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

LOUISIANA

INITIAL MEDICAL LICENSURE PROGRAM

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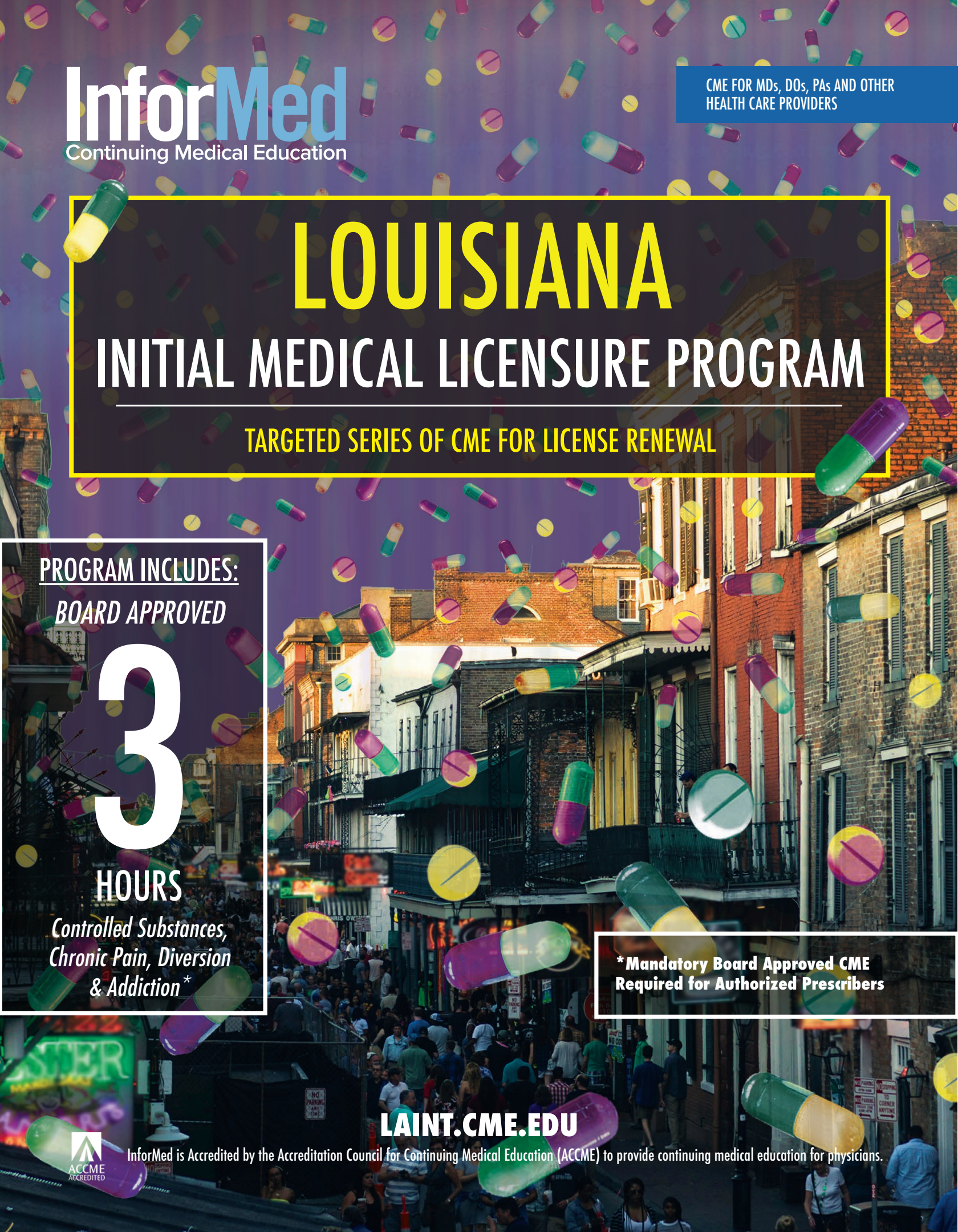

PROGRAM INCLUDES:

BOARD APPROVED

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HOURS

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***Mandatory Board Approved CME Required for Authorized Prescribers**

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ACCME ACCREDITED

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

CONTINUED

LOUISIANA

01 **BEST PRACTICES FOR PRESCRIBING CONTROLLED SUBSTANCES**

COURSE ONE | 3 CREDITS*

SATISFIES CONTROLLED SUBSTANCE REQUIREMENT

39 **LEARNER RECORDS: ANSWER SHEET & EVALUATION**

REQUIRED TO RECEIVE CREDIT

*This course is approved by the Louisiana State Board of Medical Examiners to satisfy the mandatory three (3) hour CME requirement on best practices for prescribing controlled substances, drug diversion, addiction treatment and treatment of chronic pain.

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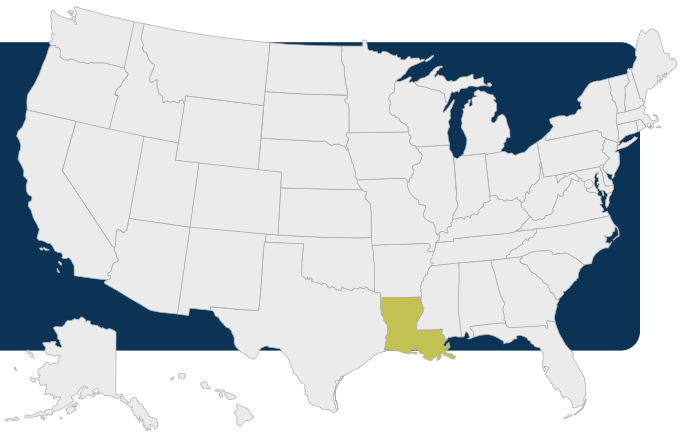

Louisiana Professional License Requirements

LOUISIANA PHYSICIANS CONTINUING MEDICAL EDUCATION REQUIREMENTS

Subject to the waiver of and exceptions to CME prescribed by §§445 and 447 and the special requirements attendant to initial renewal of licensure specified in §449, every physician seeking the renewal or reinstatement of licensure, to be effective on or after January 1, 2002, shall annually evidence and document, upon forms supplied by the board, the successful completion of not less than 20 hours of board approved CME.

MANDATORY CME REQUIREMENT FOR INITIAL CDS PRESCRIBERSS

As a condition of medical license renewal, Initial Licensees with a Controlled Dangerous Substance (CDS) license in Louisiana are required to complete at least three (3) hours of Board approved continuing medical education (CME) that includes the following topics: best practices for the prescribing of CDS, drug diversion training, appropriate treatment for addiction, and the treatment of chronic pain. This course is a one-time requirement under current law and will be considered a part of, and not in addition to, the prescriber's annual CME requirement. Initial licensees must fulfill the requirement upon the first medical license renewal after obtaining a CDS license.

What This Means For You:

As a condition of medical license renewal, Initial Licensees with a CDS license must complete a one-time requirement of three (3) hours of continuing medical education on best practices for prescribing controlled substances, chronic pain, diversion and addiction upon the first medical license renewal after obtaining a CDS license. For verification on Board approved courses, see https://www.lsbme.la.gov/content/board-approved-cme-courses-cds-requirements

COMPLETION DEADLINE:

Prior to 2021 Medical License Renewal

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ABOUT US

For more than 51 years InforMed has been providing high-level education activities to physicians and other health care 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 Louisiana Medical Professionals,

InforMed is pleased to offer this collection of CME activities for physicians that are licensed by the state of Louisiana. The uniquely tailored curriculum is customized to the educational needs of the Louisiana 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 Louisiana State Board of Medical Examiners. Licensees who complete this program optimize their learning path while satisfying professional credentialing requirements for three (3) hours on best practices for the prescribing of controlled substances, chronic pain, diversion and addiction. 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.

-InforMed CME Team

COMPLETION INSTRUCTIONS

- **ONLINE:** Visit LAINT.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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Inquiries related to any part of the program or associated materials including, but not limited to, interpretation of any ACCME, AMA, ABMS Specialty Boards, FDA, federal, state, and/or regulatory agency standards and statues may be submitted in writing to: Legal Compliance and Rulings, 1015 Atlantic Boulevard #301, Jacksonville, FL 32233

BEST PRACTICES FOR PRESCRIBING CONTROLLED SUBSTANCES

COURSE DATES:	MAXIMUM CREDITS:	FORMAT:
Release Date: 12/2018 Review Date: 12/2020 Exp. Date: 12/2022	*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 prescribed controlled substances.

COURSE OBJECTIVE

The purpose of this course is to educate prescribers on best practices for the safe prescribing of controlled substances, including opioid analgesics. The course focuses on regulatory and legal framework, current best practices for prescribing controlled substances, pharmacologic (non-opioid and opioid analgesics) and non-pharmacologic therapies for pain management, diversion and treatment of substance use disorders.

HOW TO RECEIVE CREDIT:

- Read the course materials
- Complete the self-assessment questions at the end. A score of 80% 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, role, and need for the Controlled Substances Act (CSA) as it relates to clinical practice.
2. Explain the similarities and differences between the five (5) DEA schedules for controlled substances.
3. Describe the key steps recommended for the responsible prescribing of controlled substances.
4. Describe pharmacological treatment options for treating pain, anxiety disorder, insomnia, narcolepsy, and attention-deficit hyperactivity disorder.
5. Describe the fundamental concepts of pain management, including definitions and mechanisms of pain.
6. Identify the range of therapeutic options for managing pain, including non-pharmacologic approaches and pharmacologic (non-opioid and opioid analgesics) therapies.
7. 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.
8. Describe how to safely and effectively manage patients on opioid analgesics in the acute and chronic pain settings, including assessing, initiating therapy, titrating, ongoing and discontinuing use.
9. Describe at least four (4) practices clinicians can use to minimize diversion of controlled substances.
10. Identify the six (6) approved pharmacotherapies for treating alcohol and opioid use disorders.

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

3

CONTROLLED SUBSTANCES

SPECIAL APPROVAL

This course is approved by the Louisiana State Board of Medical Examiners to satisfy the mandatory (3) three hour CME requirement on best practices for prescribing controlled substances, drug diversion, addiction treatment and treatment of chronic pain.

Initial Licensees with a CDS license in Louisiana must complete a one-time requirement of at least three (3) hours of Board approved CME on best practices for prescribing controlled substances, drug diversion, addiction treatment and treatment of chronic pain.

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:

- Melissa B. Weimer, DO, MCR, FASAM
- Stephen Braun
- Beth Dove
- Joseph J. McGurrin

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 Consumer Healthcare.

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

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. 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.[1] In 2017, the most recent data available at the time the writing of this monograph, an estimated 6 million Americans aged 12 and older misused a prescription drug at least once in the previous month, which is more than the number of Americans using cocaine, heroin, hallucinogens, and inhalants, combined [2] By drug category, this misuse translated into:

- 3.2 million people aged 12 and older misusing prescription opioid pain relievers within the past month, and 11.1 million people with prescription opioid misuse in the previous year
- 1.7 million people misusing prescription tranquilizers (e.g., benzodiazepines, muscle relaxants)
- 1.8 million people misusing prescription stimulants (e.g., methylphenidate, amphetamine)
- 400,000 people misusing prescription sedatives (sleep-aides, e.g., zolpidem)

In all, more than 6 million Americans are misusing prescription drugs (including opioids),.[3]

Data on the rates of prescription drug misuse in Louisiana differ from those available at the national level (and are more limited), but suggest similar concerns. Estimates based on the 2016-2017 Survey on Drug Use and Health and other databases show that in Louisiana in 2017:

- 307,000 people had a substance use disorder (any type)
- 158,000 people aged 12 and older misused prescription pain relievers and 27,000 had an opioid use disorder (OUD)
- 47,600 people died in 2017 from an opioid drug-related overdose (includes both prescription and non-prescription opioids), a 12.4% increase from the previous year[4]
- The age-adjusted overdose rate in Louisiana in 2017 was 24.5 per 100,000 persons, significantly higher than the national average of 21.7 per 100,000 persons[4]

Opioid analgesics are currently in the spotlight of both government and popular attention, nationally and in Louisiana, 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.

