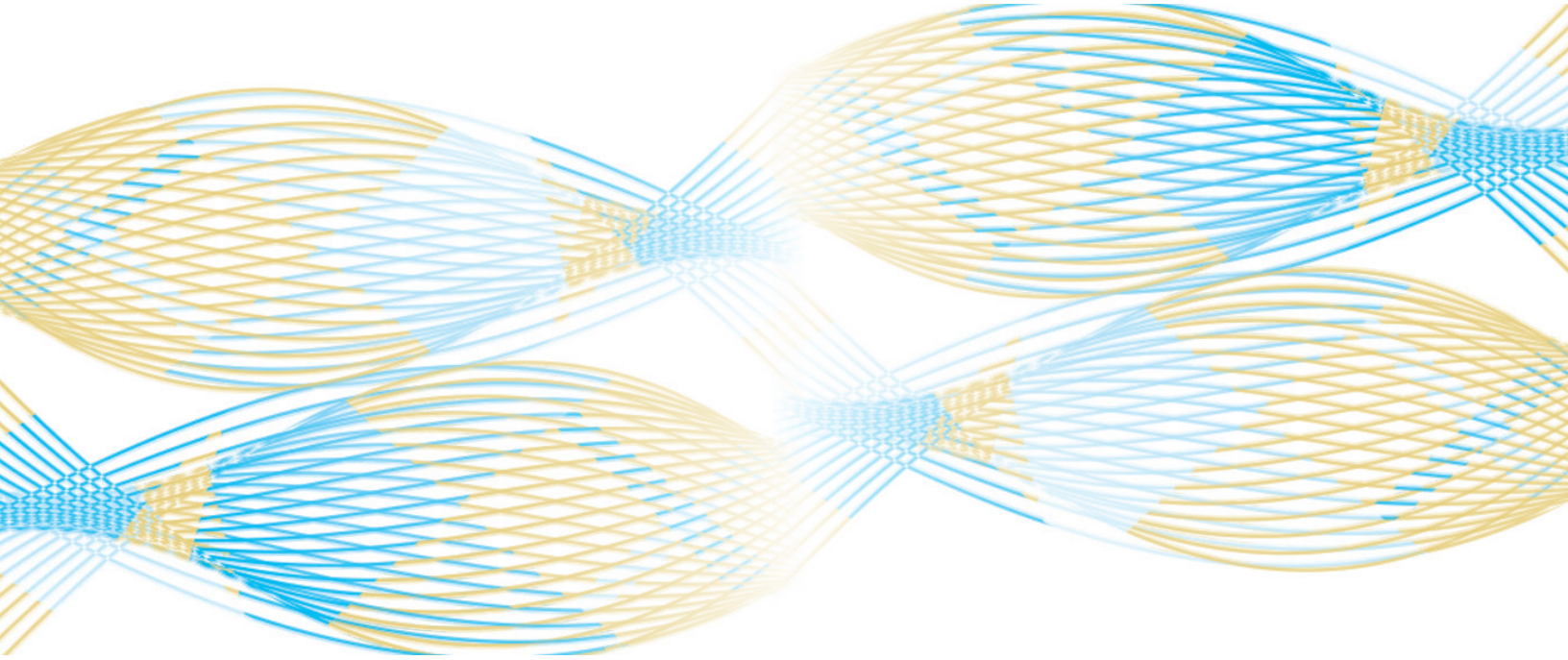
SoonerCare
Oklahoma Health Care Authority

PAIN MANAGEMENT PROGRAM



Oklahoma HealthCare Authority

DISCLAIMER

This toolkit comprises publicly available resources that the Oklahoma Health Care Authority (OHCA) has compiled for the convenience of our providers. It is intended to serve as a starting point for providers in the development of their own protocols for use in treating chronic pain patients. The resources provided herein are not exhaustive. Providers are encouraged to review additional resources and to contact chronic pain professionals for further assistance in developing their own practices. Inclusion of a resource does not mean OHCA endorses the entity that created the material. This toolkit is also not a guarantee of payment by the OHCA. This means that if a provider follows a protocol recommended by an included resource, it is not guaranteed that the services will be paid for by OHCA.

For questions or comments regarding this toolkit, please contact: MD-DDSInquires@okhca.org. Remember, this email address is for questions and comments only, please do not send in patient-specific information or questions regarding billing.

This ToolKit has been personalized for Dr. _____

Oklahoma HealthCare Authority

Telligen®

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Telligen®

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EXAMPLE ONLY

*These components have been taken from various research articles from various academic/research institutions.

