adverse effects that are less than, or comparable to, existing non-opioid analgesics.[71]

But the evidence for a benefit of cannabinoids on acute pain, is extremely limited and mixed. A small double-blind, cross-over study in 18 females and experimentally-induced mild acute pain found no significant analgesic effect of oral cannabis extract.[72] Another randomized, double-blind study with 15 healthy volunteers using smoked cannabis found no analgesic effect with low doses of cannabis, a modest effect with moderate doses, and enhanced pain responses with high doses.[73] The authors of a 2017 review on cannabis and pain conclude that cannabis may have a narrow therapeutic window as a pharmacotherapy for chronic pain but that much more research is needed to inform physician recommendations to patients regarding the analgesic efficacy of cannabis.[74]

A systematic review of both randomized trials (47) and observational studies (57) in patients with chronic noncancer pain published through July 2017 found moderate evidence that cannabinoids can exert analgesia.[75] Cannabis preparations, however, may pose both short-term and long-term risks. Short-term effects include impaired memory, motor coordination, and judgment. Paranoid ideation and psychotic symptoms, while rare, may occur with high doses of THC. Possible long-term effects include impaired brain development in young adults, potential for habituation, and increased risk of anxiety or depression. Abrupt cessation of marijuana in long-term users may cause withdrawal symptoms such as anxiety, irritability, craving, dysphoria, and insomnia. There is an increased risk of chronic bronchitis, respiratory infections, and pneumonia with inhaled products.[76]

Nonetheless, the use of cannabis may have an opioid-sparing effect at a population level. The use of medical cannabis has been associated with a 25% reduction in opioid overdose mortality in states that legalized medical use.[77]

FDA-approved cannabinoids include dronabinol (Marinol), indicated for second-line treatment of chemotherapy-induced nausea and vomiting, and anorexia-associated weight loss in patients with HIV. Nabilone (Cesamet) is indicated for chemotherapy-induced nausea and vomiting. Common side effects include dizziness/vertigo and euphoria. Dronabinol may cause nausea/vomiting, abdominal pain, and abnormal thinking. Nabilone may cause ataxia and dry mouth.[76,78,79] None of these are indicated for the treatment of pain. When recommending cannabis for patients with chronic pain, clinicians should inform patients that the analgesic properties of cannabis are only attributed to the CBD component, not the THC component.

Ketamine

Ketamine has been used as a general anesthetic since the 1960s, but its use in subanesthetic concentrations for analgesia has grown rapidly in recent years, due, in part, to efforts to reduce the risks of chronic opioid use.[80] Ketamine has been successfully used to treat such acute pain conditions as sickle cell crises, renal colic, and trauma.[80] Recently the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists released the first joint recommendations for subanesthetic ketamine (including transdermal ketamine) for acute pain with the following guidelines:[80]

- Indications
  - Perioperative use in surgery with moderate to severe postoperative pain
  - Perioperative use in patients with opioid tolerance
  - Adjunct in opioid-tolerant patients with sickle cell crisis
  - Adjunct in patients with obstructive sleep apnea
- Dose
  - Bolus IV: up to 0.35 mg/kg
  - Infusion: up to 1 mg/kg/hour
- Contraindications
  - Poorly-controlled cardiovascular disease
  - Pregnancy
  - Psychosis
  - Severe hepatic disease
  - Elevated intracranial pressure
  - Elevated intraocular pressure

Opioids

Mechanism of Action

Opioids exert their analgesic effects by acting on the mu, kappa, and delta opioid receptors. Individual agents may be classified as agonists or partial agonists of those receptors:[81]

Agonists (e.g., morphine, codeine, hydromorphone, hydrocodone) stimulate at least one of the opioid receptors and provide continued analgesia with increasing doses.

Partial agonists (e.g., buprenorphine) have high affinity at mu-receptors, have a ceiling for analgesic effect, and are less likely to cause respiratory depression.

Opioids are classified by the Drug Enforcement Agency (DEA) according to their presumed abuse and addiction potential, although the evidence base for making these differentiations continues to evolve (Table 2). Tramadol, for example, is now known to have as much potential for abuse as opioids in more restrictive classes, although its DEA classification has not changed.[82]

Table 2. Common opioids by schedule[81]

Schedule	Description	Opioid
Schedule I	No medical use, lack of accepted safety, and a high potential for abuse	Heroin
Schedule II	High potential for abuse, which may lead to physical or psychological dependence	Hydrocodone Oxycodone Morphine Hydromorphone Tapentadol Methadone Fentanyl
Schedule III	Less potential for abuse than schedules I and II, low to moderate physical dependence and high psychological dependence	Buprenorphine Codeine + acetaminophen
Schedule IV	Lower potential for abuse than schedule III medications	Tramadol

Relative effectiveness

The analgesic efficacy of opioids for treating acute pain have been known for centuries and they continue to be reliable agents for moderate-to-severe acute pain, although they are not without risks. But the evidence for opioid efficacy for acute pain cannot be extended to chronic pain. Neuronal and physiologic adaptations to long-term opioid use can result in reduced analgesic effectiveness, or even, paradoxically, increased pain or sensitivity to pain.[18] Opioid-induced hyperalgesia is different pharmacologically from the phenomenon of opioid tolerance, although both can lead to an increased need for opioids and disentangling the two, clinically, can be difficult.[83]

For chronic pain, the evidence that opioids reduce pain and improve function more than placebo is relatively weak. A 2018 systematic review and meta-analysis of 96 trials comparing various opioids vs. placebo or non-opioid analgesics in 26,169 patients with chronic noncancer pain found that opioids may slightly reduce pain and increase physical functioning compared to placebo, but not compared to non-opioids.[13] In 76 trials comparing opioids vs. placebo with follow-up ranging from 1 to 6 months, the reduction in pain scores with opioids (on a 10-point scale) was only 0.69 points, which is below the generally-accepted 2-point minimum clinically important difference for pain. Physical function scores (on a 100-point scale) improved with opioids by 2.04 points, which, again, may not be clinically important. The risk of vomiting with opioids, however, was more than 4 times higher than with placebo.[13]

The same meta-analysis compared opioids to non-opioid analgesics including NSAIDs, TCAs, anticonvulsants, and synthetic cannabinoids. No significant differences were found in physical functioning scores for any of the comparisons, and no significant differences were found in pain scores for comparisons with NSAIDs, TCAs, or cannabinoids.[13]

The Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial randomized 240 patients with moderate to severe chronic low back pain or knee or hip osteoarthritis to regimens of morphine, oxycodone, or hydrocodone or non-opioid analgesics (e.g., acetaminophen, NSAIDs, antidepressants, anti-epileptics) and followed them for 1 year.[14] At 3, 6, 9, and 12 months there were no significant differences in pain scores. At 1 year, pain intensity was significantly better in the non-opioid group. No differences in treatment response were seen in analyses by pain condition. The authors concluded that their results "do not support initiation of opioid therapy for moderate-to-severe chronic back pain or hip or knee osteoarthritis pain."[14]

Opioid formulations

Prescription opioids are available in immediate-release and extended-release/long-acting (ER/LA) formulations (Table 3). Immediate-release agents are recommended in opioid-naïve patients and for all acute pain conditions, with ER/LA agents reserved for patients or conditions in which the longer duration of action and smoother pharmacodynamics are preferred.[45] A trial comparing immediate release to an ER/LA opioid did not find evidence that the continuous, time-scheduled use of ER/LA opioids was more effective or safer than intermittent use of the immediate-release opioid.[84] According to the FDA, ER/LA opioids should only be used for patients who tolerate 60 morphine milligram equivalents per day (MMED) for at least one week.[85]

Efforts to create formulations with lower risks of abuse have met with limited success. For example, ER Oxymorphone was removed from the market after reports of intravenous abuse of the oral formulation.[86] Abuse-deterrent or tamper-resistant formulations do not prevent patients from developing opioid dependence, opioid use disorder, or simply taking too much of an opioid by mouth.[87,88] No prospective randomized clinical trials or rigorous observational studies have measured the impact of abuse-deterrent opioids on the risk of abuse or misuse. As of August 2018, eight opioids with abuse-deterrent properties have been approved by the FDA.[89]

Table 3. Immediate-release vs. extended-release/long-acting opioids

Immediate-release formulations	Extended-release/ Long-acting formulations
Codeine	Buprenorphine transdermal patch
Hydrocodone + acetaminophen	Fentanyl transdermal patch
Hydromorphone	Hydrocodone ER
Levorphanol	Hydromorphone ER
Meperidine	Methadone
Morphine	Morphine ER
Oxycodone	Morphine ER + naltrexone
Oxymorphone	Oxycodone ER
Tapentadol	Oxycodone ER + naloxone
Tramadol	Oxymorphone ER
	Tapentadol ER
	Tramadol ER

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 2.

Case Study 2

Instructions: Review the case below and consider the questions that follow.

Ralph is an 83-year-old who lives at home with his wife. He has a history of cardiovascular disease and, 10 years earlier, had successful quadruple bypass surgery. He takes the following medications: fish oil, a statin, a thiazide diuretic, low-dose aspirin, and a non-benzodiazepine sedative to help him sleep. Lately he has been complaining of increasing pain and stiffness in his right knee and hip. He is physically deconditioned due to a lack of exercise, in part because walking is painful. He asks if you can prescribe something to ease his pain.

1. **Ralph a good candidate for an ER/LA opioid? Why, or why not?**

2. **Is he a better candidate for an immediate-release opioid? Why or why not?**

3. **Would Ralph's current medication need to be adjusted if he were to be prescribed an ER/LA opioid?**

4. **What kinds of non-opioid treatments might be tried to help Ralph with his pain?**

Atypical opioids: tramadol and tapentadol

Tramadol and tapentadol are mu receptor agonists and norepinephrine reuptake inhibitors. Their mechanisms of action are unknown, but their analgesic effects are similar to morphine. Patients taking tramadol should be monitored for nausea, vomiting, constipation, and drowsiness, all of which are similar to side effects with opioids.[90] There is potential risk of serotonin syndrome when tramadol is combined with SSRIs, SNRIs, or tricyclic antidepressants.[91]

As noted above, tramadol is classified as Schedule IV, which has led some to view it as less potent or safer than other opioids. The 2016 National Survey on Drug Use and Health, however, found that 1.7 million people in the U.S. aged > 12 years reported misusing tramadol products (e.g., Ultram, Ultram ER, Ultracet) in the previous year.[82] In addition, a 2019 cohort study of 88,902 patients with osteoarthritis showed increased risks of death at one year compared to NSAIDs naproxen, diclofenac, and celecoxib.[92]

Abrupt cessation of tramadol is associated with opioid withdrawal, restlessness, and drug cravings (similar to those associated with other opioids) as well as hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and numbness/tingling in extremities (which are less typical of other opioids).[93]

Tapentadol is FDA-approved for treating neuropathic pain, although it is also used for musculoskeletal pain. A 2015 Cochrane review of 4 randomized trials with 4,094 patients with osteoarthritis or back pain found modest reductions in pain with tapentadol vs. placebo.[94]

Problematic opioid use

Although evidence for the long-term effectiveness of opioids for chronic pain is weak, evidence for opioid-related harms is abundant and strong. In a 2007 study assessing behaviors indicative of opioid misuse, many patients in primary care practices reported having engaged in aberrant behaviors with opioids one or more times (Table 4).[10] It is important to recognize and differentiate problematic use from adverse side effects of opioids. For instance, tolerance and opioid withdrawal occur with long term use of prescribed opioids. Clinicians should be able to differentiate this from problematic use.

Among adults without a prescription, 41% obtained prescription opioids from friends or relatives for their most recent episodes of misuse.[95]

A 2015 meta-analysis showed that the prevalence of opioid abuse in primary care settings ranged from 0.6%-8%, and the prevalence of opioid dependence ranged from 3%-26%. In pain clinics, the prevalence of opioid abuse ranged from 8%-16%, and addiction ranged from 2%-14%.[96] In eastern Pennsylvania, the lifetime prevalence of opioid use disorder among patients prescribed long-term opioids was estimated at 35%.[9]

For prescription opioids, long-term therapy is associated with an increased risk in accidental overdose and death. A retrospective study including 9,940 patients who received three or more opioid prescriptions within 90 days for chronic pain between 1997 and 2005 found that annual overdose rates rose significantly as doses exceeded 50 MMED (Figure 5).[97]

To ensure clear communication regarding medical issues and avoid misunderstandings about the nature and risk of addiction, the American Society of Addiction Medicine recommends the following definitions to help differentiate problem use from normal use of opioids:

- **Abuse** - Any use of an illegal drug, or the intentional self-administration of a medication, for a non-medical purpose, such as altering one's state of consciousness (e.g., getting high).
- **Misuse** - Use of a medication other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.
- **Tolerance** – when the same dose of a drug given repeatedly produces a reduced biological response. This is a normal process that occurs with long term use of a prescribed opioid.
- **Physical dependence** - A state of physical adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Most importantly (and most difficult for providers to determine) this is not synonymous with addiction.
- **Opioid use disorder (addiction)** - Problematic opioid use leading to clinically significant impairment or distress, with at least two additional criteria, such as taking more opioids or for longer than prescribed, persistent desire or unsuccessful efforts to cut down or control opioid use, and craving or a strong desire or urge to use opioids, occurring within a 12-month period.

Combining opioids with sedating drugs such as benzodiazepines or alcohol increases the risk of respiratory depression and overdose death.[23] Benzodiazepines have been linked with overdose fatalities in 50-80% of heroin overdoses, and 40-80% in methadone-related deaths.[23,98] Patients prescribed benzodiazepines who are being initiated on opioids should have their benzodiazepine tapered and discontinued whenever possible. For patients being co-managed by mental health professionals, coordinate a plan regarding continuing or tapering benzodiazepines in the setting of opioid co-prescribing.

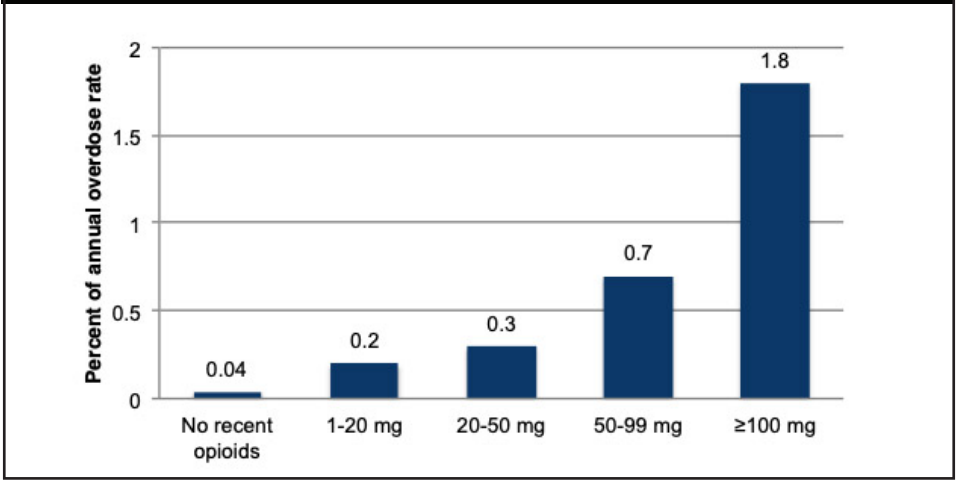
Women and opioids

Current American Pain Society-American Academy of Pain Medicine (APS-AAPM) guidelines suggest that clinicians should avoid prescribing opioids during pregnancy unless the potential benefits outweigh risks.[42] Some data suggest an

Table 4. Behaviors indicative of opioid misuse[10]

Behavior	Frequency in patients with opioid misuse
Requested early refills	47%
Increased dose on own	39%
Felt intoxicated from pain medication	35%
Purposely over sedated oneself	26%
Used opioids for purpose other than pain	18%

Figure 5. Risk of overdose rises with daily milligram morphine-equivalent dose.[97]



association between the use of long-term opioid therapy during pregnancy and adverse outcomes in newborns, including low birth weight and premature birth, although maternal factors may play a role in these associations and causality is not certain.[42] Exposure to these medications has also been associated with birth defects in some studies. Opioid withdrawal can be expected in up to half of newborns of opioid-dependent mothers (neonatal abstinence syndrome).[42] If a mother is receiving long-term opioid therapy at or near the time of delivery, a professional experienced in the management of neonatal withdrawal should be available.

Prescribers should discuss a method to prevent unintended pregnancy with every woman of child-bearing age who has reproductive capacity before opioids are initiated. The practitioner should obtain a signature indicating that any woman who wishes to become, or is at risk to become, pregnant has been educated about the risks and benefits of opioid treatment during her pregnancy.

The Tennessee Guidelines say that women of child-bearing age who have reproductive capacity should undergo a pregnancy test prior to the initiation of opioids, and that they should be asked about the possibility of pregnancy at each visit. For women who wish to avoid unintended pregnancy, use of long acting reversible contraceptives should be discussed, or referral to appropriate high risk obstetrician made.

If a female patient on an opioid plans to become, or becomes, pregnant, she should be referred to a high risk obstetrician. The OB and treating physician should work together to encourage compliance with both chronic pain management or medical replacement therapy plan, and prenatal care. A risk assessment, UDT, and CSMD check should be performed before initiating any opioid or benzodiazepine during pregnancy.

A UDT should be performed at intake to prenatal care. If positive, the mother should be referred to appropriate chronic pain management . In cases of opioid use disorder, the woman should be referred for methadone or buprenorphine treatment. The risks of Intra-Uterine Drug Exposure should be discussed, and documented, and random UDT should be performed during the prenatal course. If a woman has a positive UDT on initial prenatal visit, A UDT should be performed upon admission for delivery to help identify infants at risk for NAS.

Other adverse events

In addition to risks of misuse, addiction, respiratory depression, and overdose death, there are many well-known side effects associated with chronic opioid use that can significantly compromise quality of life, including constipation, nausea or vomiting, sedation, pruritus, erectile dysfunction, menstrual changes, fracture, immunosuppression, hallucinations, and hyperalgesia.

Gastrointestinal side effects

Constipation is one of the most common opioid-related adverse events, affecting most patients to at least some degree, and which usually does not resolve with continued exposure.[42] To mitigate this side effect, patients should use a mild stimulant laxative such as senna or bisacodyl and increase the dosage in 48 hours if no bowel movement occurs. Physicians should perform a rectal examination if no bowel movement occurs in 72 hours. If there is no impaction, consider other therapies such as an enema, suppository, or magnesium citrate.[99]

Medications for refractory, opioid-induced constipation include naloxone derivatives: naloxegol (Movantik), methylnaltrexone (Relistor), or naldemedine (Symproic). Naloxegol is an oral tablet that is used daily while methylnaltrexone is a subcutaneous injection or oral tablet used daily. Naldemedine is taken by mouth daily (0.2 mg) and may cause side effects such as abdominal pain or discomfort, diarrhea, and nausea.[97] In the COMPOSE-1 trial, patients on naldemedine had significantly more spontaneous bowel movements (defined as ≥3 per week) than those on placebo (47.6% vs. 34.6%, P=0.002).[100]

For nausea or vomiting, physicians should consider a prophylactic antiemetic, add or increase non-opioid pain control agents (e.g., acetaminophen as an opioid-sparing drug), and decrease opioid dose by 25% if analgesic is satisfactory.

Sedation

Sedation is the first warning sign of a patient being at risk for opioid overdose. Take this symptom very seriously. If a patient complains of sedation, determine whether sedation is related to the opioid, eliminate nonessential depressants (such as benzodiazepines or alcohol), reduce dose by 10%-15% if analgesia is satisfactory, add or increase non-opioid or non-sedating adjuvant for additional pain to reduce opioid dose. There is insufficient evidence to recommend opioid rotation as a possible means of reducing sedation.[45] Patients should also be co-prescribed naloxone for opioid overdose reversal.

Fracture

A retrospective cohort study over seven years compared the risk of fracture associated with starting opioids vs. NSAIDs (2,436 older adults initiated on opioids and 4,874 older adults initiated on NSAIDs). Opioids significantly increased the risk of fracture in a dose-dependent fashion. The opioid formulation mattered with much of the risk in the first month after drug initiation for short-acting opioids, though fracture increased for both long- and short-acting opioids over time.[101]

Infection

Opioids may increase risk of infection in older adults. A case-control study of 3,061 older community dwelling adults ages 64-95 years evaluated the association between pneumonia and opioid use. Current prescription opioid users had a 38% increased risk of pneumonia compared with nonusers. The risk was highest for opioid users categorized as being immunosuppressed, such as those with cancer, recent cancer treatment, or chronic kidney disease, or those receiving immunosuppressive medications or medications for HIV.[102]

Myocardial Infarction (MI)

A case-control study assessed the risk of MI among adults on opioids for chronic pain in the UK General Practice Research Database (11,693 cases with up to four matched controls). Current opioid use was associated with a 28% increased risk of MI compared to non-use.[103]

Erectile Dysfunction (ED)

In a cross-sectional analysis of 11,327 men with back pain, 909 (8%) received ED medications or testosterone. Long-term opioid use was associated with 45% greater use of medications for ED or testosterone replacement compared to patients with no opioid use. Men prescribed daily doses of 120 mg morphine or more had a 58% increase in medication for ED or testosterone compared to patients without opioid use, suggesting that dose and duration of opioid use were associated with ED.[104]

Tamper-resistant/abuse-deterrent opioids

One strategy to mitigate the risk of opioid abuse has been the development of "abuse-deterrent" formulations of opioids that make it more difficult to alter for non-oral consumption (e.g., injecting, snorting, or smoking). [105] However, these opioids are more aptly named as "tamper-resistant" formulations instead of "abuse-deterrent" since they are no less potentially addictive than regular opioids when taken by mouth.

Tamper-resistant formulations often contain a higher opioid dose than immediate-release preparations. Furthermore, most are extended-release and also considerably more expensive than generic, off-patent opioids.[105] As of this writing, only one immediate-release opioid is available in an abuse deterrent formulation (oxycodone hydrochloride [RoxyBond]).[105]

Patients on Workers' Compensation

Opioids and other associated analgesic medications represent more than 30% of drug costs in Tennessee Workers' Compensation claims, a significant portion of payments for long term claimants, and are associated with longer periods of disability and lost-work time. Effective oversight

and appropriate use of these medications reduce their abuse and diversion, return injured workers to employment sooner, decrease long term disability, improve longevity, and improve patient function.

Patients being treated under a workers' compensation program are assigned an "authorized treating physician." In Tennessee, there are educational requirements and criteria to be met in order for a physician to treat chronic pain with opioids. These requirements are similar to, but somewhat different from, those in the Department of Health Guidelines as a "Pain Medicine Specialist" and it is anticipated that future legislation will be passed to reconcile the differences.

Employers through their workers' compensation insurance carriers and utilization review companies may review Schedule II, III, and IV prescriptions for appropriateness, necessity, and efficacy after 90 days. The co-administration of other Schedule II, III, and IV medications with opioids significantly increases the probability of serious complications, including death, and should generally not be used.

If more than one provider is prescribing any of the medications listed in the Tennessee guidelines, each must access the CSMD at each visit and assure by direct telephone or face-to-face communication that each provider is aware of the safety and appropriateness of all prescribed medications given to an individual patient. This communication should occur at least quarterly and be documented in the chart. Because of the risks of treatment with these medications, it is important to set guidelines that may aid the practitioners and the injured workers in effectively and safely managing chronic pain.

Patient education

Before prescribing an opioid for pain, clinicians should discuss with patients the risks and benefits of such therapy. An important consideration in framing treatment, and a key message to communicate to patients, is that the goal is not "zero pain" but, rather, a level of analgesia that maximizes a patient's physical and mental functioning.[106] A multi-modal approach, using both drug and non-drug treatments, should be encouraged.

Here are some suggested topics for discussion with patients:[46]

- Importance of adherence to prescribed dosing regimen
- Patients should use the least amount of medication necessary to treat pain and for the
- shortest amount of time
- The risk of serious adverse events that can lead to death
- The risk of physical dependence that can occur even when product is used as recommended
- Known risk factors for serious adverse events, including signs and symptoms of overdose and opioid-induced respiratory depression, GI obstruction, and allergic reactions, among others
- The most common side effects (e.g., constipation, sexual dysfunction, respiratory depression), along with the risk of falls, working with heavy machinery, and driving
- When to call the prescriber (e.g., managing adverse events, ongoing pain)
- How to handle missed doses
- The importance of full disclosure of all medications and supplements to all HCPs and the risks associated with the use of alcohol and other opioids/benzodiazepines
- Product-specific concerns, such as not to crush or chew ER products; transdermal systems and buccal films should not be cut, torn, or damaged before use, etc.
- How to safely taper dose to avoid withdrawal symptoms
- Never share any opioid analgesic with another person
- How and when to use naloxone products and their various means of administration
- Seeking emergency medical treatment if an opioid overdose occurs
- How to seek help if an opioid use disorder develops and what treatments options are available if it does
- How to report adverse events and medication errors to FDA (1-800-FDA-1088 or online at: fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf)

In addition, patients should be educated about the safe storage and disposal of opioid medications. Safe use means following clinician instructions about dosing, avoiding potentially dangerous drug interactions (e.g., alcohol), and assuring full understanding of how the medication should be consumed or applied. Remind patients that pain medications are sought after by many people, and, therefore, opioids should be stored in a locked cabinet or, if a locked unit is not available a place that is not obvious or easily accessed by others.

Proper disposal methods should be explained:

- Follow any specific disposal instructions on the prescription drug labeling or patient information that accompanies the medication.
- Do not flush medicines down the sink or toilet unless the prescribing information specifically instructs to do so.
- Return medications to a pharmacy, health center, or other organization with a take-back program.
- Mix the medication with an undesirable substance (e.g., used coffee grounds or kitty litter) and put it in the trash, or use special drug deactivation pouches that your health care provider may recommend.

Managing acute pain

It is now becoming clear that many of the problems and risks associated with managing chronic pain with opioids are also at work in the management of acute pain with opioids. For example, a number of studies demonstrate increased risk of new persistent opioid use in opioid-naïve patients after having been prescribed opioids for acute pain.[107-110] Although the risk of opioid misuse in patients prescribed opioids for acute post-surgical or post-procedural pain is relatively small (roughly 0.6% per year)[111], the volume of such procedures (approximately 48 million ambulatory surgeries or procedures in 2010)[112] translates into large numbers of patients (i.e., approximately 160,000) who may develop dependence, abuse, or overdose every year.

A central tenet of pain management, whether acute or chronic, is that the goal of treatment is a tolerable level of pain that allows the patient maximum physical and emotional functioning with the lowest risk of side effects, progression to chronic pain, or misuse or abuse.[26] This requires an adroit balancing of patient-related factors (e.g., comorbidities, medical history, risk of abuse) and drug-related factors (e.g., potency, mechanism of action, expected side effects). A commonly-recommended way to achieve this balance is with multimodal analgesia, in which several therapeutic approaches are used, each acting at different sites of the pain pathway, which can reduce dependence on a single medication and may reduce or eliminate the need for opioids and attendant risks/side effects.[113]

Multimodal analgesia (e.g., using drugs from two or more classes, or a drug plus a non-drug treatment) can produce synergistic effects, reduce side effects, or both. One example of multimodal analgesia is the use of both an NSAID and acetaminophen, plus physical approaches (e.g., cold, compression, or elevation) to manage postoperative pain. Demonstrated benefits of multimodal analgesia include earlier ambulation, earlier oral intake, and earlier hospital discharge for postoperative patients, as well as higher levels of participation in activities necessary for recovery (e.g., physical therapy).[113]

Managing patient expectations

Patients in acute pain are understandably worried that the pain will persist or get worse with time. Physicians can reduce such fears and set realistic expectations for treatment effectiveness and healing with clear, compassionate communication couched in terms patients can easily understand. It can be helpful, for example, to share with patients the fact that most forms of acute nociceptive pain (e.g. nonspecific low back pain) are self-limited, subside within weeks, and do not require invasive interventions. (In a systematic

review of 15 prospective cohort studies, 82% of people who stopped work due to acute low back pain returned to work within one month.[114])

A systematic review of 14 controlled trials of patient education interventions for low back pain showed that structured messaging by providers can reassure patients with acute pain more than usual care/control education both in the short and long term.[115] Messaging was significantly more reassuring to patients when delivered by physicians than other primary care practitioners, and such communication reduced the frequency of primary care visits.

Non-pharmacological treatments for acute pain

When possible, non-pharmacologic methods should be used, alone or in combination with analgesics, to manage acute pain.[25] The degree to which this is possible depends on the severity, type, and origin of the pain, but many non-pharmacological approaches can be very effective and their use avoids the potential side effects and risks associated with pharmacological interventions.

Physical methods of pain management can be helpful in all phases of care, including immediately after tissue trauma (e.g., rest, application of cold, compression, elevation) and later in the healing period (e.g., exercises to regain strength and range of motion).

Non-pharmacologic methods can include:[25]

- Application of cold (generally within first 24 hours) or heat
- Compression
- Elevation
- Immobilization
- Relaxation exercises
- Distraction/guided imagery
- Acupuncture
- Massage
- Electroanalgesia (e.g., transcutaneous electrical nerve stimulation)
- Physical therapy
- Yoga

Physical therapy may be useful for a range of musculoskeletal issues and can be helpful in recovering from acute pain-producing traumas initially treated with other methods. A 2018 study reported that patients with low back pain who first consulted a physical therapist were less likely to receive an opioid prescription compared to those who first saw their primary care physician.[116]

Exercise therapy can take many forms, including walking, swimming or in-water exercise, weight training, or use of aerobic or strength-training equipment. According to a review by the Centers for Disease Control and Prevention (CDC), conditions that may improve with exercise therapy include low back pain, neck pain, hip and knee osteoarthritis pain, fibromyalgia, and migraine.[117]

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 3.

Non-opioid pharmacologic treatments for acute pain

Acetaminophen and NSAIDs

In general, mild-to-moderate acute pain responds well to oral non-opioids (e.g., acetaminophen, non-steroidal anti-inflammatories [NSAIDs], and topical agents). NSAIDs, which include aspirin and other salicylic acid derivatives, and acetaminophen are used in the management of acute pain arising from injury, arthritis, dental procedures, swelling, or surgical procedures. Although they are weaker analgesics than opioids, acetaminophen and NSAIDs do not produce tolerance, physical dependence, or addiction and they do not induce respiratory depression or constipation. Acetaminophen and NSAIDs are often added to an opioid regimen for their opioid-sparing effect. Since non-opioids relieve pain via different mechanisms than opioids, combination therapy can provide improved relief with fewer side effects.

The choice of medication may be driven by patient risk factors for drug-related adverse effects (e.g., NSAIDs increase the rate of gastrointestinal, renal, and cardiovascular events). If acetaminophen or NSAIDs are contraindicated or have not sufficiently eased the patient's pain or improved function despite maximal or combination therapy, other drug classes (e.g., opioids) are sometimes used.

Non-opioid analgesics are not without risk, particularly in older patients. Potential adverse effects of NSAIDs include gastrointestinal problems

Case Study 3

Instructions: Review the case below and consider the questions that follow.

Hannah is a 62-year-old woman who has been coping with persistent pain for more than a year since she was involved in a car accident. Her initial severe neck and low back pain was thought to be due to cervical and lumbar sprain/strain. She was prescribed a short-acting opioid, which she said helped with the pain, but led to constipation. After three months of using the opioid, Hannah decided to stop because she did not like the constipation and "brain fog" from the drug. She tried several types of alternative therapies, such as massage and acupuncture, both of which provided short-term relief, although the pain later returned. At 6 months post-accident, X-ray and MRI imaging revealed no obvious spinal pathophysiology, although Hannah reported a sharp, radiating/aching pain spreading to her legs and arms. She describes bilateral pins and needles feeling in her hands. Hannah has a BMI of 31 and has been diagnosed with metabolic syndrome. She is physically inactive but currently takes no medications.

1. **Given the subjective nature of pain, how can a clinician more objectively assess the kind of pain reported by patients such as Hannah? Given the subjective nature of pain, how can a clinician more objectively assess the kind of pain reported by patients such as Hannah?** _____

2. **Does the lack of obvious pathophysiology on imaging suggest that Hannah is having psychosomatic pain?** _____

3. **What Hannah be a good candidate for an opioid analgesic? Why or why not?** _____

(e.g., stomach upset, ulcers, perforation, bleeding, liver dysfunction), bleeding (i.e., antiplatelet effects), kidney dysfunction, hypersensitivity reactions, and cardiovascular concerns, particularly in the elderly.[118] The threshold dose for acetaminophen liver toxicity has not been established; however, the Food and Drug Administration (FDA) recommends that the total adult daily dose not exceed 4,000 mg in patients without liver disease (with a lower ceiling for older adults).[119]

The FDA currently sets a maximum limit of 325 mg of acetaminophen in prescription combination products (e.g., hydrocodone and acetaminophen) in an attempt to limit liver damage and other potential ill effects of these products.[32]

Topical capsaicin and salicylates can both be effective for short term pain relief and generally have fewer side effects than oral analgesics, but their long-term efficacy is not well studied.[120,121] Topical aspirin, for example, can help reduce pain from acute herpes zoster infection.[122] Topical NSAIDs and lidocaine may also be effective for short-term relief of superficial pain with minimal side effects. Topical agents can be simple and effective for reducing pain associated with wound dressing changes, debridement of leg ulcers, and other sources of superficial pain.[122]

Anticonvulsants

Anticonvulsants, such as gabapentin, pregabalin, oxcarbazepine, and carbamazepine, are often prescribed for chronic neuropathic pain (e.g., post-herpetic neuralgia and diabetic neuropathy) although evidence for efficacy in acute pain conditions is weak.[123] A 2017 trial, for example, randomized 209 patients with sciatica pain to pregabalin 150 mg/day titrated to a maximum of 600 mg/day vs. placebo for 8 weeks.[124] At 8 weeks there was no significant difference in pain between groups (mean leg pain intensity on a 0-10 scale 3.7 with pregabalin vs. 3.1 with placebo, P=0.19).