The United States has seen three successive waves of both legal and illegal opioid use associated with overdose deaths.[5] The first wave began in the 1990s and was due to steadily rising rates of prescription opioids. In 2010, the second wave began, characterized by sharply increasing deaths from heroin use that reached "epidemic" levels in 2011 as described by the Centers for Disease Control and Prevention (CDC).[6] The third wave began in 2013 with a 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.[7] Between 1999 and 2017, the CDC estimates that nearly 400,000 people in the United States died from such overdoses.

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."[10] 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.[10]

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.

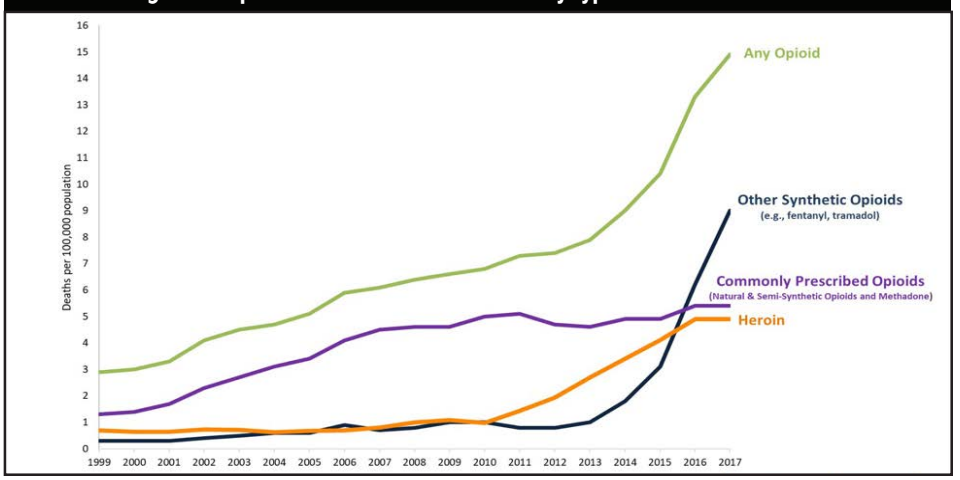
Unfortunately, many prescribers have had little or no education on substance use disorder issues, either in professional school or through recurrent training.[11] Furthermore, many prescribers are not educated or trained in prescribing practices that minimize risk with commonly misused medications. Less than half of the states have statutes or regulations that require or recommend education for prescribers of prescription pain medication.[12]

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.

Figure 1. Opioid-related overdose deaths by type in the United States[9]



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:[13]

- **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.
- **Acute pain.** Pain with an abrupt onset typically due to an obvious cause, such as an injury or surgical procedure. It generally has a short duration and usually lasts less than four weeks, improving with time.[14]
- **Chronic pain.** Pain 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.[15]
- **Chronic non-cancer pain.** Chronic pain arising from non-cancerous conditions or treatments for cancerous conditions.
- **Diversion.** The intentional transfer of a controlled substance from legitimate distribution and dispensing channels.
- Misuse/abuse. 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.
- **Recovery.** A general term associated with a wide range of addictive behaviors referring to a state in which a person has regained control over the substance or behavior (with or without medication assistance), and has returned to their previous level of personal, professional, and physical functioning.
- **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 pathophysiology of addiction involves a disorder of the brain's dopamine-mediated reward system which develops over time in response to chronically high levels of exposure to an addictive stimulus (chemical or behavioral).[16] The development of addiction typically occurs in five stages: first use, continued use, tolerance, dependence, and addiction, although the speed of progression through the stages varies markedly between individuals and in response to different kinds of addictive stimuli.[16] 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":[16]

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.[16]

The Controlled Substances Act

The federal government's first attempt at regulating medications was through the Harrison Act passed in 1914.[17] 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.[18] 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.[19]

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.[20]

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:[21]

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.[22])

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 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.

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.[21]

Table 1 lists some of the controlled substances that are commonly encountered and/or prescribed in clinical settings.

Table 1. Commonly-prescribed Controlled Substances[23]

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

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.[21] 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.[24] 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.

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.[25] 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.[26] Generally, if opioids are used at all, it is better to offer short-acting opioids PRN. Long-acting (LA) or extended-release (ER) 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.[27] 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.[28] 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.[29] 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.[2]

Side Effects

Binding of opioids to receptors in various body regions (e.g., CNS, GI tract) results in both therapeutic effects and side effects.

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)

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.[30] 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.[31] 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.[32] 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.[30]

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.[21] Because it can impair judgment and induce amnesia, particularly when combined with ethanol, flunitrazepam has been associated with sexual assault.[21]

Non-benzodiazepines are molecularly distinct from benzodiazepines, although they act on the same GABA receptor sites and produce similar sedative effects.[33] 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.[34] 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.

The diversion and abuse of carisoprodol and its adverse health effects appear to have dramatically increased in recent years.[35] 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.[30] 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.[30] Cocaine has limited medical uses as a topical local anesthetic and for reducing bleeding of mucous membranes in the mouth, throat, and nasal cavities.

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

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

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.[21] (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.[21] "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.[36]

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.[36]

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.[36]

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.

Louisiana and DEA Requirements for Prescribing Controlled Substances

Louisiana Requirements

In 2017 the Louisiana legislature passed Act 76, which revised and updated a set of requirements for prescribers related to controlled substances.[37] The major provisions:

- Prescribing practitioners applying for an initial controlled dangerous substance (CDS) license or renewing of such a license from the Louisiana Board of Pharmacy will be automatically registered as a participant in the PMP.
- A prescriber or his/her delegate must access and review a patient's record in the PMP prior to prescribing any opioid for the patient, and must access and review the record in the PMP at least every 90 days if the patient's course of treatment continues for more than 90 days.
- The requirement does not apply if:
  - The drug is prescribed to a hospice or any other patient diagnosed as terminally ill
  - The drug is prescribed or administered for the treatment of cancer-related chronic or intractable pain
  - The drug is ordered or administered to a patient being treated in a hospital
  - The PMP is not accessible or not functioning due to an electronic issue (however, the prescriber must check the PMP after electronic accessibility has been restored, and note the cause for the delay in the patient's chart
  - No more than a single 7-day supply of the drug is prescribed or administered to a patient

In addition, as a condition to license renewal, all practitioners with a CDS license are required to obtain 3 hours of continuing education pertaining to drug diversion training, best practices regarding prescribing of controlled substances, appropriate treatment for addiction, and any other matters pertaining to the prescribing of CDS that are deemed appropriate by the licensing board. The CME is a one-time requirement and the 3 credit hours are considered among, and not in addition to, those required by the licensing board for license renewal. The CME requirement can be waived if the practitioner submits a certification form developed by the licensing board, attesting that she/he has not prescribed, administered or dispensed a CDS during the entire applicable reporting period. This certification will be verified by the board through the PMP.

Act 76 makes professional licensing boards responsible for developing rules and enforcement of the new requirements.

DEA Requirements

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."[38] 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.[39] 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).[40] 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:[3]

- 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:[3]

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

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.[41] 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."[3]

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.[3] There are, however, recurring patterns that suggest inappropriate prescribing of controlled substances by a clinician:[3]

- 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.[3]

See Louisiana Administrative Code 46 "Professional and Occupational Standards", Part XLV "Medical Professions", Chapter 69 for state specific requirements on "Prescription, Dispensation, and Administration of Medications." (http://www.lsbme.la.gov/sites/default/files/documents/Rules/Individual%20Rules/Physicians%20Feb%202017.pdf)

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.[3] 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.[3]

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.[23] 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.[39] 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.[42] 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.[38]

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

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.[43]

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.[44] 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.[45]

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).[46]

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.

PLEASE SPEND THE ALLOTTED TIME ON CASE STUDY 1.

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.

Case Study Exercise 1

Instructions: Spend 15–20 minutes reading the case study below, reviewing the mental health assessment tools, and considering the questions that follow.

Harold, a well-dressed 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. He was diagnosed with metastatic prostate cancer 17 years ago, but 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."

Mental Health Assessment Tools

1. 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. One link to this screening tool: cqaimh.org/pdf/tool_phq2.pdf
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 if it is positive. It's easy to score and use and available at: integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf
3. Zung Self-Rating Depression Scale (Zung). This is a 20-item written questionnaire available at: mentalhealthministries.net/resources/flyers/zung_scale/zung_scale.pdf
4. Hamilton Depression Rating Scale (Ham-D). This is 21-item screening questionnaire. Scores <7 are normal. http://img.medscape.com/pi/emed/ckb/psychiatry/79926-1889862-1859039-2124408.pdf
5. Generalized Anxiety Disorder 7-item Scale (GAD) available at: integration.samhsa.gov/clinical-practice/GAD708.19.08Cartwright.pdf
6. Primary Care PTSD (PC-PTSD). This is a four-item screening test for post-traumatic stress disorder available at: integration.samhsa.gov/clinical-practice/PC-PTSD.pdf

Question 1: Which of these tools might be appropriate to use with Harold? _____

_____

Question 2: How might Harold's mental health issues interact with the management of his pain? _____

_____

Question 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 DSM-5 to diagnose his mental status; or asking questions aimed at assessing his level of physical and social functioning.) _____

_____

Medication adherence and other drug use can be assessed using regular urine drug screenings PMP queries, and pill counts (i.e., medication reconciliation). The American Medical Association defines "medication reconciliation" as "…making sense of a patient's medications and resolving conflicts between different sources of information to minimize harm and maximize therapeutic effects."[47]

PLEASE SPEND THE ALLOTTED TIME ON CASE STUDY EXERCISE 2.

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.

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: _____

Case Study Exercise 2 (Continued)

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? _____

_____

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 overdos
- 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.[48] 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.[49]

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.

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.

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.

Prescription Drug Monitoring Programs (PDMPs)

PDMPs are state-operated databases that collect information on dispensed medications. 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).[50]

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).

Louisiana's PDMP was established in 2006 to improve the state's ability to identify and inhibit the diversion of controlled substances and other drugs of concern in an efficient and cost-effective manner that would not interfere with the use of these drugs for legitimate purposes.[51]

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."[52]

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."[12]

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.

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.

See Louisiana Administrative Code 46 "Professional and Occupational Standards", Part XLV "Medical Professions", Chapter 69 "Prescription, Dispensation, and Administration of Medications", Subchapter C for state specific requirements on "Mandatory Access and Review of Prescription Monitoring Program Data." (http://www.lsbme.la.gov/sites/default/files/documents/Rules/Individual%20Rules/Physicians%20Feb%202017.pdf)

Act 82 (HB 192) establishes a seven-day limit on first-time prescriptions of opioids for acute pain, with a prescriber option to override the limit when medically necessary with a note in the patient's chart.

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.[10] 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.[42] 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.[2]

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.[29]

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

Overview of Pain Management

The practice of pain management requires an understanding of 2 competing public health problems: the high prevalence and burden of pain and the risks associated with opioid analgesics and other controlled substances often used to treat pain. All healthcare providers (HCPs) who treat pain with opioids are called upon to familiarize themselves with best practices to increase patient and societal safety while boosting patient outcomes for pain relief, function, and quality of life.