Example

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EXAMPLE ONLY

*These components have been taken from various research articles from various academic/research institutions.

Example

Amended 12/01/2015

*OKLAHOMA ADMINISTRATIVE CODE
TITLE 435. STATE BOARD OF MEDICAL LICENSURE AND SUPERVISION

INDEX

contractor or other indirect assistant incidental to the ultimate disposal of human tissue by any of the designated methods.

[**Source:** Added at 10 Ok Reg 1527, eff 4-26-93]

435:10-7-10. Annual reregistration

(a) On an annual basis, each person licensed by the Board shall reregister with the Board. Reregistration shall be conducted during the month of initial licensure of each individual licensee by the Board. Each licensee shall provide to the Board all information required by the Board pursuant to statute, 59 O.S. ss 495a.1, in a form approved by the Board. The Board's staff shall prorate all fees for reregistration periods to equal the actual reregistration period during the period of transition from the uniform June annual reregistration period to the new period of reregistration based upon month of initial licensure.

(b) It shall be the affirmative duty of each licensee to comply with reregistration requirements. No grace period beyond that provided by law shall be allowed. The Board will not hear requests for extensions for reregistration or exemption from any reregistration requirement that the licensee did not receive reregistration materials.

[**Source:** Added at 12 Ok Reg 767, eff 1-5-95 (emergency); Added at 12 Ok Reg 1235, eff 5-15-95]

435:10-7-11. Use of controlled substances for the management of chronic pain

The Board has recognized that principles of quality medical practice dictate that the people of the State of Oklahoma have access to appropriate and effective pain relief and has adopted the following criteria when evaluating the physician's treatment of pain, including the use of controlled substances:

(1) **Evaluation of the patient.** A medical history and physical examination must be obtained, evaluated and documented in the medical record. The medical record should document the nature and intensity of the pain, current and past treatments for pain, underlying or coexisting diseases or conditions, the effect of the pain on physical and psychological function and history of substance abuse. The medical record also should document the presence of one or more recognized medical indications for the use of a controlled substance.

(2) **Treatment plan.** The written treatment plan should state objectives that will be used to determine treatment success, such as pain relief and improved physical and psychosocial function, and should indicate if any further diagnostic evaluations or other treatments are planned. After treatment begins, the physician should adjust drug therapy to the individual medical needs of each patient. Other treatment modalities or a rehabilitation program may be necessary depending on the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.

(3) **Informed consent and agreement for treatment.** The physician should discuss the risks and benefits of the use of controlled substances with the patient, persons designated by the patient or with the patient's surrogate or guardian if the patient is without medical decision-making capacity. The patient should receive prescriptions from one physician and one pharmacy whenever possible. If the patient is at high risk for medication abuse or has a history of substance abuse, the physician should consider the use of a written agreement between physician and patient outlining patient responsibilities, including:

(A) urine/serum medication levels screening when requested;
(B) number and frequency of all prescription refills; and
(C) reasons for which drug therapy may be discontinued (e.g. violation of agreement)

(4) **Periodic review.** The physician should periodically review the course of pain treatment and any new information about the etiology of the pain or the patient's state of health. Continuation or modification of controlled substances for pain management therapy depends on the physician's evaluation of progress toward treatment objectives. Satisfactory response to treatment may be indicated by the patient's decreased pain, increased level of function or improved quality of life. Objective evidence of improved or diminished function should be monitored and information from family members or other caregivers should be considered in determining the patient's response to treatment. If the patient's progress is unsatisfactory, the physician should assess the appropriateness of continued use of the current treatment plan and consider the use of other therapeutic modalities.

(5) **Consultation.** The physician should be willing to refer the patient, as necessary, for additional evaluation and treatment in order to achieve treatment objectives. Special attention should be given to those patients with pain who are at risk for medication misuse, abuse or diversion. The management of pain in patients with a history of substance abuse or with a comorbid psychiatric disorder may require extra care, monitoring, documentation and consultation with or referral to an expert in the management of such patients.

(6) **Medical records.** Records should remain current and be maintained in an accessible manner, readily available for review. The physician should keep accurate and complete records to include:

(A) the medical history and physical examination (including vital signs),
(B) diagnostic, therapeutic and laboratory results,
(C) evaluations, consultations and follow-up evaluations,
(D) treatment objectives,
(E) discussion of risks and benefits,
(F) informed consent,
(G) treatments,
(H) medications (including date, type, dosage and quantity prescribed),
(I) instructions and agreements and
(J) periodic reviews.