Potential side effects of anticonvulsants include sedation, dizziness, and peripheral edema. Pregabalin and gabapentin also have some abuse potential in the general population because some users report euphoric effects, and abrupt cessation of anticonvulsants may precipitate withdrawal symptoms.[123]

Cannabis

As noted above, the evidence base for cannabinoid efficacy on acute pain, is extremely limited and mixed. A small double-blind, cross-over study in 18 females and experimentally-induced mild acute pain found no significant analgesic effect of oral cannabis extract.[72] Another randomized, double-blind study with 15 healthy volunteers using smoked cannabis found no analgesic effect with low doses of cannabis, a modest effect with moderate doses, and enhanced pain responses with high doses.[73] Much more research is needed before cannabis in any form can be recommended for treatment of acute pain.[74]

Opioids for acute pain

Reasons for caution

Opioids are commonly prescribed for pain, with nearly two thirds (64%) of the public reporting being prescribed an opioid for pain at some point in their lives.[125] However, this approach is not as safe and effective as once thought, and high-dose prescriptions or prolonged use not only increase the risk of misuse, addiction, or overdose, they may actually increase pain and pain sensitivity.[126,127]

Recent evidence suggests that opioids may not be more effective for moderate to severe pain than non-opioid pain regimens.[128,129] A randomized trial of 416 patients with acute extremity pain found no clinically important differences in pain reduction at two hours after single-dose treatment with ibuprofen and acetaminophen vs. three different opioid and acetaminophen combination analgesics .

Physical dependence can readily occur after use of opioids at a sufficient dose (e.g., 30mg of oxycodone) for just a few days. In addition, side effects of opioid use include constipation, confusion/gait instability, respiratory depression, pruritus, erectile dysfunction, and fractures, all of which may be more problematic in older patients and occur at higher rates than with non-opioid analgesics.

A cross-sectional study compared common side effects experienced during the first week of treatment with opioid analgesics vs. non-opioid analgesics in patients over age 65 with acute musculoskeletal pain.[130] The intensity of six common opioid-related side effects were significantly higher with opioids. (A limitation of this study is that it could not assess severe but less common adverse events associated with NSAIDs and acetaminophen, including the risk for gastrointestinal bleeding, acute kidney injury, and hepatotoxicity.)

In a retrospective study of 12,840 elderly patients with arthritis, opioid use was associated with an increased risk relative to non-opioids for cardiovascular events, fracture, events requiring hospitalization, and all-cause mortality.[131]

High-intensity prescribing of opioids (high doses or high numbers of pills prescribed) for acute pain is associated with greater likelihood of long-term opioid use.[132,133] In a retrospective analysis of a national sample of opioid-naïve Medicare beneficiaries who received emergency treatment from 2008 through 2011, initial exposure to an opioid was a strong predictor of subsequent long-term use.

The risk of prolonged opioid use is particularly high after arthroscopic joint procedures. In a 2019 case-control study of 104,154 opioid-naïve adults, 8,686 (8.3%) developed new prolonged opioid use (continued opioid use between 91 and 180 days after shoulder arthroscopy).[134] Subgroups at higher risk for long-term use included women, those with a history of alcohol use disorder, those with a mood disorder, and those with an anxiety disorder.

Opioid choices for acute pain

If an opioid is deemed necessary to treat moderate-to-severe acute pain, the following general principles are recommended:

- Avoid extended-release and long-acting opioids such as methadone, fentanyl patches, and ER/LA versions of opioids such as oxycodone or oxymorphone.
- Avoid co-prescribing opioids with other drugs known to depress central nervous system function (e.g., benzodiazepines)
- Limit the dose and quantity of opioids to address the expected duration and severity of pain (usually less than 7 days).
- Combine opioids with other treatments (e.g., non-pharmacologic options such as exercise or cognitive behavioral therapy, NSAIDs, or acetaminophen).
- Closely monitor patients with impaired hepatic or kidney function if they are prescribed opioids, and adjust the dose or duration accordingly

Immediate-release agents are strongly preferred because of the higher risk of overdose associated with ER/LA agents. A cohort study of 840,000 opioid-naïve patients over a 10-year span found that unintentional overdose was 5 times more likely in patients prescribed ER/LA agents compared to immediate-release opioids.[140]

Little high-quality evidence exists to support the choice of any one opioid over another for acute pain. However, some opioids are associated with more adverse events. For example, codeine is not preferred due to differential metabolism to the active ingredient, morphine. It is associated with a risk of both under-treatment in usual doses (due to CYP2D6 mutations) and overtreatment (in ultra-rapid metabolizers of CYP2D6). [141]

Meperidine is associated with an increased risk of post-operative delirium[142] due to its long half-life and its active metabolite, normeperidine, which is a central nervous system stimulant.[143]

Opioid dosing for acute pain

The amount of opioid prescribed should relate to the level of pain expected from the injury or procedure. Injuries or procedures involving bones and joints tend to be more painful than those involving soft tissues.[144]

Table 5 illustrates the wide range of expected pain and associated recommended opioid doses for some common surgeries or procedures.

Managing chronic non-cancer pain

Management of chronic non-cancer pain begins by establishing individualized treatment goals, exploring non-opioid treatment options, and addressing comorbid depression and anxiety, if present. Pain management goals may include both pain and functional targets, with the understanding that being 100% pain free is not realistic. Functional goals should focus on activities that are meaningful to the patient and attainable based on the severity of the painful condition. Multi-modal approaches that include non-drug and drug interventions are recommended.[42]

Be aware that comorbid conditions such as depression and anxiety can impact pain management. (In a study of 250 patients with chronic pain and moderate depression, using antidepressant therapy reduced pain levels before analgesic interventions were added.[146])

For patients with intractable, moderate-to-severe chronic noncancer nociceptive pain unresponsive to non-opioid treatment options, a trial of opioids may be indicated guided by the following principles (each detailed below):

- Discuss risks and benefits of opioid use
- Establish a written treatment agreement
- Check or monitor opioid use
- Use caution with dose escalation
- Prescribe naloxone if at risk for overdose
- Screen for opioid misuse or abuse using history and, ideally, a validated questionnaire, as well as urine drug testing
- Taper or discontinue opioids when possible

Discussing opioid risks and benefits

Educate patients about the risks and benefits of opioid use prior to initiating opioids and discuss them at each subsequent visit. For many patients, the risks of opioid therapy outweigh the benefits. However, for some patients with nociceptive, or even neuropathic, chronic pain, intermittent use of low-dose opioids on an as-needed basis may be a reasonable approach.

Establishing a written treatment agreement

Written documentation of all aspects of a patient's care, including assessments, informed consent, treatment plans, and provider/patient agreements, are a vital part of opioid prescription "best practices." Such documentation provides a transparent and enduring record of a clinician's rationale for a particular treatment and provides a basis for ongoing monitoring and, if needed, modifications of a treatment plan.[26]

Many computerized systems are now available for the acquisition, storage, integration, and presentation of medical information. Most offer advantages that will benefit both patients and prescribers, such as maintaining up-to-date records, and providing instant availability of information relevant to prescribing or treatment. Although automation can help, clear documentation is not dependent on electronic record-keeping; it merely requires a commitment to creating clear and enduring communication in a systematic fashion. Good documentation can be achieved with the most elaborate electronic medical record systems, with paper and pen, or with dictated notes. Clinicians must decide for themselves how thoroughly, and how frequently, their documentation of a patient's treatment should be.

Table 5. Opioid dose recommendations for post-procedural pain[145]

Procedure	Number of oxycodone 5 mg tablets (or equivalent)
Dental extraction	0
Thyroidectomy	5
Breast biopsy or lumpectomy	5
Lumpectomy plus sentinel lymph node biopsy	5
Hernia repair (minor or major)	10
Sleeve gastrectomy	10
Prostatectomy	10
Open cholecystectomy	15
Cesarean delivery	15
Hysterectomy (all types)	15
Cardiac surgery via median sternotomy	15
Open small bowel resection	20
Simple mastectomy with or without sentinel lymph node biopsy	20
Total hip arthroplasty	30
Total knee arthroplasty	50

Informed Consent

Informed consent is a fundamental part of planning for any treatment, but it is particularly important in long-term opioid therapy, given the potential risks of such therapy. At its best, consent also fortifies the clinician/patient relationship. Prescribers must be able to answer with confidence four key questions when obtaining informed consent in the context of treatment with opioids:[147]

1. Does the patient understand the various options for treatment?
2. Has the patient been reasonably informed of the potential benefits and risks associated with each of those options?
3. Is the patient free to choose among those options, free from coercion by the healthcare professional, the patient's family, or others?
4. Does the patient have the capacity to communicate his or her preferences—verbally or in other ways (e.g., if the patient is deaf or mute)?
5. Is there a proxy available if the patient cannot provide consent due to cognitive impairment?

Documentation related to these key areas can be accomplished by creating a separate paper or electronic informed consent form or by incorporating informed consent language into a larger treatment plan or patient/provider agreement.

Patient-Provider Agreements

A written agreement between a clinician and a patient about the specifics of their pain treatment with opioids can help clarify the plan with the patient, the patient's family, and other clinicians who may become involved in the patient's care.[26] Such agreements can also reinforce expectations about the appropriate and safe use of opioids. Caution must be exercised, however, to ensure that patient/provider agreements are not used in a coercive way to unethically place patients in the position of having to agree to its terms or else lose an important component of their treatment (or even lose all treatment).[147]

Although evidence is lacking about the most effective methods to convey the information included in most patient-provider agreements, such agreements have been widely used and are recommended by regulators and many experts on treatment guidelines for long-term opioid therapy.[42] The Veterans Administration and U.S. Department of Defense chartered an expert panel to undertake a systematic review of existing medical literature on this subject. In the clinical practice guidelines resulting from that work, the panel concluded that opioid treatment agreements are a standard of care when prescribing long-term opioid therapy.[147]

Provider/patient agreements have many potential advantages, including:[26]

- Allowing treatment to start on a note of mutual respect and partnership
- Enhancing transparency
- Engaging patients in a collaborative education and decision-making process
- Helping to set functional goals and clarifying the clinician's and patient's roles and responsibilities in attaining these goals
- Documenting acceptance of treatment risks and benefits
- Documenting informed consent
- Helping avoid misunderstandings that may occur over long treatment time periods
- Providing a foundation for subsequent decisions about changes in medications or termination of treatment

Clinicians should strive to craft agreements that serve their patients' best interests and avoid coercive or punitive language. Thus, agreements should avoid:

- Putting all burden on the patient rather than sharing it between patient and clinician
- Framing the agreement in terms of punishments for possible future crimes or difficulties
- Using language that is stigmatizing, dominating, or pejorative
- Using coercion in any way
- Imposing limitations for the clinician's convenience without clear and substantial benefit for the patient.
- Insisting on behaviors unrelated to actual use of medications
- Using the term "fired" to describe termination of treatment.
- Threatening abandonment or suggesting that patients will not have continued access to non-opioid pain relieving treatments if opioids are terminated

To be effective, written agreements must be clearly understood by the patient. This may require the provision of agreements in multiple languages. All agreements should be written at the sixth- to seventh-grade level or even lower.[148] Translators may need to be provided for speakers of other languages to ensure patient understanding and effective informed consent. A patient who does not fully understand the potential risks and benefits of a treatment cannot be truly "informed" as required by the legal and ethical guidelines for medical practice. Time must be allowed for patients to ask questions, and for prescribers to ensure patients understand what they are being told. Some, or all, of these tasks may be handled by trained personnel (or staff members) rather than clinicians.

Although the term "agreement" is generally perceived as being more patient-friendly than the word "contract," clinicians should understand that, from a legal standpoint, any written or oral agreement between a prescriber and a patient may be considered a binding "contract."[149] Clinicians should ensure that the terms in any agreement are understood by the patient, and are acceptable, attainable, and consistent with high-quality practice.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 4 ON THE NEXT PAGE.

Creating individualized function-based pain treatment plans

Once a patient has been assessed and accepted as a candidate for chronic opioid therapy, and after informed consent has been obtained for such treatment, a written plan for implementing the treatment should be drafted. Such plans typically include a statement of the goals of therapy. These goals should be written carefully in light of the inherent subjectivity of pain. Since pain itself cannot be measured objectively, framing treatment goals solely in terms of pain relief means that such goals cannot be objectively confirmed.

Although a patient's subjective pain and suffering are obviously important factors, only the functional impact of the pain can be measured and used to create objective treatment goals. This impact takes many forms, but typically chronic pain erodes foundations of daily life, such as physical activity, concentration, emotional stability, interpersonal relationships, and sleep. This can, in turn, degrade functioning at work or in the home, which can lead to depression, anxiety, insomnia, and even suicide. Clinicians should know that even relatively modest reductions in pain can translate into significant functional improvements as pain rating declines.[26] A 20% reduction in a pain score (i.e., roughly two points on the standard 0-10 pain scale) may be acceptable if it produces significant functional benefits for a patient.

Framing treatment goals in terms of improved patient functioning, rather than merely pain relief, offers two primary advantages to clinicians:

- Prescribing decisions (or decisions to terminate treatment) are based on outcomes that can be objectively demonstrated to both clinician and patient (and, possibly, to the patient's family)
- Individual differences in pain tolerance become secondary to the setting and monitoring of treatment goals, since subjectively perceived levels of pain are not the primary focus in determining functionality.

Basing treatment plans on functional goals is especially valuable in the context of prescribing opioid pain medications, because such goals may help determine whether a patient has an opioid use disorder because patients with OUD often have decreased functioning, while effective pain relief typically improves functioning.

Functional decline itself may result from a range of problems, including inadequate pain relief, non-adherence to a regimen, function-limiting side effects, or untreated affective disorders. Sometimes impaired functioning is the result of OUD, and these objective results may shed valuable light on an otherwise confusing presentation of a patient's pain symptoms.

Functional treatment goals should be realistic. Progress in restoring function is usually slow and gains are typically incremental. Chronic non-cancer pain is often marked by long-standing physical and psychological deconditioning, and recovery may require reconditioning that may take weeks, months, or years. It is much better to set goals that are slightly too low than slightly too high. Raising goals after a patient has "succeeded" in achieving them is far more motivational and encouraging than lowering goals after a patient has "failed." Table 6 illustrates some simple functional goals and ways they might be verified.

Table 6: Example of functional goals and evidence used to assess progress[26]

Functional Goal	Evidence
Begin physical therapy	Letter from physical therapist
Sleeping in bed as opposed to lounge chair	Report by family member or friend (either in-person or in writing)*
Participation in pain support group	Letter from group leader
Increased activities of daily living	Report by family member or friend
Walk around the block	Pedometer recordings or written log of activity
Increased social activities	Report by family member or friend
Resumed sexual relations	Report by partner
Returned to work	Pay stubs from employer or letter confirming the patient is off of disability leave
Daily exercise	Gym attendance records or report from family member or friend

** Involving other persons requires explicit permission from the patient, and this permission should be documented.*

Case Study 4

Janet is an 82-year-old Caucasian woman. Her husband died of an ischemic stroke five years ago, and now her son Tim, who lives nearby, looks after her. Janet has had chronic left hip pain ever since a hip fracture repair two years ago developed a serious infection. She comes in to see you with Tim because she is having worsening pain. Although she has always been quick-witted and articulate, in recent years Janet has had memory problems, often pausing in mid-sentence as she searches for a name or word that's "right on the tip of her tongue." She views these memory lapses as completely normal, although Tim finds them worrisome. According to Janet, the pain medication she was prescribed (short-acting hydrocodone/acetaminophen) is not enough to quell the pain in her hip (she says both are now hurting). According to Tim, however, Janet often forgets how much medicine she has taken. Tim feels Janet is relying too heavily on the analgesics—he believes strongly that much of Western medicine is misguided, overly invasive, overly reliant on "pills for everything." Janet dismisses Tim's concerns and presses for a long-acting opioid she saw advertised on television.

Instructions: Review the sample controlled substance patient agreement below, then answer the questions on the next page that follow related to the "Janet" scenario above.

SAMPLE PATIENT AGREEMENT:

PATIENT NAME: _____

PRIMARY CARE PHYSICIAN/SITE:_____

I understand that this agreement between myself; and (insert name of medical office/group) is intended to clarify the manner in which chronic (long- term) controlled substances will be used to manage my chronic pain. Chronic controlled substance therapy for patients who do not suffer from cancer pain is a controversial issue.

I understand that there are side effects to this therapy; these include, but are not limited to, allergic reactions, depression, sedation, decreased mental ability, itching, difficulty in urinating, nausea and vomiting, loss of energy, decreased balance and falling, constipation, decreased sexual desire and function, potential for overdose and death. Care should be take when operating machinery or driving a car while taking these medications. When controlled substances are used long-term, some particular concerns include the development of physical dependence and addiction. I understand these risks and have had my questions answered by my physician.

I understand that my (insert name of medical group) health care provider will prescribe controlled substances only if the following rules are adhered to:

- All controlled substance prescriptions must be obtained from your (insert name of medical group) primary care provider. If a new condition develops, such as trauma or surgery, then the physician caring for that problem may prescribe opioids for the increase in pain that may be expected. I will notify my primary care physician within 48-hours of my receiving an opioid or any other controlled substance from any other physician or other licensed medical provider. For females only: If I become pregnant while taking this medicine, I will immediately inform my provider and my obstetrician and obtain counseling on risks to the fetus.
- I will submit urine and/or blood on request for testing at any time without prior notification to detect the use of non-prescribed drugs and medications and confirm the use of prescribed ones. I will submit to pill counts without notice as per provider's request. I will pay any portion of the costs associated with urine and blood testing that is not covered by my insurance.
- All requests for refills must be made by contacting my (insert name of medical group) primary care provider during business hours at least 3-workdays in advance of the anticipated need for the refill. All prescriptions must be filled at the same pharmacy, which is authorized to release a record of my medications to this office upon request. A copy of this agreement will be sent to my pharmacy.
- Pharmacy name/address/telephone:
- The daily dose may not be changed without my (insert name of medical group) primary care provider's consent. This includes either increasing or decreasing the daily dose.
- Prescription refills will not be given prior to the planned refill date determined by the dose and quantity prescribed. I will accept generic medications.
- Accidental destruction, loss of medications or prescriptions will not be a reason to refill medications or rewrite prescriptions early. I will safeguard my controlled substance medications from use by family members, children or other unauthorized persons.
- You may be referred to an appropriate specialist to evaluate your physical condition.
- You may be asked to have an evaluation by either a psychiatrist or psychologist to help manage your medication needs.
- If your provider determines that you are not a good candidate to continue with the medication, you may be referred for further evaluation or treatment. .
- These medications may be discontinued or adjusted at your provider's discretion.
- I understand that it is my provider's policy that all appointments must be kept or canceled at least 2-working days in advance. I understand that the original bottle of each prescribed controlled substance medication must be brought to every visit.
- I understand that it is my provider's policy that all appointments must be kept or canceled at least 2-working days in advance. I understand that the original bottle of each prescribed controlled substance medication must be brought to every visit.
- I understand that I am responsible for meeting the terms of this agreement and that failure to do so will/may result in my discharge as a patient of (insert name of medical group). Grounds for dismissal from (insert name of medical group) include, but are not limited to: evidence of recreational drug use; drug diversion; altering scripts; obtaining controlled substance prescriptions from other providers without notifying this office; abusive language toward staff; development of progressive tolerance; use of alcohol or intoxicants; and engagement in criminal activities.
- I understand that I am responsible for meeting the terms of this agreement and that failure to do so may result in my provider no longer prescribing for me.

Patient's Signature: _____ Date: _____

Case Study 4 (Continued)

Questions for case study:

1. **Would this agreement be appropriate for use with Janet?**

2. **Would this agreement need to be modified in any way because of the specifics of Janet's case?**

3. **Would it be prudent to include a family member in the discussion about treatment and to serve as a witness to the agreement?**

The responsibility for obtaining evidence of success in meeting a functional goal lies with the patient and should be made explicit in the prescribing agreement. If a patient is unable to document or achieve the progress outlined in a treatment plan, this may suggest a need for goal readjustment.

Components of an Effective Treatment Plan

The creation of an effective function-based treatment plan must be a collaboration between patient and clinician. A patient's pain score will be just one of many variables to be considered in framing goals. These goals should be realistic, meaningful to the patient, and verifiable. The details of a function-based treatment plan are necessarily specific to the patient, but one way to initiate the process is to begin with the question: "What do you hope to do as a result of treatment that you can't do now?"

The treatment plan can include a discussion of, and the setting of expectations about, periodic re-assessment of goals. Patients may stabilize at a certain level of function, and the clinician and patient together must decide if this is acceptable or whether changes are needed.

As is the case in drafting other types of patient/provider documents, patients should be reminded of the benefits and risks of a chosen therapy. With opioids, these include the realities of tolerance and physical dependence and the potential need to taper the medication slowly to avoid withdrawal. Patients must also be educated about the possibility that opioids may be either ineffective or have intolerable adverse effects, and that there is also the possibility of problematic use, which could lead to misuse, abuse, or, less commonly, OUD.

Another critical component of any treatment plan is a description of how treatment with an opioid medication might be terminated. Stopping opioid therapy in cases of chronic non-cancer pain is often more difficult than starting it. Being clear about the conditions under which opioid therapy will end is important because opioids are not curative, have no standard duration of treatment, and may be associated with substantial risks.

Termination may be required for many reasons, including:

- Healing or resolution of a specific pathology underlying the pain
- The experience of intolerable side effects
- Lack of adequate response to a medication in terms of either pain relief or functional improvement (called therapeutic failure)
- Evidence of non-medical use of the medication, abuse, inappropriate use, or OUD

If inappropriate use of a prescription medication is discovered, treatment may be suspended, although provisions should be in place for continuation of some kind of pain treatment and/or referral to other professionals or members of a pain management team. Some clinicians may be willing and able to continue a regimen of opioid therapy even after the discovery of aberrant behavior if done with intensified monitoring, patient counseling, and careful documentation of all directives. This level of vigilance and risk management, however, may exceed the abilities and resources of the average prescriber. In such cases, referral to a provider with specialized skill or experience in dealing with high-risk patients may be prudent.

The intensity and frequency of monitoring recommended in a treatment plan is dependent on an assessment of the patient's risk for abuse, diversion, or addiction. Tools and techniques similar or identical to those used during an initial assessment of a patient's risk can be used to re-assess or monitor risk on an on-going basis.[150]

States vary in their requirements for intervals at which follow-up visits are required when controlled substances such as opioid medications are prescribed. Although federal law allows for a 90-day supply of prescriptions for patients receiving schedule II drugs (who are otherwise deemed safe to have this amount), state law can vary from 30 days to 6 months. In cases where state and federal law conflict, the most restrictive rule prevails.[150]

Initiating therapy

Key Principles of initiation

1. Opioids should only be prescribed if the benefits of the treatment appear to outweigh the risks because national data suggest an increased risk for overdose starting at 40 MEDD in opioid naïve patients, with greatest risk in the first 2 weeks of treatment.[15] The risk of overdose increases ten-fold at 100 MEDD, although data from Tennessee suggest this ten-fold risk may start closer to 81 MEDD.[15]
2. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days in some instances is appropriate and should be documented in the medical record.
3. Primary care providers treating chronic pain with opioids should generally prescribe immediate-release opioids instead of ER/LA opioids (deviations from this general rule should be documented).
4. Prescribers who are not pain medicine specialists should not prescribe methadone for a chronic pain condition.
5. Any product containing buprenorphine, whether with or without naloxone, may only be prescribed for a use recognized by the FDA. Buprenorphine/naloxone combination should be avoided for the treatment of chronic pain.

6. Benzodiazepines should be generally avoided in combination with chronic opioid therapy. When the opioid dose reaches 120mg morphine equivalent dose/day (MEDD) and the benzodiazepines are being used for mental health purposes, the provider should refer the patient to a mental health professional to assess necessity of the benzodiazepine medication.
7. Although methadone is a viable treatment option, it should be reserved for the treatment of addiction. However, methadone may be used by a pain specialist for treatment of pain. A pain specialist should understand the complexities of methadone. The decision to treat should consider all available treatments.
8. If the prescribed treatment deviates from recommended guidelines, the reasons should be documented in the medical record.

The initiation of opioids should be presented to the patient as a therapeutic trial, the results of which will determine whether opioid treatment is continued. When initiating opioid therapy, the lowest dose of opioids should be given to an opioid-naïve patient and then titrated to effect.

Informed consent for the use of opioids in treating pain must be obtained prior to initiating treatment. Informed consent documents typically cover: potential risks and anticipated benefits of opioid therapy, potential side effects, likelihood of physical dependence, risk of over-sedation, pregnancy, risk of impaired motor skills, risk of addiction and death.

A written treatment agreement should be used with the patient at the time opioids are first prescribed for chronic pain. Treatment agreements typically cover reasons for which opioids may be discontinued, the practice policy on early refills, policy on lost prescriptions or medications, expectations for safe storage of medications, use of one pharmacy, and expectations about periodic drug testing. The treatment agreement should include an expectation that a female patient will tell the provider if she wishes to avoid unintended pregnancy and if she becomes pregnant.

No provider is obligated to continue opioid therapy that has been initiated by another provider. If the initial evaluation of the patient does not support the need for opioids, a discussion about risks and possible treatment of withdrawal should be included in the documentation of clinical reasoning for opioid cessation.

Providers must continually monitor the patient for signs of abuse, misuse or diversion. An unannounced UDT (or a comparable oral fluids test) should be done twice a year at a minimum.

Monitoring opioid use

Follow-up appointments should occur one to four weeks after initiation of opioids or with dose changes; maintenance therapy visits should occur at least every three months. Each visit should include an assessment using a pain and function tool, questions about side effects, evaluation of overdose risk, and discussions about how the medication is being used.[23]

Many strategies to monitor opioid use and ensure patient safety have been recommended. However, simply asking patients how they are using the medication, how often they take it, how many pills they take at one time, and what triggers them to take the medication, can identify patients who may be misusing opioids or need changes to their pain management plan. Other ways to objectively monitor opioid use are checking prescription drug monitoring programs, completing urine drug screens, or random pill counts.

Relatively infrequent monitoring may be appropriate for low-risk patients on a stable dose of opioids (i.e., 1-2 times a year). More frequent or intense monitoring is appropriate for patients during the initiation of therapy or if the dose, formulation, or opioid medication is changed. Patients who may need more frequent or intense monitoring (i.e., 4-6 times a year) include:[26]

- Those with a prior history of an addictive disorder, past abuse, or other aberrant use
- Those in an occupations demanding mental acuity
- Older adults
- Patients with an unstable or dysfunctional social environment
- Those with comorbid psychiatric or medical conditions

It is important to recognize that urine drug testing is expensive and not all insurance companies will pay for frequent testing. Discuss the cost of testing with patients. Also, only order the test that is necessary. It is not necessary to order quantitative testing on patients as this test can be very expensive. For low-risk patients urine drug screening, even done as a point of care test, may be sufficient.

Trust is a necessary part of any patient/clinician relationship, but studies suggest that in the context of controlled substances, it is unwise to rely on a patient's word that medications are being consumed as prescribed. Although the use of more objective ways to monitor adherence to medication regimens is an imperfect science, such methods remain an essential component of periodic review. Multiple objective methods to assess adherence exist, but there is no single "best" approach and all such methods have both advantages and potential drawbacks.

Drug testing should be approached in a consensual manner as part of an agreed-upon treatment plan and with the idea that such testing benefits both the patient and the provider. The potential benefits of clinical drug testing include:[26]

- Serving as a deterrent to inappropriate use
- Providing objective evidence of abstinence from non-prescribed controlled substances
- Monitoring response to opioid treatment
- Assisting with a diagnosis
- Helping patients allay concerns by family members, employers, or law-enforcement
- Demonstrating to regulatory authorities a clinician's dedication to monitoring "best practices"

In the context of family practice settings (and even pain specialist settings) unobserved urine collection is usually an acceptable procedure for drug testing. Prescribers, however, should be aware of the many ways in which urine specimens can be adulterated. Specimens should be shaken to determine if soap products have been added, for example. The urine color should be noted on any documentation that accompanies the specimen for evaluation, since unusually colored urine could indicate adulteration. Urine temperature and pH should be measured immediately after collection when possible.[150]

One way to reduce the risk of urine test false positives or false negatives is to develop a relationship with a single laboratory, become familiar with its testing tools and threshold values, and use the same screening (presumptive) and confirmatory (definitive) tests regularly to build familiarity with the range of normal results.[150] Quantitative testing is not necessary and can not be used to determine if a patient is taking a specific dose of a medication.

Prescribers should be familiar with the metabolites associated with each opioid that may be detected in urine, since the appearance of a metabolite can be misleading (Table 7). A patient prescribed codeine, for example, may test positive for morphine because morphine is a metabolite of codeine. Similar misunderstandings may occur for patients prescribed hydrocodone who appear

Table 7: Metabolites of common opioid analgesics[150]

Drug	Metabolites
Morphine	Morphine Hydromorphone Codeine
Codeine	Codeine Morphine Hydrocodone
Hydrocodone	Hydrocodone Hydromorphone 6-Hydrocodol
Oxycodone	Oxycodone Oxymorphone Hydrocodone

positive for hydromorphone or oxycodone and oxymorphone.

Opioid rotation and equianalgesic dosing

"Opioid rotation" means switching from one opioid to another in order to better balance analgesia and side effects. Rotation may be needed because of a lack of efficacy (often related to tolerance), bothersome or unacceptable side effects, increased dosing that exceeds the recommended limits of the current opioid (e.g., dose limitations of co-compounded acetaminophen), or inability to absorb the medication in its present form (i.e., if there is a change in the patient's ability to swallow, switch to a formulation that can be absorbed by a different route such as transdermal.)

Because of the large number of variables involved in how any given opioid will affect any given patient, opioid rotation must be approached cautiously, particularly when converting from an immediate-release formulation to an ER/LA product. As noted previously, equianalgesic charts must be used carefully, and titration must be done carefully and with appropriate monitoring. In some cases, because of the risk of potential harm during the time of rotating from one chronic opioid regimen to another, it may be wise to initially use lower doses of an ER/LA opioid than might be suggested by equianalgesic charts, while temporarily liberalizing, as needed, the use of a short-acting opioid.[151] This would then be followed by gradual titration of the LA opioid to the point where the as-needed short-acting opioid is incrementally reduced, until no longer necessary.

Equianalgesic dosing charts help clinicians determine the appropriate starting dose of an opioid when changing routes of administration or when changing from one opioid drug to another. Such charts must be used carefully, however. A high degree of variation has been found across the various charts and online calculator tools, and may account for some overdoses and fatalities.[151] The optimal dose for a specific patient must be determined by careful titration and appropriate monitoring, and clinicians must be mindful that patients may exhibit incomplete cross-tolerance to different types of opioids because of differences in the receptors or receptor sub-types to which different opioids bind.[151] In addition, the patient's existing level of opioid tolerance must be taken into account. Printed equianalgesic charts are common, and online calculators are also freely available (a common one can be accessed at clincalc.com/Opioids). The CDC provides a helpful guide to opioid conversions available at: www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf. Always work with a clinical pharmacist if you do not have a lot of experience with opioid rotation as this can be a risk factor for unintentional opioid overdose.

How to recognize and intervene upon suspicion or identification of an OUD

Whenever a clinician considers treating pain with a controlled substance, such as an opioid, risk of misuse or diversion is always a possibility, no matter how remote, and must be assessed. Exactly whom to suspect and when to be proactive in investigating risk factors is an area of great debate. To date, no convincing data exist to support the strategy of focusing on any one specific population or setting—which means that prescribers must be vigilant with all patients. The concept of "universal precautions" has been applied to this approach, which means that any patient in pain could have a drug misuse problem—just as any patient requiring a blood draw for a simple lab test could have HIV.[152] Treating everyone with the same screens, diagnostic tests, and administrative procedures can help remove bias and level the playing field so everyone is treated equally and screened thoroughly.

Nonetheless, it is also true that some patient characteristics are predictive of a potential for drug abuse, misuse, or other aberrant behaviors. The factor that appears to be most strongly predictive in this regard is a personal or family history of alcohol or drug abuse.[42] Some studies have also shown that younger age and the presence of psychiatric conditions are also associated with aberrant drug-related behaviors.[42]

In evaluating patients with chronic pain for risk of addiction or signs that they may be abusing a controlled substance, it may be helpful to consider the sets of characteristics listed in Table 8.

Signs of physical dependence include the appearance of an abstinence syndrome with abrupt cessation or diminution of chronic drug administration and is not the same as OUD, a condition where patients lose control of their opioid use or compulsively use opioids. The nature and time of onset of this syndrome vary with drug actions and half-life. Slow tapering of the drug (e.g., 10-15% reduction in dosage per day or every other day) usually avoids the appearance of an abstinence syndrome.

Although not usually encountered in patients without a history of drug abuse, the administration of some drugs (e.g., opioids) may cause OUD. Signs of drug craving and/or drug-seeking behavior (e.g., missed appointments with after-hour calls for prescription renewals; solicitation of prescriptions from multiple physicians; reports of lost, destroyed, or stolen medications; selling and buying drugs off the street)[153] should alert the clinician to such a possibility. It is critical that OUD be diagnosed because it is a serious, but very treatable, condition and failure to treat it will hinder efforts to manage pain.

Managing Non-Adherent Patients

Patients who exhibit aberrant drug-related behaviors or non-adherence to an opioid prescription should be monitored more closely than compliant patients. Concern that a patient is non-adherent should prompt a thorough evaluation. The way clinicians interact with patients can affect the relationship (for better or worse) and influence treatment outcomes. A clinician's negative reactions to non-adherence might include anger at the patient, disappointment and sadness at the apparent betrayal of trust, or fear that the patient's behavior could expose the provider to legal jeopardy.[26]

Before accusing a patient of not adhering to a prescribed regimen, clinicians should assess the situation fully. Possible reasons for non-adherence include:

- Inadequate pain relief
- Misunderstanding of the specifics of the prescription
- Misunderstandings related to lack of fluency with English

Table 8: Characteristics of chronic pain patients vs. patients with an OUD[150]

Patient with chronic pain	Patient with an opioid use disorder
Medication use is not out of control	Medication use is out of control
Medication use improves quality of life	Medication use impairs quality of life
Wants to decrease medication if adverse effects develop	Medication use continues or increases despite adverse effects
Is concerned about the physical problem being treated with the drug	Unaware of or in denial about any problems that develop as a result of drug treatment
Follows the practitioner-patient agreement for use of the opioid	Does not follow opioid agreement
May have left over medication	Does not have leftover medication
	Loses prescriptions
	Always has a story about why more drug is needed

- Attempts to "stretch" a medication in order to save money
- Cultural or familial pressure not to take a medication
- Stigma about taking a pain medication
- Overmedication and fears about addiction
- Misunderstanding of a prescription by a caregiver who has taken responsibility for daily apportioning of medications
- Confusion between two medications that look very similar to each other

The use of patient–provider agreements and/or informed consent documents can help clinicians navigate the uncertainties that can arise in cases of real or apparent non-adherence, and may help make the process less confrontational. Consultation with an addiction medicine specialist or psychiatrist may be necessary if addiction is suspected or if a patient's behavior becomes so problematic that it jeopardizes the clinician/patient relationship.