Close to 100 million Americans suffer from some type of ongoing pain.[90] In National Health Interview Survey Data, 25 million respondents reported living with daily pain, and more than 14 million reported the highest level of pain.[91] The higher the impact and severity of pain, the greater the costs in terms of disability, health status, quality of life, and use of health care services.[92]

Pain is even more common in military veterans, particularly those who have served in recent conflicts: 66% reported pain in the previous 3 months and 9% had the most severe pain.[93] Certain populations are more vulnerable than others to developing more severe chronic pain and disability, including women, older adults, and racial and ethnic minorities.[94] Members of some groups, including racial and ethnic minorities and children are also at risk for having their pain undertreated.[94]

Pain care is most effective when it combines multiple disciplines and utilizes a broad range of evidence-based pharmacologic and nonpharmacologic treatment options.[90,91] For acute pain and for some chronic pain, unresponsive to nonopioid therapies, opioids may form part of a customized treatment plan. Some patients report improved pain and quality of life with opioids.[96] However, opioids also bring well-documented risks that include misuse, abuse, opioid-use disorder (OUD), and overdose death. Approximately 11.5 million Americans, or 4.3 percent of the population, misused prescription opioids in 2016.[97] Furthermore, of 42,000 opioid-related deaths in 2016, 40% involved prescription opioids.[98]

HCPs must acquire the necessary knowledge to consider all available therapies and to create a comprehensive treatment plan, prescribing opioids only when the benefits outweigh the risks. When a trial of potentially long-term opioids is selected, HCPs should be better equipped to recognize and manage any adverse events that may arise during the course of opioid therapy.[94]

See Louisiana Administrative Code 46 "Professional and Occupational Standards", Part XLV "Medical Professions", Chapter 69 "Prescription, Dispensation, and Administration of Medications", Subchapter B for state specific requirements on "Medications Used in the Treatment of Non-Cancer-Related Chronic or Intractable Pain." (http://www.lsbme.la.gov/sites/default/files/documents/Rules/Individual%20Rules/Physicians%20Feb%202017.pdf)

Pain Definitions and Mechanisms

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[90] As such, pain is protective and essential for survival, serving as a useful warning signal that something has gone wrong. Pain is also a subjective experience with an emotional component. There are no precise clinical markers for pain, which is experienced by the individual as a constellation of biological, psychological, and social factors.

Pain varies by type and mechanism:[90]

- Acute pain has a sudden onset and expected short duration, though episodes may recur
- Chronic pain lasts longer than normal healing and is generally diagnosed after persisting from 3-6 months
- Nociceptive pain is the normal response to any type of stimulus that results in tissue damage
- Visceral pain is nociceptive pain that arises from the body's organs (may be cramping, throbbing, vague)
- Somatic pain, whether superficial or deep, is nociceptive pain that results from issues within the body's bone, joints, muscles, skin, or connective tissue (may be localized and stabbing, aching, throbbing)
- Neuropathic pain results from damage to or abnormal processing of the peripheral or central nervous system (CNS) (may be sharp, stabbing, burning, tingling, numb)
- Referred pain spreads beyond the initial injury site

Chronic pain's many possible causes include injuries, malignancies, diseases that flare up, medical treatments or surgeries, or inflammation that appears as a result of injury or chronic disease. Chronic pain may even occur in the absence of a defined injury or cause.

Ongoing pain can modify the CNS, through which pain is sensed, transmitted, modulated, and interpreted.[90] When the nociceptors, or sensory receptors, become sensitized, they discharge more frequently. In peripheral sensitization, this state of heightened neuron excitability occurs at the site where the pain impulse originated in the body; in central sensitization, it occurs in the spinal neurons, which begin to fire spontaneously, resulting in pain that intensifies and lasts far longer than the stimulus applied.[90] Sensitization can result in hyperalgesia, where response to pain-causing stimuli is intensified, and allodynia, a pain response to stimuli that normally are not painful.[90] Therefore, the resulting pain comes not just from an injury site but from neural impulses. The pathologies created by central sensitization can persist and continue to generate pain impulses indefinitely, far outlasting pain's usefulness as a warning signal.

Chronic pain may be primarily nociceptive, neuropathic, or have mixed nociceptive-neuropathic characteristics. Examples of nociceptive or inflammatory pain include postoperative pain, arthritis, mechanical low back pain, sickle cell crises, and pain from traumatic injuries. Causes of peripheral neuropathic pain include postherpetic neuralgia and diabetic neuropathy. Central neuropathic pain triggers include spinal cord injury, trigeminal neuralgia, and multiple sclerosis.

Creating a Treatment Plan

Acute pain is generally manageable with rest, over-the-counter (OTC) medications or a short course of stronger analgesics, and resolution of the underlying cause (e.g., trauma, surgery, illness). Prompt management of acute pain is necessary to prevent progression to a chronic state.

With chronic pain, it is essential to treat the cause of pain, whenever a cause can be diagnosed, in addition to managing the pain. When the pain is moderate-to-severe in intensity, it requires a biopsychosocial model of comprehensive treatment in recognition of its complex contributors.[90] The complexity of the pain experience involves emotions, attitudes, presence of confounding psychiatric and anxiety conditions, history of response to pain, current living conditions, and many other factors. The presence of a psychiatric condition does not mean the pain the patient is experiencing is not real. Chronic pain affects relationships, work, sleep, function, overall health, and quality of life. This complexity is why a comprehensive approach to pain management should factor in the many contributors from the biological, psychological, and social domains.[90] It is also why patients often respond better to a combination of therapeutic modalities rather than a unimodal medication regimen.

A number of guidelines have been developed by professional medical societies, states, and federal agencies to assist HCPs in setting and executing treatment plans for prescribing opioids for chronic pain.[15,92-95] Common recommendations include:

- Conduct a physical exam
- Collect pain history, medical history, and family/social history
- Consider all treatment options, weighing benefits and risks of opioid therapy, and prescribe opioids only when nonpharmacologic or nonopioid treatments are ineffective
- Obtain informed consent and implement pain treatment agreements
- Start patients on the lowest effective dose
- Conduct urine drug testing (UDT), when appropriate
- Check prescription drug monitoring programs (PDMPs) to identify past and present opioid prescriptions at initial assessment and during the monitoring phase
- Monitor pain and treatment progress with documentation, using greater vigilance at higher doses
- Use safe and effective methods for discontinuing opioids (e.g., tapering, making appropriate referrals to substance abuse treatment or other services)
- Pay close attention to drug-drug and drug-disease interactions
- Recognize special risks with fentanyl patches and methadone
- Titrate slowly and cautiously
- Consider using an opioid-specific risk assessment

The goals of treatment should be meaningful to the patient and contain pain relief and functional components.[15,95] Even patients with pain conditions or injuries that make complete cessation of pain unlikely can set goals such as sleeping through most nights, returning to work, walking a set distance, or participating more fully in family activities. The self-efficacy involved in collaborating on these goals can help patients gain greater control over their pain and their lives.

Informed consent is critical to a treatment plan containing a trial or continuation of opioid therapy.[15,94,96] Treatment plans should be revisited and adjusted frequently to ensure goals are being met and any adverse effects of therapy are addressed.

Nonpharmacologic Approaches

A number of nonpharmacologic and self-management treatment options are available, which may be used alone or as part of a comprehensive pain management plan. Evidence-based nonpharmacologic options for acute and chronic pain, include:[97]

- Acupuncture therapy
- Chiropractic and osteopathic manipulation
- Massage therapy
- Physical therapy
- Exercise
- Mind/body therapies (e.g., mindfulness-based-stress reduction, cognitive-behavioral therapy)
- Movement therapies (e.g., yoga, Tai chi)
- Injection treatments

Patients may find helpful a combination of approaches that include nutritional support, healthy lifestyle changes, patient education, sleep hygiene instruction, and relaxation and visualization techniques.

Interventional techniques range from the less invasive such as injections (nerve blocks, trigger point injections, epidural steroid injections, joint blocks), transcutaneous electrical nerve stimulation, and various approved medical devices to the more invasive such as surgeries, implantable spinal pumps, and implantable spinal electronic stimulators or peripheral nerve stimulators.

Rather than thinking of these treatments as "alternatives" to conventional treatment, HCPs are encouraged to review the evidence base[97] and consider a trial of 1 or more nonpharmacologic therapies. Unfortunately, barriers are common in obtaining insurance coverage and reimbursement for nonpharmacologic therapies, and access to trained professionals in these care options is sometimes limited.[93] The modalities of cognitive-behavioral therapy, physical therapy, certain injections, exercise and electrical stimulation are generally recognized and covered as having benefit for chronic pain.[97]

Less invasive measures for pain management should be considered first.[15] Education can be an effective means to patient self-management; for example, instruction in proper posture and movement techniques along with advice to remain active are recommended for the treatment of persistent low-back pain.

Nonopioid Pharmacologic Analgesic Therapy

Nonopioid pharmacologic treatments for pain include:

Acetaminophen (ACET) for pain without inflammation. All ACET products carry an FDA-required black box warning highlighting the potential for severe liver damage and potential for allergic reactions.[98] Dose levels from all medication sources should be evaluated to avoid exceeding the recommended daily dosage.

Nonsteroidal anti-inflammatory drugs (NSAIDs), which includes cyclooxygenase-2 (Cox-2) inhibitors, for pain and inflammation. Risks are elevated with NSAIDs for heart attack, stroke, gastrointestinal bleeding or perforation, and renal and cardiovascular abnormalities, particularly at higher doses and longer duration of use.[15] An FDA-required black box warning for all marketing NSAIDs highlights the potential for increased risk of cardiovascular events and serious, potentially life-threatening gastrointestinal bleeding associated with their use.

Skeletal muscle relaxants for pain and muscle spasm for short-term use. Sedation is a common adverse effect. Particular CNS risks are notable with carisoprodol (toxicity) and benzodiazepines (substance dependence and respiratory depression leading to overdose) when prescribed in combination with opioids.[97]

Antidepressants (serotonin and norepinephrine reuptake inhibitors [SNRIs] and tricyclics) used in low doses for insomnia and neuropathic pain. Depending on class, risks may include anticholinergic effects, sexual dysfunction, weight gain, emotional blunting, and suicidal thoughts.[97]

Anticonvulsants, such as gabapentin and pregabalin, have mild-to-moderate benefit for neuropathic pain and adverse effects that include drowsiness and cognitive slowing.[97]

Topical medications include lidocaine, ketamine, capsaicin, and anti-inflammatory drugs such as ketoprofen and diclofenac. Anti-inflammatory topicals are proven beneficial for musculoskeletal pain as is capsaicin for neuropathic pain.[97]

Many guidelines recommend NSAIDs and ACET as first-line therapies for low-back pain and osteoarthritis, and anticonvulsants and antidepressants as first- and second-line therapies for neuropathic pain with appropriate risk mitigation.[15]

Analgesic Effects of Opioids

Understanding the variety of opioid products, delivery systems, and formulations that are available to treat pain can assist HCPs in drug selection to maximize analgesia and minimize or prevent adverse effects. Opioids achieve an analgesic effect primarily by inhibiting nociceptive transmission in the CNS. They do this by binding to and activating receptors within the endogenous opioid system. Mu, kappa, and delta are the 3 primary opioid receptor types that mediate analgesia. Drugs that bind to these receptors are classified as full agonists, partial agonists, mixed agonist-antagonists, and antagonists (Table 4). Opioids used in clinical practice are typically full mu-agonists that bind selectively to the mu-opioid receptor. When an antagonist occupies the receptor, it displaces the agonist, and is associated with abstinence syndrome (withdrawal). Partial agonists, such as buprenorphine, have high receptor occupancy, some antagonistic effects, and low intrinsic activity at the site.