(7) **Compliance with controlled substances laws and regulations.** To prescribe, dispense or administer controlled substances, the physician must be licensed in Oklahoma and comply with applicable federal and state regulations. Physicians are referred to the Physicians Manual of the U.S. Drug Enforcement Administration for specific rules governing controlled substances as well as applicable state regulations.

[**Source:** Added at 16 Ok Reg 2003, eff 6-14-99; Amended at 22 Ok Reg 2096, eff 6-25-05]

435:10-7-12. Establishing a physician/patient relationship; exceptions

A physician/patient relationship is established when a physician agrees by direct or indirect contact with a patient to diagnose or treat any condition, illness or disability presented by a patient to that physician, whether or not such a presenting complaint is considered a disease by the general medical community. The physician/patient relationship shall include a medically

STATE OF OKLAHOMA

TITLE 510. STATE BOARD OF OSTEOPATHIC EXAMINERS

(b) Noting in this Section shall preclude the doctor's right to use human tissue for the treatment of disease or injury. Likewise, the doctor shall have the right to assist in arranging appropriate donations through the process of the Anatomical Board, under the provisions of the Anatomical Gift Act or the preservation of human tissue for other legitimate educational purpose in any accredited educational endeavor.
(c) In no event shall any person knowingly dispose of any human tissue in a public or private dump, refuse or disposal site or place open to public view.

[Source: Added at 13 Ok Reg 2225, eff 6-27-96]

510:5-5-4. Violations

Any osteopathic physician who violates or whose employees or agents violate this subchapter shall, upon conviction in a hearing before the Board, be fined an amount not to exceed Ten Thousand Dollars ($10,000.00).

[Source: Added at 13 Ok Reg 2225, eff 6-27-96]

510:5-5-5. Compliance

A presumption of compliance occurs once the attending physician has executed one of the methods of handling described in 510:5-5-3 and his responsibility is deemed fulfilled. In no event shall the osteopathic physician be responsible for the acts or omissions of any other licensed professional, independent contractor or other indirect assistant incidental to the ultimate disposal of human tissue by any of the designated methods.

[Source: Added at 13 Ok Reg 2225, eff 6-27-96]

SUBCHAPTER 7. UNPROFESSIONAL CONDUCT RELATING TO PRESCRIBING OR DISPENSING DANGEROUS DRUGS

Section

510:5-7-1. Unprofessional conduct relating to prescribing or dispensing dangerous drugs

The Board has the right to refuse to issue, renew or reinstate a license and may revoke a license or impose other appropriate sanctions for unprofessional conduct. In addition to those acts of unprofessional conduct listed in Title 59 O.S., Section 637 the following acts shall be included without limiting, in any way the Board's ability to interpret other acts as unprofessional conduct:

(1) Indiscriminate or excessive prescribing, dispensing or administering controlled dangerous drugs.

(2) Issuing prescriptions for controlled dangerous drugs to minors in violation of Title 63 O.S.

(3) Purchasing, prescribing, dispensing, or administering any controlled dangerous drug or other regulated substance in Schedule I through V, as those schedules are defined in Title 63 O.S. Chapter 2, Sections 2-101 et seq. for the physician's personal use unless it is prescribed, dispensed or administered by another physician who is licensed to do so.

(4) The delegation of authority to another person for the signing of prescriptions, whether controlled dangerous substances or otherwise.

(5) Any violation of any provisions of Title 63 O.S., Chapter 2, Sections 2-101 et seq or the Uniform Controlled Dangerous Substances Act.

[Source: Added at 13 Ok Reg 2225, eff 6-27-96]

SUBCHAPTER 9. PRESCRIBING FOR INTRACTABLE PAIN

Section

[Source: Codified 6-25-99]

510:5-9-1. Purpose

The purpose of this subchapter is to provide guidelines and requirements for osteopathic physicians who prescribe for chronic, intractable pain.

510:5-9-2. Guidelines and requirements

This rule requires that diagnosis be documented, it requires that certain records be maintained, and it requires that the physician must discuss the risks and benefits with the patient or the patient's guardian.

(1) To treat a patient's intractable pain, as long as the benefit of the expected relief outweighs the risk, even if the use of the drug increases the risk of death, so long as it is not furnished for the purpose of causing, or the purpose of assisting in causing death, the physician may prescribe or administer Schedule II, III, IV or V controlled dangerous substances or other pain relieving drugs in higher than normal dosages when, in that physician's judgment, the higher dosages are necessary to produce the desired therapeutic effect.