Treatment Termination

Reasons for discontinuing an opioid analgesic can include the healing of or recovery from an injury, medical procedure, or condition; intolerable side effects; lack of response; or discovery of misuse of medications. Regardless of the reason, termination should be accomplished so as to minimize unpleasant or dangerous withdrawal symptoms by tapering the opioid medication slowly, by carefully changing to a new formulation, or by effectively treating an opioid use disorder if it has developed. Approaches to weaning range from a slow 10% reduction per week to a more aggressive 25 to 50% reduction every few days.[42] In general, a slower taper will produce fewer unpleasant symptoms of withdrawal; however, this may not be the safe course of action for a patient experiencing harmful side effects or who has OUD.

Opioid therapy must be discontinued or re-evaluated whenever the risk of therapy is deemed to outweigh the benefits being provided. A clinician may choose to continue opioid treatment with intensified monitoring, counseling, and careful documentation if it is deemed in the best interest of the patient. This requires, however, careful consideration and a well-documented risk management plan that addresses the greater resources necessary for opioid continuation following evidence of misuse.

If termination of the provider/patient relationship is deemed necessary (though it rarely is), clinicians must ensure that the patient is transferred to the care of another provider and ensure that the patient has adequate medications to avoid unnecessary risk, such as from uncontrolled or unpleasant withdrawal. Practitioners can be held accountable for patient abandonment if medical care is discontinued without justification or adequate provision for subsequent care.

Role of ER/LA opioids and methadone

ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine. A 2015 study found a higher risk for overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with immediate-release opioids.[140] As noted above, continuous, time-scheduled use of ER/LA opioids is not more effective or safer than intermittent use of immediate-release opioids, and ER/ LA opioids increase risks for opioid misuse or addiction.[45]

The Tennessee guidelines suggest that ER/LA opioids should be reserved for severe, continuous pain, not for acute pain conditions.[15] Additional caution is required when prescribing ER/LA opioids in older adults or patients with renal or hepatic dysfunction because decreased clearance of drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations.

When an ER/LA opioid is prescribed in the primary care setting, using an agent with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk (i.e., the unusual characteristics of methadone and transdermal fentanyl make safe prescribing of these medications for pain more challenging).[45]

The use of methadone for chronic pain in primary care should generally be avoided because of higher methadone-related risks for QTc prolongation and fatal arrhythmias.[45] Equianalgesic dose ratios are highly variable with methadone, making conversion from other opioids difficult, with attendant increased risk of overdose. While methadone-related death rates decreased 9% from 2014 to 2015 overall, the rate increased in people ≥65 years of age.[154] If methadone is considered, refer patients to pain management specialists with expertise in using this medication.

BEFORE MOVING ONTO THE NEXT SECTION, PLEASE COMPLETE CASE STUDY 5.

Case Study 5

Instructions: Review the case below and consider the questions that follow.

Zeke is a 25-year-old construction worker who is currently taking workman's compensation to recover from a compound fracture of his right foot and ankle sustained when a cement block slipped off of a pallet and landed on his foot. The fractures required two surgeries to correct, with the implantation of several internal fixation devices. Zeke was prescribed a short-acting opioid after each surgery, which he has continued to use. He has been regularly attending physical therapy sessions to restore muscle tone in his right leg, but has come into the clinic today seeking an ER/LA opioid. The short-acting medication, he says, is "choppy" and allows his pain to return at the end of each dosing cycle. He says friends have suggested that a long-acting opioid would be easier to use and would provide him more steady pain relief.

1. **What steps might you take before agreeing to a trial of an ER/LA medication for Zeke?**

2. **What specific kind of ER/LA medication might be most appropriate for Zeke if no contraindications were found in the pain and substance abuse assessment?**

3. **Name three specific functional goals that might be used as the basis for a pain management agreement with Zeke.**

Protecting against opioid-induced adverse events

The Veterans Administration/Department of Defense (VA/DoD) clinical practice guideline outlines a number of evidence-based strategies to reduce opioid-related adverse effects (Table 9).[155] Prophylaxis for constipation—the most common opioid-induced adverse event—has been facilitated by the approval of methylnaltrexone subcutaneous administration and naloxegol oral administration for patients with chronic non-cancer pain. Other, less expensive medications like senna and docusate, are also effective to guard against constipation.

Both male and female patients on long-term opioid therapy are at risk for hypogonadism, thus current guidelines suggest that the endocrine function of all patients should be assessed at the start of long-term opioid therapy and at least annually thereafter. The symptoms of hypogonadism in both genders may include fatigue, mood changes, decreased libido, loss of muscle mass, and osteoporosis. Although there are insufficient data to recommend routine endocrine screening of asymptomatic patients, current guidelines do recommend such testing for patients exhibiting any of the aforementioned signs and symptoms.[42]

Naloxone for opioid overdose

Naloxone (e.g., Narcan) is an opioid antagonist that quickly reverses the effects of opioid overdose. Naloxone is increasingly available to first responders, patients, and friends and family members of those prescribed opioids, and a generic formulation of nasal-spray naloxone was approved by the FDA in April, 2019.[156] Tennessee allows licensed healthcare providers to prescribe Narcan for persons at risk of overdose or family members, friends, or others in a position to help the person at risk.[15]

- Patients at risk of overdose includ those:
- With renal or hepatic dysfunction
- Taking opioid doses >50 MMED
- Co-prescribed benzodiazepines or other sedating medications
- With a history of overdose or OUD
- Starting treatment for opioid use disorder

Many states allow patients, family members, caregivers, and/or friends to request naloxone from their local pharmacist. Anyone receiving naloxone should be taught how to use the device and about the common signs of overdose (slow or shallow breathing, gasping for air, unusual snoring, pale or bluish skin, not waking up or responding, pin point pupils, slow heart rate). A variety of naloxone products are available. The intranasal device with atomizer and intramuscular (IM) shots require the most manipulation in order to administer. Intranasal naloxone and the auto-IM injector are easier to use, but vary greatly in terms of price and insurance coverage.

Depending on the opioid involved in the overdose, more than one dose may be required. All patients who receive naloxone reversal should be taken to an emergency room in case additional doses of naloxone or other medical support is needed.

When to consult a pain specialist or refer

Many acute or chronic pain conditions are relatively straightforward and can be effectively treated by primary care clinicians. But some painful conditions, and some patients, pose considerable complexities, and in such cases clinicians should consider referring the patient to a pain specialist (assuming one is available in the geographic area) or other professionals with expertise in specific areas of need. Some examples of conditions or patients in which referral may be warranted include:

- Phantom limb pain
- Severe neuropathic pain
- Severe low back and neck pain, or radicular pain the arms or legs
- Intractable headache
- Visceral pain
- Significant joint pain
- Unrelieved chronic pain
- Patients with pain who also have an OUD being treated with medication-assisted therapy
- Patients with mental disorders that interfere with their ability to adhere to and/or comprehend recommended treatments
- Older adults with polypharmacy and/or significant comorbidities for which typical analgesics may be contraindicated
- Patients with end-of-life pain using levels of opioid analgesics that pose a significant risk of severe or fatal respiratory depression

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Table 9: Recommendations for preventing or treating opioid-induced side effects[155]

Constipation	Methylnaltrexone or naloxegol Prophylactic mild peristaltic stimulant (e.g. bisacodyl or senna) If no bowel movement for 48 hours, increase dose of bowel stimulant If no bowel movement for 72 hours, perform rectal exam If not impacted, provide additional therapy (suppository, enema, magnesium citrate, etc.)
Nausea or vomiting	Consider prophylactic antiemetic therapy Add or increase non-opioid pain control agents (e.g. acetaminophen) If analgesia is satisfactory, decrease dose by 25% Treat based on cause
Sedation	Determine whether sedation is due to the opioid – if so, lower opioid dose immediately Eliminate nonessential CNS depressants (such as benzodiazepines) Reduce dose by 20-30% Add or increase non-opioid or non-sedating adjuvant for additional pain relief (such as NSAID or acetaminophen) so the opioid can be reduced Change opioid Prescribe naloxone
Pruritus	Consider treatment with antihistamines Change opioid
Hallucination or dysphoria	Evaluate underlying cause Eliminate nonessential CNS acting medications
Sexual dysfunction	Reduce dose Testosterone replacement therapy may be helpful (for men) Erection-enhancing medications (e.g., sildenafil)

Case Study 6

Instructions : Review the case below and consider the questions that follow.

Clara is a 77-year-old who has been diagnosed with lumbar spinal stenosis, which is causing a burning pain that radiates across her back and down into her buttocks. She has stage 2 kidney failure, although she is not on dialysis. In the previous two years, she has fallen twice at home, sustaining a subdural hematoma on one occasion and a sprained shoulder on the other. She lives alone and is fiercely independent, continuing to drive and adequately maintaining activities of daily living. She has tried numerous non-drug treatments for her pain, including physical therapy, acupuncture, massage, yoga, and even medical cannabis (which she said did help with the pain, but which she didn't continue because she didn't like the cognitive effects). She continues to have pain which disrupts her sleep and reduces her incentive to walk.

1. **Would treatment with an NSAID be appropriate for Clara? Why or why not?**

2. **Would treatment with an ER/LA opioid be appropriate for Clara? If so, what specific route of administration and/or agent might be best?**

3. **What aspects of Clara's case should be considered when thinking about an initial dose selection of an ER/LA medication?**

Who are pain medicine specialists?

Pain Medicine is the medical specialty dedicated to the prevention, evaluation and treatment of people with chronic pain. While most physicians, advanced practice nurses, and physician assistants have some training and experience in the management of chronic pain, Pain Medicine Specialists (physicians) have fellowship training from The American Board of Medical Specialties (ABMS), the American Osteopathic Association (AOA), or additional training in pain medicine sufficient to obtain ABPM diplomate status. They may use medications, procedural interventions, or sometimes integrative therapies. Current protocols regarding the delineation of prescribing authority to and supervision of Advanced Practice Nurses with certificate of fitness for prescribing and Physicians Assistants for prescribing to treat chronic pain continue to apply. Pain Medicine Specialists may deal with patients being treated with more than 90 milligram morphine equivalents daily dose because they are at least eleven times more likely to suffer an adverse effect including overdose death.

In Tennessee, Pain Medicine Specialists are allowed to treat patients with any level of opioid analgesic. Non-pain medicine specialists who want to treat patients with more than 120 milligram morphine equivalents daily dose (MEDD) must first consult with a Pain Medicine Specialist, and if treating a patient requiring more than 120 MEDD for more than six months, they must obtain at least one annual consultation with a Pain Medicine Specialist.

Ongoing opioid therapy for chronic non-malignant pain

Key Principles

1. All chronic opioid therapy should be handled by a single provider or practice and all prescriptions should be filled in a single pharmacy, unless the provider is informed and agrees that the patient can go to another pharmacy for a specific reason.
2. Opioids should be used at the lowest effective dose. If the patient is not achieving analgesic benefit at these doses, it may be that opioids are not effective for his or her pain.
3. A provider should not use more than one short-acting opiate concurrently. If a provider deems it necessary to do so then the medical reasons should be clearly documented.

Documentation of the discussion of the five A's (analgesia, activities of daily living, adverse side effects, aberrant drug-taking behaviors and affect) at initiation of chronic opioid therapy and at follow up visits should be included in the medical record.

Patients on opioid doses of 120mg MEDD or greater should be referred to a pain specialist for a consultation and/or management. If a provider cannot make the required consultation as outlined above, then he/she shall clearly document why not. Clinicians should review the patient's history of controlled substances using the CSMD to monitor for potentially dangerous combinations.

Providers must continually monitor the patient for signs of abuse, misuse or diversion. A UDT (or a comparable oral fluids screen or test) should be done twice a year at a minimum.

Based on the combined information of patient behavior, collateral information, the CSMD results, the UDT (or OFT) results and past records, an ongoing risk assessment should be made about a patient's risk of misuse, abuse or diversion of medications. The prescribing of opioids, if medically indicated, should take this risk assessment information into account on an ongoing basis. Adjustments to the patient's treatment should occur in a timely manner based on this information. Inconsistent results from the treatment plan should be addressed immediately and documented action taken as appropriate.

Emergency department physicians should keep the specialist and the primary care provider informed about changes in a patient's condition and any emergent incidents or conditions. Opioids should be discontinued when the risks, side effects, lack of efficacy or presence of medication or aberrant behavior outweigh the benefits. Opioids sometimes have to be discontinued due to financial or third-party coverage issues. A taper of opioids may or may not be indicated, depending on the clinical situation. Appropriate documentation of CSMD query should be included in the medical record. For patients with substance use disorders, clinicians should offer (or refer to) evidence-based treatment programs and/or refer to an addiction specialist.

Medically directed opioid tapering

Patients who do not achieve functional goals on stable or increasing opioid doses or those with unacceptable side effects, should have the opioid tapered or discontinued. Patients sometimes resist tapering or discontinuation, fearing increased pain. However, a 2017 systematic review found that dose reduction or discontinuation resulted in reduced pain (eight studies), improved function (five studies) and improved quality of life (three studies).[157] A 2018 retrospective study of 551 veterans with chronic pain (mostly musculoskeletal) assessed pain one year before, and one year after discontinuation of long-term opioids (MMED 75.8 mg).[158] Pain was assessed on a 0-10 scale with higher score indicating worse pain. The mean overall pain score at the time of discontinuation was 4.9, and pain scores dropped during discontinuation by a mean of 0.2 points/month. Patients with moderate pain experienced the greatest reduction in pain after discontinuation.

Recommendations for tapering schedules vary. A 10% decrease weekly is recommended, based on years of opioid use (i.e., 10% decrease monthly for patients using opioids ≥4 years). For patients on high-dose opioids (i.e., ≥90 MMED), taper 10% until patient is taking 30% of the total initial dose, then recalculate 10% taper based on the new total opioid dose to slow taper.[157,159] The rate of opioid taper should be adjusted based on patient-specific factors such as the severity of withdrawal symptoms.

A structured support program for opioid tapering may improve outcomes. A small trial of 35 patients with long-term opioid use compared a structured intervention including weekly individual counseling sessions vs. standard care and found reduced opioid doses in the intervention group at 34 weeks (mean 100 MMED vs. 138 MMED) although the difference was not statistically significant at 34 weeks.[160] Pain scores decreased in both groups by about one point on a 10-point scale (not significant).

In 2019 the FDA, recognizing the risks associated with abrupt discontinuation of opioid analgesics, required new labeling for opioid analgesics to guide prescribers about safe tapering practices.[161] The key elements include:[161]

- Do not abruptly discontinue opioid analgesics in patients physically dependent on opioids. Counsel patients not to discontinue their opioids without first discussing the need for a gradual tapering regimen.
- Abrupt or inappropriately rapid discontinuation of opioids is associated with serious withdrawal symptoms, uncontrolled pain, and suicide.
- Ensure ongoing care of the patient and mutually agree on an appropriate tapering schedule and follow-up plan.
- In general, taper by an increment of no more than 10-20% every 2-4 weeks.
- Pause taper if the patient experiences significantly increased pain or serious withdrawal symptoms.
- Use a multimodal approach to pain management, including mental health support (if needed).
- Reassess the patient regularly to manage pain and withdrawal symptoms that emerge and assess for suicidality or mood changes.
- Refer patients with complex comorbidities or substance use disorders to a specialist.

Addiction medicine primer

Opioid use disorder (OUD)

OUD is a problematic pattern of opioid use that causes significant impairment or distress.[162] (Note: OUD was previously termed by DSM-IV "opioid abuse," "opioid dependence," or "opioid addiction," but in this learning activity we use OUD because this is the term used in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5].) As with other chronic diseases, OUD usually involves cycles of relapse and remission.

OUD is a chronic brain disease resulting from the effects on prolonged opioid use on brain structure and function that causes significant negative personal, economic, and social consequences.[163] Rates of OUD diagnoses have increased 4-5 fold in recent years, according to market research and insurance company data.[164-166] Most people with OUD, or who misuse opioids, obtain the drugs from prescriptions (36.1%) or from friends and relatives (53.1%).[82]

DSM-5 diagnosis of OUD is based on clinical evaluation and determination that a patient has problematic opioid use leading to clinically significant impairment or distress involving at least two of the following within a 12-month period:[162]

- Opioids taken in larger amounts, or for longer periods, than intended
- Persistent desire or unsuccessful attempts to control or reduce use
- Significant time lost obtaining, consuming, and recovering from opioids
- Craving or a strong desire or urge to use opioids
- Failure to complete obligations (i.e., work, home, or school) due to opioids
- Persistent or recurrent social or interpersonal problems due to opioids
- Giving up enjoyable social, work, or recreational activities due to opioids
- Recurrent opioid use in situations in which it is physically hazardous (e.g., driving)
- Continued use despite a physical or psychological problem caused by or worsened by opioid use
- Tolerance (unless opioids are being taken as prescribed)
- Using opioids to prevent withdrawal symptoms (unless opioids are being taken as prescribed)

OUD is not a binary diagnosis, rather it exists as a continuum, with DSM-5 describing 3 levels of severity:

- Mild OUD (2-3 criteria)
- Moderate OUD (4-5 criteria)
- Severe OUD (≥ 6 criteria)

More than 2 million Americans have OUD, and the number is growing.[82] OUD can be effectively managed with medication-assisted treatment (MAT), but only an estimated 20% of adults with OUD currently receive such treatment.[167]

Medications to treat OUD

The FDA has approved three medications for treating OUD: buprenorphine, methadone, and extended-release naltrexone (Table 10). Buprenorphine and methadone can reduce opioid cravings and all three can prevent misuse.[163] Each medication has a unique mechanism of action and involve different formulations, methods of induction and maintenance, patterns of administration, and regulatory requirements.

Table 10. Available FDA-approved medications for OUD[163]

Buprenorphine • Buprenorphzne/naloxone buccal film (Bunavail) • Buprenorphine/naloxone sublingual film (Suboxone, generics) • Buprenorphine/naloxone sublingual tablets (Zubsolv, generics) • Buprenorphine sublingual tablets (generics) • Buprenorphine subdermal implant (Probuphine) • Buprenorphine extended-release subcutaneous injection (Sublocade)
Methadone • Tablets (Dolophine, MethaDose, generics) • Oral concentrate (MethaDose, generics)
Naltrexone extended-release injection (Vivitrol)

Methadone

Methadone is a synthetic, long-acting opioid agonist that fully activates mu-opioid receptors in the brain.[168] This activity reduces the unpleasant/dysphoric symptoms of opioid withdrawal, and, at therapeutic doses, it blunts the "highs" of shorter-acting opioids such as heroin, codeine, and oxycodone. Patients do not have to experience opioid withdrawal before starting methadone. It may, however, take days to weeks to achieve a therapeutic dose, which requires individualized monitoring in order to minimize cravings and reduce the risk of relapse.

In the United States, outpatient methadone treatment for OUD can only be given to persons enrolled in state- and federally-certified opioid treatment programs/clinics. (Methadone can be provided when patients are admitted to a hospital for treatment of other conditions or in emergencies).[169] Most patients are required to visit a methadone clinic every day to receive their dose. Eventually, stable patients may receive take-home doses if they meet certain criteria, such as having a stable period of good functioning without illicit drug use.[44] In addition, patients prescribed methadone are usually required to attend regular counseling sessions with clinic providers.

As a full agonist, methadone sustains opioid tolerance and physical dependence, thus missing doses may precipitate opioid withdrawal. Overdose risk is highest in the first two weeks of methadone treatment,[170] after which risk is significantly lower compared to people who are not in treatment.[171,172]

Common side effects of methadone are constipation, vomiting, sweating, dizziness, and sedation. Although respiratory depression can be induced by methadone, the FDA advises that methadone not be withheld from patients taking benzodiazepines or other central nervous system depressants because the risk of overdose is even higher among patients not on methadone for OUD.[173] The other potential harms of methadone include hypogonadism, which is a potential side effect of chronic use of any opioid, and QTc segment prolongation.

Buprenorphine

Buprenorphine is a high-affinity partial opioid agonist at the mu-opioid receptor as well as an antagonist of the kappa opioid receptor.[174] Like methadone, buprenorphine can relieve opioid withdrawal symptoms, and, because of its partial agonist effect, it can reduce the rewarding effect of other opioids used simultaneous with buprenorphine. Buprenorphine's partial agonist status also translates into a lower risk of respiratory depression compared to methadone and other opioids,[175] and a therapeutic dose may be achieved within a few days.[176]

Buprenorphine is available as sublingual tablets, sublingual/buccal films, subdermal implants, or extended-release subcutaneous injection. Some film and tablet formulations are combined with the opioid antagonist naloxone to discourage misuse by crushing and injecting the medication. (A buprenorphine-only patch [Butrans] is only FDA-approved as an analgesic.) Some forms of buprenorphine can be self-administered by patients after filling their prescription at regular pharmacies.

In order to prescribe buprenorphine, physicians in the United States must complete an 8-hour training and apply for a waiver (informally called an X-waiver) from the Drug Enforcement Administration (for details see "Obtaining an X-waiver" section below). The Comprehensive Addiction and Recovery Act of 2016 authorized nurse practitioners and physician assistants to be eligible to apply for training and X-waivers, although the associated required training is 24 hours.[177]

As with methadone, buprenorphine sustains opioid tolerance and physical dependence in patients, so discontinuation can lead to withdrawal—although buprenorphine's withdrawal syndrome may be less severe. The most common side effects are constipation, vomiting, headache, sweating, insomnia, and blurred vision. One risk of buprenorphine (as well as naltrexone) is the risk of precipitating opioid withdrawal at first dose if the patient has recently used either prescription or illicit drugs, due to buprenorphine's partial-agonist properties high binding affinity for the opioid receptor.[163] Thus, a patient must be in mild to moderate withdrawal prior to initiation to avoid precipitating withdrawal. The risk of opioid overdose declines immediately when patients with OUD initiate buprenorphine treatment.[172] The risk of hypogonadism is lower with buprenorphine compared to methadone, and buprenorphine is not associated with QTc prolongation or cardiac arrhythmias.[178]

The various non-oral routes of buprenorphine avoid the significant hepatic metabolism inherent with oral administration, and appear to be largely equivalent in their efficacy for maintaining abstinence and reducing risk of overdose. For example, a randomized trial comparing buprenorphine implant to sublingual buprenorphine found higher levels of negative urine screens and abstinence with the implant, but the differences did not reach statistical significance.[179] (Note that use of implantable agents require stabilization on sublingual doses first.)

"Buprenorphine treatment provides one of the rare opportunities in primary care to see dramatic clinical improvement: it's hard to imagine a more satisfying clinical experience than helping a patient escape the cycle of active addiction."
--Wakeman et al. NEJM 2018;379(1):1-4

Extended-release naltrexone

Naltrexone is not an opioid. It is a full antagonist of the mu-opioid receptor, which blocks both the euphoric and analgesic effects of all opioids, including endogenous opioids (i.e., endorphins) and also reduces cravings for opioids.[174] Naltrexone does not cause physical dependence, nor does it produce any of the rewarding effects of opioids. Patients may try to use opioids while on extended-release naltrexone, but it is unlikely that they will experience any rewarding effects from such use, unless the binding affinity of naltrexone is overcome.[163] The most common side effects of extended-release naltrexone are injection site pain, nasopharyngitis, insomnia, and toothache.

Treatment initiation requires a 7-10 day period during which the patient is free from all opioids, including methadone and buprenorphine. This is usually achieved with medically-supervised withdrawal followed by at least 4 to 7 days without any opioids (including methadone and buprenorphine). This process is a very significant barrier to naltrexone use.[163]

Naltrexone is currently available both as a once-daily oral tablet and in a once monthly, extended-release depot injection. The oral formulation, however, was found to be no better than placebo in a 2011 Cochrane review of 13 trials with 1,158 participants,[180] and only the extended-release formulation has been approved for OUD by the FDA. Patients may have an increased risk of overdose when they approach the end of the 28-day period of the extended-release formulation.[181]

No special training is required for medical providers to prescribe naltrexone. Although randomized trials in participants without OUD have shown an increased risk for dysphoria and/or depression with naltrexone therapy, a small trial of 80 patients with OUD found no increased risk of depression with daily oral naltrexone compared to continuation of methadone therapy,[182] and depression is not a contraindication to the use of naltrexone.

Naloxone vs. Naltrexone:
What's the difference?

Naloxone (Narcan) is an opioid antagonist given by injection or nasal spray to reverse overdoses. It acts within minutes and lasts for only about an hour due to rapid metabolism.

Naltrexone has a very similar chemical structure to Naloxone and is also an opioid antagonist, but it acts more slowly and lasts longer. Extended-release naltrexone is used clinically to block cravings for opioids and other drugs.

Comparative efficacy

A 2016 Cochrane review of six trials (n=607) of patients with prescription opioid misuse found no significant differences between methadone and buprenorphine. The mean study duration was 24 weeks, and no significant differences were found for days of unsanctioned opioid use, self-reported opioid use, or positive urine screens for opioid use.[183]

Evidence for the efficacy of medication-assisted treatment (MAT)

Abundant evidence from decades of randomized trials, clinical studies, and meta-analyses suggests that agonist or partial-agonist opioid treatment used for an indefinite period of time is the safest option for treating OUD.[163,176] (The evidence base for extended-release naltrexone is much less robust.)[163]

As demonstrated by the studies and trials detailed below, people with OUD treated with methadone or buprenorphine are less likely to die, less likely to overdose, and more likely to remain in treatment. MAT is also associated with lower risks for HIV and other infections, and improved social functioning and quality of life compared to people not on MAT.[44]

A small trial in Sweden randomized 40 adults with OUD to daily buprenorphine 16 mg sublingually for one year vs. a six-day taper of buprenorphine followed by placebo.[184] After one year, 75% of patients on buprenorphine remained in treatment and were abstinent vs. 0% in the placebo group, and 20% of those in the placebo group died.

A prospective cohort study following 15,831 patients with OUD treated with buprenorphine for up to 4.5 years showed that the rate of overdose mortality was four times higher in patients who stopped taking buprenorphine (4.6 deaths per 1000 person years, 95% CI 3.9-5.4 deaths per 1000 person years) compared to patients who remained on the medication (1.4 deaths per 1000 person years, 95% CI 1-2 deaths per 1000 person years).[172]

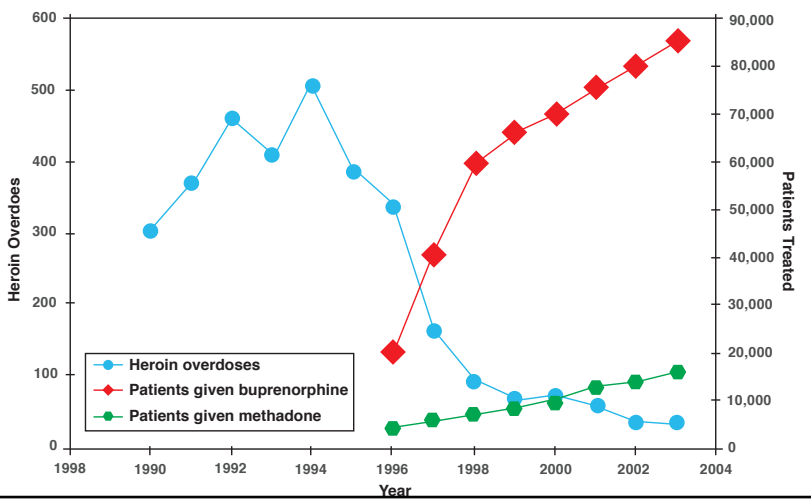
Compelling evidence also comes from population-level studies. Facing rising levels of heroin overdoses in the 1990s, France, in 1996, increased the availability of methadone and buprenorphine by allowing primary care physicians to prescribe both medications without getting additional certifications (both medications were also subsidized by the government).[185] As illustrated in Figure 6, heroin deaths declined rapidly as use of MAT increased.

Methadone and buprenorphine have also been shown to improve treatment retention. One trial randomized 247 patients to three groups: counseling alone, counseling plus methadone 20 mg/day, or counseling plus methadone 50 mg/day.[186] Both methadone doses were more effective than counseling alone at 20 weeks ($P<0.05$ for both comparisons). A trial of buprenorphine/naloxone randomized 329 patients to referral alone, a brief intervention, or buprenorphine and found similarly significant improvements in treatment retention after 30 days.[187]

Data suggest that MAT is more effective than psychotherapeutic interventions alone, and is just as effective whether psychotherapeutic interventions are used concurrently with medication treatment or not. For example, data from Massachusetts Medicaid beneficiary claims between 2004 and 2010 show significantly lower relapse rates with both buprenorphine and methadone compared to a behavioral health intervention alone.[188]

Although the evidence base for intramuscular naltrexone is less robust than for methadone or buprenorphine, it has been shown to significantly decrease opioid misuse in patients with mild-to-moderate OUD.[163] For example, one trial randomized 250 patients with OUD who completed inpatient detoxification (≥ 7 days off all opioids) to 24 weeks of naltrexone intramuscular injection (380 mg/month) vs. placebo.[189] At follow-up, 90% in the naltrexone group were abstinent compared to 35% in the placebo group.

Figure 6. Impact on heroin overdoses with rising use of methadone and buprenorphine[185]



OUD Management

Following a diagnosis of OUD, a management plan should be created that includes the following components:[44]

- Assessment for, and treatment of, medical and psychological comorbidities
- Use of motivational interviewing techniques to promote safer behaviors and to encourage patient engagement with treatment
- Education about opioid overdose
- Naloxone prescription
- Education about safer injection drug techniques and sources of sterile needles
- In-person follow-up, regardless of whether the patient was referred for specialty treatment

If a provider cannot prescribe buprenorphine because they do not have an X-waiver, they can still support the patient's path to recovery by taking the following steps:[44]

- Assess and treat comorbid conditions.
- Use motivational interviewing techniques to promote safer behaviors and encourage participation in MAT.
- Educate the patient about ways to reduce overdose risk.
- Prescribe naloxone to the patient and/or family members.
- Inform patients who inject drugs about ways to access sterile injecting equipment (if available).
- Refer patient to a treatment center providing MAT.
- Schedule follow-up visits regardless of referral status.

Naloxone is recommended for anyone who:

- Is in treatment for OUD
- Has a history of opioid overdose
- Is using ≥ 50 MME/day
- Is using any opioid and also has COPD, sleep apnea, other respiratory conditions, renal or hepatic dysfunction, or a mental health condition
- Has a co-prescription for benzodiazepine
- Has lost tolerance (e.g., recently released from prison or detox program)
- Is a family member/significant other of person in treatment for OUD

A 2019 study found a significant association between the adoption of state laws providing direct authority to pharmacists to prescribe naloxone and lower rates of fatal overdoses.[190] In states with such policies, opioid-related fatal overdoses dropped by 0.387 per 100,000 people ≥ 3 years after adoption of the laws.

Treatment selection

Medication choice for treatment of OUD is guided by severity of the OUD, patient need for additional psychosocial support and/or monitoring, patient preference, logistical concerns, and patient

willingness to undergo full opioid withdrawal (in the case of extended-release naltrexone). Although MAT is sometimes provided along with behavioral or cognitive-behavioral therapy, it is so effective that it should be offered whether or not psychosocial treatment is available.[191] The choice of treatment should always be a shared decision between the health care professional.

Treatment with buprenorphine

For providers with an X-waiver, the following steps are recommended upon a diagnosis of OUD:[44]

- Determine the severity of OUD using DSM-5 criteria.
- Review the Tennessee CSMD.
- Conduct patient history and review of systems.
- Conduct targeted physical exam for signs of opioid withdrawal, intoxication, injection, or other consequences of misuse.
- Order appropriate laboratory tests including urine or oral fluid drug tests, liver function tests, and tests for hepatitis B, hepatitis C, and HIV.

Buprenorphine treatment typically occurs in three phases:

The Induction Phase is the medically monitored initiation of buprenorphine treatment performed at home by a patient, in a physician's office, or in a certified opioid treatment program. The medication is administered when a person with OUD has not used any opioids for 12 to 24 hours and experiences mild-to-moderate withdrawal symptoms.

The Stabilization Phase begins after a patient is on a stable dose that reduces illicit use, decreases cravings, and minimizes side effects. The buprenorphine dose may need to be adjusted to achieve these goals during this phase.

The Maintenance Phase occurs when a patient is doing well on a steady dose of buprenorphine. The length of time of the maintenance phase is tailored to each patient and guidelines and could be indefinite due to the high risk of relapse (see section below on Tapering Protocols).

Psychosocial treatments

Psychosocial and/or behavioral interventions can be used in combination with medications in order to treat the "whole patient" (e.g., comorbid psychiatric symptoms, social support needs). The National Academy of Sciences, however, notes that psychosocial services may not be available to all patients and recommends that that the lack of such supports should not be a barrier to using MAT.[163]

For example, a 2012 trial randomized 230 adults with OUD to one of three groups: methadone without extra counseling vs. methadone with standard counseling vs. methadone with counseling in the context of smaller case loads.[192] At one-year follow-up there were no significant differences between the groups in rates of retention in treatment or urine tests positive for opioids. Three other randomized trials comparing buprenorphine with medical management alone vs. buprenorphine plus cognitive behavioral therapy or extra counseling sessions also found no significant differences in key opioid-related outcomes.[193-195]

Nonetheless, psychosocial, behavioral, and peer-support interventions may have many profoundly important benefits for patients beyond strictly opioid-related outcomes, such as improving self-confidence, self-advocacy, general quality of life, and improvements in legal, interpersonal, and occupational functioning.[163] Some guidelines and authors advocate for the use of psychosocial interventions, but suggest that the lack of such interventions at a given place or time should not be a barrier to the use of MAT.[163,196]

Tapering protocols

OUD guidelines do not recommend a duration of MAT treatment, which could be for an indefinite period of time because of the high risk of relapse with discontinuation.[163] For example, a population-based retrospective study of 14,602 patients who discontinued methadone treatment found that only 13% had successful outcomes (no treatment re-entry, death, or opioid-related hospitalization) within 18 months of taper.[197]

Nonetheless, some patients may want to stop opioid agonist therapy. An ideal time frame for a trial of MAT tapering has not been established. Tapering should always be at the patient's discretion, and all decisions should be based on a thorough dialogue between patient and provider. Goals should be framed functionally, for example maintaining employment, avoiding using illicit opioids or other drugs, continuing with social/emotional support programs, etc.