Table 4. Opioid Analgesic Classifications

Type	Generic Name	Notes/Cautions
Pure agonists	Codeine Dihydrocodeine Fentanyl Hydrocodone Hydromorphone Levorphanol Meperidine* Methadone Morphine Oxycodone Oxymorphone Propoxyphene	*Not recommended for long-term treatment or in patients with renal compromise due to toxicity risks
Agonist-antagonists	Partial agonist: Buprenorphine Mixed agonist-antagonists: Butorphanol Dezocine Nalbuphine Pentazocine	May produce abstinence with physical dependence
Pure antagonists	Naloxone Naltrexone	Administered to reverse opioid effects
Other	Tramadol Tapentadol	Dual action mu-agonist and serotonin–norepinephrine reuptake inhibitor Dual action mu-agonist and norepinephrine reuptake inhibitor

In addition to use in pain treatment, methadone and buprenorphine are used to treat OUD, a process known as medication-assisted treatment (MAT) when combined with behavioral therapy.[99] Kappa opioid receptor agonists (including levorphanol, pentazocine, and butorphanol) have been used clinically but are associated with side effects such as dysphoria and hallucinations.

Initiating Opioids: Acute Pain Setting

For acute pain, the therapeutic goal is to prescribe the lowest dose that controls pain for a duration that lasts only as long as the acute phase. Prescriptions beyond 3 days are usually unnecessary. Be aware that localities and states may have strict regulations governing maximum duration of prescriptions.

The most recent VA/DoD practice guideline recommends against utilizing Opioid Therapy for Acute Pain. However, there are certain situations in which opioids may be necessary therapy for acute pain, even when substantial risk factors exist. It is important to incorporate opioid risk mitigation strategies into opioid prescribing for acute pain. These strategies should include patient education, use of non-opioid adjunctive therapy, and structured reassessment of opioid risks and benefits for all on acute OT. Also, consider checking the PDMP and performing a UDT.

For those at higher risk of adverse events related to opioid therapy, the following strategies may help to decrease opioid-related overdose events and unintended long-term use: checking the PDMP, performing a UDT, placement in an inpatient setting or monitored environment, and/or providing OEND. Monitoring standards with administration of OT for acute pain vary depending on a number of factors including the setting, specifics of the painful insult, patient medical factors, and selected medication potency/dose/route of administration/adjunct selection.

VA/DoD practice guideline recommendation on Opioid Therapy for Acute Pain:

- Recommend alternatives to opioids for mild-to-moderate acute pain.
- Use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain.
- If take-home opioids are prescribed, we recommend that immediate-release opioids are used at the lowest effective dose with opioid therapy reassessment no later than 3-5 days to determine if adjustments or continuing opioid therapy is indicated.
- Patient education about opioid risks and alternatives to opioid therapy should be offered

Initiating Opioids: Chronic Pain Setting

Treatment of patients who have active cancer or who need palliative or end-of-life care is not addressed in this activity. For patients with chronic noncancer pain (CNCP) in the outpatient setting, opioids are not considered first-line therapy.[101,102]

The class of ER/LA opioids has some commonalities that limit their usage:[129,108]

- Not for use as needed
- Not for mild pain or pain that is not expected to persist for an extended duration
- Not for use to treat acute pain
- Not for use in opioid-naïve patients: tolerance is critical to safe use (see individual product PI for criteria for strengths, daily doses, special populations, and product-specific safety concerns)

The HCP may consider a trial of long-term opioid therapy (LTOT) as 1 therapeutic option if the patient's pain:[100]

- Is severe and ongoing or recurs frequently
- Diminishes function or quality of life
- Is unrelieved or likely to be unrelieved by nonopioid therapies

The HCP should consider the following questions:

- Do medical comorbidities increase risk of side effects?
- Do other therapies have better or equal evidence for the particular pain type and condition?
- Do reasonable alternatives to LTOT exist? Are they available?
- Do anticipated therapeutic benefits of LTOT outweigh known risks?
- Does thorough patient evaluation indicate the patient is likely to adhere to the treatment plan?

The patient's pain type and previous treatments tried should be evaluated to see if opioid therapy is likely to be effective. For example, one might first try an anticonvulsant for trigeminal neuralgia, a disease-modifying drug for rheumatoid arthritis, a corticosteroid for polymyalgia rheumatica, or various rescue and preventive medications for migraine and stress-related headache.[100] Opioids, if administered, are best when used at the lowest effective dose and combined with modalities from other disciplines.[100,102]

Prescribers should be knowledgeable about general characteristics, toxicities, and drug interactions for ER/LA opioid analgesic products. Additionally, clinicians should recognize specific characteristics of ER/LA opioid analgesic products they prescribe, including: Drug Substance, Formulation, Strength, Dosing Interval, Key Instructions, Specific Information About Conversion Between Products Where Available, Specific Drug Interactions, Use In Opioid-Tolerant Patients, Product-Specific Safety Concerns, And Relative Potency To Morphine.

For further detailed information, prescribers can refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

Assessing Patients in Pain

Initial patient evaluation includes taking a medical and pain history, performing a physical exam, and conducting appropriate diagnostic testing when indicated. The evaluation should include chief complaint, prior diagnostic findings, results and analyses of laboratory tests and screenings, all previous treatments tried, and comorbid conditions (including medical, psychiatric, mood and sleep disorders). One should obtain a complete history of current and past substance use and misuse to include prescription drugs, illegal substances, alcohol, and tobacco. Social history is also relevant to include employment, marital history, and family status.[93] Women should be screened for contraceptive use and pregnancy or breastfeeding status or intent.[15]

Pain is assessed by onset, location, intensity, quality, duration, radiation, and variations. Patients should be asked what relieves or increases the pain, how it affects their daily lives and functioning, and what goals they have for pain relief and improved function. A number of pain assessment tools are available to be incorporated into routine clinical practice. The Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) are sensitive, validated, and widely-used, quick tools to measure pain severity.[100] The Brief Pain Inventory (BPI) has good sensitivity, reliability, and validity for pain severity and interference-with-function items, including assessments of mood and sleep.[101,102] The McGill Pain Questionnaire (MPQ), also available as a short form, assesses additional pain descriptors (sensory, evaluative, and affective).[100] With good validity and reliability, the MPQ is useful for facilitating description of the subjective pain experience but requires a good vocabulary when self-administered. An instrument to assess how well patients cope with chronic pain is the Multidimensional Pain Inventory (MPI), which categorizes patients into 3 coping styles: Adaptive, Dysfunctional, and Interpersonally Distressed and has been validated for multiple chronic pain conditions.[103,104]

Patients also should be evaluated for psychosocial, psychiatric, and social factors that can impact pain, including anxiety, post-traumatic stress disorder (PTSD), and depressive symptoms or disorders. The 9-item Patient Health Questionnaire (PHQ-9) and its variations are brief, reliable, and valid measures to identify depression.[15,105] One PHQ-9 item addresses suicidal ideation, an important assessment for patients with chronic pain.[106] The Generalized Anxiety Disorder (GAD)-7 and GAD-2 are validated and recommended to assess for generalized, panic, and social anxiety disorders and PTSD.[15,107]

Additional helpful screening tools are the reliable and valid Beck Depression Inventory II (BDI-II) self-report measure of depression severity,[108] and the Beck Anxiety Inventory (BAI),[109] which emphasizes somatic components of anxiety.

Even more in-depth pain assessment is offered through newer systems such as the Stanford-developed and implemented Collaborative Health Outcomes Information Registry through the use of item banks that capture many physical, psychological, and social functioning domains.[110]

Clinicians can screen patients for their risk of (or presence of) a substance use disorder with the Screening, Brief Intervention and Referral to Treatment (SBIRT) evidence-based tool, which typically takes 5-10 minutes to administer.[111] SBIRT has been endorsed by the Substance Abuse and Mental Health Services Administration (SAMHSA).[112] SAMHSA recommends universal screening for substance use disorders, which includes OUD, with tools such as SBIRT because of the high prevalence of these disorders in patients visiting primary care settings. In contrast, universal screening with urine, blood, or oral fluid tests is not recommended in primary care.[112]

Other tools for universal substance abuse screening include:

- 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)

Risks and warnings with opioids

Even at prescribed doses, opioid analgesics carry the risks of misuse, abuse, OUD, respiratory depression, overdose, and death. Terminology related to opioid use and misuse is shown in Table 5. The risks apply to all brand-name and generic extended release/long-acting (ER/LA) and immediate-release (IR) opioids.[99,113] Opioid combination products containing acetaminophen also carry warnings of the potential for severe liver damage.[98] Particular care and increased monitoring are essential during opioid dose initiation, upward titration, rotation, and addition of other CNS-depressant medications. Studies show patients are particularly vulnerable to respiratory depression at these times.[114,115] In addition, patients may suffer harm that includes abstinence syndrome, increased pain, and distress if opioids are suddenly discontinued or tapered too rapidly. An FDA boxed warning details the risks of prescribing opioids and benzodiazepines together, a combination of medications that has increased in recent years but which is associated with extreme sleepiness, respiratory depression, coma, and death.[116]

Common adverse drug reactions with opioids include lightheadedness, dizziness, sedation, nausea and vomiting, drowsiness, mental clouding, constipation, hormonal deficiencies, pruritis, and myoclonus.[15]

The disease of OUD is diagnosed using DSM-5 criteria: A minimum of 2–3 criteria are required for a mild substance-use disorder (SUD) diagnosis, while 4–5 is moderate, and 6–7 is severe;[120] OUD is specified instead of SUD, if opioids are the drugs of abuse. Addiction, while not a DSM-5 diagnosis, is still a term that is used and generally describes a severe OUD. The presence of tolerance and physical dependence are not in themselves indicators that an OUD has developed.

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

Initial Dosing and Dose Titration

For outpatient chronic pain management, opioids are typically administrated through the oral, transmucosal, and transdermal routes. Each route has advantages and disadvantages and safety concerns, some of which are intrinsic to all opioids and some of which are specific the route.

Table 5. Definitions Related to Opioid Use and Misuse

Term	Definition
Tolerance[117]	A physiologic state of adaptation in which exposure to the opioid results in diminution of its effects over time In patients with "analgesic tolerance," increased doses of opioid are needed to maintain pain relief
Physical dependence[117]	A physiologic state characterized by abstinence syndrome (withdrawal) if treatment with an opioid is stopped or decreased abruptly, or if an antagonist is administered
Abuse[118]	The intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect
Misuse[118]	The intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse
Addiction[119]	Chronic disease characterized by compulsive, or uncontrollable, drug seeking and use despite harmful consequences and long-lasting changes in the brain
Criteria for Opioid-Use Disorders from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[120]*	1. Opioid taken in larger amounts or over a longer period than intended 2. Persistent desire or unsuccessful efforts to cut down or control opioid use 3. A lot of time spent obtaining, using, or recovering from the effects of the opioid 4. Craving or a strong desire to use opioids 5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home 6. Continued use despite persistent or recurring social or interpersonal problems caused or exacerbated by opioid use 7. Stopping or reducing important social, occupational, or recreational activities due to opioid use 8. Recurrent use of opioids in physically hazardous situations 9. Continued use despite knowledge of having persistent or recurrent physical or psychological problems cause or worsened by opioid use 10. Tolerance as defined by either a need for markedly increased amounts to achieve intoxication or desired effect or by markedly diminished effect with continued use of the same amount. (Does not apply when used appropriately under medical supervision) 11. Withdrawal manifesting as either characteristic syndrome or the substance is used to avoid withdrawal (Does not apply when used appropriately under medical supervision)

Case Study Exercise 3

Instructions: Spend 5 minutes reading the case study below and considering the questions that follow.