(2) The determination of intractable pain must include a complete medical history and physical examination which includes an assessment of the patient's pain, physical and psychological function, substance abuse history, underlying or co-existing diseases or conditions and the presence of a recognized medical indication for the use of an analgesic.

(3) The treatment plan must state objectives by which treatment success can be evaluated, such as pain relief and or improved physical and psychological function, and must indicate what further diagnostic evaluations or other treatments are planned. The drug therapy must be tailored to the individual needs of each patient.

(4) The course of treatment and any new information about the etiology of the intractable pain must be reviewed periodically, at least annually, with consideration given to referral for a current second opinion. The continuation or modification of treatment will depend on the results of this review and the evaluation of the patient's progress toward the treatment objectives. If the patient has not improved, the physician must assess the appropriateness of continuing the current therapy and the trial of other modalities.

(5) The management of intractable pain in patients with a history of substance abuse requires extra care, monitoring, documentation and consultation with addiction medicine specialists, and may include the use of agreements between the physician and patient specifying rules for medication use and consequences for its misuse.

(6) The physician must discuss the risks and benefits of the use of controlled substances with the patient or the patient's guardian and obtain informed consent prior to proceeding if it substantially increases the risk of death.

(7) Accurate and complete records documenting these requirements must be kept.

(8) To prescribe controlled substances, the physician must be licensed in Oklahoma, have a valid controlled substances registration and comply with federal and state regulations for issuing controlled substances prescriptions.

(9) Expert clinical testimony may be used to prove a violation of this rule. As used herein, a "clinical expert" is a physician who, by reason of specialized education or substantial relevant experience in pain management, has knowledge regarding current standards, practices and guidelines.

(10) Nothing in this rule shall limit a physician's authority to prescribe or administer prescription drug products beyond the customary indications as noted in the manufacturer's package insert for use in

treating intractable pain, provided the drug is recognized for treatment of intractable pain in standard reference compendia or medical literature.

510:5-9-3. Violations

The violation of any provision of this subchapter shall constitute unprofessional conduct, for which an application for licensure or reinstatement may be denied and for which appropriate sanctions may be imposed.

SUBCHAPTER 11. MEDICAL MICROPIGMENTATION

Section

[Source: Codified 9-13-02 ------- Pending final revocation]

SUBCHAPTER 13. ADVERTISING BOARD CERTIFICATION

Section

510:5-13-1. Requirements of Representation

An osteopathic physician's authorization of or use of the term "board certified," or "diplomate," or any similar word or phrase in any advertising for his or her osteopathic medical practice shall constitute misleading or deceptive advertising unless the osteopathic physician discloses the complete name of the specialty board or certifying organization which conferred the certification and the specialty board or certifying organization, so named, meets requirements in paragraphs 1 and 2 of this section:

(1) The certifying organization is a member of the Bureau of Osteopathic Specialists or the American Board of Medical Specialties, or the American Association of Physician Specialists.

(2) The certifying organization requires that its applicants be certified by a separate certifying organization that is a member of the Bureau of Osteopathic Specialists or the American Board of Medical Specialties or American Association of Physician Specialists and the certifying organization meets the criteria set forth in Section B, below.

510:5-13-2. Requirements of Certifying Organizations

Each certifying organization that is not a member board of the Bureau of Osteopathic Specialists or the American Board of Medical Specialties or American Association of Physician specialists must meet each of the requirements set forth in paragraphs 1 through 5 of this section:

(1) The certifying organization requires all physicians who are seeking certification to successfully pass a written or an oral examination or both, which test the applicant's knowledge and skills in that specialty or subspecialty area of osteopathic medicine. All or part of the examination may be delegated to a testing organization. All examinations require a psychometric evaluation for validation;

Oklahoma Opioid Prescribing Guidelines

Note: These guidelines do not replace clinical judgment in the appropriate care of patients. They are not intended as standards of care or as templates for legislation, nor are they meant for patients in palliative care programs or with cancer pain. The recommendations are an educational tool based on the expert opinion of numerous physicians and other health care providers, medical/nursing boards, mental and public health officials, and law enforcement personnel in Oklahoma and throughout the United States.[1,2,3]