Misconceptions about OUD Treatment

Stigma and misunderstanding surround the issues of addiction in general and OUD in particular.[163] These include counterproductive ideologies that portray addiction as a failure of will or a moral weakness, as opposed to understanding OUD as a chronic disease of the brain requiring medical management, which is no different, in principle, from the approach used to manage other chronic diseases such as diabetes or hypothyroidism. Some stigma and misunderstanding may arise from a lack of awareness of how treatment of OUD has evolved in the past 15 years.[198] Table 11 summarizes some common misconceptions about OUD treatment.

Addressing stigma

High levels of stigma persist among some medical professionals and recovery communities toward people with OUD and medications used to treat OUD.[163] A 2016 national opinion survey (n=264) found that 54% of respondents thought people addicted to opioid pain relievers were to blame for their addiction, 46% felt such people are irresponsible, and 45% said they would be unwilling to work closely with such people.[200]

A 2014 survey of 1,010 primary care physicians found similar, or even higher, levels of stigma related to people with OUD.[201] Interviews with patients using methadone for OUD confirm that this group experiences high rates of stigma and discrimination related to their medication use in interactions with the public and with health care professionals,[202] which erodes their psychological well-being and may inhibit them from entering treatment.[163]

Table 11. Misconceptions vs. realities of OUD treatment[199]

Misconceptions	Reality
Buprenorphine treatment is more dangerous than other chronic disease management.	Buprenorphine treatment is less risky than many other routine treatments, such as titrating insulin or starting anticoagulation and easier to administer. It is also safer than prescribing many opioids (e.g., oxycodone, morphine).
Using methadone or buprenorphine is simply a "replacement" addiction.	Addiction is compulsive use of a drug despite harm. When taken as prescribed, methadone and buprenorphine improve function, autonomy, and quality of life and patients using these drugs do not meet the definition of addiction.
Detoxification for OUD is effective.	No data show that detoxification programs are effective for OUD, and, in fact, such interventions may increase the risk of overdose death by eliminating tolerance.
Prescribing buprenorphine is time consuming and burdensome.	Buprenorphine treatment can be readily managed in a primary care setting, and in-office induction or intensive behavioral therapy are not required for effective treatment.

Health care professionals can combat stigma by examining their own attitudes and beliefs and by consciously and consistently using neutral, "person-first," and non-stigmatizing language (Table 12).

Pregnancy and OUD

The prevalence of OUD among pregnant women, while low in absolute terms, quadrupled from 0.15% in 1999 to 0.65% in 2014, with large variability across states.[204] Overdose is one of the leading causes of maternal deaths in the United States, with the rate of overdose lowest in the third trimester (at 3.3/100,000 person-days) and highest 7 to 12 months after delivery (12.3/100,000 person-days).[205] Pregnant women with untreated OUD have up to six times more maternal complications than women without OUD, including low birth weight and fetal distress, while neonatal complications among babies born to mothers with OUD range from neonatal abstinence syndrome and neurobehavioral problems to a 74-fold increase in sudden infant death syndrome.[206]

Both methadone and buprenorphine are recommended for treating OUD in pregnancy to improve outcomes for both mother and newborn.[163] The efficacy and safety of methadone treatment for OUD in pregnant women was established in the 1980s, showing that maternal and neonatal outcomes in women on methadone treatment during pregnancy are similar to women and infants not exposed to methadone.[207]

More recent research suggests that buprenorphine treatment has similar, or superior, benefits in this population. An RCT with 175 pregnant women with OUD found that neonates of women on buprenorphine required 89% less morphine, had shorter hospital stays, and received a shorter duration of treatment for neonatal abstinence syndrome compared to neonates of women treated with methadone (other outcomes and adverse events were similar between the two groups).[208]

The safety of extended-release naltrexone has not yet been established for pregnant women, and naltrexone is currently not recommended for the treatment of OUD in pregnant women.[163]

Despite this solid evidence base, most pregnant women with OUD do not receive any treatment with medications.[209] Among women who do receive treatment during pregnancy, many fall out of treatment during the post-partum period due to gaps in insurance coverage and other systemic barriers. An integrated approach with close collaboration between OUD treatment providers and prenatal providers has been described as the "gold standard" for care, and further research is needed to investigate interventions that could help to increase treatment retention.[163]

Treating acute pain in patients on MAT

Some physicians may not prescribe effective opioid analgesia for patients with OUD on MAT due to concerns about respiratory depression, overdose, or drug diversion. As a result, this population is at particular risk of under-treatment for acute pain.

Physicians may also mistakenly assume that acute pain is adequately controlled with the long-term opioid agonist (i.e., methadone) or partial-agonist (i.e., buprenorphine). Although potent analgesics, methadone and buprenorphine have an analgesic duration of action (four to eight hours) that is substantially shorter than their suppression of opioid withdrawal (24 to 48 hours).[210]

Non-opioid analgesics (e.g., acetaminophen and NSAIDs) are first-line options for treating acute pain in this population. For moderate-to-severe pain not adequately controlled with non-opioids, however, judicious use of opioid analgesics should be considered. Patients on MAT generally have a high cross-tolerance for analgesia, leading to shorter durations of analgesic effects. Higher opioid doses administered at shorter intervals may thus be necessary. Concomitant opioids can be given for pain to a patient prescribed buprenorphine, but typically hydromorphone or fentanyl may be the most effective due to competitive binding at the opioid receptor.

Since extended-release naltrexone will block the effects of any opioid analgesics, acute pain in such patients (e.g., that associated with dental work, surgery, or traumatic injury) should be treated with regional analgesia, conscious sedation, non-opioid analgesics, or general anesthesia.[44]

If opioids are deemed necessary for patients on methadone or buprenorphine, clinicians should verify the patient's methadone or buprenorphine dose, and ensure that naloxone is available. Clinicians should inform the program or prescribing physician about the addition of new opioids, as this may affect subsequent urine screening.

Managing end-of-life pain

Patient-Centered Treatment Goals

Although pain relief is often considered—and may sometimes be—an end unto itself, pain management and control of symptoms at the end of life may be more appropriately viewed as means of achieving the more primary goal of improving or maintaining a patient's overall quality of life. The meaning of "quality of life" varies, not just from patient to patient, but even between the phases of an illness experienced by a single patient.

A focus on quality of life is important because sometimes a patient may have priorities that compete with, or supersede, the relief of pain. For example, the end of life can be an extremely important and meaningful time.[211] For some patients, mental alertness sufficient to allow maximal interactions with loved ones may be more important than physical comfort. Optimal pain management, in such cases, may mean lower doses of an analgesic and the experience, by the patient, of higher levels of pain. At the end of life, decisions about pain relief must be more than usually balanced with a mindful consideration of the patient's own values and desires.

Defining clear patient-centered goals of care is a first step to developing an optimal pain management strategy at the end of life. These goals should be guided by four core ethical values that apply broadly, but are particularly important at the end of life:[212]

- Autonomy of the patient
- Beneficence (the physician's obligation to promote patient welfare)
- Justice
- Non-malfeasance (avoiding harm)

Table 12. Alternatives to stigma-reinforcing words and phrases[203]

Avoid these terms	Use these instead
Addict, user, drug abuser, junkie	Person with opioid use disorder or person with opioid addiction, patient
Addicted baby	Baby born with neonatal abstinence syndrome
Opioid abuse or opioid dependence	Opioid use disorder
Problem	Disease
Habit	Drug addiction
Clean or dirty urine test	Negative or positive urine drug test
Opioid substitution or replacement therapy	Opioid agonist treatment
Treatment failure	Treatment attempt, return to use, relapse
Being clean	Being in remission or recovery

These four values are embodied in the question at the core of any consideration of an end-of-life intervention: do the expected benefits outweigh the expected burdens from the patient's perspective?[213] This question applies as much to minor interventions such as phlebotomy as to more complex interventions such as chemotherapy or surgery.

Answering this question requires that clinicians understand what a particular patient would consider a "benefit" or a "burden" and what the patient's goals are. The question also can seldom be answered with absolute certainty since the outcomes, particularly of complex interventions, are inherently difficult to predict. In developing plans of care, therefore, clinicians must engage with the patient (or designated surrogate) to carefully consider the patient's values, beliefs, and priorities (Table 13). In the end, clinicians can only provide the best information and estimates they can. The patient (or surrogate) must weigh the options and make the decision.

Table 13. Potential patient-centered goals of care[213]

Longer life
Symptom relief
Time at home
Ability to travel
Mental clarity
Physical mobility
Ability to interact with loved ones
Minimizing burdens on loves ones
Personal/Spiritual growth
"Dignity" (though meanings will vary)

Assessing Pain at the End of Life

The end of life is often characterized by a reduced level of consciousness or complete lack of consciousness. This can make assessments of pain very challenging. If a patient is not alert enough to communicate, nonverbal signs or cues must be used to determine if the patient is experiencing pain and to what degree an analgesic approach is effective. In general, even ambiguous signs of discomfort should usually be treated, although caution must be exercised in interpreting such signs.[213] Patients who are actively dying may groan or grunt in ways that suggest they are in pain, although such sounds may, in fact, be the normal expressions attendant to the last moments or hours of life.

Signs of discomfort that are accompanied by more rapid breathing or heart rate should be taken more seriously. Likewise, if physical stimulation of the patient (i.e. during bathing) causes signs of discomfort, increased analgesia may be warranted. Prolonged rapid breathing (> 20/min.) may be uncomfortable because of muscle fatigue and it may therefore be reasonable, even in the absence of other evidence of discomfort, to titrate a pain medication with a target respiratory rate of 15 to 20/minute.[213]

Treatment Options

Opioids are often valuable for providing effective analgesia at the end of life, and opioid formulations are available in such variety in the U.S. that, typically, a pain regimen can be tailored to each patient. Because there is great between-patient variability in response to particular opioid agents no specific agent is superior to another as first-line therapy. Although morphine was previously considered the "gold standard," it is now recognized that the most appropriate agent is the opioid that works for an individual patient.[214]

Morphine and other opioids are available in a wide range of formulations and routes of administration, including oral, parenteral, and rectal delivery. Both rectal and transdermal routes can be especially valuable at the end of life when the oral route is precluded because of reduced or absent consciousness, difficulty swallowing, or to reduce the chances of nausea and vomiting.[214] When selecting an opioid, clinicians should also consider cost, since expensive agents can place undue burden on patients and families.

Some opioids may not be appropriate in the end-of-life setting. For example, meperidine is not recommended in cancer pain management due to the neurotoxic effects of its metabolites.[215] Mixed agonist-antagonist opioid analgesics, including butorphanol, nalbuphine, and pentazocine, are not recommended in cancer pain management.[214]

Opioid-related side effects must be considered in advance of treatment and steps must be taken to minimize these effects to the extent possible, since adverse effects contribute significantly to analgesic nonadherence. This is particularly true for constipation and sedation. Tolerance rarely develops to constipation and therefore it must be prevented and, if unsuccessful, treated aggressively.

A stimulant, such as methylphenidate or dextroamphetamine, might be added to offset sedative effects, typically starting at a dose of 5 to 10 mg once or twice daily. One study found that with proper timing, the administration of methylphenidate did not disrupt sleep.[216]

Other adverse effects, including respiratory depression, are greatly feared and may lead to clinician under-prescribing and reluctance by patients to take the medication, despite the rarity of this event in persons with cancer.[217] Despite this fear, studies have revealed no correlation between opioid dose, timing of opioid administration, and time of death.[218]

Adjuvant Analgesics

Although opioid medications are central to pain management at the end-of-life, many other classes of medications have proven to be effective and, in some cases, preferable to opioids (Table 14). Some exert a direct analgesic effect mediated by non-opioid receptors centrally or peripherally. Other adjuvant "analgesics" have no direct analgesic qualities but may provide pain relief indirectly by affecting organs or body systems involved in painful sensations.

Corticosteroids can play a valuable role in treating end-of-life pain related to neuropathic pain syndromes, pain associated with stretching of the liver capsule due to metastases, for treating bone pain (due to their anti-inflammatory effects) as well as for relieving malignant intestinal obstruction.[219] Dexamethasone produces the least amount of mineralocorticoid effect and is available in a variety of delivery forms, including oral, intravenous, subcutaneous, and epidural.[214]

Local anesthetics may be useful in preventing procedural pain and in relieving neuropathic pain. Local anesthetics can be given topically, intravenously, subcutaneously, or spinally. Both gel and patch versions of lidocaine have been shown to reduce the pain of postherpetic neuropathy and cancer-related neuropathic pain.[220]

NMDA antagonists (dextromethorphan, amantadine, and ketamine) are believed to exert their analgesic effects by blocking receptors for glutamate and other excitatory amino acids at the level of the spinal cord. Ketamine is the most commonly-used agent, and can be administered in a variety of routes. A general recommendation is to reduce the opioid dose by approximately 25% to 50% when starting ketamine to avoid sedation.[221] Although a Cochrane review found insufficient trials to determine its safety and efficacy in relieving cancer pain, case reports and small studies suggest that intravenous or oral ketamine can be used in adults and children with cancer for the relief of intractable neuropathic pain or to reduce opioid doses.[221]

In recent years there has been a resurgence of interest in the use of cannabinoids for the relief of pain and the end of life.[222] Two oral cannabinoid preparations are FDA-approved and available in the US, and an oromucosal preparation is available in Canada and several European countries. These routes of administration avoid the potential hazards and dosing uncertainties involved with inhaled forms of raw cannabis.

Cannabinoids have been shown to exert no appreciable effects on opioid plasma levels and may augment the efficacy of oxycodone and morphine in patients suffering from a variety of chronic pain conditions, potentially allowing a reduction in the opioid doses used in such patients.[223]

Table 14. Adjuvant analgesics of end-of-life pain[214]				
Drug Class	**Agent**	**Route of Administration**	**Potential adverse effects**	**Indications**
Antidepressants	Nortriptyline	Oral	Anticholinergic effects	Neuropathic pain
	Desipramine	Oral	Cardiac arrhythmia	
	Venlafaxine	Oral	Nausea, dizziness	
	Duloxetine	Oral	Nausea	
Anti-epilepsy drugs	Gabapentin	Oral	Dizziness	Neuropathic pain
	Pregabalin	Oral	Dizziness	
Corticosteroids	Dexamethasone	Oral/IV	"Steroid psychosis"	Neuropathic pain, cerebral edema, spinal cord compression, bone pain, visceral pain
Lidocaine	Lidocaine patch	Topical	Erythema (rare)	Neuropathic pain
	Lidocaine infusion	IV	Perioral numbness, cardiac changes	Intractable neuropathic pain
NMDA antagonists	Ketamine	Oral/iv	Hallucinations	Unrelieved neuropathic pain; need to reduce opioid dose
Bisphosphonates	Pamidronate	IV	Pain flare, osteonecrosis	Osteolytic bone pain
	Zoledronic acid	IV		
Cannabinoids	THC (Marinol)	Oral	Dizziness, nausea, tachycardia, euphoria	Nausea, loss of appetite, spasticity, neuropathic pain
	Nabilone (Cesamet)	Oral		
	THC (Sativex) (note: not available in the U.S.)	Oromucosal spray		

The authors of a recent review of the role of cannabinoids in hospice and palliative care concluded: "Many patients in a palliative care setting who are currently on long-term opioids for chronic pain could potentially be treated with either cannabis alone or in combination with a lower dose of opioids. From a pharmacological perspective, cannabinoids are considerably safer than opioids and have broad applicability in palliative care."[222]

Complementary and Alternative Therapies

A wide range of complementary and alternative therapies (CAT) are commonly used in end-of-life care. A 2010 study found that 41.8% of all hospice care providers offered some form of CAT.[224] More than half of providers that offered CAT offered massage, supportive group therapy, music and pet therapy, and guided imagery and relaxation. CAT interventions are aimed at reducing pain, inducing relaxation, and enhancing a sense of control over the pain or the underlying disease. Breathing exercises, relaxation, imagery, hypnosis, and other behavioral therapies are among the modalities shown to be potentially helpful to patients.[214]

Physical modalities such as massage, use of heat or cold, acupuncture, acupressure, and other physical methods may be provided in consultation with physical or occupational therapy. These treatments can enhance patients' sense of control as well as greatly reduce the family caregivers' sense of helplessness when they are engaged in pain relief. A 2008 study found that both massage and "simple touch" induced statistically significant improvements in pain, quality of life, and physical and emotional symptom distress over time without increasing analgesic medication use.[225]

Psychosocial interventions for end-of-life pain may include cancer pain education, hypnosis and imagery based methods, and coping skills training.[226] Educational programs are one of the most common interventions to address cancer pain barriers, and current studies provide high-quality evidence that pain education is feasible, cost-effective, and practical in end-of-life settings.[226]

Managing pain in intensive care units

Several studies show that most US adults wish to die at home,[227] and yet more than half of deaths occur in hospitals, most with ICU care.[228] When curative approaches are not expected to be successful, a transition to primary comfort-focused care and the withdrawal of ineffective or burdensome therapies is often necessary. Although guidelines and detailed strategies have been developed for analgesic therapy during the removal of life-sustaining interventions, communication about what to expect and how things may proceed remain paramount to negotiating this care transition.[229] Some patients and families may be able to have meaningful interactions at the end of life, and thus brief interruption of sedatives and analgesics may be reasonable.

Rarely are dying ICU patients able to self-report information about their pain. Thus it is incumbent on the critical care health professionals, perhaps with the assistance of the patient's family members, to assess pain without self-report input from the patient. Two pain assessment instruments have been validated for use in the ICU setting: the Behavioral Pain Scale and the Critical-Care Pain Observation Tool. Both tools describe specific observations that the patient's ICU care providers (including family members or loved ones) can make that, when present, could indicate the patient is experiencing pain such as grimacing, rigidity, wincing, shutting of eyes, clenching of fists, verbalization, and moaning.[230]

Reports by family members or other people close to a patient should not be overlooked. In the Study to Understand Prognosis and Preference for Outcomes and Risks of Treatment (SUPPORT) study, surrogates for patients who could not communicate verbally had a 73.5% accuracy rate in estimating presence or absence of the patient's pain.[231]

Ethical considerations

A potential barrier to good pain management at the end of life is the misconception on the part of providers, family members, or both, that an escalation of pain medications or other palliative therapies will unethically hasten or cause death. Although ethical and legal consensus upholds the appropriateness of withdrawing unwanted or unhelpful therapies to avoid the prolongation of the dying process and the administration of medications with the intent of relieving suffering, such concerns may mitigate optimal administration of therapies.[229] When providers administer pain medications and other palliative therapies to a dying patient, the

intent should explicitly be on relief of symptoms, and communication with the family must stress this goal, even if the possibility exists that such treatments could hasten death.[232]

Contrary to fears among patient and their families, research suggests that aggressive pain management at the end of life does not necessarily shorten life. In fact, pain management may be life-prolonging by decreasing the systemic effects of uncontrolled pain that can compromise vital organ function.[232]

If a patient experiences intense pain, discomfort or other undesirable states at the end of life despite the best efforts of pain management providers, palliative sedation (also known as terminal, continuous, controlled, or deep-sleep sedation) is an option. Palliative sedation is the intentional sedation of a patient suffering uncontrollable refractory symptoms in the last days of life to the point of almost, or complete, unconsciousness and maintaining sedation until death—but not intentionally causing death.[233] Although palliative sedation may bring intolerable suffering to an end and allow people to die peacefully, it nonetheless can be challenging to put into practice and has been criticized as "slow euthanasia."[233]

Acknowledging the inherently complex and subjective nature of decisions about palliative sedation, guidelines have nonetheless been developed to help guide responsible use of this alternative. Guidelines suggest that palliative sedation should only be considered when:[233]

- The patient is terminally ill
- Death is expected within hours or days
- The patient is suffering acute symptoms unresponsive to therapy
- Consent is obtained from the patient or his/her proxy
- The withdrawal of food and water is discussed
- Families are informed that the patient will likely not regain consciousness and will die
- Causing death is not the intention even though it may not be possible to achieve adequate symptom control except at the risk of shortening the patient's life
- The degree to which palliative sedation is used, and the manner in which it is used, must, in the end, be a matter of clinical judgment on the part of individual physicians.

Emergency room patients

Pain is a frequent complaint of emergency room (ER) patients, and ER physicians are among the higher prescribers of opioids to patients ages 10-40.[234] ER physicians, however, face considerable challenges in determining a patient's appropriateness for opioid therapy. A medical history is often lacking, and the physician seldom knows the patient personally. Time constraints, as well, can preclude the kinds of careful assessment and evaluation recommended for responsible opioid prescribing. Because of this, current guidelines from the American College of Emergency Physicians include the following recommendations:[235]

- ER/LA opioid medications should not be prescribed for acute pain
- Tennessee's CSMD should be used to help identify patients at high risk for opioid abuse or diversion
- Opioids should be reserved for more severe pain or pain that doesn't respond to other analgesics
- If opioids are indicated, the prescription should be for the lowest effective dose and for a limited duration (e.g., < 1 week).

Children and adolescents

Chronic pain is estimated to affect 5% to 38% of children and adolescents.[236] The Tennessee Department of Health believes that appropriate pain care for acute and chronic pain should be available to all children.[15] These pain conditions can be from congenital diseases (e.g., sickle cell disease), where pain begins in the infant or toddler age period; chronic noncongenital diseases (e.g., juvenile idiopathic arthritis, fibromyalgia, inflammatory bowel disease); or primary chronic pain conditions (e.g., headaches, chronic abdominal pain, chronic musculoskeletal pain).

The origin of pain conditions in the pediatric age group is important because the developing pediatric nervous system can be especially vulnerable to pain sensitization and development of neuroplasticity.[237] Data support the finding that early neonatal and childhood pain experiences can alter pain sensitivity in later life. Poor pain management in children can put them at risk for persistent pain and increased impairment as they transition into adulthood and may even be linked to the development of new chronic pain conditions.[238]

The application of the biopsychosocial model to pediatric pain care is therefore vital.[1] Psychological conditions resulting from chronic disease and pain syndromes can contribute to long-term pain. These psychological conditions can include difficulty coping, anxiety, and depression. Incorporation of parents and family into pain care is especially important in the pediatric population because childhood pain can be affected by family and parental factors, including family functioning and parental anxiety, and depression.

Appropriate pain management in childhood is imperative because children's early pain experiences can shape their response to pain as adults. It is of utmost importance to introduce comprehensive pain care early in the pediatric age group to optimize patients' quality of life now and in the future.[1]

Older adults

The prevalence of pain among community-dwelling older adults has been estimated between 25% and 50%.[239] The prevalence of pain in nursing homes is even higher. Unfortunately, managing pain in older adults is challenging due to: underreporting of symptoms; presence of multiple medical conditions; polypharmacy; declines in liver and kidney function; problems with communication, mobility, and safety; and cognitive and functional decline in general. Special considerations exist for pain assessment, acute pain management, specific conditions causing persistent pain, medication classes, interventional strategies, and managing addiction in older adults.[240]

Acetaminophen is considered the drug of choice for mild-to-moderate pain in older adults because it lacks the gastrointestinal, bleeding, renal toxicities, and cognitive side-effects that have been observed with NSAIDs in older adults (although acetaminophen may pose a risk of liver damage at high or prolonged doses). Opioids must be used with particular caution, and clinicians should "Start low, go slow" with initial doses and subsequent titration. Clinicians should consult the American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults for further information on the many medications that may not be recommended.[31]

The many challenges of pain management in older adults, only sketched here, suggest that early referral and/or consultation with geriatric specialists or pain specialists may be advisable.

Conclusions

Managing pain is particularly challenging in Tennessee, which is grappling with an epidemic of opioid misuse and overdose. This learning activity has reviewed an evidence-based path forward, based on a biopsychosocial model of pain, and an emphasis on holistic assessment, individualized treatment planning, and multi-modal therapeutic approaches.

Physicians and caregivers need to base pain treatment plans on realistic functional goals and the level of pain management needed to reach those goals using a shared decision-making approach. As detailed in this activity, chronic pain syndromes respond differently to available pharmacologic and non-pharmacologic treatments, but, in general, non-drug options (which can be as effective as drug options) should be tried first when possible. When drug options are considered, it is important to maximize non-opioid options before prescribing opioids. For selected patients requiring opioids, the risk of long-term opioid treatment should be minimized through patient education, screening of high-risk patients for OUD, continuous monitoring, use of alternative non-opioid options, and careful tapering when appropriate.

Since much acute pain is self-limiting and remits with healing (typically within a month), helping patients frame expectations about acute pain and pain relief can provide reassurance and reduce fear, worry, and distress. Multimodal approaches should be used to manage acute pain, combining non-drug (e.g. interventional procedures, physical rehabilitation, and psychological support) as well as appropriate drug-based options. Opioid analgesics should be reserved for severe pain that does not respond to all other approaches, and then should be used at the lowest doses, and shortest durations, appropriate for the pain intensity expected with the precipitating event.

More than 2 million people in the United States are estimated to have OUD. Medication-assisted treatment with methadone and buprenorphine works: it alleviates withdrawal symptoms, reduces opioid cravings, increases abstinence, and saves lives. These medications also help people improve their functionality and quality of life, and can allow them to reintegrate with their families, jobs, and communities. Most people with OUD in the United States, however, receive no treatment at all, and only a tiny minority of clinicians have obtained the X-waivers needed to prescribe buprenorphine.

This document has laid out the evidence supporting these conclusions and provides the basis for improved treatment and reduced risk, both for patients and the state of Tennessee at large.

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TENNESSEE CLINICAL PRACTICE GUIDELINES FOR MANAGING CHRONIC PAIN

Self-Assessment

Choose the best possible answer for each question and mark your answers on the Self-Assessment answer sheet at the end of this book. There is a required score of 70% or better to receive a Certificate of completion.

1. **Which type of pain is characterized by aberrant signal processing in the peripheral or central nervous system?**
   A. Nociceptive pain
   B. Acute pain
   C. Neuropathic pain
   D. Chronic non-cancer pain

2. **What is the likely physiological basis for opioid-induced hyperalgesia?**
   A. Upregulation of nociceptive pathways in peripheral and central nervous systems
   B. Downregulation of nociceptive pathways in dorsal horn neurons
   C. Increased release of substance-P in neuronal synapses of peripheral and central nervous system neurons
   D. Disinhibition of neuropathic pain pathways in central nervous system

3. **What term describes the phenomenon of pain being caused by a normally innocuous stimulus such as light touch?**
   A. Allodynia
   B. Hyperalgesia
   C. Hypoalgesia
   D. Referred pain

4. **Non-pharmacologic methods for treating acute pain are appropriate for which phase of healing?**
   A. Immediately after tissue trauma
   B. > 48 hours after tissue trauma
   C. Late healing phase for recovery of function
   D. Immediately after tissue trauma as well as in late healing phase

5. **What is one suggestion for a way to augment opioid treatment in order to help improve a patient's pain and function?**
   A. Use an every-other-day dosing pattern for the opioid, alternating with an NSAID analgesic
   B. Rotate the route of administration every 6 weeks
   C. Add a long-acting opioid to a prescription for an immediate-release opioid
   D. Try concurrent non-pharmacologic approaches such as exercise or cognitive behavioral therapy

6. **Which statement best summarizes the finding about opioids for chronic pain?**
   A. Opioid analgesics should be confined to use in patients with neuropathic, as opposed to nociceptive, pain syndromes
   B. Chronic non-cancer pain can be effectively treated with immediate-release opioid agents, but should not be treated with long-acting or extended-release formulations
   C. No evidence shows a long-term benefit of opioids in pain and function versus no opioids although extensive evidence shows the potential harms of opioids
   D. Evidence supports the use of opioid analgesics for long-term non-cancer chronic pain except in patients with pre-existing substance use disorders

7. **Long-acting (LA) and extended-release (ER) formulations of opioids should not be used for _____?**
   A. Treating acute pain
   B. Treating cancer pain
   C. Treating end-of-life pain
   D. Treating chronic non-cancer pain

8. **Which class of patients might require more frequent or intense monitoring when prescribed an opioid analgesic?**
   A. Young adults
   B. Older adults
   C. Female patients
   D. Patients with hypertension

9. **In Tennessee non-pain medicine specialists are not allowed to treat patients requiring more than _____.**
   A. ≥ 40 MMED
   B. ≥ 60 MMED
   C. ≥ 90 MMED
   D. ≥ 120 MMED

10. **Which of the following topics should be routinely covered as part of patient education about opioid analgesics?**
    A. Background information about acute vs. chronic pain
    B. Criteria for Opioid Use Disorder
    C. Safe medication disposal
    D. Difference between nociceptive and neuropathic pain

11. Which of the following is an example of a functional goal?

A. Reduced anxiety about pain
B. Reduced need for rescue analgesia
C. Reduced daily dose of opioid analgesic
D. Walking around the block

12. Which of the following is a possible reason for prescribing naloxone to a patient who has been prescribed an opioid analgesic?

A. The patient is taking a dose of an opioid < 50 MMED
B. The patient has recently been released from prison
C. The patient has history of hypertension
D. The patient has a concurrent prescription for an SSRI antidepressant

13. The availability of naloxone was increased in 2019 by an FDA decision that _____.

A. Allowed naloxone to be sold over the counter
B. Approved a generic formulation of nasal-spray naloxone
C. Allowed registered nurses to prescribe naloxone
D. Provided government subsidy to increase production of naloxone

14. Opioid pain medications should not be combined with _____?

A. Benzodiazepines
B. Stimulant medications
C. SSRI antidepressants
D. Anti-hypertensive medications

15. Although the absolute risk for inducing opioid misuse or addiction due to prescriptions of opioids for acute pain is low, the large number of such prescriptions means that approximately how many people are at risk each year?

A. 260,000
B. 160,000
C. 60,000
D. 6,000

16. According to the 2019 Tennessee guidelines, what amount of opioid analgesic is appropriate for most painful conditions?

A. 2-day supply
B. 3-day supply
C. 5-day supply
D. 7 day supply

17. Which of the following characteristics is typical of patients who are addicted to a pain medication??

A. Medication use improves quality of life
B. Follows practitioner-patient agreement for opioid use
C. Medication use continues or increases despite adverse effects
D. Has left-over medication at each visit

18. Which of the following medications is a full mu-receptor agonist used to treat Opioid Use Disorder?

A. Methadone
B. Buprenorphine
C. Extended-release naltrexone
D. Naloxone

19. For which of the following must clinicians obtain a special waiver from the DEA prior to being able to prescribe the medication?

A. Methadone
B. Buprenorphine
C. Extended-release naltrexone
D. Naloxone

20. Which of the following medications can be self-administered by patients with a medication obtained from a regular pharmacy?

A. Methadone
B. Buprenorphine
C. Extended-release naltrexone
D. Naloxone

EVIDENCE-BASED GUIDANCE ON RESPONSIBLE PRESCRIBING, EFFECTIVE MANAGEMENT, AND HARM REDUCTION

COURSE DATES:	MAXIMUM CREDITS:	FORMAT:
Release Date: 10/2018 Exp. Date: 09/2021	*3 AMA PRA Category 1 Credits™*	Enduring Material (Self Study)

TARGET AUDIENCE

This course is designed for all physicians and health care providers involved in the treatment and monitoring of patients prescribed controlled substances.

COURSE OBJECTIVE

The purpose of this course is to educate health care providers about the requirements of the Controlled Substances Act and safe prescribing practices for both opioid and non-opioid controlled substances. In addition, some of the medical conditions for which controlled substances are most commonly prescribed will be reviewed, along with recommendations for responsible management of these conditions with specific controlled substances.

HOW TO RECEIVE CREDIT:

- Read the course materials
- Complete the self-assessment questions at the end. A score of 70% is required.
- Return your customer information/ answer sheet, evaluation, and payment to InforMed by mail, phone, fax or complete online at course website under NETPASS.

LEARNING OBJECTIVES

Completion of this course will better enable the course participant to:

1. Explain the purpose and role of the Controlled Substances Act (CSA) as it relates to clinical practice.
2. Explain the similarities and differences between the 5 DEA schedules for controlled substances.
3. Know what pieces of information must be included on all prescriptions for controlled substances.
4. Describe at least four signs that a controlled substance may be inappropriately prescribed.
5. Describe the key steps recommended for the responsible prescribing of controlled substances.
6. Describe pharmacological treatment options for treating pain, anxiety disorder, insomnia, narcolepsy, obesity, and attention-deficit hyperactivity disorder.

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DISCLAIMER

Introduction

The use of controlled substances is a major public health issue in the United States. These are drugs regulated by the government for use as prescription medications under the care of a medical provider. Unfortunately, such drugs are not always taken by those to whom they were prescribed, they are not always taken as directed, and, even when used as directed, they can lead to serious adverse effects, including physical dependence, addiction, or death.

Every year, millions of people use prescription medications for the first time, whether illicitly or prescribed. In 2016, the most recent data available at the time of the writing of this monograph, there were:[1]

- 2.1 million new users of prescription opioid pain relievers
- 1.4 million new users of prescription tranquilizers (benzodiazepines, muscle relaxants)
- 294,000 new users of prescription sedatives (sleep-aides, e.g., zolpidem)

While most people who use prescription drugs do not develop unhealthy patterns of use, a significant fraction do, and a significant fraction of the drugs themselves become diverted, intentionally or not, and fall into the hands of people with existing patterns of misuse or addiction.[2] In 2016, an estimated 3.3 million people were currently misusing opioid pain relievers, 2 million were misusing tranquilizers, 1.7 million were misusing stimulants, and 497,000 people wvere misusing sedative-hypnotics.[3] In all, more than 6 million Americans are misusing prescription drugs (including opioids), which is more than the number of Americans using cocaine, heroin, hallucinogens, and inhalants, combined.[4]

Opioid analgesics are currently in the spotlight of both government and popular attention because of the extreme toll these drugs are taking in terms of addition, overdose, and association with subsequent use of heroin and other illicit drugs. But, as the numbers just cited illustrate, opioids are not the only problematic class of controlled substances being prescribed by health care professionals. Non-opioid controlled substances are a diverse group of agents that include anxiolytics (e.g., alprazolam, diazepam, and lorazepam) sedative-hypnotics (including zolpidem and eszopiclone), muscle relaxants (e.g., barbiturates such as carisoprodol), and stimulants (including amphetamine, methylphenidate, and appetite suppressants such as phentermine).