Woman, 28, presents with low-back pain of 2 months duration. Pain is intermittent and aching. Pain intensity is typically 5-10 VAS but spikes to 7-10 after shifts in the call center where she works. The pain came on suddenly without an instigating trauma. She has no radicular symptoms. The pain is helped by yoga stretching and occasional OTC ACET and worsened by periods of prolonged sitting. Her sleep is interrupted by the need to change position in the night, and she reports sleeping 2 uninterrupted hours on average before waking; 5 hours total sleep per night is usual. She awakes unrefreshed and feels her ability to cope with stress is suffering as a result. She has a husband and 3-year-old son but does not join them for dinner as she used to, because she feels the need to lie down in the evening from the pain and fatigue. She has a history of major depression (1 episode in college) and smokes 1 pack of cigarettes daily. She reports no recreational drug use and drinks beer only on the weekends.

On her initial visit, which of the following therapies would you be likely to discuss/recommend?

a. IR opioid plus muscle relaxant
b. ER opioid plus IR opioid for breakthrough pain
c. Exercise/physical therapy, option for standing desk, NSAID
d. Antidepressant for pain and benzodiazepine for insomnia

Commentary on Exercise 3: Nonpharmacologic remedies and treatment plans that address underlying causes are preferred. Trialing an NSAID that helps with inflammation, plus adding gentle movement therapies and addressing work-related triggers, may help the patient manage her pain. A CNS-depressant such as a benzodiazepine is not a first-line therapy for insomnia that appears to have an underlying cause (pain) that should be addressed.

Short-acting opioids (SAOs) are preferred and considered safer when initiating a therapeutic trial of opioids.[93] Commonly prescribed SAOs include IR morphine, hydromorphone, oxymorphone, codeine, fentanyl, hydrocodone, and oxycodone.[121] Codeine, hydrocodone, and oxycodone are also available in combination with ACET or an NSAID, which limit daily dose due to risk for liver and gastrointestinal toxic effects.[121] In pain management, IR opioids, are indicated for pain severe enough to need opioid treatment and for which nonopioid treatments are ineffective or not tolerated.[99] They have a short half-life and duration of action (typically 2 to 4 hours), and are often prescribed to take as needed every 4 to 6 hours.[99] Patients with no or limited exposure to opioids should be initiated at the lowest dose and titrated slowly to minimize adverse effects.[93]

If patients require long-term maintenance and pain is severe enough to require around-the-clock analgesia that is not adequately relieved by SAOs or other therapies, consider a transition to ER/LA opioids with scheduled dosing.[113] ER/LA opioids are not indicated for acute pain and are for use only in patients who are already tolerant to opioids, with rare exceptions.[122] It is critical also that HCPs be aware that all transdermal fentanyl and hydromorphone ER products are for use only in opioid-tolerant patients and never for acute or short-term pain.[122] Transmucosal IR fentanyl is also for use only in opioid-tolerant patients. Adult patients are considered opioid tolerant if they have received the following dosages of opioids (or equianalgesic dosages of other opioids) for at least 1 week:[15,122]

- 60 mg daily of oral morphine
- 25 mcg per hour of transdermal fentanyl
- 30 mg daily of oral oxycodone
- 8 mg daily of oral hydromorphone
- 25 mg daily of oral oxymorphone

Product information for individual formulations contain guidance on degree of opioid tolerance necessary for administration and minimum titration intervals.

Dose titration is individualized depending on efficacy, tolerability, and presence of adverse effects. Patients should be monitored carefully, particularly within 24 to 72 hours of opioid initiation or upward titration. Patients who require repeated dose escalations to achieve sufficient pain relief should be reevaluated for the cause, and the risk-to-harm benefit of LTOT should be reconsidered.[93]

Altering oral ER/LA opioids by cutting, chewing, or dissolving in liquids can release a potentially toxic dose of active ingredient.[122] Transdermal systems and buccal films should not be cut, torn, or damaged before use.

Methadone for pain presents special clinical challenges due to a long and variable half-life, risk for toxicity due to accumulation in plasma concentrations during the longer time (several days) necessary to achieve steady-state, and risk for cardiac toxicities due to prolongation of the QTc interval.[93,123,124] Methadone-related deaths have occurred in disproportionate numbers relative to the frequency with which it is prescribed for pain.[15] Methadone is only for patients whose severe pain is unrelieved by other opioids. Methadone administration requires close monitoring during initiation and dose changes, and caution in patients with heart disease or taking medications with concurrent QTc interval effects. If deemed necessary, methadone should be started at a very low dose (e.g., ≤15 mg/day in divided doses) and slowly titrated (e.g., by no more than 25%-50%, no more frequently than weekly.[93,123] Bear in mind pain relief from a methadone dose lasts only 4 to 8 hours, but methadone remains in the body much longer (8 to 59 hours).[124] Patients should be counseled never to exceed prescribed dose, and methadone doses are scheduled, not taken as needed. Practitioners without experience and knowledge of methadone should seek expert consultation before prescribing.[123] Most opioids fall into Category C, indicating evidence of potential harm to the fetus from animal studies. Oxycodone is an exception, listed as a Category B medication with no evidence of harm to the fetus from animal studies.[125] Codeine and tramadol should be avoided in breastfeeding women due to risks to the infant from ultra-rapid CYP2D6 metabolism in some women.[15] In CYP2D6 ultra-rapid metabolizers, codeine changes to morphine and tramadol to M1 faster than in other people, which can result in high and unsafe levels of morphine and M1 in blood and breast milk.[126]

Considerations with opioids in special populations

Women should be given information on the potential effects of LTOT for current or future pregnancies, including the risks of life-threatening neonatal opioid withdrawal syndrome (NOWS).[15] Babies born to women who are taking opioids are at risk for birth defects (including neural tube defects, congenital heart defects, and gastroschisis), preterm delivery, poor fetal growth, and stillbirth.[15]

During pregnancy, HCPs and patients together should carefully weigh risks and benefits when making decisions about whether to initiate opioid therapy.[15]

When caring for pregnant women who are taking opioids, HCPs should arrange for delivery at a facility prepared to evaluate and treat NOWS.[15] In pregnant women with OUD, the risk of opioid exposure from MAT should be discussed and balanced against the risk of untreated OUD, which might lead to illicit opioid use associated with outcomes such as low birth weight, preterm birth, or fetal death.[127]

Several states pain management guidelines recommend the following measures when treating women of child-bearing age:[128]

- Every woman with reproductive capacity should discuss with the HCP a method to prevent unintended pregnancy when initiated on opioids
- Agreement should be obtained to inform the HCP if the woman becomes or intends to become pregnant while taking opioids
- Women who plan to become pregnant should be counseled on the risks of opioid exposure to the fetus and referred to an obstetrician
- The obstetrician and HCP should work together to encourage compliance with chronic pain management and prenatal care
- All newly pregnant women should have a urine drug test administered by the appropriate women's health provider
- If a urine result is positive for unprescribed controlled substances or illicit drugs during a prenatal visit, the woman should have another upon admission for delivery to help identify the infant at risk for NOWS

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

Patients with renal and hepatic impairment need extra caution in initiation and titration of opioid doses and increased monitoring.[15] In patients with renal compromise, accumulation resulting in toxicity has been observed in case studies; monitoring for opioid toxicity and use of nonopioids when possible are advised.[129]

Avoid LTOT in children and adolescents for most chronic pain problems.[95] Accidental exposure to and ingestion of opioids can result in death.

Genetic and phenotypic variations influence how quickly or well individuals metabolize opioids and other drugs.[130] Medical conditions, including kidney and liver disease, also cause variations in opioid metabolism.[130] Pharmacogenetic testing is available to help guide clinical decision making. For example, the FDA has approved tests to determine whether a patient is a CYP2D6 ultra-rapid metabolizer.[126] However, little data exist to inform the practice of pain management, and these tests are not routinely performed.[131] Testing may help HCPs make individual treatment decisions while keeping in mind genetics is only one of many factors affecting drug metabolism and responses.

Older adults (≥65 years) require cautious opioid dosing and management as they may have numerous co-occurring medical problems with treatments that increase the risk for polypharmacy and harmful drug interactions.[93] Polypharmacy increases patient risk by complicating renal and hepatic physiology (i.e., pharmacodynamics/pharmacokinetic) which may, in turn, decrease the effectiveness of an analgesic, intensify the analgesic effect, or increase the potential for adverse events such as falls or cognitive clouding. In addition, prescription drug or other substance abuse may be difficult to spot, mimicking symptoms of common conditions such as dementia, diabetes, and depression. Initial doses should be 25–50% lower than in those who are younger.[95]

Cancer survivors should be evaluated for a recurrence or secondary malignancy with any new or worsening pain symptoms.[95]

Sleep disorders co-occur frequently with chronic pain. For patients with moderate or severe sleep-disordered breathing, avoid LTOT whenever possible.[15] Some clinicians recommend that all patients who are considered for LTOT receive a sleep study prior to therapy or when higher dosages are considered.[123]

For patients who experience a nonfatal opioid overdose during pain management, it is recommended to work to reduce opioid dose and discontinue opioids whenever possible.[15]

Ensure that the patient is optimally treated for depression and other mental health disorders: Consider using tricyclic or SNRI antidepressants for combined analgesic and antidepressant effects.[15]

Absolute contraindications for LTOT include:[94]

- Known hypersensitivity to active ingredients or other components of opioid analgesics
- Significant respiratory depression or compromise
- Acute or severe bronchial asthma
- Known or suspected paralytic ileus and gastrointestinal obstruction
- Evidence for or history of diversion of controlled substances (e.g., forged prescriptions, pharmacy robberies, selling own prescription drugs, theft of others' drugs)

The Department of Veterans Affairs/Department of Defense (VA/DoD) practice guideline lists concomitant use of benzodiazepines as a contraindication to initiating LTOT.[94]

Pharmacokinetics (PK) influence the bioavailability of a drug, the production and elimination of metabolites, and the activity of metabolic enzymes.[130] Most opioids are metabolized through the liver microsomal cytochrome P-450 (CYP) system with CYP2D6 or CYP3A4 being responsible for much metabolism of opioids and many other drugs. Certain clinical applications are relevant. Slow metabolizers of CYP2D6 may gain little benefit from codeine, for example. Opioids metabolized through the CYP450 system, including codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone, may have heightened or reduced CYP450-associated effects with drug combinations, while morphine, oxymorphone, and hydromorphone are not as prone to such interactions.[132]

Drug interactions and other safety issues

The risk of drug interactions with an opioid is determined largely by which enzyme systems metabolize the opioid.[130] Interactions with inhibitors or inducers of certain enzymes may produce clinically relevant effects.[130]

- Potential drug–drug interactions raise great concern when prescribing opioids as follows:[122]
- CNS-depressants including alcohol, benzodiazepines, sedatives, hypnotics, tranquilizers, and tricyclic antidepressants can potentiate sedation and respiratory depression caused by opioids.
- Alcohol exposure can rapidly release or increase drug level of some ER opioid formulations
- Combining opioids with monoamine oxidase inhibitors (MAOIs) increase respiratory depression effect; may cause serotonin syndrome with certain opioids
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone
- Initiating CYP 3A4 inhibitors or discontinuing CYP 3A4 inducers can result in higher than expected opioid blood levels leading to overdose

To prescribe safely, one should also comprehend a drug's effects within the body or pharmacodynamics, such as binding action to opioid and other receptors and the location of the binding action.[130] Essentially, all opioid drugs have similar pharmacodynamic actions, although individual response may vary. Both PK and PD contribute to the onset and duration of various effects, such as analgesia, as well as the vulnerability to toxicity.