Physicians and other health care providers play important roles in the nationwide effort to stem the tide of inappropriate use of controlled substances. Survey data show that over half of the nonmedical users of pain relievers, tranquilizers, stimulants, and sedatives obtained their prescription drugs "from a friend or relative for free."[5] In a follow-up question, three quarters or more of these respondents indicated that their friend or relative had obtained the drugs from one doctor.[5]

Health care providers can help reduce diversion of controlled substance by thoroughly understanding both the regulatory frameworks surrounding controlled substances as well as the most recent professional guidance for prescribing, monitoring, and managing controlled substances in clinical situations.

Unfortunately, many prescribers have had little or no education on substance use disorder issues, either in professional school or through recurrent training.[6] Furthermore, many prescribers are not educated or trained in prescribing practices that minimize risk with commonly misused medications. Less than half of the states have statutes or regulations that require or recommend education for prescribers of prescription pain medication.[7]

This monograph addresses this common gap in professional knowledge and presents the latest evidence-based guidance and "best practices" for responsibly prescribing the most commonly misused controlled substances. It will review the substances themselves, provide context for the current legal framework governing controlled substances, and summarize the ways clinicians can help limit misuse or help patients who have developed unhealthy patterns of use with these drugs. (Note: cannabis is a controlled substance, can be legally prescribed for a range of medical indications in a number of states, and, like any drug, can also lead to unhealthy patterns of use or behavior. This monograph, however, does not cover cannabis because the legal, medical, and cultural dimensions of this drug are in such dynamic flux at the time of this writing.)

Definitions

Because the problematic side of controlled substances involves misuse, physical dependence, and addiction, it is important to be clear about what these, and related terms, mean. The American Society of Addiction Medicine (ASAM), the American Academy of Pain Medicine (AAPM), and the American Pain Society (APS) have recommended the following definitions:[8]

- **Aberrant drug-related behavior.** A behavior outside the boundaries of an agreed-upon treatment plan.
- **Abuse.** Any use of a drug, or the intentional self-administration of a medication, for a nonmedical purpose such as pleasure-seeking or altering one's state of consciousness.
- **Addiction.** A chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations, characterized by behaviors that include one or more of the following: craving, impaired control over drug use, compulsive use, and continued use despite harm.
- **Diversion.** The intentional transfer of a controlled substance from legitimate distribution and dispensing channels.
- **Misuse.** Use of a medication other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.
- **Physical Dependence.** A state of physical adaptation (tolerance) that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Physical dependence is not the same thing as addiction.
- **Tolerance.** A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

The Diagnostic and Statistical Manual 5th Edition (DSM 5) categorizes addictive disorders by the specific substance misused, e.g., alcohol use disorders, opioid use disorders, and others. The diagnostic criteria from the DSM 5 for substance use disorder are as follows: "A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period":[9]

1. More of the substance taken or they are taken over a longer period than planned
2. The patient has difficulty cutting down or controlling use
3. Large amounts of time are invested in attempting to obtain, use, or recover from, using
4. Craving
5. Use causes a failure to fulfill roles at work, school, or home
6. Continued use despite having social or interpersonal problems caused by use
7. Social, occupational, or recreational activities given up because of use
8. Use even when physically hazardous
9. Use despite physical or psychological problems caused by substance use
10. Tolerance, as defined by the need for an increased amount to achieve intoxication, or decreased effect with continued use of the same amount of a substance. (This criteria is exempted from consideration if a drug or substance is being taken under the guidance of a medical professional.)
11. Withdrawal symptoms upon cessation of use, or substances taken to avoid withdrawal. (This criteria is exempted from consideration if a drug or substance is being taken under the guidance of a medical professional.)

The severity of substance use disorders can be described by the number of criteria the patient meets. A patient with mild disorder meets 2-3 criteria, moderate disorder meets 4-5 criteria, and a patient with severe disorder meets 6 or more criteria.[9]

The Controlled Substances Act

The federal government's first attempt at regulating medications was through the Harrison Act passed in 1914.[10] The Harrison Act criminalized what, at that time, was considered to be the "recreational" use of opium, morphine, and cocaine. While these drugs could still be legally obtained, physicians, dentists and veterinary surgeons were now required to register, document, and pay taxes on any packages containing these drugs. Over the next few years, thousands of prescribers who did not comply with the law were arrested, convicted, and jailed.

In 1970, the United States government passed the Federal Comprehensive Drug Abuse Prevention and Control Act. Now known as the Controlled Substances Act (CSA), the law consists of three parts, including rehabilitation services for people with substance use disorder, the regulation and distribution of controlled substances, and regulation of the importation and export of controlled substances.[11] The Drug Enforcement Administration (DEA) administers all parts of the CSA. The CSA is continually updated to add, remove, or transfer over 160 substances across schedules. This monograph reflects the most recent issue of Title 21 Code of Federal Regulations (CFR) Part 1300. It is limited to describing the controlled substances most frequently encountered by health care providers and is not a comprehensive list.[12]

Since many controlled drugs are important tools in the clinician's pharmaceutical armamentarium, the CSA attempts to balance two competing needs: to maintain an adequate and uninterrupted supply of these controlled substances for legitimate purposes while simultaneously reducing their diversion and abuse.[13]

The CSA places all substances which were in some manner regulated under existing federal law into one of five schedules (with the exceptions of alcohol and tobacco). This placement is based on the substance's perceived medical use, potential for abuse, safety, and dependence liability. The law also provides a mechanism for new substances to be added to or transferred between schedules or for substances to be removed from control.

In determining into which schedule a drug or other substance should be placed, or whether a substance should be decontrolled or rescheduled, certain factors are required to be considered, including:[14]

1. The drug's actual or relative potential for abuse
2. Scientific evidence of the drug's pharmacological effect, if known
3. Its history and current pattern of abuse
4. The scope, duration, and significance of abuse
5. What, if any, risk there is to public health
6. The drug's psychic or physiological dependence liability
7. Whether the substance is an immediate precursor of a substance already controlled

After considering the above listed factors, the DEA administrator may make specific findings concerning the drug or other substance. This will determine into which schedule (if any) the drug or other substance will be placed.

Schedules of Controlled Substances

Controlled substances under the CSA are classified into one or more of five schedules.

Schedule I Substances

Substances in this schedule are deemed to have a high potential for abuse, have been determined to have no currently-accepted medical use in the United States, and evidence for their safe use under medical supervision has not been accepted. Some examples of substances listed in schedule I are: heroin, lysergic acid diethylamide (LSD, i.e. "acid"), peyote, and 3,4-methylenedioxymethamphetamine (MDMA, i.e."ecstasy"). (Note: government-approved scientific and clinical research is currently underway with some Schedule I drugs, such as LSD, exploring their utility to treat a variety of mental health disorders, including addiction, the results of which may alter their classification in the future.[15])

Schedule II Substances

Substances in this schedule are considered to have a high potential for abuse which may lead to psychological or physical dependence, and yet the drug or substance also has one or more currently accepted medical use in the United States. Examples include many opioid pain medications, and stimulants such as amphetamine, methamphetamine, methylphenidate, and cocaine.

Schedule III Substances

Substances in this schedule have less potential for abuse than substances in schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence. These substances also have currently accepted medical uses in the United States. Examples include buprenorphine and products containing not more than 90 mg of codeine per dosage unit (i.e. Tylenol with codeine®). Examples of schedule III non-opioid drugs include benzphetamine, ketamine, and anabolic steroids such as oxandrolone.

> ***Did You Know?***
>
> Some drugs or substances appear in two or more schedules, depending on the specifics of their formulation. For example, raw cannabis is listed as Schedule I, although products containing one or more of the active ingredients in cannabis (i.e., tetrahydrocannabinol, or THC) are listed as Schedule III. Likewise, gamma-hydroxybutyric acid (GHB) as a street drug is Schedule I, although when formulated in a product for clinical use it is listed as Schedule III.

Schedule IV Substances

Substances in this schedule are thought to have a low potential for abuse relative to substances in schedule III, and have currently accepted medical uses in the United States. Examples include alprazolam, clonazepam, diazepam, lorazepam, phenobarbital, temazepam, and triazolam.

Schedule V Substances

Substances in this schedule have a low potential for abuse relative to substances listed in schedule IV. These are generally used for antitussive, antidiarrheal, and analgesic purposes. Examples include cough preparations containing not more than 200 mg of codeine per 100 milliliters or per 100 grams.

Classes of Controlled Substances

The CSA regulates five classes of drugs:

- Opioids
- Sedative-Hypnotics
- Stimulants
- Hallucinogens
- Anabolic steroids

With the exception of anabolic steroids, controlled substances are abused to alter mood, thought, and feeling through their actions on the central nervous system (brain and spinal cord). Some of these drugs alleviate pain, anxiety, or depression. Some induce sleep and others energize. Though most controlled substances can be therapeutically useful, the "feel good" effects of these drugs may contribute to their potential for abuse.

The extent to which a substance can reliably produce intensely pleasurable feelings (euphoria) increases the likelihood of that substance being abused.[14]

Table 1 lists some of the controlled substances that are commonly encountered and/or prescribed in clinical settings. Note that some substances, such as many common products that emit fumes that can be inhaled to alter consciousness, are not scheduled because doing so would impede legitimate commerce.[14] New substances are continually being either discovered or invented which have abuse potential and, thus, the list of controlled substances continues to grow.

Opioids

Opioids are used to treat moderate to severe pain that does not respond to non-opioids alone. They are often combined with non-opioids because this permits use of lower doses of the opioid (i.e., dose-sparing effect). Nearly all types of pain respond to opioids; however, nociceptive pain is generally more responsive to opioids than neuropathic pain, which may require higher doses of opioids.[17] Opioids play a major role in the treatment of acute pain (e.g., trauma, postoperative pain), breakthrough pain, cancer pain, and some types of chronic non-cancer pain. Opioids may also help relieve certain types of neuropathic pain, such as the acute pain of herpes zoster.'

Table 1. Commonly-prescribed Controlled Substances[16]		
Schedule	Substance	Common Name
II	Hydrocodone	Vicodin, Norco (with acetaminophen)
II	Oxycodone	Oxycontin, others
II	Morphine	Duramorph, Infumorph, Arymo ER, others
II	Hydromorphone	Exalgo, others
II	Amphetamine	Dexedrine, Adderall
II	Lisdexamfetamine	Vyvanse
II	Methylphenidate	Concerta, Ritalin, Methylin
II	Phenobarbital	Nembutal
III	Buprenophine	Suboxone, Buprenex, Butrans, others
III	Codeine	
III	Anabolic steroids	Anabolic steroids
III	Chlorphentermine	Pre-Sate, Lucofen, Apsedon, Desopimon
III	Dronabinol	Marinol
IV	Tramadol	Ultram, ConZip
IV	Alprazolam	Xanax
IV	Barbital	Veronal, Plexonal, Barbitone
IV	Carisoprodol	Soma
IV	Chlordiazepoxide	Librium, Libritabs, Limbitrol, SK-Lygen
IV	Clonazepam	Klonopin, Clonopin
IV	Diazepam	Valium, Diastat
IV	Lorazepam	Ativan
IV	Midazolam	Versed
IV	Modafinil	Provigil
IV	Phentermine	Ionamin, Fastin, Adipex-P, Zantryl
IV	Phenobarbital	Phenobarbital
IV	Temazepam	Restoril
IV	Zaleplon	Sonata
IV	Zolpidem	Ambien, Ivadal, Stilnoct, StilNox
IV	Zopiclone	Lunesta
V	Pregabalin	Lyrica

Opioids as a class include many specific agents available in a wide range of formulations and routes of administration, including:

- Oral (e.g., tablets, capsules, solutions, lollipops)
- Transdermal
- Transmucosal
- Rectal
- Intrathecal

Combination products join an opioid with a non-opioid analgesic, usually for use in patients with moderate pain. Using a combination product when dose escalation is required risks increasing adverse effects from the non-opioid co-analgesic, even if an increase of the opioid dose is appropriate. In such cases, using a pure opioid is preferable. Care, in particular, must be given to not exceed maximal daily doses of acetaminophen.

In their daily practice, clinicians who treat patients with opioid pain medications must balance pain relief with the risks associated with opioid analgesics.

The term "pharmacovigilance" refers to the range of procedures and processes used to achieve this goal. These procedures need not be burdensome and are akin to similar risk/benefit calculations required in the prescription of a great many other therapeutic agents.[18] What makes opioids of particular concern is the fact that they are highly sought-after by people who use drugs and criminal elements in society. In addition, opioids have a wide range of potential adverse effects that can expose a patient to serious morbidity and even mortality.

Risk is increased among: older adults; those with impaired renal or hepatic function; individuals with obesity, cardiopulmonary disorders, sleep apnea, or mental illness; and in patients who combine opioids with other respiratory depressants such as alcohol, sedative-hypnotics, benzodiazepines, or barbiturates.

Extended-release/long-acting opioids

Little evidence exists that specific analgesic formulations or dosing schedules affect efficacy or addiction risk (aside from those specifically made to reduce abuse risk), so selection of agent should be based on the patient's pain complaint, lifestyle, and preferences.[19] Generally, if opioids are used at all, it is better to offer short-acting opioids PRN (Table 2). Extended-release (ER) or long-acting (LA) opioids (with duration of action typically between 4 and 72 hours) may be helpful for patients who have difficulty managing an "as needed" regimen, or who are physically dependent on opioid analgesics and require continued use to maintain their functioning.

Scheduled long-acting opioids have the advantage of producing a steady state, without the cycling effect of pain relief and withdrawal associated with short-acting opioids, which could, theoretically, lead to problematic behavior patterns.[20] With ER/LA agents, however, patients may end up using more drug than is actually needed, and physiological adaptations to the steady state may ultimately decrease efficacy.[21] Clinicians should warn patients that oral ER/LA opioids should not be broken, chewed, or crushed, and patches should not be cut or torn prior to use, since this may lead to rapid release of the opioid and could cause overdose or death.

Prescribers considering ER/LA opioid products should consider carefully the general characteristics, toxicities, and drug interactions for these agents. [For detailed information on current ER/LA opioid analgesics, see the FDA Blueprint for Prescriber Education, available at: https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf]. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for safer administration of opioid analgesics. Methadone can be an effective opioid, for example, but it must be prescribed carefully and with full knowledge of its highly variable pharmacokinetics and pharmacodynamics.

Abuse-deterrent formulations

Concern about opioid misuse and abuse has spurred efforts to create abuse-deterrent opioid formulations. Two agents commonly available, which are co-formulated with an opioid antagonist are Targiniq ER (oxycodone and naloxone) and Embeda ER (morphine and naltrexone). The abuse-deterrent forms of long-acting oxycodone also contain a polymer that makes the pill difficult to crush, snort, or melt for injection. Transdermal opioid formulations were thought to be less vulnerable to misuse, but such formulations can be abused.[22] Abuse-deterrent opioid formulations do not prevent users from simply consuming too much of a medication or using it without a prescription.

In 2016, the most commonly misused subtype of prescription pain relievers consisted of hydrocodone products (6.9 million abusers), which include Vicodin®, Lortab®, Norco®, Zohydro® ER, and generic hydrocodone.[23]

Side Effects

Binding of opioids to receptors in various body regions (e.g., CNS, GI tract) results in both therapeutic effects and side effects. Potential side effects of opioids as a class include respiratory depression, sedation, mental clouding or confusion, nausea, vomiting, constipation, itching, and urinary retention. With the exception of constipation, these side effects tend to subside with time. Constipation is so common, in fact, that when patients use opioids and do *not* have constipation, clinicians should consider possible reasons ranging from rapid bowel transit time to drug diversion. Constipation requires proactive treatment, with stimulating laxatives prescribed at the time of initiating opioids, and frequent re-evaluation. With the exception of constipation, uncomfortable or unpleasant side effects may potentially be reduced by switching to another opioid or route of administration (such side effects may also be alleviated with adjunctive medications).

Use caution when prescribing opioids to patients with conditions that may be complicated by adverse effects from opioids, including chronic obstructive pulmonary disease (COPD), congestive heart failure, sleep apnea, current or past alcohol or substance use disorder, mental illness, advanced age, or patients with a history of renal or hepatic dysfunction.

All newly pregnant women should have a urine drug test administered by the appropriate women's health provider. In addition, providers should discuss a birth control plan to prevent unintended pregnancy with every woman of child-bearing age who has reproductive capacity when opioids are initiated due to the high likelihood of neonatal abstinence syndrome in children whose mothers use opioids throughout their pregnancies. Finally, it is not recommended that chronic pain be treated with controlled substances through telemedicine.

All chronic opioid therapy should be handled by a single provider or practice and all prescriptions should be filled in a single pharmacy, unless the provider is informed and agrees that the patient can go to another pharmacy for a specific reason.

Sedative-Hypnotics

Sedative-hypnotics, lower arousal levels and reduce nervous system excitability via a range of pharmacological mechanisms, the most prominent of which are facilitation of gamma-aminobutyric acid (GABA) receptors, opioid receptors, or inhibition of glutamatergic or catecholaminergic activity.[24] Although widely-prescribed for their anxiety-relieving, muscle-relaxing, and sleep-inducing properties, sedative-hypnotics are also widely abused for these properties as well as their abilities to induce euphoria. Because ethanol acts on many of the same neuronal receptor targets as many of the sedative-hypnotics, lethal synergistic effects may occur.

Barbiturates were the first class of synthetic sedative-hypnotics to be introduced and many specific types with varying durations of action are FDA-approved for indications such as the relief of anxiety, the promotion of sleep, or the treatment of epilepsy. Benzodiazepines were discovered in the 1950s and have largely eclipsed barbiturates for a range of indications including anxiety, insomnia, muscle spasms, alcohol withdrawal, and as premedication for certain medical or dental procedures.[25] Although initially thought to be less prone to induce tolerance and dependence than barbiturates, benzodiazepines are now recognized to be just as liable to diversion and abuse.[26] Benzodiazepines are categorized as either short-, intermediate- or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are used for the treatment of anxiety, though they are not effective for long term treatment of anxiety.[24]

Flunitrazepam (Rohypnol®) is a benzodiazepine that has never been approved by the FDA in the United States, but which is available by prescription in other countries and also as illegal preparations.[14] Because it can impair judgment and induce amnesia, particularly when combined with ethanol, flunitrazepam has been associated with sexual assault.[14]

Non-benzodiazepines are molecularly distinct from benzodiazepines, although they act on the same GABA receptor sites and produce similar sedative effects.[27] Common non-benzodiazepines include zolpidem (Ambien®), Zaleplon (Sonata®) and Eszopiclone (Lunesta®).

Gamma-hydroxybutyric acid (GHB) and its chemical analogs are widely used, both as a prescription medicine (Xyrem®), and as industrial solvents or components in many commercial products. Sold as a liquid or as a powder that is dissolved in another liquid and swallowed, GHB induces euphoric and calming effects as well as amnesia.

Carisoprodol is a centrally-acting skeletal muscle relaxant whose primary active metabolite is meprobamate, a substance with well established abuse potential similar to that of benzodiazepines.[28] A number of reports show that carisoprodol has been abused for its sedative and relaxant effects, to augment or alter the effects of other drugs, and by the intentional combination of carisoprodol and other non-controlled medications because of the relative ease (as compared to controlled substances) of obtaining prescriptions.

Quick Sedative-Hypnotics Facts

Physical signs of depressant overdose:
- Shallow respiration
- Clammy skin
- Dilated pupils
- Weak and rapid pulse
- Slurred speech
- Loss of motor coordination
- Blurred vision
- Nausea
- Vomiting
- Low blood pressure

Drugs causing similar effects:
- Alcohol (ethanol)
- Antihistamines
- Certain antipsychotics

Available forms:
- Tablets
- Capsules
- Syrups
- Injectable liquids

Table 2: Long Acting vs. Immediate Release Opioids

Long acting opioids	Immediate release opioids
Buprenorphine patch (Butrans)	Codeine (generics)
Fentanyl patch (Duragesic)	Fentanyl – transmucosal (Abstral, Actiq, Fentora, Lazanda, Onsolis, Subsys)
Hydrocodone (Zohydro ER)	Hydrocodone+acetaminophen (generics, Norco, Vicodin, Xodol)
Hydromorphone ER (generics, Exalgo)	Hydromorphone (generics, Dilaudid)
Methadone (generics, Dolophine, Methadose)	Levorphanol (generics)
Morphine ER (generics, Avinza, Kadian, MS Contin)	Meperidine (generics, Demerol, Meperitab)
Oxycodone (Oxycontin)	Morphine (generics)
Oxymorphone ER (generics, Opana ER)	Oxycodone (generics, Roxicodone)
Tapentadol (Nucynta ER)	Oxymorphone (generics, Opana)
Tramadol ER (generics, ConZip, Ultram ER)	Tapentadol (Nucynta)
	Tramadol (generics, Ultram)

The diversion and abuse of carisoprodol and its adverse health effects appear to have dramatically increased in recent years.[29] Clinicians have begun to see a withdrawal syndrome consisting of insomnia, vomiting, tremors, muscle twitching, anxiety, and ataxia in patients who abruptly cease intake of large doses of carisoprodol. Hallucinations and delusions may also occur. The withdrawal symptoms are very similar to those described for meprobamate withdrawal, suggesting that what may actually be occurring is withdrawal from meprobamate accumulated as a result of intake of excessive amounts of carisoprodol. However carisoprodol itself is capable of modulating GABA function, and this may contribute both to the drug's abuse potential and to the occurrence of a withdrawal syndrome with abrupt cessation of intake.

Stimulants

Stimulants induce a range of effects on the body and mind by enhancing activity of the central and peripheral nervous systems. Common effects, which vary depending on the stimulant in question, may include: enhanced alertness, wakefulness, endurance, productivity, and motivation; increased sexual arousal, locomotion, heart rate, and blood pressure; and diminished appetite. Many stimulants temporarily improve mood or induce feelings of euphoria.

Stimulants exert their effects through a number of different pharmacological mechanisms, the most prominent of which are facilitation of norepinephrine and/or dopamine activity, adenosine receptor antagonism, and nicotinic acetylcholine receptor agonism.[24] Not all stimulants are listed as controlled substances. Caffeine, theophylline, and nicotine are widely used and legally available. Amphetamines and methylphenidate are controlled substances but are also widely-prescribed to treat attention-deficit disorders, sleep disorders such as narcolepsy and shift-work disorders, and as adjuvant medications for depression, especially treatment-resistant depression.[24] Cocaine has limited medical uses as a topical local anesthetic and for reducing bleeding of mucous membranes in the mouth, throat, and nasal cavities. Other stimulants such as crack cocaine have no approved medical uses.

The clandestine production of amphetamines in the past decade has increased dramatically, particularly the production of methamphetamine, which is a potent central nervous system stimulant and highly addictive.[14] (Note that a single brand of methamphetamine, Desoxyn®, is approved by the FDA for the treatment of attention deficit disorders.)

So-called "bath salts" are synthetic stimulants, also known as synthetic cathinones, which is the active chemical found naturally in the khat plant.[14] "Bath salts" are sold as powders, tablets, or capsules under various brand names. They are usually ingested by sniffing/snorting, though they can also be taken orally, smoked, or put into a solution for injection.

Tolerance to higher doses of stimulants can develop quickly, as can psychological dependence. Abrupt cessation of stimulants is typically followed by a "crash" of depression, anxiety, extreme fatigue, and drug craving. Accidental death may be caused by cardiovascular collapse, dehydration, or high fever (physical exertion increases the hazards of stimulant use because of the effects of stimulants on the body's hypothalamic temperature-regulation mechanisms).

Gabapentinoids such as pregabalin (Lyrica®) as well as the original agent gabapentin (Neurontin®) are approved to treat a variety of conditions, including post-herpetic neuralgia, fibromyalgia, and neuropathic pain associated with diabetes, and some literature suggests that clinicians may be prescribing these drugs off-label as alternatives to opioids.[30] Currently in Schedule V, in 2016, gabapentin was the 10th most commonly-prescribed medication in the United States: 64 million gabapentin prescriptions were dispensed, up from 39 million in 2012.[30]

Although data are limited, they suggest that gabapentinoid abuse and misuse may be growing, both when taken alone and in combination with opioids, benzodiazepines, or other central nervous system depressants. Drug users say gabapentin pills, known as "johnnies" or "gabbies," which often sell for less than a dollar each, enhance the euphoric effects of heroin and when taken alone in high doses can produce a marijuana-like high.[30]

Quick Stimulant Facts

Physical signs of stimulant overdose:
- Tremors
- Headache
- Flushed skin
- Chest pain with palpitations
- Excessive sweating
- Vomiting
- Abdominal cramps

Drugs causing similar effects:
- Although often classified as a hallucinogen, MDMA (ecstasy) is a stimulant and can induce responses similar to classic stimulants

Available forms:
- Tablets
- Capsules
- Powder
- "Rocks"
- Injectable liquids

DEA Requirements for Prescribing Controlled Substances

To be eligible for DEA registration and legally prescribe controlled substances, a health care provider must meet certain requirements. He or she "must be a physician, dentist, veterinarian, hospital, or other person licensed, registered, or otherwise permitted by the United States or the State in which he or she practices to dispense controlled substances in the course of professional practice."[31]

Tolerance v. Addiction

Tolerance is an unavoidable neurophysical adaptation of the brain to the presence of a drug. As a result, patients can be expected to need higher doses of medication to obtain the same effect. Tolerance also implies that a person will experience withdrawal symptoms if a drug is suddenly stopped.

Addiction is the compulsive seeking and use of a drug despite continuing harm and dysfunction. Continued use of a substance by someone who is addicted decreases their functioning; use of a substance by a non-addict typically improves functioning.

As a result, a prescriber who does not have a professional license or whose professional license has been temporarily suspended cannot hold a DEA license or legally prescribe controlled substances. Similarly, prescribers must have a DEA license in the state where they are professionally licensed.

Providers must be aware of regulatory developments and legislation associated with the prescribing requirements for controlled substances.[32] This section will review the appropriate documentation for writing prescriptions, DEA prescriber registration, renewal, and revocation of registration.

Rules for Documentation

All prescriptions for controlled substances must be either typed or written in ink or indelible pencil, though some states (e.g., New York) mandate that all prescriptions for controlled substances be sent via electronic prescription (i.e., e-prescribed).[33] Although a designated individual may write the prescription, it must be manually signed by the responsible provider. All prescriptions must contain the following elements:
- Prescriber's name, address, and DEA registration number
- Manual signature of prescriber
- Patient's name and address
- Date of issue
- Drug name
- Drug strength
- Dosage
- Quantity prescribed
- Number of refills (may be 0)
- Directions for use

Schedule II controlled substance prescriptions must be written and signed by the prescriber. Under certain very strict circumstances, they can be e-prescribed, but the electronic medical record is required to have specific authentication steps. Schedule II medications cannot be refilled; they require a new prescription each time they are filled. In case of emergency, the prescriber may telephone the prescription for a schedule II controlled substance into the pharmacy but the prescriber must follow up with a written prescription within seven days. Schedule III and IV controlled substance prescriptions may be written, called in or faxed to the pharmacy, and they

have a maximum of five refills in six months. Prescriptions for schedule V controlled substances do not have a limit on refills.

Registration, Renewal, and Termination of DEA License

To prescribe controlled substances, practitioners must be registered with the DEA. There are three ways to obtain DEA Form 224 and apply for registration:[4]

- DEA Diversion Web Site: DEAdiversion.usdoj.gov
- DEA field office
- Registration Call Center: 1-800-882-9539

Once obtained, the Certificate of Registration (DEA Form 223) must be kept at the registered location and be easily retrieved for official inspection. DEA registration should be renewed every three years using DEA Form 224a. The DEA will mail the renewal form to the address listed on the current registration 45 days before the expiration date. The renewal can be completed online at DEAdiversion.usdoj.gov, or the printed renewal form can be mailed to:

Drug Enforcement Administration
Registration Unit
Central Station
P.O. Box 28083
Washington, D.C. 20038-8083

Prescribers are required to update the DEA if they change their business address or discontinue their business.

Revoking a DEA License

The DEA can deny, suspend, or revoke registration if the prescriber has committed any of the following:[4]

1. Falsified the DEA application
2. Been convicted of a felony associated with a controlled substance
3. Lacks a state practitioner license or registration
4. Cannot participate in Medicaid or Medicare
5. Acted in a way that is inconsistent with public interest, including sustaining state licensing or professional disciplinary society sanctions or being convicted of a federal or state crime associated with controlled substances

Locum Tenens

Health care providers who are working in a locum tenens capacity must understand the laws surrounding their DEA registration. Physicians who function in a locum tenens capacity temporarily substitute for a permanently employed physician while he or she is on leave. Some locum tenens physicians may also provide temporary care in a short-staffed hospital or clinic. If these practitioners work within a single state, they must be licensed and registered within that state.[34] If they register at one location in the state but practice at a different location, they are not required to re-register with the DEA. However, if they work throughout the U.S. and administer, dispense, or prescribe controlled substances in several states, they must obtain a separate DEA registration in each state where they work, use the hospital's DEA license if the hospital agrees, or transfer their DEA registration from one state to another.

Appropriate and Inappropriate Prescribing Practices

The legal standard that a controlled substance may only be prescribed, administered, or dispensed for a legitimate medical purpose by a provider acting in the usual course of professional practice has been construed to mean that the prescription must be "in accordance with a standard of medical practice generally recognized and accepted in the United States."[4]

Federal courts have long recognized that it is not possible to define the phrase "legitimate medical purpose in the usual course of professional practice" precisely enough to cover all of the varied situations providers may encounter in clinical practice.[4] There are, however, recurring patterns that suggest inappropriate prescribing of controlled substances by a clinician:[4]

- An inordinately large quantity of controlled substances prescribed or large numbers of prescriptions issued compared to other providers in an area
- No physical examination given
- Advising a patient to fill prescriptions at different pharmacies
- Issuing prescriptions knowing that the patient was delivering the drugs to others
- Issuing prescriptions in exchange for sex or money
- Prescribing controlled drugs at intervals inconsistent with legitimate medical treatment
- The use of street slang rather than medical terminology for the drugs prescribed
- No logical relationship between the drugs prescribed and treatment of the condition allegedly existing

Each case must be evaluated on its own merits in view of the totality of circumstances particular to the provider and patient. Regulatory agencies, for example, are typically aware that what constitutes "an inordinately large quantity of controlled substances," can vary greatly from patient to patient. A particular quantity of a powerful Schedule II opioid might be blatantly excessive for the treatment of mild temporary pain, and yet be insufficient to treat the unremitting pain of a cancer patient.[4]

Regulations Pertaining to Internet Access to Controlled Substances

In 2008, an amendment to the CSA was passed to add new regulatory requirements and criminal provisions designed to combat the proliferation of so-called "rogue Internet sites."[14] The Ryan Haight Act made it illegal to dispense controlled substances in all schedules via the Internet. An online pharmacy is defined as a person, entity, or Internet site, whether in the United States or abroad, that knowingly or intentionally delivers, distributes, dispenses, or offers to deliver, distribute, or dispense, a controlled substance by means of the Internet.

This law became effective April 13, 2009. As of that date, it is illegal under federal law to deliver, distribute, or dispense a controlled substance by means of the Internet unless the online pharmacy holds a modification of DEA registration authorizing it to operate as an online pharmacy.

Security Requirements Related to Controlled Substances

The CFR requires all registrants to provide effective controls and procedures to guard against theft and diversion of the controlled substances they store or handle. Factors used to determine the adequacy of these security controls include:[4]

- The location of the premises and the relationship such location bears on security needs
- The type of building and office construction
- The type and quantity of controlled substances stored on the premises
- The type of storage medium (safe, vault, or steel cabinet)
- The control of public access to the facility
- The adequacy of registrant's monitoring system (alarms and detection systems)
- The availability of local police protection

Registered health care providers are required to store Schedule II through V controlled substances in a securely locked, substantially constructed cabinet. In order to maximize security related to controlled substances, DEA recommends that health care providers not employ any of the following persons if they will have potential access to controlled substances:

- Any person who has been convicted of a felony offense related to controlled substances
- Any person who has been denied a DEA registration
- Any person who has had a DEA registration revoked
- Any person who has surrendered a DEA registration for cause

Lastly, practitioners should notify the DEA field office in their area of the theft or significant loss of any controlled substances upon discovery.[4]

Disposal of Controlled Substances

A practitioner may dispose of out-of-date, damaged, or otherwise unusable or unwanted controlled substances, including samples, by transferring them to a registrant who is authorized to receive such materials.[4] These registrants are referred to as "Reverse Distributors." The practitioner should contact their local DEA field office for a list of authorized Reverse Distributors. Schedule I and II controlled substances should be transferred via the DEA Form 222, while Schedule III–V compounds may be transferred via invoice. The practitioner should maintain copies of the records documenting the transfer and disposal of controlled substances for a period of two years.[4]

Guidelines for Prescribing Controlled Substances

Patients have long turned to health care providers to relieve suffering or improve their health or general functioning. However, health care providers face challenges when they prescribe controlled substances to their patients to help achieve these ends. Providers find themselves balancing issues of safety, a complex array of therapeutic options, compliance with governmental regulation and a mandate to alleviate patient suffering.

Since the Controlled Substances Act was passed in 1970, more than 160 medications have been added, transferred, or removed from the lists of controlled substances.[16] As part of their obligation to be responsible health care providers, prescribers must be aware of new legislation and regulatory requirements associated with practicing medicine.[32] However, prescribers are not always aware of the latest additions, changes, and deletions made in the schedules of non-opioid controlled substances. Nevertheless, the Drug Enforcement Agency can punish prescribers who fail to comply with the latest updates by revoking their prescribing license, closing their businesses, implementing fines, or inflicting prison time. These negative outcomes may be prevented if prescribers educate themselves about which medications are on the controlled substances list and how to safely prescribe them to patients.

Health care providers who prescribe controlled substance to patients must understand all of the associated risks. For example, in one study examining the interaction between prescribing physicians and older patients on chronic anxiolytics, the prescribing physicians continued prescribing anxiolytic medications to their patients because they believed that elderly patients were at low risk of addiction.[35] This practice is problematic, however, because even though the patients were at low risk of addiction they were also at increased risk of falls, motor vehicle collisions, and functional decline associated with the substances being prescribed.

Before a provider prescribes a controlled substance, he or she must understand all alternative treatments and be able to justify why the patient requires a controlled substance. Once a physician accurately diagnoses a disease, he or she cannot simply prescribe a controlled substance, but must remain updated on all of the latest management options including lifestyle changes, medical management, or surgical interventions. Moreover, health care providers are obligated to thoroughly document the patient history, physical examination and alternative treatments before prescribing a controlled substance.[31]

PLEASE SPEND THE ALLOTTED TIME ON EXERCISE 1.

Harm Reduction and Risk Mitigation

Providers should consider and implement risk mitigation strategies prior to prescribing controlled substances. Clinical decision making should remain patient-centered including focusing on patient safety. Risk mitigation strategies alone or in combination improve patient safety. The strategies and their frequency should be commensurate with risk factors and include:

- An informed consent conversation covering the risks and benefits of treatment with a controlled substance as well as alternative therapies
- Ongoing, random urine drug testing (including appropriate confirmatory testing), although providers should be aware that such testing can be expensive and is not always covered by a patient's insurance
- Checking state prescription drug monitoring programs
- Monitoring for overdose potential and suicidality
- Providing overdose education
- Prescribing naloxone rescue medication if indicated

Case Study Exercise 1

Instructions: Spend 5–10 minutes reviewing the case study below and considering the questions and commentary that follow.
Jenny Cook is a 42 year old woman who has recently relocated and become your patient. On her first visit to your clinic, she reports that her personal health has been quite good, except for an extra 100 pounds that she has been struggling to lose since she gained weight in college 20 years ago. She is sedentary and works at an office job, but she says she walks at the high school track for at least 30 minutes, 3 times a week. She reports, however, that she has been feeling a strange "fluttering" in her chest during those walks for the past 6 months. She doesn't think it is anything serious, but decided to mention it anyway.

Question 1: What follow-up questions do you have about the patient's chief complaint? _____

Commentary on Question 1: The patient's chief complaint is the "fluttering" she has in her chest while exercising. Although she alludes to weight gain, it is important for you to investigate her possible arrhythmia first. As always, you must ask about the nature, timing, exacerbating and relieving factors associated with her "fluttering." You should also ask her about any co-morbid conditions, past medical history, past surgical history, family history of heart disease or thyroid disease, and if she is taking any medications. When she tells you her medications, you must evaluate the side-effect profile of each medication.

Except for the extra weight, the patient denies any past medical or past surgical history. She does not have any allergies to medications, and she regularly takes a birth control pill, multivitamin, and phentermine. She requests re-fills on all of her medications. When you ask her how long she has been taking phentermine, she responds that she has been taking it on and off since it was initially prescribed for her by the health care provider at University Health Services. She had been taking the combination fenfluramine/phentermine (fen-phen), but stopped when that drug was taken off the market. However, a friend of hers, who is a nurse practitioner, began prescribing phentermine to Jenny again 5 years ago. Now that Jenny has moved to a different state, her friend told her that she could no longer prescribe phentermine because it is a controlled substance.

Question 2: Describe any concerns you have about the patient's health history? _____

Commentary on Question 2: Although the patient denies any past medical problems, she has been taking phentermine for many years. Phentermine is a non-opioid stimulant controlled substance used for weight loss. It was previously approved as a combination medication with the drug fenfluramine to create fen-phen. Fen-phen was taken off the market when several studies showed that its side-effect profile included significant cardiac complications, with valvular regurgitation impacting over 20% of patients.[36] Although the combination drug was taken off the market, patients who used to take the medication are still at risk for adverse events. You should be concerned that this patient did not undergo a cardiac evaluation after discontinuing fen-phen. In addition, phentermine is not meant to be used long-term, and patients who are currently taking this drug should be carefully monitored. This patient has been taking the drug chronically, and she was not monitored appropriately by a health care provider. (Case study continues later in this monograph.)

Evaluation and Risk Assessment

A Universal Precautions approach to prescribing controlled substances assumes that all patients are capable of prescription drug misuse and that procedures should be implemented to mitigate this risk. These procedures include making a clear diagnosis of the disorder being treated, assessing risk of drug misuse, obtaining informed consent regarding the abuse liability of controlled substances, and continually re-evaluating treatment effectiveness and patient adherence.[37]

Health care providers must perform and document a complete history and physical in accordance with the usual course of professional practice before legally prescribing any controlled substances. The documented history should include a description of the patient's chief complaint, attempted treatments, and co-morbid conditions. The physical examination should be used to identify co-morbid conditions and should include a neurological assessment.

Essential questions about symptoms include:

- What are the symptoms?
- When did the symptoms start?
- Was there an inciting event?
- How do symptoms impact daily life?
- What did the patient do in response to the symptoms?
- Has the patient been treated for this problem in the past?
- If so, were they prescribed a controlled substance?
- Who prescribed the controlled substance and at what doses?

Questions to consider when taking a history include:

- Does the patient have any other medical disorders?
    - Specifically for sedatives, any respiratory disorders, frequent falls, or cognitive issues?
    - Specifically for stimulants, any cardiovascular issues?
- Does the patient have a history of substance use disorders, including tobacco use?
    - Is there evidence in the chart of a history of a substance use disorder that the patient may not be disclosing? Do they have a collateral contact, such as a spouse, to verify this? Is a urine drug screening needed to confirm?
- Has the patient ever had an opioid (or other substance) overdose?
- Does the patient have a history of psychiatric disorders? If so, is the disorder currently active? Is there any potential for suicide?
- Is the patient prescribed other central nervous system (CNS) depressants?
- Is there evidence of drug diversion in the past?
- Is there a family history of substance use disorders?
- Are there children in the household?
- Can medications be secured?
- Is there a history of trauma or abuse?

If the patient is currently taking a controlled substance, the provider should ask for the name and location of the previously treating physician and, if available, check a prescription monitoring program (PMP) to corroborate that information. The health care provider must learn if the patient has attempted other treatment modalities, including dietary modification, physical therapy, behavioral therapies, medical management with a non-controlled substance, or surgical intervention. The provider should also ask if the patient's symptoms improved or deteriorated in response to prior interventions.

In order to safely manage the patient, the health care provider should find out if the patient is suffering from any co-morbid diseases or conditions, including a history of substance use disorders or harm related to substance use.

To safely treat patients with controlled substances, providers should be aware of risk factors for overdose and addiction. Addiction risk factors include a personal or family history of any substance use disorder (including current tobacco use), and psychiatric comorbidity.[38] Chronic respiratory illness, acute psychiatric instability, uncontrolled suicidality, active substance use disorder, concomitant use of benzodiazepines or other known CNS depressants (including alcohol) and known diversion in the past are other relative contraindications to controlled substance prescribing.[39]

Providers should also perform a directed physical exam and review any additional diagnostic studies or labs the patients may have required in the past. Patients may need to undergo additional imaging or diagnostic testing. As above, a urine drug screen may be needed at baseline when there is a high suspicion of an active substance use disorder (alternatively, and less subjectively, all patients may be required to submit a baseline urine drug screen). On physical examination, the health care provider should be vigilant for signs of intoxication or withdrawal, track marks from injection drug use, bruising from needles, and physical exam findings that do not fit with the presenting complaint (for example, the patient is at an appropriate weight but seeking weight reduction).[40]

Once a rigorous clinical assessment has established a clear indication for the prescription, the clinician and patient must balance the potential benefit of the medication in treating the diagnosis with the risks inherent to the medication including addiction and overdose. Although most risk-management screening tools are designed for prescribing opioids, they can also be modified and applied to screen patients for risk of misuse of non-opioid controlled substances. The most common of these are the Opioid Risk Tool (ORT), the DIRE Score, and the Screener and Opioid Assessment for Patients with Pain (SOAPP). It should be noted that these tools assess risk and should not be used to determine whether or not opioids should be prescribed.

Several mental health assessment tools are available and may be prudent to use if there is suspicion of an underlying psychiatric disorder, which may enhance risk of misuse of controlled substances, if left untreated.

Provider/Patient Agreements

Once the patient has been selected for management with any controlled substance, a robust treatment agreement should be used to build trust in the patient-physician relationship and to clarify expectations. Treatment agreements consist of informed consent language, descriptions of the treatment and what to expect, responsibilities of both parties, reasonable alternatives, benefits, and risks. While data supporting the effectiveness of treatment agreements are lacking, they are considered a standard practice. Possible side effects, including addiction and overdose, need to be fully and clearly explained, both in writing and verbally.

Continual assessment of adherence and effectiveness of the treatment with a controlled substance is crucial. A functional assessment of changes in daily activities, quality of life, and medication side effects is helpful in weighing the effectiveness of the prescribed medication. Medication adherence and other drug use can be assessed using regular urine drug screenings PMP queries, and pill counts.

PLEASE SPEND THE ALLOTED TIME ON EXERCISE 2 ON THE NEXT PAGE.

Case Study Exercise 2

Instructions: Spend 10–15 minutes reviewing the sample controlled substance patient agreement below, then answer the questions that follow related to the "Janet" scenario above:

Janet is an 82-year-old Caucasian woman. Her husband died of an ischemic stroke five years ago, and now her son Tim, who lives nearby, looks after her. Janet has had chronic left hip pain ever since a hip fracture repair two years ago developed a serious infection. She comes in to see you with Tim because she is having worsening pain. Although she has always been quick-witted and articulate, in recent years Janet has had memory problems, often pausing in mid-sentence as she searches for a name or word that's "right on the tip of her tongue." She views these memory lapses as completely normal, although Tim finds them worrisome.

According to Janet, the pain medication she was prescribed (short-acting hydrocodone/acetaminophen) is not enough to quell the pain in her hip (she says both are now hurting). According to Tim, however, Janet often forgets how much medicine she has taken. Tim feels Janet is relying too heavily on the analgesics—he believes strongly that much of Western medicine is misguided, overly invasive, overly reliant on "pills for everything." Janet dismisses Tim's concerns and presses for a long-acting opioid she saw advertised on television.

SAMPLE PATIENT AGREEMENT: Controlled Substance Treatment

PATIENT NAME: _____

PRIMARY CARE PHYSICIAN/SITE: _____

I understand that this agreement between myself; and (insert name of medical office/group) is intended to clarify the manner in which chronic (long-term) controlled substances will be used to manage my chronic pain. Chronic controlled opioid therapy for patients who do not suffer from cancer pain is a controversial issue.

I understand that there are side effects to this therapy; these include, but are not limited to, allergic reactions, depression, sedation, decreased mental ability, itching, difficulty in urinating, nausea and vomiting, loss of energy, decreased balance and falling, constipation, decreased sexual desire and function, potential for overdose and death. Care should be taken when operating machinery or driving a car while taking these medications, particularly if you feel impaired. When controlled substances are used long-term, some particular concerns include the development of physical dependence and addiction can occur. I understand these risks and have had my questions answered by my health care provider.

I understand that my (insert name of medical group) health care provider will prescribe controlled substances only if the following rules are adhered to:

- All controlled substance prescriptions must be obtained from your (insert name of medical group) primary care provider. If a new condition develops, such as trauma or surgery, then the health care provider caring for that problem may prescribe opioids for the increase in pain that may be expected. I will notify my primary care provider within 48-hours of my receiving an opioid or any other controlled substance from any other licensed medical provider. For females only: If I become pregnant while taking this medicine, I will immediately inform my obstetrician and obtain counseling on risks to the baby.
- I will submit urine and/or blood on request for testing at any time without prior notification to detect the use of non-prescribed drugs and medications and confirm the use of prescribed ones. I will submit to pill counts without notice as per health care providers' request. I will pay any portion of the costs associated with urine and blood testing that is not covered by my insurance.
- All requests for refills must be made by contacting my (insert name of medical group) primary care provider during business hours at least 3-workdays in advance of the anticipated need for the refill. All prescriptions must be filled at the same pharmacy, which is authorized to release a record of my medications to this office upon request. A copy of this agreement will be sent to my pharmacy.
- Pharmacy name/address/telephone:
- The daily dose may not be changed without my (insert name of medical group) primary care provider's consent. This includes either increasing or decreasing the daily dose.
- Prescription refills will not be given prior to the planned refill date determined by the dose and quantity prescribed. I will accept generic medications.
- Accidental destruction, loss of medications or prescriptions will not be a reason to refill medications or rewrite prescriptions early. I will safeguard my controlled substance medications from use by family members, children or other unauthorized persons.
- You may be referred to an appropriate specialist to evaluate your physical condition.
- You may be asked to have an evaluation by either a psychiatrist or psychologist to help manage your medication needs.
- If your provider determines that you are not a good candidate to continue with the medication, you may be referred to a detoxification program or evaluation by a pain management center.
- These medications may be discontinued or adjusted at your provider's discretion.

I understand that it is my provider's policy that all appointments must be kept or canceled at least 2-working days in advance. I understand that the original bottle of each prescribed controlled substance medication must be brought to every visit.

I understand that I am responsible for meeting the terms of this agreement and that failure to do so will/may result in my discharge as a patient of (insert name of medical group). Grounds for dismissal from (insert name of medical group) include, but are not limited to: evidence of recreational drug use; drug diversion; altering scripts; obtaining controlled substance prescriptions from other providers without notifying this office; abusive language toward staff; development of progressive tolerance; use of alcohol or intoxicants; and engagement in criminal activities.

Patient's Signature: _____ Date: _____

Question 1: Would this agreement be appropriate for use with Janet? _____

_____

Question 2: Would this agreement need to be modified in any way because of the specifics of Janet's case? _____

_____

Question 3: Would it be prudent to include a family member in the discussion about treatment and to serve as a witness to the agreement?

_____

Patient Education About Controlled Substances

Responsible prescribing of controlled substances requires clinicians to fully educate patients about the many issues related to safe use, storage, and disposal of such substances. Not only will educating patients possibly improve their adherence to any medication regimen, it may prevent accidental overdose or inadvertent diversion to non-authorized users.

Controlled substances of all kinds require a higher level of care and responsibility on the part of patients due to their potential for misuse or abuse. Hence, education about safe use, storage, and disposal should be part of every provider-patient interaction involving these substances. This education may include verbal instructions delivered by a prescriber, nurse or other trained clinic staff person, written handouts, guidance through other media (such as DVDs or the Internet), or referral to other resources (such as a local clinic webpage or national resources). All patient-directed materials should be written at a 6th-7th grade reading level, or lower depending on patient literacy.

Patients should be instructed about the proper use and administration of any prescribed controlled substances, including special directions about timing of doses, whether to administer the medication with food or without, and any foods or other medications to avoid while administering.

Here are some other key ideas to convey to patients about proper use:

- Read the prescription container label each time to check dosage
- Never use medicines after the expiration date
- Never share medicines with others
- Do not take a medicine with alcohol or other sedatives
- Do not take a medicine to promote sleep (unless it has been specifically prescribed for that use)
- Never break, chew, or crush medicines
- Transdermal products may be affected by external heat, fever, and exertion, which can increase absorption of a medication, leading to a potentially fatal overdose
- Transdermal products with metal foil backings are not safe for use in MRI scanners

Patients should be continually reminded that sharing, selling, or giving away controlled substances is against the law and poses significant hazards not just to the recipient of the medications, but to society at large.

Health care providers must also educate patients about the importance of proper storage of controlled substances. Even children or close relatives can be tempted to use medications they have not been prescribed, and these are often the way controlled substances become available to non-authorized uses. It is best if all controlled substances are stored in a locked cabinet or other secure storage unit. Storage areas should be cool, dry, and out of direct sunlight. Remind patients not to store medications in their car, to keep medications in the original containers, and to avoid storing medications in the refrigerator or freezer unless specifically directed to do so by a healthcare provider or pharmacist. Patients, family members, or care-givers should also monitor pill containers so they will know if any pills are missing.

Educating patients about proper disposal of unused controlled substances is also important. The U.S. Food and Drug Administration recommends a variety of disposal methods, depending on the specific drug being disposed.[41] Some states, however, may have different or more stringent guidelines. California, for example, instructs consumers not to flush any medicines down the toilet or drain. If flushing medicines is not allowed in your state, instruct patients to follow the instructions of a pharmacist for disposal or to mix the medicines with an undesirable substance, such as used coffee grounds, put the mixture into a disposable container with a lid or a sealable bag, and place it in the trash. (Note: in 2014, the DEA loosened regulations to allow pharmacies, hospitals, clinics, and other authorized collectors to serve as drop-off sites for unused prescription drugs).

The DEA sponsors the National Take Back Initiative which coordinates periodic take-back programs at thousands of state and local law enforcement agencies across the country. More information about these programs can be found at: deadiversion.usdoj.gov/drug_disposal/takeback/index.html.

Urine drug screening

Urine drug screening is noninvasive and widely available. Urine drug testing should be used to screen for the presence of prescribed and non-prescribed medications and illicit drugs. Urine drug testing does not definitively confirm whether prescription drug misuse has occurred and does not diagnose the presence of a substance use disorder, and, thus, should be used only as one tool to assess adherence or for the presence of a substance use disorder.

In the context of family practice settings, unobserved urine collection is usually an acceptable procedure for drug testing. Prescribers, however, should be aware of the many ways in which urine specimens can be adulterated. Specimens should be shaken to determine if soap products have been added, for example. The urine color should be noted on any documentation that accompanies the specimen for evaluation, since unusually colored urine could indicate adulteration. If possible, urine temperature and pH should be measured immediately after collection.[42]

One way to reduce the risk of urine test false positives or false negatives is to develop a relationship with a single laboratory, become familiar with its testing tools and threshold values, and use the same screening and confirmatory tests regularly to build familiarity with the range of normal results. Providers should only order the minimum necessary testing on a regular basis, however, as lab costs due to unnecessary testing can become quite expensive. For low risk patients, the number of tests needed per year may be as few as 2, or every 6 months. It is also generally not necessary to obtain quantitative results to confirm medication adherence.

Prescribers should be familiar with the metabolites associated with each opioid that may be detected in urine, since the appearance of a metabolite can be misleading. A patient prescribed codeine, for example, may test positive for morphine because morphine is a metabolite of codeine. Similar misunderstandings may occur for patients prescribed hydrocodone who appear positive for hydromorphone or oxycodone and oxymorphone. If questions arise, it is important to reach out to the lab toxicologist for consultation. Additionally, it is not recommended that providers make decisions about patient care solely based on the result of one urine drug test. It is important to interpret the results with other clinical information.

Table 3: Metabolites of Common Opioid Pain Medications

Drug	Metabolites
Morphine	Morphine Hydromorphone Codeine
Codeine	Codeine Morphine Hydrocodone
Hydrocodone	Hydrocodone Hydromorphone 6-Hydrocodol
Oxycodone	Oxycodone Oxymorphone Hydrocodone

Source: Webster LR, and Dove B. Avoiding Opioid Abuse While Managing Pain. Lifesource. 2007.

Prescription Drug Monitoring Programs (PDMPs)

PDMPs are state-operated databases that collect information on dispensed medications. The first PDMP was established in 1939 in California, and by 1990 another eight state programs had been established.[43] PDMPs periodically send reports to law enforcement, regulatory, or licensing agencies as part of efforts to control diversion of medication by prescribers, pharmacies, and organized criminals. Such diversion can occur through medication or prescription theft or illicit selling, prescription forgery or counterfeiting, nonmedical prescribing, and other means, including diversion schemes associated with sleep clinics (sedative-hypnotics and barbiturates), weight clinics (stimulants), and pain clinics (opioid medications).[43]

The first PDMPs, which were paper-based, did not provide reports to healthcare providers for use during individual patient care; however, today's electronic databases have a variety of features that make them practical for such care. Depending on the particular state law, the types of professionals who may register

to access PDMP records include prescribers (e.g., primary care doctors, nurse practitioners, physician assistants), dispensers (e.g., pharmacists), medical examiners, practitioner licensure board members, third-party payers, public health and safety agency representatives, and law enforcement and drug court personnel.[2] Most PDMPs permit providers to delegate access to a mid-level practitioner, such as a registered nurse or a pharmacy technician.[2] In more than half of states, prescribers and pharmacists are required to register with their respective PDMP; in some of these states, registrants are also required to access the PDMP for a patient's prescription history before prescribing or dispensing controlled substances.[2]

PDMPs Today

PDMP databases in most states are housed within a licensing or public health agency; in a few states, they are located within a law enforcement agency. Most states track prescriptions for Schedule II–V controlled medications, and some also track unscheduled medications with misuse potential (e.g., ephedrine, which can be used to make methamphetamine).

Most PDMPs update their data on a daily or weekly basis, enabling prescribers and dispensers to assess a patient's recent patterns of use or misuse. Systems are evolving toward even more frequent updating; in 2012, Oklahoma became the first state to institute real-time reporting, with prescription data available within 5 minutes after medication is dispensed.[44] Real-time reporting can offer some advantages; in particular, emergency department care providers can find near real-time prescription histories for patients presenting for acute care.

Some state PDMPs provide batch reporting; this is a utility that enables prescribers to obtain summary histories for a group of patients, such as those scheduled for upcoming appointments. The practitioner can review the summaries to determine whether a full report should be ordered for any particular patient.

Most state PDMPs are authorized to send unsolicited reports to providers, licensing boards, or law enforcement agencies when a prescriber's or prescription recipient's activity exceeds thresholds established by the PDMP.[45] Unsolicited reports can alert healthcare providers to intervene with patients whose prescription-related behavior may suggest substance misuse, whereas unsolicited reports to investigative agencies or licensure boards can support investigations into potential drug diversion or problematic prescribing.

More than half of the states are building systems to allow for data sharing across systems, agencies, and states.[7] Benefits of this system integration include the following: providers can obtain patient prescription history within the electronic health record system instead of logging into two separate systems; state Medicaid agencies can share information with federal health service providers (e.g., U.S. Department of Veterans Affairs, Indian Health Service); and adjacent states are able to share information to address illicit cross-border prescription filling or to provide for better coordination of the care that a patient is receiving in different states.

Collecting data

Pharmacies must submit required data to their state's PDMP for each prescription they dispense for specified controlled substances. Pharmacies in the U.S. Department of Veterans Affairs and in the Indian Health Service are also authorized to submit data to PDMPs, and such pharmacies in many states do so.[7] Depending on a state's legislative requirements, the following entities/ individuals may also be required to submit prescription data when dispensing controlled substances: emergency departments, wholesale distributors, licensed hospital pharmacies, physicians, veterinarians, dentists, and medical and behavioral health service providers.

Information collected typically includes date dispensed, patient, prescriber, pharmacy, medication, and quantity. This information is submitted to databases in electronic form. The intervals at which pharmacies are required to submit data vary by state.

Typically, prescriptions for intravenous medications and those filled by hospice palliative care are not submitted to PDMPs. In addition, federal confidentiality rules exempt medications dispensed at opioid treatment programs (OTPs)—that is, when a medication for the treatment of a substance use disorder (e.g., methadone, buprenorphine) is dispensed at an OTP, patient-identifying information is not submitted to the PDMP. There are some exceptions specified in the federal regulations.

OTP-based prescribers may access PDMP information to help manage the care of their patients, and the Substance Abuse and Mental Health Services Administration (SAMHSA) encourages them to do so.[1] It is especially important that OTP-based physicians and physicians who are qualified to prescribe buprenorphine for opioid use disorder (i.e., physicians who have received a waiver under the Drug Addiction Treatment Act of 2000) access the PDMP, because these physicians are the only practitioners who have full knowledge of their patients' controlled medication histories.

Privacy and security

States work hard to ensure the privacy and security of health information to prevent identity theft and medical fraud. One such safeguard is that many PDMPs are prohibited from providing identifying information about individual patients or practitioners in reports to law enforcement agencies, except in specified situations such as in response to a subpoena or for an active case investigation. Such prohibitions are also intended to protect confidentiality and avoid potential targeting of providers engaged in legitimate prescribing and dispensing activities.

Using PDMP data

PDMP reports can be used by a healthcare practitioner with other support tools (e.g., documentation templates, patient data reports and summaries, computerized alerts and reminders) when screening a new patient or monitoring a current patient. The practitioner can review the patient's prescription record from the PDMP to confirm or augment information provided by the patient's own reports and the medical exam. Providers can promote patients' acceptance of this tool by proactively informing them that PDMP data are routinely checked for all patients to enhance care and that confidentiality and privacy are protected by law and regulation.

For example, when treating for chronic pain, a practitioner can check the state PDMP for data on the patient's history of prescriptions for controlled substances. This information can be used to determine whether the patient is already receiving opioid medications or other medications that, when combined with an opioid prescription, might put him or her at risk for overdose. The Centers for Disease Control and Prevention (CDC) advises: "Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months."[46]

Whether updated in real time or at some other regular interval, a PDMP provides longitudinal information from which a healthcare practitioner can identify patterns of inappropriate prescription medication use or risky substance use behavior. PDMP data may suggest that a patient has an uneventful prescription history, giving confidence to the practitioner that the patient has a legitimate need for any scheduled prescription medications under consideration.

The data can also reveal whether the patient has been prescribed medication that may create a risk for interaction with a medication the practitioner is considering prescribing. For example, the data can suggest the total level of morphine equivalent to which a patient already has access and whether the patient has access to other medication(s) that may, in combination, put the patient at risk for overdose. Another potential use of the data is to determine whether a patient has failed to fill a prescription for medication previously prescribed by that practitioner; in such situations, the practitioner can initiate a conversation about why the patient is not taking the medication as indicated.

A practitioner can also use PDMP data to monitor patients with suspected or known substance use disorders by checking patient records for medically unwarranted concurrent use of prescription medication (e.g., high doses of several prescriptions, including long- and short-acting opioids as well as benzodiazepines) and use of multiple prescribers or pharmacies.

Other indicators of potentially problematic prescription use that a practitioner can look for when reviewing PDMP data include early refills and dose escalation.

Behavior that suggests substance misuse, a substance use disorder, or diversion is known as aberrant drug-related behavior. PDMP data can alert a practitioner to aberrant behavior such as doctor shopping (obtaining overlapping prescriptions from different doctors for intended nonmedical use) or pharmacy shopping (visiting multiple pharmacies to fill prescriptions); these are called "multiple provider episodes."

PDMP data are best used in conjunction with other sources of information, including clinical assessment, before making any determinations about aberrant behavior, because no validated and standardized criteria for the threshold of questionable activity have been established. A patient who has obtained prescriptions from multiple providers is not necessarily a "doctor shopper"; the patient could have legitimately received prescriptions from different specialists for diverse conditions (e.g., a terminal disease or disorder, chronic pain, postsurgical pain). There are also plausible reasons why a patient might fill prescriptions at multiple pharmacies (e.g., because different pharmacies may be closer to work or home, because a particular pharmacy offered a coupon). For these reasons, a proposed operational definition of shopping behavior for medications at high risk for misuse or diversion is having "overlapping prescriptions written by different prescribers and filled at three or more pharmacies."[7]

When PDMP data, combined with other information, indicate that a patient may be engaging in aberrant behavior, the practitioner can use this information in the medical setting with the patient as a basis for an immediate conversation or intervention. To ensure that the patient does not misuse prescribed medication, the practitioner can monitor PDMP data in conjunction with urine drug testing and use of a treatment agreement (a contract between patient and practitioner on what each of them will do).

Before prescribing an opioid for pain, the practitioner can assess PDMP data to ensure that a patient is not obtaining, through other prescribers, medication with sedative effects (e.g., other opioids, benzodiazepines), which could heighten risk of overdose when used simultaneously with the opioid. PDMPs provide another valuable function in that providers can use them to periodically review their own prescribing record, to confirm that their Drug Enforcement Administration (DEA)-controlled substance number has not been used illegally by another person.

Not only prescribers but also pharmacists are enhancing patient care through their use of PDMPs. For example, pharmacists can identify interaction risks from multiple prescriptions. Pharmacists can also initiate conversations with patients whose prescription use patterns indicate possible substance misuse, and they can refer such patients for screening and counseling and link them with informational resources on substance use disorders and substance use disorder treatment. Alternatively, they can contact the patient's prescriber, who may be best positioned to provide resources or referrals. Pharmacists can also use PDMP data to flag suspicious prescribing patterns that may indicate aberrant, illicit, or unsafe prescribing by medical professionals.

Evidence for Effectiveness

Provider surveys, case studies, state evaluations, and other reports offer growing evidence that individual state databases are reducing diversion while also improving individual clinical decision making and prescribing practices and lowering rates of admissions for substance use treatment.[8]

For example, after New York and Tennessee required prescribers to consult their state's database before prescribing pain medications, the percentage of patients with multiple provider episodes (receiving prescriptions from five or more prescribers or filling prescriptions at five or more pharmacies in a 3-month period) dropped 75% and 36%, respectively.[47]

Evidence from states with mandates also suggests that PDMP use supports appropriate prescribing and dispensing. In the 1-year period beginning 2 months after Kentucky's mandate on enrollment and use of its PDMP went into effect (in July 2012), overall dispensing of controlled substances in the state declined 8.5 percent. In approximately the same period, prescriptions for buprenorphine (a medication used in treatment of opioid use disorder) increased nearly 90 percent.[47] According to the PDMP Center for Excellence, these two data points indicate that the PDMP mandate suppresses inappropriate prescribing but does not impinge on legitimate prescribing.[47]

PDMP use may also be a factor in reducing mortality associated with opioid use. A 2016 study of 34 states (32 with PDMPs) found that the rate of opioid-related deaths declined in states in the year after PDMP implementation. States whose PDMPs had more robust features (e.g., more frequently updated data) experienced greater reductions in deaths compared with states whose PDMPs did not have those features.[48]

Ohio's experience indicates that PDMPs can be a significant tool in a broader program to encourage and enforce safe prescribing practices. In 2011, the state adopted rules that mandate prescriber and dispenser use of the PDMP under certain conditions. At the same time, the state instituted other measures designed to curb misuse of prescription drugs, including crackdowns on pill mills (physicians, clinics, or pharmacies that prescribe or dispense controlled medications inappropriately or for nonmedical reasons), licensing restrictions on pain management clinics to prevent over prescription of opioid pain medications, and the institution of a drug take-back program. In the first quarter of 2014 alone, the PDMP received requests for 2 million reports.[48]

A concern that has been raised about PDMPs is that they could suppress the availability of opioid medication for legitimate cases of pain. A 2016 study found that across 24 states implementing PDMPs, a sustained 30 percent reduction in the rate of prescribing Schedule II opioids occurred; however, there was no significant impact on the overall prescribing of pain medication (the study did not evaluate whether patients' pain was effectively managed).[49]

One small study (N=179) of patients presenting with nonacute pain conditions in an emergency department found that in 41 percent of the cases, clinicians altered their prescribing plan after consulting the state's PDMP; changes went in both directions, with the planned opioid prescribing reduced in 61 percent of the cases and increased in 39 percent.[50]

Other initial studies indicate that PDMPs do not have a suppressive effect, although they may affect the types of opioids that are prescribed.[7] A 2009 study found that, between 1997 and 2003, compared with states without PDMPs, states with PDMPs had a smaller number of shipments per capita (from suppliers to distributors such as pharmacies) for oxycodone (a medication highly associated with drug diversion) and reduced admissions for the treatment of prescription opioid misuse. At the same time, overall opioid shipments increased, indicating no chilling effect on the prescribing of opioids overall. According to a study on Project Lazarus—a program in Wilkes County, NC, that combines PDMP surveillance data with public health education, prevention, and treatment efforts—overdose deaths in the county declined 69 percent from 2009 to 2011, even though the number of opioid prescriptions remained nearly level and was higher than the state average.

In a pilot study of the Indiana PDMP in 2012, physicians reported that the clinical care they provided was enhanced by use of PDMPs; depending on their patients' clinical needs, physicians both reduced (by 58%) and increased (by 7%) the number of prescriptions written or number of pills dispensed.

Another concern is the perception that increased prescription monitoring through PDMPs may be a factor that causes people who are dependent on prescription opioids to switch to heroin use, contributing to heroin-related overdose deaths (the rate of heroin-related deaths almost tripled from 2010 through 2013). However, according to an analysis of 2002–2011 data from the National Survey on Drug Use and Health, of people who initiate nonmedical use of pain relievers, only 3.6% transition to heroin use within 5 years of initiation. According to the report Trends in Heroin Use in the United States: 2002 to 2013, "The concern that efforts to prevent the illegal use of prescription opioids are causing people to turn to heroin is not supported by the trend data. . . . Although research indicates that people who previously misused prescription pain relievers were

more likely to initiate heroin use than people who had not misused prescription pain relievers, most people who misuse prescription pain relievers do not progress to heroin use."[51]

Furthermore, according to a 2016 review article, implementation of most policy decisions aimed at reducing rates of nonmedical use of opioid medications occurred after heroin use rates had begun trending upward.[52] The authors point to heroin's increased accessibility, reduced price, and high purity as factors that may have contributed to increases in the drug's use. In addition, the review highlighted studies of Florida and Staten Island, NY, that found that policy-induced reductions in the rates of opioid prescribing were associated with reductions in overall opioid-related deaths (that is, deaths related to either heroin or opioid medication use). Based on the overall findings of the review, the authors recommended enhanced use of PDMPs as part of a comprehensive strategy.

Accessing PDMPs

A healthcare provider must enroll in a PDMP to become an authorized user before obtaining access to its data. Typically, the enrollment procedure involves certifying credentials, authenticating providers through proper identification, and establishing secure system access through passwords and/or biomarkers. These procedures are intended to restrict entry to users with legitimate purposes for accessing the data. Several states have developed streamlined registration systems that make enrollment easier, while still maintaining confidentiality and security.

PDMP use complements other measures that providers can take to prevent misuse and diversion of prescription medications and to help ensure the safety of patients using them. PDMPs are an increasingly valuable and easy-to-use resource for healthcare providers who prescribe and dispense controlled medication. Regulation and oversight of these databases ensure that the benefits for clinical care do not jeopardize patient privacy and security. Providers are encouraged to register to use their state's PDMP and to routinely query the database in regard to their patients' prescription histories. This practice can help curtail prescription medication misuse and diversion, reduce risk of substance use disorders, and prevent opioid overdoses and deaths

Condition-specific recommendations

General considerations

Drugs with the highest risk for addiction typically elicit rapid dopamine release in the midbrain. Therefore, potent high-dose immediate-onset medications have greater abuse liability than do their less-potent lower-dose extended-release counterparts.

It should be remembered that controlled substances are often the last therapeutic option that should be considered to manage a disease or condition, with behavioral, non-pharmacologic, and non-controlled medications tried prior to a trial of any controlled substances. Health care providers should be aware of all the available treatment options for each disease and be able to justify why they believe a controlled substance is the best therapeutic intervention. Providers should also understand the side-effects of each medication and how to monitor controlled substances for signs of misuse, addiction or abuse.

Anxiety

The CSA lists numerous anxiolytics as controlled substances. Scheduled drugs include the benzodiazepines, barbiturates, and so-called "z-drugs" such as zolpidem, zaleplon and eszopiclone. Benzodiazepines such as alprazolam, clonazepam, diazepam and lorazepam have largely replaced barbiturates for the short-term treatment of anxiety.[53] Because many anxiolytics have sedating properties, these medications are also commonly used as sleep-inducing (hypnotic) agents.