Daily dosage thresholds are now common and may be part of state law. Some states have limits ranging between ≥50 morphine milligram equivalents (MME)/day to ≥90 MME/day. The CDC, as well as a consensus panel of the American Association of Pain Medicine, recommend prescribing opioids only if nonopioids are ineffective, exercising caution at any dose, prescribing the lowest effective dose, reassessing risk vs. benefit at ≥50 morphine milligram equivalents (MME)/day, avoiding increasing dosage to ≥90 MME/day or carefully considering rationale.[15,133] It must be reemphasized that these recommended ceiling doses do not remove the necessity of exercising caution at any dose or the importance of individualizing the dose. The 2016 CDC guidelines (and AAPM consensus statement) suggest that for most painful conditions (barring major surgery or trauma) a 3-day supply should be enough, although many factors must be taken into account (for example, some patients might live so far away from a health care facility or pharmacy that somewhat larger supplies might be justified).[52,133]

Medication errors may result from miscommunication, packaging design, confusion caused by similar drug names, and other sources.

Opioid Rotation

A patient who suffers inadequate analgesia or intolerable side effects from one opioid may benefit from rotation to a different opioid, because individual opioid response varies from one drug to another.[130] Because mu-agonists produce varied effects, switching a patient to a different drug may allow for pain control at lower doses. Care must be taken in switching to a different opioid, because tolerance to a particular opioid drug does not translate to tolerance to another – a concept known as incomplete cross-tolerance. Patients should be monitored especially closely during any dose or formulation changes.

Equianalgesic dosing tables, conversion charts, and calculators allow for the conversion of any opioid dose to the standard value of morphine, referred to as morphine milligram equivalents (MME) or morphine equivalent doses (MED). Equianalgesic dose tables have limitations in that supporting studies were conducted on single doses in patients with limited opioid exposure and did not incorporate needs for chronic dosing.[134]

When using equianalgesic dosing tables as a starting point for opioid rotation, HCPs are advised to reduce the dose (≥25% to 50% is advised, more with methadone) when converting to the new opioid.[93] A greater reduction is advised in patient who are older or medically frail. A 75% to 90% reduction[134] or considering the patient opioid naïve is advised for rotating to methadone followed by careful monitoring.[93] Conversions to transdermal routes of fentanyl and buprenorphine require special considerations: HCPs should closely follow instructions in the prescribing information.

Informed Consent and Treatment Agreements

Patients started on LTOT should be informed of the potential risks and benefits. The most serious risk with any opioid is respiratory depression leading to death. Patients who have never taken opioids or whose medications or doses will be changed should be counseled to expect short-lived or lasting sedation or other cognitive effects. In addition, it is recommended to include product-specific risks (such as dangers of chewing an ER formulation) in the informed consent document.

An informed consent form should be signed by the patient and retained in the medical record. Items recommended in informed consent include:[93,94,135]

- Potential risks and benefits of opioid therapy
- Risks of OUD, overdose, and death even at prescribed doses
- That evidence for benefit of opioids for LTOT in CNCP is limited
- Nonpharmacological and nonopioid therapeutic options for pain treatment
- Potential side effects (both short and long term) such as cognitive impairment and constipation
- The likelihood that tolerance and physical dependence will develop
- Risks of drug interactions and over-sedation
- Risks of impaired motor skills affecting driving, operating machinery, and other tasks
- Serious adverse effects
- Signs and symptoms of overdose
- Risks when combining opioids with other CNS-depressants, including benzodiazepines and alcohol
- The importance of disclosing all medications and supplements
- How to handle missed doses

Opioid treatment agreements (OTAs) that spell out patient and provider expectations and responsibilities are recommended by most opioid guidelines.[93,95]

Recommendations of what an OTA should contain include:[135]

- Treatment goals in terms of pain management, restoration of function, and safety
- Patient's responsibility for safe medication use (not taking more than prescribed; dangers of using in combination with alcohol, cannabis, or other substances like benzodiazepines; not altering pills)
- Instructions for secure storage and safe disposal
- Patient's responsibility to obtain prescribed opioids from only 1 clinician or practice
- Patient's responsibility of getting the prescriptions filled at only 1 pharmacy
- Patient's agreement to periodic drug testing
- Prescribing policies, including handling of early refills and replacement of lost or stolen medications
- Reasons for which drug therapy may be changed or discontinued, including violation of the treatment agreement
- Statement that treatment may be discontinued without agreement by the patient
- HCPs availability policy, including responsibility to make available a covering clinician to care for unforeseen problems and to prescribe scheduled refills
- Education of the patient that the complete elimination of pain should not be expected

Patients should be counseled never to share opioids with any other person. Leftover opioids in the household pose dangers to children and pets, who may ingest them accidentally. Opioids that are unsecured may be stolen by family members or visitors. Opioids should be stored in a locked area or safe that is not available or visible to family members or visitors.[93] Leftover opioids, including transdermal fentanyl patches, should not be placed in the trash but should be taken to an authorized drug take-back facility or, if one is not available, flushed down the toilet or washed down the drain immediately.[136] Call 1-800-882-9539 or visit the website (https://www.deadiversion.usdoj.gov/drug_disposal/index.html) of the Drug Enforcement Administration (DEA) for more information about drug disposal, National Prescription Drug Take-Back Day events, and local DEA-authorized collectors.

Naloxone Administration

Naloxone can be used to save lives during overdose, and its presence increases safety for the patient and others who live in or visit the home.[15] Take-home naloxone is recommended with the presence of opioid overdose risk factors, such as history of overdose, history of SUD, clinical depression, opioid dosages ≥50 MME/day, or concurrent benzodiazepine use[15] or with evidence of increased risk by other measures. Approved naloxone products have 3 delivery formulations. One is an injectable delivery system that requires professional training to administer. Two easily administered products are an auto-injection device that provides verbal instructions to the user once activated and a nasal spray that requires no assembly.

Patients given an automatic injection device or nasal spray should keep the item available at all times.[114] Naloxone administration can cause withdrawal symptoms, and people who have been administered naloxone should have follow-up medical care. Laws vary by state regarding immunity for physicians or laypeople administering naloxone and can be checked here: http://www.pdaps.org/datasets/laws-regulating-administration-of-naloxone-1501695139.

Signs of an opioid overdose include:[123,137]

- Small, constricted "pinpoint pupils"
- Falling asleep or loss of consciousness
- Slow, shallow breathing
- Choking or gurgling sounds
- Limp body
- Pale, blue, or cold skin
- Snoring heavily and cannot be awakened
- Periods of ataxic (irregular) or other sleep-disordered breathing
- Trouble breathing
- Dizziness, confusion or heart palpitations

Patients and their caregivers and other family members should be counseled to do the following if an opioid overdose is suspected:[137]

- Call 911 immediately
- Administer naloxone if available
- Try to keep the person awake and breathing
- Lay the person on his or her side to prevent choking
- Stay with him or her until emergency workers arrive

Examples of informed consent and agreement documents are available online from the New Hampshire Medical Society at https://www.nhms.org/content/examples-opioid-informed-consent-agreement. These may be combined into one document and adapted to the HCPs needs and preferences.

The FDA Patient Counseling Guide: What You Need to Know About Opioid Pain Medicines and product-specific Medication Guide should be given to patients, who, along with their caregivers, should be encouraged to read these materials. Prescribers may download a medication guide for patients at http://www.accessdata.fda.gov/scripts/cder/daf/ and the Patient Counseling Guide can be found at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_Analgesic_2018_09_18_Patient_Counseling_Guide.pdf.

Reporting adverse events

All suspected adverse events and reactions with opioids may be reported directly to the FDA's MedWatch Reporting System by calling 1-800-FDA-1088 (1-800-332-1088); by going online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm; or by mail using the Form FDA 3500 available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf.

Ongoing Management of Patients on Opioid Analgesics

Patients on long-term opioid therapy should be monitored regarding potential misuse and abuse as well as for therapeutic goals of pain relief and function. The CDC has issued a guideline stating that patients on opioid therapy should be reevaluated within 1-4 weeks of initiation or dosage change and every 3 months thereafter to ensure benefits outweigh risks.[15] Other guidance has recommended using risk stratification to set clinic visit frequency and other monitoring measures as determined by patient risk category (low, moderate, or high risk) during initial screening and clinical follow-up.[93] The clinical principle is that patients with more comorbidities or higher abuse risk require more stringent monitoring measures and more frequent follow-up than patients with less risk for harm.

HCPs should evaluate and document effects of LTOT on include analgesia, daily activities, adverse effects, aberrant drug-related behaviors, cognition, function, and quality of life. Tools available to assist with frequent reassessment and documentation include the Pain Assessment and Documentation Tool (PADT)[138] and the COMM.[139] Keep in mind patients may misuse opioids for various reasons that include misunderstanding of medical instructions, unauthorized self-medication of pain, mood, or sleep problems, wish to avoid withdrawal symptoms, desire for psychoactive reward such as euphoria, compulsive use due to OUD, and illegal diversion for financial gain.[140]

One monitoring tool that may be helpful is the "5 A's" created by the Federation of State Medical Boards.[141] This tool involves regular assessments of:

1. Activity
   a. What progress has been made toward functional goals such as sitting tolerance, standing tolerance, walking ability, and performance of activities of daily living?
2. Analgesia
   a. How does the patient rate the following in the past 24 hours on 0-10 scale (10 being worst pain possible): Average pain? Worst pain?
   b. How much relief have pain medications provided as a percentage of total pain (e.g., 10%, 50%, 75%, 100%?)
3. Adverse effects
   a. Has the patient had adverse effects such as constipation, nausea, dizziness, drowsiness?
4. Aberrant behaviors
   a. Has patient taken medications as prescribed?
   b. Has patient exhibited any problematic behaviors or signs of misuse/abuse, such as increased use of alcohol or other drugs, unsanctioned dose escalation, reports of lost prescriptions or frequent requests for early refills?
5. Affect
   a. Is pain affecting the patient's mood or causing any anxiety or depression?

Ongoing periodic monitoring should incorporate checks of the PDMP and UDT.[142] The recommended frequency for periodic review of PDMP data ranges from every prescription to every 3 months.[15] A consensus-based recommendation for UDT frequency is to test every patient at least 1 time annually and higher-risk patients from 2 to 3 times annually.[142] It is best to present UDT, PDMP data, and other monitoring measures to patients as a routine, consensual part of medical care using nonjudgmental language.

Results of a UDT are used to identify the presence of prescribed medications and the use of unauthorized prescription and illegal drugs. The UDT may also help guide clinical decisions, serving as alert to potential drug-drug interactions. The first step is generally immunoassay testing that can be done at the point of care (POC) and help quickly establish whether a new patient has recently ingested illegal drugs or other opioid and prescription drugs.[142] The immunoassay detects certain drug classes but typically cannot isolate specific opioids.

If results of a POC test are inconsistent with medical direction, the next step is a quantitative evaluation, usually via gas chromatography/mass spectrometry (GC/MS) technology or liquid chromatography dual mass spectrometry (LC/MS/MS). These tests are more specific than immunoassay and can detect actual drugs and their metabolites. Some laboratories offer definitive testing via LC-MS/MS that may be given as the initial test; however, most guidelines still suggest immunoassay ahead of confirmatory testing due to cost concerns.[142]

Healthcare providers should exercise caution in interpreting UDT results, recognizing limitations and taking care not to stigmatize patients but to base interpretation on objective results.[15] Limitations of UDT include:[142]

- Cross-reactivity with other drugs or substances
- Potential for false positives (e.g., poppy seeds positive for opiates)
- Potential for false negatives
- Variable drug metabolism
- Laboratory error

Unexpected results, such as the absence of prescribed medications that could indicate diversion, should be discussed with the patient and documented in the record along with plans to address the results.

In the presence of ongoing or severe ADRBs, HCPs should consider that patient suffering may be linked to OUD or other SUD or psychiatric disorders. Criteria of an OUD may be reviewed in Table 5.

Signs and symptoms seen in a clinical scenario include:[120]

- Taking opioids compulsively and long term for no legitimate medical purpose
- If pain is present, taking opioids in excess of prescription
- Obtaining opioids from unauthorized sources
- Falsifying or exaggerating medical problems to receive opioids
- Significant tolerance and physical dependence (also occurs in non-SUD patients)
- Conditioned responses of craving that persist after cessation

Other circumstances that may accompany OUD include:[120]

- History of drug-related crimes
- History of legal problems
- Marital problems, including divorce
- Unemployment and irregular employment

When an active SUD or a recent SUD history is present, HCPs should strongly consider referral to SUD specialists and pain specialists regarding pain management and/or tapering opioids and managing pain with nonopioid therapies.[15]

Discontinuing Opioids

Reasons to discontinue opioid therapy may include failure to achieve sufficient analgesia, intolerable side effects, resolution of pain, development of OUD, or repeated or egregious ADRBs.

Serious nonadherence to the treatment plan or other unsafe ADRBs include:[93]

- Repeatedly increasing dose without HCP knowledge
- Sharing medications
- Unapproved opioid use
- Use of illicit drugs
- Obtaining opioids from unauthorized sources
- Prescription forgery
- Multiple episodes of losing prescriptions
- Polysubstance abuse

Before initiating opioid therapy, HCPs should have an exit strategy in place to humanely taper opioids and treat pain or refer for treatment with alternatives to opioid therapy. In an outpatient setting, taper should be done to avoid opioid withdrawal in physically dependent patients. Approaches range from a slow 10% dose reduction per week to a more rapid 25% to 50% reduction every few days.[93] It may be medically risky to abruptly discontinue opioids in a physically dependent patient. Taper may be accomplished in a rehabilitation setting if the patient is unable to reduce opioid dose.

Consider the expert-consensus guidelines below:[94,123]

- Evaluate comorbidities, the patient's psychological condition, and other relevant factors before beginning the taper
- Educate the patient and family about the taper protocol
- When safety allows, consider a 5% to 20% reduction every 4 weeks. Individualize this schedule based on patient needs and symptoms. Some patients may tolerate a faster taper, while others may need to slower the dose adjustments to monthly rather than weekly
- Managing opioid abstinence syndrome if symptoms (e.g., nausea, diarrhea, muscle pain, myoclonus) occur, using nonopioid analgesics and adjuvant agents
- Referral for counseling or other support during the taper if there are significant behavioral issues
- For complicated withdrawal symptoms, refer the patient to a pain specialist or chemical dependency center

Referral should include, as indicated, treatment of OUD, which may include MAT, or management of psychiatric illnesses.[114] Diversion of opioids or other controlled substances is a contraindication for continuing opioid therapy.[94]

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.[149]

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, which can be used at any stage of treatment, including maintenance treatment, 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).[143] 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. (See Table 6 for a summary of medications used to treat alcohol and opioid use disorders [no medications are approved as of this writing to treat marijuana, stimulant, or other substance use disorders].)[144]

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.[145] 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.[146] 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.[147]

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.[147,148] 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.[144] 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.[144]

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.[144] 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.[144]

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.[144]

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.[149] 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.

Table 6: Pharmacotherapies for treating alcohol and opioid use disorders[144]				
Medication	**Use**	**Dosage Form**	**DEA Schedule***	**Application**
Buprenorphine-Naloxone	Opioid use disorder	Sublingual film**: 2mg/0.5mg, 4mg/1mg, 8mg/2mg, and 12mg/3mg Sublingual tablet: 1.4mg/0.36mg, 2mg/0.5mg, 2.9/0.71mg, 5.7mg/1.4mg, 8mg/2mg, 8.6mg/2.1mg, 11.4mg/2.9mg Buccal film: 2.1mg/0.3mg, 4.2mg/0.7mg, 6.3mg/1mg	CII	Used for detoxification or maintenance of abstinence for individuals aged 16 or older. Physicians who wish to prescribe buprenorphine, must obtain a waiver from SAMHSA and be issued an additional registration number by the U.S. Drug Enforcement Administration (DEA)
Buprenorphine Hydrochloride	Opioid use disorder	Sublingual tablet: 2mg, 4mg, 8mg, and 12mg	CIII	This formulation is indicated for treatment of opioid dependence and is preferred for induction. However, it is considered the preferred formulation for pregnant patients, patients with hepatic impairment, and patients with sensitivity to naloxone. It is also used for initiating treatment in patients transferring from methadone, in preference to products containing naloxone, because of the risk of precipitating withdrawal in these patients.
		Probuphine® implants: 80mgx4 implants for a total of 320mg		For those already stable on low to moderate dose buprenorphine. The administration of the implant dosage form requires specific training and must be surgically inserted and removed.
Methadone	Opioid use disorder	Tablet: 5mg, 10mg Tablet for suspension: 40mg Oral concentrate: 10mg/mL Oral solution: 5mg/5mL, 10mg/5mL Injection: 10mg/mL	CII	Methadone used for the treatment of opioid addiction in detoxification or maintenance programs shall be dispensed only by Opioid Treatment Programs (OTPs) certified by SAMHSA and approved by the designated state authority. Under federal regulations it can be used in persons underage 18 at the discretion of an OTP physician.
Naltrexone	Opioid use disorder; alcohol use disorder	Tablets: 25mg, 50mg, and 100mg Extended-release injectable suspension: 380mg/vial	Not Scheduled under the Controlled Substances Act	Provided by prescription; naltrexone blocks opioid receptors, reduces cravings, and diminishes the rewarding effects of alcohol and opioids. Extended- release injectable naltrexone is recommended to prevent relapse to opioids or alcohol. The prescriber need not be a physician, but must be licensed and authorized to prescribe by the state.
Acamprosate	Alcohol use disorder	Delayed-release tablet: 333mg	Not Scheduled under the Controlled Substances Act	Provided by prescription; acamprosate is used in the maintenance of alcohol abstinence. The prescriber need not be a physician, but must be licensed and authorized to prescribe by the state
Disulfiram	Alcohol use disorder	Tablet: 250mg, 500mg	Not Scheduled under the Controlled Substances Act	When taken in combination with alcohol, disulfiram causes severe physical reactions, including nausea, flushing, and heart palpitations. The knowledge that such a reaction is likely if alcohol is consumed acts as a deterrent to drinking

Notes: **This dosage form may be used via sublingual or buccal routes of administration; sublingual means placed under the tongue, buccal means applied to the buccal area (in the cheek). Source: Adapted from Lee et al., (2015).120

Approved for clinical use in October 2002 by the FDA, buprenorphine represents the latest advance in MAT.[149] 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.[149] 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:

- 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:[149]

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 > 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.

Preventing Diversion

The prescribing of opioids and other controlled substances brings with it the risk for diversion, which is the act of removing the medication from its intended and lawful use. Diversion is associated with increased harms from illicit use as well as increased costs, to patients and society. It is estimated that the diversion of controlled prescription drugs and subsequent abuse costs both public and private medical insurers $72.5 billion each year.[150] Commonly-diverted drugs include the opioids oxycodone, hydrocodone, and methadone, the central nervous system depressants butalbital, diazepam, and alprazolam, and the stimulants methylphenidate and amphetamine.[151] To be lawful, the prescribing of controlled substances, including opioids, must occur for a legitimate medical purpose in the usual course of professional practice.[152] The responsibility of the prescribing clinician includes reasonable measures to prevent abuse and diversion. Because diversion poses risks for patients, health care workers and other facility employees, and the public at large, it is important for prescribing clinicians to remain alert to signals and address them. Physicians can report lost or missing drugs directly to the DEA via an online system (available at: https://apps2.deadiversion.usdoj.gov/TLR) or by phone: 800-882-9539.

Under no circumstances may a clinician prescribe an opioid or other controlled substance with the knowledge that the medication will be diverted. Drug diversion is a crime with serious consequences that may occur in a variety of settings and at any point along the drug's supply chain.[153] Systemically, reducing diversion requires cooperation from multiple stakeholders, including government agencies, state legislators, pharmaceutical retailers, physicians and other clinicians, patients, pharmacists, and pharmaceutical companies.[154]

In hospital and acute care settings

Opioids are frequently left over from surgeries, trauma treatments, and other acute pain treatment clinical scenarios.[155,156] From 33–75% of opioids prescribed after shoulder surgery remain unused, and half of prescribed opioids remain unused after outpatient dental surgery.[154] Many people save opioids in the event they may need them in the future, frequently storing the medications in unlocked locations in the home.[154] These opioids and other controlled substances, which linger in medicine cabinets, can then become a significant source for diversion. The National Survey on Drug Use and Health reported that 60% of adults who misused opioids did not have a prescription, and 41% obtained their most recent misused opioids for free from friends or relatives.[157]

The CDC has proposed certain prescribing durations for episodes of surgical or other acute pain treatment to reduce the quantity of unused opioids. The CDC guideline states the following:[15]

- When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of IR 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 7 days will rarely be needed.

Patients should be counseled never to share opioids with any other person and to store opioids in a locked area away from other family members and visitors.[93] Leftover opioids, including transdermal fentanyl patches, should not be placed in the trash but should be taken to an authorized drug take-back facility or, if one is not available, flushed down the toilet or washed down the drain immediately.[136] More information about drug disposal and national drug take-back events is available by calling 1-800-882-9539 or visiting the website (https://www.deadiversion.usdoj.gov/drug_disposal/index.html) of the Drug Enforcement Administration.

In clinicians' offices

Opioids are the most diverted of controlled substances, and most diversion of opioids occurs in outpatient settings.[153] Other drug classes with high diversion potential include hallucinogens, stimulants, anabolic steroids, and other CNS depressants.

Diversion by patients or persons posing as patients can take the form of visiting multiple providers to receive prescriptions, drug theft, prescription pad theft and forgery, and stealing prescription drugs. Any formulation may be misused or diverted: Extended-release (ER) opioids contain a higher dose per unit, which makes them attractive to manipulate and abuse; however, immediate-release (IR) opioids are more frequently prescribed and widely available and are generally preferred by nonmedical users.[154]

Clinical practices to minimize diversion include the following:[158]

- Caution when prescribing to patients who request combinations of drugs that may enhance effects, such as opioids with benzodiazepines
- Thorough documentation when prescribing or choosing not to prescribe opioids
- Keeping a DEA registrant or license number confidential unless disclosure is required
- Protecting access to prescription pads
- Ensuring that prescriptions are written clearly to minimize the potential for forgery
- Moving to electronic prescribing so that paper prescriptions are not required
- Adhering to strict refill policies and educating office staff
- Using PDMPs to monitor new patients and on refilling or adding new medications
- Referring patients with extensive pain management or prescription needs to specialists in relevant fields
- Collaborating with pharmacy benefit managers and managed care plans that seek to determine medical necessity of prescriptions

Generally speaking, risk mitigation measures to prevent nonmedical or other problematic opioid use by the patient are also helpful in determining whether a patient -- or a person posing as a patient -- is diverting controlled substances. These measures include opioid treatment agreements to lay out consequences of illegal behavior and initial, random, and ongoing checks of the state PDMP and UDT as appropriate. Diversion is one possible explanation if UDT results show the prescribed medications are not present. One should bear in mind, however, that the absence of the prescribed medication is not in itself proof of diversion (or hoarding for later use) but is one possible explanation that should be considered in context with other clinical signs. When diversion has occurred, immediate discharge from care is warranted.[94]

By facility health care workers

Unfortunately, the diversion of opioids by health care workers from their places of employment is not uncommon. A single provider may have multiple opportunities to divert drugs when procuring them from storage, preparing or administering them, and disposing of drug waste. Theft of patients' medication is one form of health care worker diversion. Another is tampering or replacing the patient's intended medication with another substance in order to use (i.e., inject) the patients' medication for themselves. Tampering is particularly dangerous and includes the risk the patient may be exposed to infections.