Anxiety disorders share features of excessive fear and anticipation of future threat. Fear leads to autonomic arousal, a feeling of imminent danger, and an impulse to escape. Physical symptoms associated with anxiety include chest tightness, dyspnea, tachycardia, flushing, dry mouth, tremor, dizziness, blurry vision, nausea or vomiting, abdominal pain, diarrhea, and urinary urgency.[54]

Fear and anxiety can be non-pathologic, transient emotions. In contrast, pathologic anxiety disorders persist for longer than six months, exist when certain behaviors are no longer developmentally appropriate, or are out of proportion to the threatening event or object. They must also cause distress, significantly alter the patient's routine, and diminish his or her functioning in everyday life. Examples of anxiety disorders include separation anxiety disorder, specific phobias, social anxiety disorder, panic disorder, agoraphobia, substance/medication-induced anxiety disorder, and generalized anxiety disorder (GAD). Obsessive compulsive disorders and trauma-related disorders are also common causes of anxiety symptoms, though DSM 5 has separated them from other anxiety disorders.

Although anxiety disorders are very common, little progress has been made in developing new anxiolytics over the past 50 years.[55] Anxiolytics form a heterogeneous group of agents with a wide range of efficacy and some of these medications are controlled substances with a high potential for morbidity and mortality. Barbiturates and benzodiazepines are commonly prescribed for patients suffering from anxiety. However, selective-serotonin uptake inhibitors (SSRIs) and behavioral interventions may be more effective, may have better long-term responses, and have a much smaller abuse potential.[56]

Barbiturates

Barbiturates were commonly used in the past as sedatives and hypnotics. However, they have serious safety problems and have been replaced by benzodiazepines outside the operating room. Barbiturates pose a risk of coma in high doses, induce tolerance, possess drug-interfering metabolites, create physical dependency, and incite severe withdrawal symptoms. Side-effects of these agents include drowsiness, decreased concentration, nausea, and dizziness. CNS, cardiovascular, and respiratory depression may cause overdose death.

Withdrawal from barbiturates can cause seizures, delirium, anxiety, weakness, restlessness, tremors, nausea, vomiting, cardiac arrest, and death. Barbiturates are still being used for surgical anesthesia and phenobarbital is used cautiously as an anticonvulsant. Carisoprodol is still prescribed as a muscle relaxant. It lacks effectiveness as a long term agent and should be used only for short periods, avoided in the elderly, and avoided in patients with substance use disorders. It is metabolized to meprobamate, which, though it was marketed as safer than barbiturates, has most of the pharmacological effects and dangers of barbiturates.

Benzodiazepines

Benzodiazepines have largely replaced barbiturates for short-term treatment of anxiety although they have a significant risk of morbidity and mortality, including addiction, injuries due to side-effects, potentially lethal interactions with other substances, and a risk of death from overdose. In 2010, 29% of overdose deaths in the United States involved benzodiazepines, though 77% of those deaths also involved opioid analgesics. When not used in combination with other drugs, benzodiazepines are implicated in only 3.7% of drug overdoses.[57]

In 2010, 2.2% of Americans misused tranquilizers, of which benzodiazepines were the major constituent. Nearly 10% of these individuals met criteria for a benzodiazepine use disorder.[5] In a case-control study, risk factors for death from prescribed drug overdose included one or more sedative/hypnotic medication prescriptions, male sex, older age, increased number of prescriptions, higher dose of opioid analgesics, and a prescription for buprenorphine, fentanyl, hydromorphone, methadone, or oxycodone.[58] Benzodiazepines produce behavioral disinhibition and amnesia and can enhance opioid-induced euphoria. Thus patients misusing both benzodiazepines and opioids may lose track of how much they have taken and be inclined to take more. Side-effects of long-term benzodiazepine use include tachycardia, hypertension, rebound anxiety, agitation, disorientation, hallucinations, and seizures.[59]

Before prescribing benzodiazepines, providers should obtain a current list of medications, and discuss and document the patient's drug and alcohol history. Concomitant use of benzodiazepines and

alcohol can increase the risk of overdose death and the provider may be held liable for unsafe prescribing practices if he or she has failed to document and address these risk factors.[60] Benzodiazepines should only be prescribed with extreme caution to patients with past or current alcohol use disorder. In one pilot study, an audit of medical clinic records showed that 57% of the records did not contain any information about the patients' alcohol use and the remaining records only provided limited information that was insufficient to safely prescribe benzodiazepines.[60]

Approximately one-third of patients who have long term use of benzodiazepines will experience withdrawal symptoms within two to 10 days of stopping use. Some patients will experience withdrawal symptoms on tapering benzodiazepines to a lower dose. Withdrawal symptoms include hyperarousal symptoms, such as insomnia, anxiety, photophobia, heightened sensitivity to sound, unsteadiness, and seizures.[61] Patients in a nationwide study in Switzerland who abused benzodiazepines described self-medication for anxiety and insomnia as the primary motivation for misusing this controlled substance.[62] Most patients began taking benzodiazepines after their provider prescribed the medication, and the prescribing provider usually detected the misuse.[62]

Benzodiazepines should be prescribed for short-term use only and very cautiously in older adults. Chronic daily use of benzodiazepines can lead to a profound physical dependence that is difficult to address. Adverse events associated with benzodiazepine use in older adults include motor vehicle collisions, falls, cognitive difficulties, delirium, sleep disturbances, drug-drug interactions, and impaired function.[35] Studies of older patients who are taking benzodiazepines show that they come to rely on them for any anxiety symptoms, deny the presence of side-effects and are reluctant to taper or discontinue use even when they understand the risks of continued use.[63] Health care providers prescribe these medications because they view them as effective, rapidly acting, and eliciting strong patient satisfaction.[64] Providers may minimize risks of these medications and may not view them as problematic in older patients because of the relatively low risk of addiction. As a result, they may not monitor these patients stringently or try to wean them off of long-term use of these drugs. These beliefs contradict practice guidelines and do not meet standard of care.

Insomnia

Insomnia is the most common sleep disorder and chronic insomnia is described as insomnia lasting longer than three months that is not better explained by use of substances, medications, or by another disorder.[65] The routine evaluation of insomnia involves obtaining a thorough history and performing a physical examination. In obtaining a history, the health care provider should ask questions about medical and psychiatric co-morbidities including sleep apnea (the STOP-Bang questionnaire [stopbang.ca] is a good sleep apnea screening tool for primary care), substance use disorders, and stress. The provider may want to discuss the patient's sleep habits with the patient's partner or caregiver in case he or she has noticed any sleep abnormalities such as snoring, sleep apnea, sleepwalking, or unusual limb movements. Physical examination should include a neurological exam and an assessment for comorbidities. The provider should ask the patient about prescribed medications, caffeine intake, alcohol intake, and herbal supplements.

Initial treatment for chronic insomnia should involve cognitive behavioral therapy for insomnia (CBT-I), which is multimodal treatment involving education, stimulus control instructions, time-in-bed restriction, and relaxation training. [66] Some patients take over-the-counter antihistamines, opioids, or drink alcohol in an effort to treat insomnia. Providers should discourage patients from using opioids or alcohol as sleep agents. Antihistamines reduce sleep quality and produce residual daytime drowsiness, making them a poor choice for treating insomnia. Although benzodiazepines are commonly prescribed for their hypnotic properties, patients should not rely on benzodiazepines to treat chronic insomnia, and providers should preferentially prescribe non-benzodiazepine sleep agents, and then only for acute insomnia and for intermittent use for no more than 3-4 weeks.[65] Although the margin of safety for both benzodiazepines and benzodiazepine receptor agonists (so-called Z-drugs) is relatively wide, adverse effects may include anterograde amnesia, complex sleep-related behaviors, falls, cognitive impairment, respiratory depression, and rebound insomnia.[23]

Pharmaceutical intervention for treating insomnia should be used when non-pharmaceutical treatments are ineffective, when insomnia significantly interferes with function, or when the underlying cause is addressed but insomnia persists.[67] Health care providers should prescribe the lowest effective dose and for a short duration. The provider should avoid prescribing hypnotics for patients who have an underlying history of respiratory depression, myasthenia gravis, substance use disorder, or acute cerebrovascular accident.

Temazepam

Temazepam is a benzodiazepine used to treat patients with insomnia who wake up frequently during the night.[68] Its peak sedative effect occurs 2-3 hours after it is taken, so patients must take this medication several hours before bedtime. It is a schedule IV controlled substance.

Z-Drugs

Like benzodiazepines, the Z-drugs (Zolpidem, Zaleplon, and Eszopiclone) enhance the effect of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter. Because they modulate a more specific GABA receptor subtype, the Z-drugs were thought to be less addictive and have less abuse potential than benzodiazepines. Evidence shows, however, that they elicit a similar behavioral profile including reinforcing effects, abuse potential, tolerance, physical dependence, and subjective effects.[69] While Z-drug addiction is uncommon, the risk increases at higher doses and in patients with a history of substance use disorders.[69] They can all cause withdrawal symptoms if abruptly discontinued after prolonged use. Side-effects are similar in all three and can include nightmares, agitation, hallucinations, dizziness, daytime drowsiness, headache and gastrointestinal problems.

Other agents

Doxepin is appropriate for sleep maintenance insomnia and may be useful for patients with contraindications to benzodiazepines or Z-drugs.[70] Other agents that may be effective for chronic insomnia include suvorexant, remelteon, and low doses of the sedating antidepressants trazodone and mirtazapine.[22]

Narcolepsy

Narcolepsy is characterized by neural dysregulation of the sleep-wake cycle. As a result, individuals suddenly fall asleep in the middle of the day in "sleep attacks" and experience episodes of extreme daytime sleepiness.[71] Males and females are equally affected, and narcolepsy is a life-long chronic condition that often begins between the ages of 7 and 25 years. Associated symptoms include vivid dreams, hallucinations, and total paralysis immediately before falling asleep or after waking. Some people with narcolepsy also have cataplexy, a loss of voluntary muscle tone that makes the sufferer limp and unable to move. These patients suffer from poor sleep in general and often enter REM sleep several minutes after falling asleep, in contrast to people with normal sleep cycles who enter REM sleep 80-100 minutes after falling asleep.

To diagnose narcolepsy, health care providers must take a careful sleep history to determine if shift-work, circadian rhythm abnormalities, or pre-existing sleep deprivation are present. The provider should note any symptoms consistent with cataplexy. Excessive daytime sleepiness and cataplexy are pathognomonic for this disease. Approximately half of patients have all four symptoms of hallucinations, sleep paralysis, cataplexy, and excessive daytime sleepiness.[72] Preschool-age children may have different symptoms, including inattentiveness, emotional lability, and hyperactivity.[73]

Patients may be sent home with a sleep journal and asked to keep track of their sleep patterns for several weeks.[71] A thorough physical examination must be performed to exclude any other underlying disease state that may cause similar symptoms, although cataplexy is rarely found outside of narcolepsy.

Treating narcolepsy is difficult because this disease is due to permanently low hypocretin levels.[71]

Although bench scientists are working on stem-cell therapies to replace hypocretin-producing cells, currently-approved treatments focus on alleviating symptoms. Patients with narcolepsy find this disease highly disruptive to their everyday function. They may fall asleep during work or school, in the middle of a conversation, or during a meal. More dangerously, they may fall asleep while driving or operating heavy machinery.

While they are awake, many patients describe persistent mental cloudiness, loss of concentration, fatigue, and extreme exhaustion. Therefore, health care providers prescribe treatments such as modafinil/armodafinil, amphetamines, SSRI's, and TCA's to improve wakefulness during the day. At night, patients with narcolepsy experience disrupted sleep, with hallucinations, paralysis, insomnia, and other sleep difficulties. Consequently, other treatments, including behavioral interventions, attempt to improve duration and quality of sleep. Sodium oxybate is the only medication approved in the United States to treat cataplexy.

First-line agents for patients with excessive daytime sleepiness are modafinil/armodafinil alone or in combination with sodium oxybate.[74] Alternative treatments include amphetamines (including methylphenidate), SSRI's, and TCA's.

Modafinil/armodafinil

Modafinil and armodafinil (r-enantiomer) have replaced amphetamines to become the first-line stimulants for patients with narcolepsy.[75] These medications reduce excessive daytime drowsiness and improve alertness with a better side-effect profile than amphetamines. They share a mechanism of action with amphetamines, namely blocking dopamine reuptake, though the observed effects are much milder.[76] Modafinil is a schedule IV controlled substance. It has been shown to have similar mood elevating properties, though to a lower degree.[76] Withdrawal symptoms include anhedonia, lethargy, anxiety and insomnia.

Sodium oxybate

Sodium oxybate (gamma hydroxybutyrate, GHB, Xyrem) is a sedative approved to decrease daytime sleepiness and cataplexy in the United States.[75] It restores sleep continuity, decreases hallucinations, and reduces sleep paralysis. Sodium oxybate must be administered twice per night because of its short half-life, and dose titration can be challenging. Side-effects include nocturnal confusion, sleepwalking, dizziness, nausea and enuresis. Patients who are taking this medication should avoid alcohol and other sedating medications because overdose of sodium oxybate can lead to fatal respiratory depression. These safety concerns mean that the medication is tightly restricted and classified as a schedule III controlled substance, although in a recent analysis, rates of addiction are relatively low, <1%.[77]

Methylphenidate and amphetamine

Amphetamines block dopamine reuptake or increase dopamine synaptic release, which can improve alertness, decrease appetite, and reduce daytime drowsiness. Side-effects include neurological, cardiovascular, and gastrointestinal symptoms. Neurological symptoms range from insomnia, irritability, tremor, and dizziness to confusion, delirium, panic, and suicidal ideation. Cardiovascular side-effects can be serious, including cardiac arrhythmias, hypertension, angina, and circulatory collapse. Amphetamines should not be prescribed or administered to patients with cardiovascular disease or who are taking MAO-inhibitors. Lastly, patients taking amphetamines may experience anorexia, nausea/vomiting, abdominal pain or diarrhea. Chlorpromazine, an alpha-blocker, is the antidote for amphetamine overdose.

Though the percentage of past month users of prescription stimulants has remained stable, the Drug Abuse Warning Network data show that the number of emergency room visits related to nonmedical use of prescription stimulants has increased 189% since 2004.[78] The misuse of stimulants is most common in adolescents and is often associated with the desire for cognitive enhancement and euphoria.[14] Use patterns tend to coincide with examination periods and as a means to counter the effects of binge drinking and marijuana use.[79] As with opioids, immediate-release formulations have more abuse liability, and long-acting and tamper-resistant formulations have been developed to discourage misuse. Stimulants should be prescribed with caution and closely monitored in patients with a history of substance use disorder.

Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-Deficit/Hyperactivity Disorder is one of the most commonly-diagnosed disorders of childhood. According to the CDC, 11% of children between the ages of 4 and 17 (6.4 million children) have been diagnosed with ADHD in the United States.[80] Boys are twice as likely as girls to receive a diagnosis and the average age of diagnosis is 7 years old. Furthermore, the rate of diagnosis has been increasing 5% per year since 2003.

ADHD treatment involves both medical and behavioral interventions, with about half of preschoolers with ADHD taking a medication for this disease in 2011.[80] Health care providers frequently prescribe amphetamines and methylphenidate, schedule II controlled substances, for the management of ADHD.

Neurobiological findings in children with ADHD include delayed brain maturation, inhibitory control defects, noradrenergic dysfunction, and dopaminergic dysfunction.[81] However, the diagnosis of ADHD remains a clinical diagnosis. The American Academy of Pediatrics recommends that primary care providers consider evaluating pediatric patients between the ages of 4 and 18 who present with academic or behavioral problems and symptoms of inattention, hyperactivity, and impulsivity.[82] Providers should use the criteria for a diagnosis of ADHD as described in the DSM 5. These criteria for diagnosing ADHD require a persistent pattern of inattention and/or hyperactivity-impulsivity. For a diagnosis of inattention, at least six out of nine symptoms must have been present for the past six months in children younger than 17 years. These symptoms must be developmentally inappropriate and disrupt school/work and social life.

ADHD can have predominantly inattentive presentation, predominantly hyperactive/impulsive presentation, or combined presentation. Providers should document the severity of ADHD, ranging from mild to severe depending on the number of symptoms and impairment of social or occupational functioning. They should also make sure to assess the child and rule out other causes of symptoms or co-morbid conditions, such as deafness or cognitive delay.

Guidelines suggest that health care providers should take an interdisciplinary approach to treating ADHD. Educational interventions, behavioral approaches, and medication all may have roles in managing this disorder. For children ages 4-5 years, the health care provider should prescribe behavior therapy to be administered by the parent and/or teacher as first-line intervention. If the child continues to have moderate or severe functional disturbance or there is no improvement in behavior, the provider may prescribe methylphenidate. For older children, ages 6-11 years, the health care provider should prescribe teacher and/or parent administered behavioral intervention, FDA approved medication, or both. Evidence is strongest for prescribing stimulants, followed by, in descending order of efficacy for adolescents, atomoxetine, extended release guanfacine, and extended release clonidine. The values and preferences of the patient and family are critical factors in deciding whether or not to initiate medication.[83]

Behavioral interventions are preferred to medication as the initial intervention for preschool children with ADHD and are adjuncts to medication for school-aged children and adolescents.[83]

The choice of the initial medication depends upon a number of factors, including:[83,84]

- The duration of desired coverage (completion of homework or driving may require coverage into the evening)
- The ability of the child to swallow pills or capsules
- The time of day when the target symptoms occur
- The desire to avoid administration at school
- Coexisting tic disorder
- Coexisting emotional or behavioral condition
- Potential adverse effects
- History of substance use disorders in patient or household member: avoid stimulants or use stimulants with less potential for abuse (slow-release, long acting)

- Preference of the child/adolescent and his/her parent/guardian
- Expense (in general, short acting stimulants are least expensive)

Methylphenidate and amphetamine

In one study evaluating the role of psychostimulants (such as methylphenidate, dexamphetamine, and modafinil) in managing co-morbid ADHD and non-ADHD disorders, these medications improved concentration, mood, and cognitive function while decreasing fatigue.[85] Side-effects include anorexia, sleep difficulties, abdominal pain, and headaches. Some children have diminished height with long-term use.[82] Psychiatric symptoms in younger children may include mood lability and dysphoria. Although rare, hallucinations and psychotic symptoms have been reported as a side-effect of stimulant use. Health care providers and parents are most concerned about reported cases of sudden cardiac death in previously healthy children who had been prescribed stimulants to treat ADHD. Providers must make sure to ask the child and parents about any specific cardiac symptoms or history of cardiovascular disease in the child. Furthermore, providers must obtain a thorough family history and ask about any cases of sudden death in the family, hypertrophic cardiomyopathy, Wolf-Parkinson-White syndrome, or long QT syndrome. Health care providers should avoid prescribing stimulants if they are concerned about increased risk of side-effects or potential for substance misuse or diversion.[86]

When prescribing stimulants, it is not only important to establish an accurate diagnosis of ADHD, but also to monitor symptoms and for evidence of misuse.[83] Stimulant diversion and misuse can be minimized, to some extent, by prescribing long-acting stimulants with less potential for abuse, and by keeping track of prescription dates.[87,88] Having open discussions with parents and patients about the risk of misuse and diversion is helpful, such that patients can be prepared if they are asked to sell their medications and so that parents are aware of the risks.[87]

The nonmedical use of prescription stimulants represents the second most-common form of illicit drug use in college, second only to marijuana use.[89] A 2008 study showed that lifetime rates of diversion ranged from 16% to 29% of students with stimulant prescriptions who were asked to give, sell, or trade their medications.[88] Risk factors for diversion in this study included white race, being a members of a fraternity or sorority, individuals with lower grade point averages, use of immediate-release compared to extended-release preparations. Reported reasons for use, misuse, and diversion of stimulants include to concentrate, improve alertness, "get high," or to experiment.[88]

Evaluation for substance use disorders and binge drinking should also be undertaken when prescribing stimulants for ADHD. Although there is a higher risk of misuse and diversion of stimulants in those with a history of substance use disorders, it should be noted that a critical risk factor for having ongoing substance use disorders in adulthood is the persistence of ADHD symptoms and adequate treatment of ADHD in childhood is associated with a lower risk of subsequent drug and alcohol use disorders.[88]

Atomoxetine

Atomoxitine is generally less effective than stimulants for ADHD symptoms.[82] It is a non-stimulant norepinephrine reuptake inhibitor that can be used as second-line medical management of ADHD. Side-effects include gastrointestinal distress, somnolence, and anorexia. Rare side-effects include increase in suicidal ideation and drug-induced hepatitis. Atomoxitine may be more appropriate than stimulants for patients with a personal or family history of substance use disorders, or if there is concern for misuse or diversion due to its longer-acting effects.

ER Guanfacine

Extended release guanfacine is a non-stimulant adrenergic agonist.[82] It is used to treat hypertension, anxiety, and ADHD. Side-effects include somnolence and dry mouth.

ER Clonidine

Like guanfacine, clonidine is an alpha-agonist that can be used to treat mild to moderate hypertension, as well as ADHD.[68] Side-effects include mild sedation and dry mouth, but the patient may experience rebound hypertension if clonidine is abruptly withdrawn. Alpha-2-adrenergic agonists usually are used when children respond poorly to a trial of stimulants or atomoxetine, have unacceptable side effects, or have significant coexisting conditions.

Obesity

Obesity is a complex chronic disease that is becoming increasingly common internationally and in the United States. The World Health Organization (WHO) reports that more than 1.9 billion people worldwide are obese or overweight, and the worldwide prevalence of obesity doubled between 1980 and 2014.[90] In the United States, approximately 34.9% of adults, or 78.6 million people, have obesity.[91] People who suffer from obesity have significant increases in morbidity and mortality.[90]

Weight loss can significantly improve obesity-associated morbidity and mortality. Patients with obesity or overweight are at risk for type 2 diabetes, weight loss of 2.5-5 kg over at least two years can decrease the risk of obesity-associated type 2 diabetes by 30-60%.[92] Similarly, in overweight or obese adults with or without cardiovascular risk factors, lipid levels improve in a dose-response manner with weight loss.

In order to effectively treat obesity, health care providers should understand the appropriate behavioral and dietary changes patients must make in order to lose weight and maintain weight loss. They should also understand when it is appropriate to recommend medical management or surgical intervention, and the risks and benefits of those interventions.

Obesity can be very challenging to treat, in part because of physiological mechanisms that cause the human body to resist weight loss. Providers must learn the necessary skills for how to motivate patients while also respecting their autonomy. Effective management often involves interdisciplinary teamwork with nutritionists and other trained consultants.

Treatment for obesity includes dietary restriction, comprehensive lifestyle intervention, medical management, and surgical intervention. Here we focus just on medical management with controlled substances.

In 2011, 2.74 million patients were having their morbid obesity treated pharmacologically.[93] Pharmaceutical interventions for weight reduction may suppress appetite, reduce absorption, or increase energy expenditure.[94] Medications currently approved for pharmacological weight management include short-term use of phentermine, orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide.[95] Placebo-controlled trials show clinically meaningful weight loss ranging from 37–47% for lorcaserin, 35–73% for orlistat, and 67–70% for maximally dosed phentermine/topiramate-ER.[93] Phentermine, an anorexic agent used to treat obesity, is classified as a schedule III controlled substance.

Phentermine

Phentermine is an anorexic agent. It reduces food intake by causing early satiety. It is an amphetamine-like drug that interferes with norepinephrine release. A similar drug, sibutramine was withdrawn from the market in 2010 because of its association with increased risk of cardiovascular events and stroke. Phentermine/topiramate was approved by the Food and Drug Administration (FDA) in 2012. It is well-tolerated with dose-dependent adverse events. Safety concerns include tachycardia, teratogenicity, metabolic acidosis, psychiatric disorders, and cognitive adverse events.[3] It should not be used in patients with cardiovascular disease (hypertension or coronary heart disease) or in pregnant women because of an increased risk of orofacial clefts in infants exposed to the combination drug during the first trimester of pregnancy.

PLEASE SPEND THE ALLOTTED TIME ON EXERCISE 3 ON THE NEXT PAGE.

Case Study Exercise 3

Instructions: Spend 10–15 minutes reviewing the continuation case study below and considering the questions and commentary that follow.

Jenny returns for a follow-up visit after completing a cardiovascular evaluation, which you ordered because of her heart-flutter symptoms and previous use of fen-phen. Even though her evaluation was negative for abnormalities, she has thought about the risks of phentermine and decided that she would like to consider alternative interventions for managing her obesity. In particular, she is concerned that her history of fen-phen use and a family history of heart disease might lead to cardiac problems in the future. You agree to not refill her prescription for phentermine.

Question 1: Describe alternative options Jenny may have for weight loss. (Options may include pharmaceutical and non-pharmaceutical alternatives.)

Commentary on Question 1: The patient's non-pharmaceutical weight loss options include dietary changes, exercise, behavioral therapy, and surgical interventions. Dietary interventions for morbidly obese women may entail caloric reduction producing at least a 500 kcal/day deficit, resulting in a goal of 1,200-1,500 kcal consumed per day. Exercise goals include at least 150 minutes of aerobic activity per week, and behavioral therapy is meant to encourage adherence to dietary changes and physical activity.[89]

The patient should discuss whether or not she is a good candidate for surgical intervention with her bariatric surgeon in order to decide if any surgical interventions may help her with weight loss.

You refer Jenny to a comprehensive lifestyle intervention program at a local academic center. There, the patient begins taking orlistat, goes on an American Heart Association-approved diet, and starts walking and jogging for 30 minutes 6 times a week. She is carefully monitored by the medical team at her comprehensive lifestyle intervention program. Two months later, Jenny returns to your clinic. She has lost 10 lbs, and she is determined to continue on her program. However, she has been having difficulty sleeping for the past month, and was wondering if you could prescribe a medication she saw advertised on television to help her sleep.

Question 2: You note that the sleep agent the patient would like you to prescribe is a schedule IV controlled substance. How would you proceed with your insomnia evaluation?

Commentary on Question 2: First, obtain a thorough history, including a sleep history, and review the patient's medical and psychiatric co-morbid conditions. The provider should ask the patient about prescribed medications, caffeine intake, alcohol intake, and herbal supplements. If anyone else knows about the patient's sleep habits, ask that person if he or she has noticed any unusual patient sleep patterns, including snoring, sleep apnea, sleepwalking, or unusual limb movements. Next, perform a physical examination including a neurological assessment to identify any co-morbidities. Consider administering an Epworth Sleepiness Scale or the STOP-Bang test to assess for sleep apnea during the clinic visit. Finally, request that the patient keep a sleep log for 2 weeks to identify patterns of sleep disruption. She should follow up in 3 weeks with the results. In the meantime, review and encourage behavioral interventions to improve sleep, include exercise, relaxation therapy, and good sleep habits.[65]

Jenny returns to see you for a follow-up visit. She is excited to be losing weight and feeling healthier than she has ever felt in her adult life. However, she has recently been considering bariatric surgery and would like to discuss her options with you. After reviewing the risks and benefits of surgical intervention with her, you both agree to wait to see if she makes significant weight-loss progress through her current program. If she changes her mind, you plan to refer her to a bariatric surgeon affiliated with the local academic center. The patient also brings the results of her sleep journal and reports that her insomnia is getting worse, despite her adherence to sleep inducing behaviors and diligent use of melatonin. She is frustrated and exhausted.

Question 3: You decide to prescribe a schedule IV controlled substance for a short time to treat the patient's insomnia. What 6 additional steps must you take to ensure you are following best practices for prescribing a controlled substance?

Commentary on Question 3: Here are the recommended steps for ensuring best practices for prescribing a controlled substance:

1. Document a thorough history and complete physical examination.
2. Discuss the side-effects and addictive potential of the controlled substance with the patient.
3. Check the prescription drug monitoring database to corroborate the patient's controlled substance history.
4. Document that you have discussed any history of substance use, concerns from the patient's family members, and details about the patient's treatment plan in the chart. Advise the patient to not use concomitant alcohol.
5. Establish guidelines and describe the duration of treatment.
6. Carefully monitor the patient for any evidence of misuse during treatment.

Pain Control

Pain remains the most common reason people seek health care.[96] In fact, the incidence of chronic pain in the U.S. is estimated to be greater than that of diabetes, heart disease, and cancer combined.[97,98] Inadequately treating pain can lead to a wide range of adverse consequences (in addition to causing needless suffering) including diminished quality of life, and a higher risk for anxiety or depression.[99] Pain is also a major cause of work absenteeism, underemployment, and unemployment.[96]

Pain must be treated, but many types of pain treatments exist. Opioid analgesics may—or may not—be the right choice, particularly for those suffering from chronic non-cancer pain. Opioids do not address all of the physical and psychosocial dimensions of chronic pain, and they pose a wide range of potential adverse effects, including challenging side effects and the risk of abuse, addiction, and death.

Many pharmacologic and non-pharmacologic approaches to treating painful conditions are available to primary care physicians. These options should be employed by using the following general principles:

- Identify and treat the source of the pain, if possible, although treatment can begin before the source of the pain is determined
- Select the simplest approach to pain management. This generally means using non-pharmacologic approaches as much as possible and/or trying medications with the least severe potential side effects first, and at the lowest effective doses
- Establish a function-based management plan if treatment is expected to be long-term

In treating pain, clinicians can avail themselves of five basic modalities of pain-management:

- Cognitive-behavioral approaches
- Rehabilitative approaches
- Complementary and alternative therapies
- Interventional approaches
- Pharmacotherapy

These options can be used alone or in combinations to maximize pain control and functional gains. Only one of these options involves medications, and opioids are only one of many types of medications with potential analgesic utility. Which options are used in a given patient depends on the type of pain, the duration and severity of pain, patient preferences, co-occurring disease states or illnesses, patient life expectancy, cost, and the local availability of the treatment option.

Because the focus of this monograph is on controlled substances, the rest of this section will review issues related specifically to the use of opioids for analgesia.

Prescribe with caution

The utility of opioid analgesics for treating chronic non-cancer pain is being increasingly questioned and a broad consensus is developing that these agents are not, in fact, suited for many patients with this type of pain. Clinical guidelines for the use of opioids in chronic non-cancer pain have shifted in recent years to focus on non-medication treatments. They have stressed the risks of opioids and strengthened procedures that prescribers should use to reduce the risk of addiction and misuse.[100,18,101]

Little evidence supports the assertion that long-term use of opioids provides clinically significant pain relief or improves quality of life or functioning for most chronic non-cancer related pain.[102] The Agency for Healthcare Research and Quality (AHRQ), for example, recently found no studies that compare opioid therapy with either a placebo or a non-opioid treatment for long-term (>1 year) pain management.[103] A Cochrane review of opioids for long-term treatment of non-cancer pain found that many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief.[102]

A large—and growing—body of evidence, on the other hand, demonstrates that opioids pose many significant risks for adverse effects, abuse, addiction, and accidental overdose leading to death from respiratory depression.

Estimating the risk that patients face of becoming addicted to opioid analgesics is difficult because rigorous, long-term studies of these risks in patients without co-existing substance-use disorders have not been conducted.[5] A few surveys conducted in community practice settings, however, estimate rates of prescription opioid abuse of between 4% to 26%.[104,105,106,107] Risk rises with higher opioid doses and longer durations of opioid use.[108]

A 2011 study of a random sample of 705 patients prescribed long-term opioid therapy for non-cancer pain found a lifetime prevalence rate of DSM-5-defined opioid use disorder of 35%.[109] The variability in such results probably reflects differences in opioid treatment duration, the short-term nature of most studies, and disparate study populations and measures used to assess abuse or addiction. Nonetheless, the levels of risk suggested by these studies are significant enough to warrant extreme caution in the prescription of any opioid for a chronic pain condition.

Caution is also required because a significant portion of patients can be expected not to use an opioid medication as prescribed. Fleming et al., conducted in-depth interviews with 801 patients prescribed long-term opioid therapy from a primary care provider and found the following:[105]

- 39% of patients increased their dose without direction from a health care provider
- 26% engaged in purposeful over-sedation
- 20% drank alcohol concurrent with opioid use
- 18% used opioids for purposes other than pain relief
- 12% hoarded their pain medications
- 8% obtained extra opioids from other doctors

The risk of overdose with opioid analgesics is significant and, as with risk of abuse/dependence, rises with both dose and duration.[110]

In addition to the risks for misuse, addiction, and overdose, opioids can exert a wide range of uncomfortable or harmful adverse effects, the most common of which are neurologic (somnolence, dizziness), endocrine (hypogonadism), gastrointestinal (nausea, vomiting, and constipation), sexual (erectile dysfunction), and cutaneous (pruritus). In randomized trials of opioids, 50%-80% of patients report an adverse side effect, and about 25% withdraw due to an adverse event.[102,111,112]

Although less common, there is also a dose-dependent increase in risk of fractures in opioid users compared to non-users, with risk highest in the period following initiation, particularly for short-acting opioids.[113,114]

An area of potential concern is the possibility that chronic opioid use may have immunosuppressive effects. Evidence from cell cultures and animal models

Calculating Morphine Milligram Equivalents (MMEs)

Calculating a patient's total daily dose of opioids is important to appropriately and effectively prescribe, manage, and taper opioid medications. This can be done with printed or online equianalgesic charts, which provide conversion factors and dose equivalents of all available opioid medications relative to a standard dose of morphine.

Care must be taken in using such charts because dose is not the only relevant variable. Clinicians must also consider the route of administration, cross tolerance, half-life, and the bioavailability of a drug. In addition, the patient's existing level of opioid tolerance must be taken into account.

Printed equianalgesic charts are common, and online calculators are also freely available (a common one can be accessed at clincalc.com/Opioids). The CDC provides a helpful guide to opioid conversions available at:
www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf

is suggestive, and this is an area requiring further investigation.[70] Dublin et al., in a population-based case-control study, found a significantly higher risk of pneumonia in immunocompetent older adults who were prescribed opioids.[115] The risk was particularly high for adults taking long-acting opioids.[115]

Initiating Treatment With Opioids

Prior to an initial prescription of an opioid pain medication, clinicians should be certain that (1) all other potentially effective treatments that offer a more optimal benefit-to-risk profile have been considered or tried; (2) a complete evaluation has been performed and fully documented; (3) the patient's level of opioid tolerance has been determined; and (4) informed consent and agreement to treat have been obtained.[18] A patient having been prescribed opioids by a previous provider is not, in and of itself, a reason to continue opioids, and no provider is obligated to continue opioid therapy that was started by another provider. In addition, the use of an opioid, if necessary, should be just one component of a treatment plan that includes other modalities of pain management, such as physical therapy, exercise, the use of heat or cold, or any of a range of other techniques that can facilitate improved function and a decreased reliance on opioids.