The risks are grave for patient trust and treatment and for clinic employee safety. Yet physicians and other clinicians rarely report their colleagues for suspected diversion or even impairment they directly observe.[153] Reasons include fear of retribution, belief that the issue is being addressed by someone else, and fear that no action will come of the report.[153]

The best way for facilities to respond is to have clear policies and procedures in place to quickly identify diversion and intervene.[153] Possibilities include urine drug screening and agreement to comply with diversion prevention policies prior to hiring in addition to ongoing random or "for cause" testing. Newly hired facility workers should receive education to prevent diversion, and that education should be ongoing. Mandatory reporting procedures and methods of surveillance, including checks of prescribing records and video surveillance, should be in place. It is important to check relevant laws in the state of practice as some states require that diversion of controlled substances be reported to federal authorities and result in loss of license to practice medicine.

Certain signs should alert supervisors to the possibility that diversion may be occurring, for example:[159]

- Removing controlled substances without a doctor's order
- Removing controlled substances for patients "not assigned" to them
- Removing controlled substances for patients that have been discharged
- Removing controlled substances and not documenting them
- Pulling excessive quantities of as-needed medication compared to other health care workers assigned to the patient
- Exhibiting discrepancies in inventory on a regular basis
- Pulling out controlled substances in lower dosages in order to obtain more pills when the exact dosage is available
- Pulling out larger dosages of injectable medications to obtain more waste
- Continuing patient complaints of pain, despite documented administration of pain medications
- Falsifying records and failing to document waste
- Removing as-needed medications too frequently, for example pulling every 2 hours when the order is for every 4 hours

Staff members other than health care workers may also divert medications. Support staff employees who may be diverting controlled substances may be spotted in areas where they are not unauthorized, may unnecessarily touch syringes, may stay late when their services are unnecessary, and may always volunteer to help or to dispose of waste.[159] If health care workers or support staff are impaired, they may appear sleepy, exhibit personality changes, commit multiple errors or be unable to perform routine tasks, take excessive sick leave or extended breaks, and be the target of multiple patients complaints.[159]

To effectively combat diversion, cooperation is necessary across multiple teams and facility divisions. The Mayo Clinic has laid out the following set of recommended steps when diversion in the workplace is suspected or identified:[153]

- Secure whatever evidence is available
- Initiate drug testing
- Initiate a discussion with the employee's supervisor
- Review of any records documenting handling of controlled substances
- Institute additional surveillance if necessary
- Initiate recurring meetings of a drug diversion response team to review findings
- Quickly remove from patient care any employee found to have diverted controlled substances
- Quickly close the case of any employee determined not to have diverted controlled substances
- Report findings to the Drug Enforcement Administration, the state pharmacy board, and local law enforcement

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.[160] (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.[25] 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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BEST PRACTICES FOR PRESCRIBING CONTROLLED SUBSTANCES

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 80% or better to receive a Certificate of completion.

1. **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%

2. **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

3. **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

4. **Drugs in which schedule are deemed to have a high potential for abuse or dependence but also have a currently accepted medical use in the US?**
   A. I
   B. II
   C. III
   D. IV

5. **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.

6. **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

7. **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

8. **If a physician is filling in for another physician in another state as part of a locum tenens arrangement, the substitute physician can legally prescribe controlled substances as long as he or she is legitimately registered with the DEA in his or her home state.**
   A. True
   B. False

9. **In an emergency, a prescriber may phone or electronically submit a prescription for a Schedule II drug to a pharmacy, but must follow up with a written prescription within 7 days.**
   A. True
   B. False

10. **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

11. **Nonpharmacologic therapies for pain treatment:**
    A. Are most effective when combined with opioid therapy
    B. Are usually covered by insurance
    C. Are encouraged as part of a comprehensive pain treatment plan
    D. Are less effective than nonopioid pharmacologic therapies

12. **Increased monitoring of patient response is essential during opioid dose initiation, upward titration, rotation, and addition of other central-nervous system depressants because:**
    A. Constipation is more common during these times
    B. Pain control is often inadequate
    C. Risk for respiratory depression is heightened
    D. Substance-use disorder is an expected outcome

13. **For which of the following pain conditions are ER/LA opioids indicated?**
    A. Acute or postoperative pain that does not resolve after 1 week
    B. As needed for severe headache or migraine pain
    C. Severe chronic pain as a first-line therapy
    D. For pain severe enough to require daily, around-the-clock, long-term analgesia for which alternative treatment options are inadequate

14. **Which of the following is true of potential drug-drug interactions with opioids?**
    A. Monoamine oxidase inhibitors are preferred antidepressants in combination with opioids
    B. Central-nervous system depressants can potentiate the respiratory depression effects of opioids
    C. Initiation of a CYP 3A4 inhibitor can result in lower blood levels of opioids
    D. Pharmacokinetic, but not pharmacodynamic, effects contribute to the onset and duration of opioid analgesia

15. **Name one (1) way patients should be monitored for adherence to medical direction during long-term opioid therapy:**
    A. Periodically check prescription drug monitoring programs
    B. Perform laboratory testing of triglycerides
    C. Document that physical dependence has not developed
    D. Periodically warn that medical marijuana use is prohibited during long-term opioid therapy

16. **Which of the following is one (1) indication for take-home naloxone with opioid prescription?**
    A. Family history of alcohol use disorder
    B. History of opioid overdose
    C. Opioid dosages ≥20 MME/day
    D. Co-prescription of a tricyclic antidepressant

17. **Urine drug testing as a monitoring measure can tell the clinician which of the following:**
    A. The types and dosages of opioids ingested by the patient
    B. Whether the patient has an opioid-use disorder
    C. Whether prescribed medications are present at the point of testing
    D. Whether the patient has been "doctor shopping"

18. **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

19. **Which of the following is NOT a practice that clinicians can use to minimize diversion of controlled substances?**
    A. Keeping DEA registrant or license number confidential
    B. Implement mandatory urine drug testing for all patients prescribed a controlled substance
    C. Protecting access to prescription pads
    D. Using PDMPs on refilling or adding new controlled substance prescription

20. **Acamprosate is a medication that can be used in the treatment of:**
    A. Marijuana use disorder
    B. Opioid use disorder
    C. Cocaine use disorder
    D. Alcohol use disorder

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LICENSE NUMBER FORMATS:

Allopathic Physician (MD):
30 followed by 4 digits (Ex: 301234) or
MD. followed by 6 digits (Ex: MD.123456)

Osteopathic Physician (DO):
30 followed by 4 digits (Ex: 301234) or
DO. followed by 6 digits (Ex: DO.123456)

DATA REPORTING: Federal, State, and Regulatory Agencies require disclosure of data reporting to all course participants. InforMed abides by each entity's requirements for data reporting to attest compliance on your behalf. Reported data is governed by each entity's confidentiality policy. To report compliance on your behalf, it's mandatory that you must achieve a passing score and accurately fill out the learner information, activity and program evaluation, and the 90-day follow up survey. Failure to accurately provide this information may result in your data being non-reportable and subject to actions by these entities.

Turn in information online or by following these easy steps:

1. Complete the customer information, self-assessment & activity evaluations on the next page.
2. Tear out the page.
3. Mail the form in the self-addressed envelope or fax.

Phone: 1-800-237-6999 ● Fax: 1-800-647-1356

LEARNER RECORDS: ANSWER SHEET & PAYMENT INFO

LOUISIANA INITIAL MEDICAL LICENSURE PROGRAM

To Receive Credit: Please ensure information entered matches the information on file with the Louisiana Medical Examiners Board. Please write legibly; failure to accurately provide this information may result in your data being non-reportable.

FIRST NAME:

LAST NAME:

EMAIL ADDRESS:

PHONE NUMBER:

LICENSE TYPE/DEGREE: (MD, DO and PA)

LICENSE STATE: (abbr.)

LICENSE NUMBER:

LICENSE EXPIRATION DATE: (MM / DD / YYYY)

MAILING ADDRESS:

CITY:

STATE: (abbr.)

ZIP CODE:

MARK ONE ANSWER PER QUESTION

BEST PRACTICES FOR PRESCRIBING CONTROLLED SUBSTANCES (PG. 36-37)

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	16.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	17.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ			18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ			19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ			20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

$50.00

PROGRAM PRICE

CHECK:

☐ CHECK ENCLOSED MADE PAYABLE TO INFORMED

OR

CREDIT CARD:

☐ VISA ☐ ☐ AMEX ☐ DISCOVER

NAME ON CARD:

TOTAL COST:

CARD NUMBER:

SECURITY CODE:

EXPIRATION DATE: /

ZIP CODE:

PROGRAM CODE: LAINT3CME

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Phone: 1-800-237-6999 ● Fax: 1-800-647-1356

LEARNER RECORDS: EVALUATION

You must complete the program evaluation and applicable activity evaluation(s) in order to earn *AMA PRA Category 1 Credit™*

For each of the objectives determine if the activity increased your: **A** Competence **B** Performance **C** Outcome **D** No Change

COURSE 1 - BEST PRACTICES FOR PRESCRIBING CONTROLLED SUBSTANCES:

		A	B	C	D
1.	Interpret regulatory and legal framework for prescribing controlled substances	◯	◯	◯	◯
2.	Explain best practices for prescribing controlled substances	◯	◯	◯	◯
3.	Assess non-pharmacological, non-opioid and opioid analgesics therapies in comprehensive pain plan for patient	◯	◯	◯	◯
4.	Initiate, manage and discontinue use of opioid analgesics	◯	◯	◯	◯
5.	Respond to addiction treatment and diversion	◯	◯	◯	◯

6. Please identify a specific change, if any, you will make in your practice related to safe prescribing of controlled substances?

_____

_____

7. What do you see as a barrier to making these changes?

_____

_____

OVERALL PROGRAM:

		Yes	No	If no, please explain:
8.	The program was balanced, objective & scientifically valid	◯	◯	_____
9.	Do you feel the program was scientifically sound & free of commercial bias or influence?	◯	◯	_____

10. How can this program be improved? _____

_____

11. Based on your educational needs, please provide us with suggestions for future program topics & formats. _____

_____

PROGRAM CODE: LAINT3CME

CUSTOMER SERVICE

We maintain a fully-staffed educational service center that course participants can contact Monday through Friday, 8:30 AM to 5:00 PM (EST) by calling toll-free at 1-800-237-6999. You can speak directly with our educational support personnel to request course materials, have tests graded, receive interactive training and interpretation of course materials, request duplicate certificates and resolve problems.

EMAIL

support@cme.edu

MAIL

1015 Atlantic Blvd #301
Jacksonville, FL 32233

PHONE/FAX

P: 1-800-237-6999
F: 1-800-647-1356

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LOUISIANA INITIAL MEDICAL LICENSURE PROGRAM

SATISFIES MANDATORY CME ON CONTROLLED SUBSTANCES

PROGRAM INCLUDES:

BOARD APPROVED

3

HOURS

*Controlled Substances, Chronic Pain, Diversion & Addiction**

***Mandatory Board Approved CME Required for Authorized Prescribers**

LAINT.CME.EDU

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