At the outset, both the clinician and the patient should view a new opioid prescription as a short-term trial of therapy. The goal of the trial is to provide data to guide decisions on the continued appropriateness of opioid medications and on the specific dose and formulation of medication used. Such a trial might be as brief as a few days or as long as several months. Opioid selection, initial dosing, and titration must be individualized to the patient's health status, previous exposure to opioids, and treatment plan. A decision to continue opioid therapy after an appropriate trial should be based on careful review of the trial outcomes. Outcomes to consider include:

- Progress toward meeting therapeutic goals
- Changes in functional status
- Presence and nature of opioid-related adverse effects
- Changes in the underlying pain condition
- Changes in medical or psychiatric comorbidities
- Degree of opioid tolerance in the patient
- Identification of altered or aberrant behaviors, misuse, or diversion

Dose Titration

Patients who are opioid-naïve or have modest previous opioid exposure should be started at the lowest dose possible of a short-acting opioid and titrated slowly upward to decrease the risk of opioid-related adverse effects.[18] If it is unclear whether a patient has recently been using opioids (either prescribed or non-prescribed), the clinician should assume that the patient is opioid-naïve (i.e., not tolerant) and proceed as just described.

Opioid tolerance should always be established before prescribing an ER/LA opioid. The selection of a starting dose and manner of titration are clinical decisions that must be made on a case-by-case basis because of the many variables involved. Some patients, such as frail older persons or those with comorbidities, may require an even more cautious therapy initiation.

Short-acting opioids are usually safer for initial therapy since they have a shorter half-life and may be associated with a lower risk of overdose from drug accumulation.

Further studies are needed to confirm more consistent control of pain and improved adherence to prescribed therapy with use of ER/LA opioids. Although low-dose, short-acting opioids may offer the greatest safety for initiating opioid therapy, clinicians must recognize that short-acting opioids are not intrinsically safer than other formulations, and stress to their patients the importance of strict adherence to prescribed doses/administration.

Tapering protocols

Clinicians prescribing opioid therapy should continually reassess the risks and benefits of treatment, and when risks are determined to outweigh benefits or when patients voice a preference for reducing their risk, opioid therapy should be tapered to a reduced dose or tapered to discontinuation. A biopsychosocial assessment including evaluation of co-occurring medical and psychiatric conditions, opioid use disorder, as well as the patient's social support system, will guide the opioid tapering process. Determination of the rate of opioid tapering takes into account many factors that include initial dose, formulations available, and risk factors that increase potential for harm.

A gradual taper pace of reducing opioid dosage by 5-20% every two to four weeks with the option to pause periodically allows time for neurobiological equilibration as well as the acquisition of new skills to manage pain and emotional distress. In some patients, a faster taper may be needed when risks are too high to consider a gradual taper; consider tapering the dose by 5-20% per day or every week in this patient population. Regardless of the initial speed of taper, the pace of taper should be reevaluated frequently and adjusted as needed to maximize safety and patient comfort as safety allows. When there is evidence of diversion or active severe opioid use disorder, opioids should be discontinued immediately and patient should be referred for treatment of opioid use disorder.

Follow-up should occur within a range of one week to one month after any opioid dosage change with the frequency and type of follow-up adjusted as needed throughout the course of the taper. Each follow-up interaction with the patient is an opportunity to provide education about self-management strategies and the risks associated with opioid therapy while optimizing whole person approaches to pain care and treatment of co-occurring medical and mental health conditions. The care team should take great efforts to ensure that the patient does not feel abandoned during the opioid tapering process by maintaining frequent contact and emphasizing that the care team will continue to pursue non-opioid pain care options during and after opioid tapering.

The risks and benefits of continuing opioid therapy should be evaluated along with the risks and benefits of tapering opioid therapy. It is important to maintain vigilance for symptoms of opioid use disorder and/or exacerbation of an underlying mental health condition that may manifest during an opioid taper. Clinicians should consider using an interdisciplinary, team-based approach that may include primary care, mental health, pain specialty/rehabilitation, pharmacy, and/or physical therapy during the opioid tapering process, and in particular for patients with significant risk factors for adverse outcomes including very high prescribed opioid doses (> 90 mg MEDD), combined use of opioids and benzodiazepines, high risk patient behaviors, and the presence of psychiatric, medical, or substance use disorder comorbidities.

Monitoring for Overdose Potential and Suicidality

Substance use disorders are a prevalent and strong risk factor for suicide attempts and suicide. Individuals at acute risk for suicidal behavior who appear to be under the influence of alcohol or other drugs, either based on clinical presentation or objective data (e.g., breath or laboratory tests), should be maintained in a secure setting like a hospital or crisis unit until intoxication has resolved. Risk assessment needs to be repeated once the patient is sober in order to determine appropriate next steps. Risk management options include, but are not limited to, admitting the patient for inpatient hospital and psychiatric care, making a referral for detoxification, or scheduling outpatient follow-up in the near future when suicidal risk is reduced.

Intentional overdose is the most common method of attempted suicide. Therefore, the possibility that an overdose event was an intentional act of self-directed violence should always be considered. Obtaining additional information from family members, treatment providers, medical records, etc., can be invaluable in making the determination between intentional and unintentional overdose in equivocal cases.

The same factors that confer risk for suicidal behavior in non-substance abusers generally also confer risk among individuals with substance use disorders. For example, depression is a potent risk factor in both substance abusers and non-substance abusers. The presence of comorbidities (e.g., substance use disorder plus mood disorder) is the rule rather than the exception in high-risk clinical populations.

With effective treatment, illnesses and perpetuating factors can be alleviated, protective factors and coping strategies can be fortified, and the patient's suicidality can resolve to a state of clinical recovery, where the acute risk has resolved and the risk of relapse has been minimized. Ongoing care may be warranted to provide early detection of recurrence.

Naloxone for overdose

Naloxone (trade name Narcan) is a high-affinity opioid antagonist used to reverse the effects of opioids. It can be administered via intramuscular, intravenous, or intranasal routes, with virtually no side effects and no effect in the absence of opioids. Counties and states that have implemented naloxone-based overdose prevention programs have significantly reduced the incidence of opioid overdose and opioid overdose-related mortality.[116,117] The effects of naloxone typically last between 30 and 90 minutes, which means the naloxone may wear off before the effects of the opioid wear off, putting the person at risk of overdose again.[118]

The American Medical Association has endorsed the distribution of naloxone to anyone at risk for having or witnessing an opioid overdose,[119] and, as of 2014, 25 states have amended or enacted laws that make it easier for health care providers to prescribe and dispense naloxone for use by patients and/or caregivers.[120]

When discussing naloxone with patients consider avoiding the single word "overdose," which has negative connotations and may be off-putting.[121] Instead, use language such as "accidental overdose," "bad reaction," or "opioid safety." For example, one might say, "Naloxone is an antidote for opioids that can be sprayed in the nose or injected if there is a bad reaction and a person cannot be woken up."

More information and many helpful resources about prescribing and using naloxone, including patient education materials, are available from: prescribetoprevent.org.

Treating pain in special populations

Opioids and pregnancy

Current guidelines suggest that clinicians should avoid prescribing opioids during pregnancy unless the potential benefits outweigh risks.[122] Some data suggest an association between the use of long-term opioid therapy during pregnancy and adverse outcomes in newborns, including low birth weight and premature birth, though co-related maternal factors may play a role in these associations and causality is not certain.[122] Exposure to these medications has also been associated with birth defects in some studies. Opioid withdrawal can be expected in up to half of newborns of opioid-dependent mothers (neonatal abstinence syndrome).[122] If a mother is receiving long-term opioid therapy at or near the time of delivery, a professional experienced in the management of neonatal withdrawal should be available if neonatal abstinence syndrome occurs.

Emergency room patients

Pain is a frequent complaint of emergency room (ER) patients, and ER providers are among the highest prescribers of opioids to patients ages 10-40.[123] ER providers, however, face considerable challenges in determining a patient's appropriateness for opioid therapy. A medical history is often lacking, and the provider seldom knows the patient personally. Time constraints, as well, can preclude the kinds of careful assessment and evaluation recommended for responsible opioid prescribing.

Because of this, current guidelines from the American College of Emergency Physicians include the following recommendations:[124]

- ER/LA opioid medications should not be prescribed for acute pain
- PDMPs should be used where available to help identify patients at high risk for opioid abuse or diversion
- Opioids should be reserved for more severe pain or pain that doesn't respond to other analgesics
- If opioids are indicated, the prescription should be for the lowest effective dose and for a limited duration (e.g., < 1 week).

Cancer pain

Pain is one of the most common—and most feared--symptoms of cancer. Pain is experienced by about 30% of patients newly-diagnosed with cancer, 30% - 50% of patients undergoing treatment, and 70% -90% of patients with advanced disease.[98] Unrelieved pain adversely impacts motivation, mood, interactions with family and friends, and overall quality of life. Survival itself may be positively associated with adequate pain control.[125] Opioid pain medications are the mainstay of cancer pain management and a trial of opioid therapy should be administered to all cancer patients with moderate or severe pain, regardless of the known or suspected pain mechanism.[126]

ER/LA opioid formulations may optimize analgesia and lessen the inconvenience associated with the use of short-acting opioids. Patient-controlled analgesia with subcutaneous administration using an ambulatory infusion device may provide optimal patient control and effective analgesia.[127] The full range of adjuvant medications covered earlier should be considered for patients with cancer pain, with the caveat that such patients are often on already complicated pharmacological regimens, which raises the risk of adverse reactions associated with polypharmacy. If cancer pain occurs in the context of a patient nearing the end of life, other treatment and care considerations may be appropriate. In these cases, patient integrated with a specialist in palliative care medicine may be advisable.

Pain at the end of life

Pain management at the end of life seeks to improve or maintain a patient's overall quality of life. This focus is important because sometimes a patient may have priorities that compete with, or supersede, the relief of pain. For some patients mental alertness sufficient to allow lucid interactions with loved ones may be more important than physical comfort. Optimal pain management, in such cases, may mean lower doses of an analgesic and the experience, by the patient, of higher levels of pain.

Since dying patients may be unconscious or only partially conscious, assessing their level of pain can be difficult. Nonverbal signs or cues must sometimes be used to determine if the patient is experiencing pain and to what degree an analgesic approach is effective. In general, even ambiguous signs of discomfort should usually be treated, although caution must be exercised in interpreting such signs.[128] Reports by family members or other people close to a patient should not be overlooked. In the Study to Understand Prognosis and Preference for Outcomes and Risks of Treatment (SUPPORT) , surrogates for patients who could not communicate verbally had a 73.5% accuracy rate in estimating presence or absence of the patient's pain.[129]

Opioids are critical to providing effective analgesia at the end of life, and they are available in such a range of strengths, routes of administration, and duration of action that an effective pain regimen can be tailored to nearly each patient. No specific opioid is superior to another as first-line therapy. Rectal and transdermal routes of administration can be valuable at the end of life when the oral route is precluded because of reduced or absent consciousness, difficulty swallowing, or to reduce the chances of nausea and vomiting.[130] When selecting an opioid, clinicians should also consider cost, since expensive agents can place undue burden on patients and families.

Fear of inducing severe or even fatal respiratory depression may lead to clinician under-prescribing and reluctance by patients to take an opioid medication.[28] Despite this fear, studies have revealed no correlation between opioid dose, timing of opioid administration, and time of death in patients using opioids in the context of terminal illness.[131] A consult with a specialist in palliative medicine in these situations may be advisable.

Older Adults

The prevalence of pain among community-dwelling older adults has been estimated between 25% and 50%.[132] The prevalence of pain in nursing homes is even higher. Unfortunately, managing pain in older adults is challenging due to: underreporting of symptoms; presence of multiple medical conditions; polypharmacy; declines in liver and kidney function; problems with communication, mobility, and safety; and cognitive and functional decline in general.

Acetaminophen is considered the drug of choice for mild-to-moderate pain in older adults because it lacks the gastrointestinal, bleeding, renal toxicities, and cognitive side-effects that have been observed with NSAIDs in older adults (although acetaminophen may pose a risk of liver damage). Opioids must be used with particular caution, and clinicians should "Start low, go slow" with initial doses and subsequent titration. Clinicians should consult the American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults for further information on the many medications that may not be recommended.[31]

Treating Substance Use Disorders, including Opioid Use Disorder

"Unfortunately, far too few people who suffer from opioid use disorder are offered an adequate chance for treatment that uses safe and effective medications," FDA Commissioner Scott Gottlieb, M.D.[133]

Although primary care clinicians have not historically been directly involved in treating substance abuse disorders, they play a critical role in recognizing early signs of these disorders, referring patients to needed services, and supporting patients in the typically lengthy process of recovery from substance use or abuse. There are now many ways that they can assist with the treatment of opioid use disorder if they obtain a physician waiver to prescribe buprenorphine.

Substance use disorders are chronic brain diseases that impair one's ability to control substance use. Repeated use of any controlled substance over time can lead to a use disorder, and long-term is by far the most powerful risk factor for developing this disorder. All persons using controlled substances are at risk for developing a use disorder, even those who take the substances as prescribed. An early sign of a developing use disorder is gradually becoming more preoccupied with substance use and spending more time seeking the drug, using it, or recovering from its effects. Persons with substance use disorder typically continue to use the drug even though they:

- Know the drug use is harmful
- Often use more than they intended
- Engage in risky behaviors such as driving while intoxicated or combining alcohol with other drugs
- Have multiple unsuccessful attempts to cut down or control substance use
- Have strong craving or urges to use one or more substances in response to withdrawal symptoms, stress, negative emotions, or cues that the drug is available

The treatment system for substance use disorders is comprised of multiple service components, which may be available to various degrees in different regions. They include the following:

- Individual and group counseling in an outpatient setting
- Inpatient rehabilitation
- Residential treatment
- Intensive outpatient treatment
- Partial hospital programs
- Case or care management
- Medication treatment
- Recovery support services
- 12-Step fellowship
- Peer supports

A person accessing treatment may not need to access every one of these components, but each can play an important role. These systems are embedded in a broader community and the support provided by various parts of that community also play an important role in supporting the recovery of people with substance use disorders.

Counseling can be provided at the individual or group level. Individual counseling often focuses on reducing or stopping substance use, skill building, adherence to a recovery plan, and social, family, and professional/educational outcomes. Group counseling is often used in addition to individual counseling to provide social reinforcement for pursuit of recovery.

Counselors provide a variety of services to people in treatment for substance use disorders including assessment, treatment planning, and counseling. These professionals provide a variety of therapies. Some common therapies include:

- Cognitive-behavioral therapy (CBT), which teaches individuals to recognize and stop negative patterns of thinking and behavior. For instance, CBT might help a person be aware of the stressors, situations, and feelings that lead to substance use so that the person can avoid them or act differently when they occur.
- Contingency management provides incentives to reinforce positive behaviors, such as remaining abstinent from substance use.
- Motivational enhancement therapy helps people with substance use disorders to build motivation and commit to specific plans to engage in treatment and seek recovery. It is often used early in the process to engage people in treatment.
- 12-step facilitation therapy seeks to guide and support engagement in 12-step programs such as Alcoholics Anonymous or Narcotics Anonymous.

Some forms of counseling are tailored to specific populations. For instance, young people often need a different set of treatment services to guide them towards recovery. Treatments for youth often involve a family component. Two models for youth that are often used in combination and have been supported by grants from the Substance Abuse and Mental Health Services Administration are the Adolescent Community Reinforcement Approach (ACRA) and Assertive Continuing Care (ACC).[134] ACRA uses defined procedures to build skills and support engagement in positive activities. ACC provides intensive follow up and home based services to prevent relapse and is delivered by a team of professionals.

Treatment provided through inpatient rehabilitation happens within specialty substance use disorder treatment facilities with a broader behavioral health focus, or by specialized units within hospitals. Longer-term residential treatment has lengths of stay that can be as long as six to twelve months and is relatively uncommon. These programs focus on helping individuals change their behaviors in a highly structured setting. Shorter term residential treatment is much more common, and typically has a focus on detoxification (also known as medically managed withdrawal) as well as providing initial intensive treatment, and preparation for a return to community-based and outpatient addiction treatment settings.

An alternative to inpatient or residential treatment is partial hospitalization or intensive outpatient treatment. These programs have people attend very intensive and regular treatment sessions multiple times a week early in their treatment for an initial period. After completing partial hospitalization or intensive outpatient treatment, individuals often "step down" into regular outpatient treatment which meets less frequently and for fewer hours per week to help sustain their recovery.

Using medication to treat substance use disorders is often referred to as Medication-Assisted Treatment (MAT). In this model, medication is used in combination with counseling and behavioral therapies. Medications can reduce the cravings and other symptoms associated with withdrawal from a substance by occupying receptors in the brain associated with using that drug (agonists or partial agonists), block the rewarding sensation that comes with using a substance (antagonists), or induce negative feelings when a substance is taken. MAT has been primarily used for the treatment of tobacco, alcohol, and opioid use disorders.

Focus on opioid use disorder

Opioid use disorder (OUD) is associated with premature death from opioid overdose and other medical complications such as AIDS, hepatitis C, and sepsis. On average, OUD carries a 40-60% 20-year mortality rate.[136] Persons with OUD are at high-risk for premature death, not only from opioid overdose, but from other consequences. Thus, providing first-line treatment is important to save lives as well as to improve quality of life.

Strong evidence supports the use of medication-assisted therapy (MAT) (e.g., methadone, buprenorphine/naloxone, naltrexone) as first-line treatment for moderate-to-severe OUD.[137] Patients and their treating clinicians may be concerned that treatments proven effective in different OUD populations may not be effective for patients with chronic pain, or may not be necessary for patients who have become addicted to prescription opioid analgesics. This concern may be unfounded and was addressed by Weiss and colleagues in the Prescription Opioid Abuse Treatment Study.[138]

In studies with patients who meet DSM 5 diagnostic criteria for opioid use disorder, buprenorphine maintenance therapy is more effective than a four-week taper with buprenorphine. MAT with moderate dose buprenorphine/naloxone and brief, structured counseling by the prescribing physician can be successful for about half of selected patients with prescription OUD, whereas withdrawal management alone, even with close weekly follow-up and counseling, is successful for less than 10% of patients.

Furthermore, the presence of chronic pain does not seem to interfere with the success of MAT.[138,139] Given the high mortality associated with OUD and the safety and efficacy of MAT for OUD in multiple clinical trials and meta-analyses, MAT is recommended for those chronic pain patients who meet DSM-5 criteria for OUD. Those who do not respond to medication management alone through a primary care provider may benefit from a comprehensive assessment and more intensive treatment of OUD and any co-occurring conditions in SUD specialty care settings.

Methadone for OUD

Methadone is a synthetic opioid agonist that has long been used to treat the symptoms of withdrawal from heroin and other opioids. Much research supports the use of methadone as an effective treatment for opioid use disorder.[135] It is also used in the treatment of patients with chronic, severe pain as a therapeutic alternative to morphine and other opioid analgesics. Any licensed physician can prescribe methadone for the treatment of pain, but methadone may only be dispensed for treatment of an opioid use disorder within licensed methadone treatment programs.[135]

Long-term methadone maintenance treatment for opioid use disorders has been shown to be more effective than short-term withdrawal management, and it has demonstrated improved outcomes for individuals (including pregnant women and their infants) with opioid use disorders.[135] Studies have also indicated that methadone reduces deaths, HIV risk behaviors, and criminal behavior associated with opioid use.

Methadone treatment programs, also known as Opioid Treatment Programs (OTPs), must be certified by SAMHSA and registered by the U.S. Drug Enforcement Administration. OTPs are predominantly outpatient programs that provide pharmacotherapy in combination with behavioral therapies. OTPs incorporate principles of harm reduction and benefit both program participants and the community by reducing opioid use, mortality, crime associated with opioid use disorders, and infectious disease transmission.[135]

Individuals receiving medication for opioid use disorders in an OTP must initially take their doses daily under observation. Initiation of methadone treatment is done slowly and carefully. Federal law prohibits a dose greater than 40 mg for patients on their first day of treatment. Dose escalation is done slowly as patients stabilize on the medication. Therapeutic doses of methadone are typically 60-90 mg/day, though some patients may need doses much higher than this. After initiation, stabilization on methadone generally takes about 2 weeks. Patients are monitored daily and given frequent urine drug tests throughout their treatment. Once patients have stabilized fully on the medication, are no longer using other opioids, and have stable living environments, they can become eligible for "take home" medication, meaning they self-administer methadone outside of the OTP. Take home approval is highly monitored and regulated. A patient receiving methadone from an OTP can only receive up to 28 days of take home medication and he/she must remain opioid abstinent at all times.[135]

Buprenorphine for OUD

Buprenorphine is a partial opioid agonist. This means that, like opioids, it can produce effects such as euphoria and respiratory depression. With buprenorphine, however, these effects are weaker than those of full opioid agonists such as heroin and methadone.[140] Buprenorphine's opioid effects increase with each dose until, at relatively moderate doses, they level off and do not cause any additional opioid effect, even with further dose increases. This "ceiling effect" lowers the risk of misuse, dependency, tolerance, and side effects.

Approved for clinical use in October 2002 by the FDA, buprenorphine represents the latest advance in MAT.[140] Medications such as buprenorphine, in combination with counseling and behavioral therapies, provide a whole-patient approach to the treatment of opioid use disorder. When taken as prescribed, buprenorphine is safe and effective.[140] Buprenorphine as an opioid use disorder treatment is carefully regulated. Qualified physicians and advanced practice providers are required to acquire and maintain certifications to legally dispense or prescribe buprenorphine.

Unlike methadone treatment, which must be performed in a highly structured clinic, buprenorphine is the first medication to treat opioid use disorder that is permitted to be prescribed or dispensed in physician offices, significantly increasing treatment access. Under the Drug Addiction Treatment Act of 2000 (DATA 2000), qualified U.S. physicians can offer buprenorphine for opioid use disorder in various settings, including in an office, community hospital, health department, or correctional facility. Government-certified opioid treatment programs also are allowed to dispense buprenorphine.

As with all medications used in MAT, buprenorphine is prescribed as part of a comprehensive treatment plan that includes counseling and participation in social support programs.

The FDA has approved the following buprenorphine products:[140]

- Bunavail (buprenorphine and naloxone) buccal film
- Suboxone (buprenorphine and naloxone) film
- Zubsolv (buprenorphine and naloxone) sublingual tablets
- Buprenorphine-containing transmucosal products for opioid use disorder
- Buprenorphine's side effects are similar to those of other opioids and can include:
- Nausea, vomiting, and constipation
- Muscle aches and cramps
- Cravings
- Inability to sleep
- Distress and irritability
- Fever

Because of buprenorphine's opioid effects, it can be misused, particularly by people who do not have an opioid use disorder. Naloxone is added to buprenorphine to decrease the likelihood of diversion and misuse. When these products are taken as sublingual tablets, buprenorphine's opioid effects dominate and naloxone is inactive. If the sublingual tablets are crushed and injected intravenously, however, the naloxone effect dominates and can cause opioid withdrawal in people who are dependent on opioids.

Buprenorphine treatment typically happens in three phases:[140]

1. The Induction Phase is the medically monitored induction of buprenorphine treatment performed in a qualified medical provider's office or certified opioid treatment program using approved buprenorphine products. The medication is administered when a person with a moderate to severe opioid use disorder has abstained from using opioids for 8 to 24 hours and is in the early stages of opioid withdrawal (identified by a Clinical Opioid Withdrawal Scale $\geq$ to 10. It is important to note that buprenorphine can precipitate acute withdrawal for patients who are not in the early stages of withdrawal and who have long-acting opioids like methadone in their bloodstream.
2. The Stabilization Phase begins after a patient has stabilized on buprenorphine, has discontinued or greatly reduced their use of the problem drug, no longer has opioid cravings, and experiences few, if any, side effects. The buprenorphine dose may need to be adjusted during this phase. Because of the long-acting nature of buprenorphine, once patients have been stabilized, they can sometimes switch to alternate-day dosing instead of dosing every day, though this is not common. In some cases patients may benefit from taking buprenorphine twice or three times a day, particularly patients with chronic pain.

3. The Maintenance Phase occurs when a patient is doing well on a steady dose of buprenorphine. The length of time of the maintenance phase is tailored to each patient and could be indefinite. Outcomes are best for patients who remain on buprenorphine maintenance treatment. Once an individual is stabilized, an alternative approach would be to go into a medically supervised withdrawal, which makes the transition from a physically dependent state smoother. People then can engage in further rehabilitation—with or without MAT—to prevent a possible relapse.

As with any other substance use disorder, treatment of opioid use disorder with buprenorphine is most effective in combination with counseling services, which can include different forms of behavioral therapy and self-help programs.

Conclusions

This monograph on best practices for prescribing controlled substances summarized the United States federal legislation governing the prescription of controlled substances and offered suggestions for how health care providers can comply with those regulations. The monograph provided a list of frequently encountered non-opioid controlled substances grouped by schedule. It reviewed the legal requirements for compliance in prescribing these substances, including how to perform critical components of the history and physical examination, assessing patients for substance use disorder risk, and documenting risk stratification. Before prescribing controlled substances, health care providers are obligated to document how they made the diagnosis and why a controlled substance is the best treatment for the patient. This monograph also reviewed some common conditions that may be treated with controlled substances.

The government frequently changes the requirements for compliance with controlled substances. Substances are added, removed, or transferred between schedules in the controlled substance list. For example, the American Medical Association, the Institute of Medicine, and the American College of Physicians have petitioned the DEA to shift cannabis from Schedule I to Schedule II in light of the voluminous testimony that this substance does have valid medical uses and to facilitate research on more effective therapeutic uses of the relevant compounds contained in raw cannabis.[141] (As noted above, this monograph does not cover cannabis because the legal, medical, and cultural dimensions of this drug are in such flux.)

In order to maintain compliance, responsible health care providers must be aware of changes in legislation and regulatory requirements associated with commonly prescribed substances. They must maintain current DEA licensure for the state in which they practice and ensure that the DEA has their most current mailing address. When prescribers fill out a prescription for a controlled substance, they must ensure that all parts of the prescription are filled out properly, and they should take schedules into account when sending prescriptions to the pharmacy or ordering re-fills. Lastly, health care providers should closely monitor patients who are taking controlled substances for signs of addiction, overdose, side-effects, and drug-drug interactions.

Clearly, the rise of substance use disorder and prescription drug abuse, and the wider use of controlled substances, is related to social, cultural, and economic forces that are larger and more powerful than any role that clinicians have in their day-to-day work with controlled substances.[18] But at the same time, clinicians can take simple steps to insure that controlled substances are prescribed safely and effectively. By so doing, those prescribers help protect their patients, society at large and themselves should they encounter the scrutiny of regulators.

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NOTES

EVIDENCE-BASED GUIDANCE ON RESPONSIBLE PRESCRIBING, EFFECTIVE MANAGEMENT, AND HARM REDUCTION

Self-Assessment

Choose the best possible answer for each question and mark your answers on the Self-Assessment answer sheet at the end of this book. There is a required score of 70% or better to receive a Certificate of completion.

21. In the United States, approximately how many non-medical users of pain relievers, tranquilizers, stimulants, and sedatives got their prescription drugs from a friend or relative for free?

A. < 10%
B. 25%
C. 35%
D. > 50%

22. What two competing needs must the CSA and regulators attempt to balance?

A. The need to contain the spiraling costs of prescription medications while also supporting the pharmaceutical industry's need to support expensive research and development efforts
B. The need to maintain an adequate supply of controlled substances for legitimate purposes while simultaneously reducing their diversion and abuse
C. The need to regulate the pharmaceutical industry while also supporting law enforcement agencies
D. The need to punish those abusing prescription medications with the need to provide adequate social support for addicts

23. Which attribute of some drugs with legitimate therapeutic uses increases their likelihood of being abused?

A. Whether the drug is compounded with another drug
B. Whether the drug produces pleasurable feelings
C. Cost of the drug to patients
D. Whether the drug, as packaged and manufactured, resembles other drugs with legitimate medical uses

24. The duration of action of ER/LA opioids is typically _____.

A. 30 – 90 min
B. 2- 4 hrs
C. 4 – 24 hrs
D. 4 – 72 hrs

25. Uncomfortable or unpleasant side effects (aside from constipation) may potentially be reduced by which two approaches?

A. Switching to another opioid or taking the opioid with food
B. Switching to another opioid or changing the route of administration
C. Adding a non-opioid analgesic or trying a complimentary therapeutic technique
D. Changing the route of administration or advising patients to avoid alcohol consumption

26. What drug class has largely replaced barbiturates as treatment for anxiety and muscle spasms?

A. Amphetamines
B. Benzodiazepines
C. Non-benzodiazepines
D. Serotonin-reuptake inhibitors

27. Which of the following items does not need to be contained in any prescription for a controlled substance?

A. Proof of informed consent
B. Patient's name and address
C. Drug strength
D. Number of refills (if any)

28. Which of the following might suggest inappropriate prescribing of controlled substances by a clinician?

A. Prescribing a drug for which no logical relationship exists with the alleged condition of a patient
B. Prescribing a substance without performing a physical examination
C. Prescribing the substance at intervals inconsistent with legitimate medical treatment
D. All of the above

29. The Ryan Haight Act made it illegal to _____.

A. Dispense controlled substances in all schedules via the Internet
B. Dispense controlled substances in a state different from the one in which a practitioner is registered
C. Dispense Schedule I substances to patients for any reason
D. Dispense controlled substances to minors

30. Which of the following is not a potential benefit of urine drug screening?

A. May deter inappropriate use
B. Provides objective evidence of abstinence from drugs of abuse
C. May demonstrate to regulatory authorities a clinician's dedication to monitoring
D. Can differentiate between opioids that a patient may be using.

31. Drugs with the highest risk for subsequent addiction slowly elicit dopamine release in the midbrain.

A. True
B. False

32. Although initially thought to be less prone to induce tolerance and dependence than barbiturates, benzodiazepines are now recognized to be just as liable to diversion and abuse.

A. True
B. False

33. Little evidence supports the assertion that long-term use of opioids provides clinically significant pain relief or improves quality of life or functioning.

A. True
B. False

34. Roughly what percent of patients reported that they increased their dose of an opioid without talking to the prescribing physician in one study?

A. 10%
B. 20%
C. 30%
D. 40%

35. When opioid treatment is initiated, it should be viewed by both patient and clinician as _____.

A. A commitment to long-term use of opioid therapy
B. A commitment to gradual titration of the opioid to reach optimal pain relief
C. A short-term trial of therapy
D. An agreement to continue therapy until adequate pain relief is achieved

36. Opioid tolerance must be demonstrated before prescribing any strength of _____.

A. A short-acting opioid
B. An ER/LA opioid
C. A combination formulation of an opioid
D. An abuse deterrent formulation of an opioid

37. What level of opioid dose is widely considered a red flag warranting more intense monitoring and/or referral to an interdisciplinary treatment team?

A. > 75 mg MEDD
B. > 80 mg MEDD
C. > 90 mg MEDD
D. >110 mg MEDD

38. What relatively new development may reduce the incidence of death from accidental overdose of an opioid medication?

A. Mandatory CPR training for patients
B. New restrictions on simultaneous prescribing of an opioid and a central nervous system depressant
C. Greater availability of 911 emergency response systems
D. Provision to patients of intranasal naloxone for home use

39. For patients at the end of life, optimal pain management may mean lower doses of an analgesic, and higher levels of pain, in order to allow the patient mental alertness sufficient for interactions with loved ones.

A. True
B. False

40. Medication-Assisted Treatment is primarily used for treating _____.

A. Tobacco use disorder
B. Opioid use disorder
C. Alcohol use disorder
D. All of the above

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MARK ONE ANSWER PER QUESTION

TENNESSEE CLINICAL PRACTICE GUIDELINES FOR MANAGING CHRONIC PAIN (P. 41-42)

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	16.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	17.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

EVIDENCE-BASED GUIDANCE ON RESPONSIBLE PRESCRIBING, EFFECTIVE MANAGEMENT, AND HARM REDUCTION (P. 70-71)

21.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	31.	Ⓐ	Ⓑ		
22.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	32.	Ⓐ	Ⓑ		
23.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	33.	Ⓐ	Ⓑ		
24.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	34.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
25.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	35.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
26.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	36.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
27.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	37.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
28.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	38.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
29.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	39.	Ⓐ	Ⓑ		
30.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	40.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

PROGRAM CODE: TN600CME For internal use only

Please complete the activity survey on the following page.

Phone: 1-800-237-6999 ● Fax: 1-800-647-1356

ACTIVITY EVALUATION(S)

For each of the objectives determine if the activity increased your: **A** Competence **B** Performance **C** Outcome **D** No Change

TENNESSEE CLINICAL PRACTICE GUIDELINES FOR MANAGING CHRONIC PAIN:

		A	B	C	D
1.	Assess patients in pain and identify the range of therapeutic options for managing pain	○	○	○	○
2.	Safely and effectively manage patients on opioid analgesics in the acute and chronic pain settings	○	○	○	○
3.	Recognize when to incorporate emergency opioid antagonists into prescribing practice.	○	○	○	○
4.	Identify and manage patients with opioid use disorder	○	○	○	○

5. Please identify a specific change, if any, you will make in your practice related to safe prescribing of opioid analgesics?

_____

_____

6. What do you see as a barrier to making these changes?

_____

_____

EVIDENCE-BASED GUIDANCE ON RESPONSIBLE PRESCRIBING, EFFECTIVE MANAGEMENT, AND HARM REDUCTION:

		A	B	C	D
7.	Describe the scope of current use and abuse of controlled substances in the U.S.	○	○	○	○
8.	Interpret regulatory and legal framework for prescribing controlled substances.	○	○	○	○
9.	Explain best practices for prescribing controlled substances.	○	○	○	○

10. Please identify a specific change, if any, you will make in your practice related to safe prescribing of controlled substances?

_____

_____

11. What do you see as a barrier to making these changes?

_____

_____

PROGRAM EVALUATION:

		Yes	No	If no, please explain:
12.	The program was balanced, objective & scientifically valid	○	○	_____
13.	Do you feel the program was scientifically sound & free of commercial bias or influence?	○	○	_____

14. How can this program be improved? _____

_____

15. Based on your educational needs, please provide us with suggestions for future program topics & formats. _____

_____

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