Opioid Treatment for Acute Pain

1. Health care providers are encouraged to consider non-pharmacological therapies and/or non-opioid pain medications. Opioids should only be used for treatment of acute pain when the severity of the pain warrants that choice.
2. By Oklahoma law, it is mandatory that providers check the Oklahoma Prescription Monitoring Program (PMP) prior to prescribing and every 180 days prior to authorizing refills for opiates, synthetic opiates, semi-synthetic opiates, benzodiazepines, or carisoprodol. More frequent checks of the PMP are recommended.
3. When opioids are started, providers should prescribe the lowest possible effective dose. Prescribe no more than a short course; most patients require opioids for no more than three days.
4. Avoid prescribing opioids to patients currently taking benzodiazepines and/or other opioids.
5. Patients should be counseled to store medications securely, never to share them with others, and to dispose of medications when the pain has resolved.
6. Long-acting or extended-release opioids should not be prescribed for acute pain.
7. Providers should provide screening, brief intervention, and referral to treatment, if indicated.
8. Continued opioid use should be evaluated carefully, including assessing the potential for abuse, if pain persists beyond the anticipated period of acute pain.
9. In general, health care providers should not provide replacement prescriptions for opioids that have been lost, stolen, or destroyed.

Opioid Treatment for Chronic Pain

1. Alternatives to opioid treatment should be tried, or previous attempts documented, before initiating opioid treatment for chronic pain.
2. By Oklahoma law, it is mandatory that providers check the Oklahoma Prescription Monitoring Program (PMP) prior to prescribing and every 180 days prior to authorizing refills for opiates, synthetic opiates, semi-synthetic opiates, benzodiazepines, or carisoprodol. More frequent checks of the PMP are recommended.
3. A comprehensive evaluation should be performed before initiating opioid treatment for chronic pain.
4. The health care provider should screen for risk of abuse or addiction before initiating opioid treatment.
5. Patients should be counseled to store medications securely, never to share them with others, and to dispose of medications when pain has resolved.
6. Long-acting or extended-release opioids are associated with an increased risk of overdose death, and should only be prescribed by health care providers familiar with their indications, risks, and need for careful monitoring.

7. A written treatment plan should be established that includes measurable goals for reduction of pain and improvement of function.
8. The patient should be informed of the risks, benefits, and terms for continuation of opioid treatment, ideally using a written and signed treatment agreement. Consider co-prescribing naloxone for patients with increased risk of opioid overdose.
9. Opioids should be initiated as a short-term trial to assess the effects of opioid treatment on pain intensity, function, and quality of life. The trial should begin with a short-acting opioid medication.
10. During the titration period, regular visits for evaluation of progress toward goals should be scheduled and the PMP should be checked more frequently.
11. Continuing opioid treatment should be a deliberate decision that takes into consideration the risks and benefits of chronic opioid treatment for that patient. Patients and health care providers should periodically reassess the need for continued opioid treatment, weaning whenever possible. A second opinion or consultation may be useful in making that decision.
12. Opioid treatment should be tapered or gradually discontinued if adverse effects outweigh benefits or if aberrant, dangerous, or illegal behaviors are demonstrated. Care should be taken when tapering opioid treatment, particularly in patients on higher dosages, the elderly, and patients who are pregnant. Abrupt discontinuation of opioids should be avoided.
13. Health care providers should consider consultation for patients with complex pain conditions, serious co-morbidities, mental illness, or a history or evidence of current drug addiction or abuse.
14. In general, health care providers should not provide replacement prescriptions for opioids that have been lost, stolen, or destroyed.
15. Health care providers should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

1. Oklahoma State Department of Health. (2013). *Oklahoma Emergency Department (ED) and Urgent Care Clinic (UCC) Opioid Prescribing Guidelines*. Retrieved from https://www.ok.gov/health2/documents/UP_Oklahoma_ED-UCC_Guidelines.pdf. Accessed July 8, 2016.
2. Oklahoma State Department of Health. (2014). *Opioid Prescribing Guidelines for Oklahoma Health Care Providers in the Office-Based Setting*. Retrieved from https://www.ok.gov/health2/documents/UP_Oklahoma_Office_Based_Guidelines.pdf. Accessed July 8, 2016.
3. Centers for Disease Control and Prevention. (2016). *CDC Guideline for Prescribing Opioids for Chronic Pai*n. Retrieved from https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm. Accessed July 8, 2016.

Opioid Prescribing Guidelines for Oklahoma Health Care Providers in the Office-Based Setting

Note: These guidelines do not replace clinical judgment in the appropriate care of patients. They are not intended as standards of care or as templates for legislation, nor are they meant for patients in palliative care programs or with cancer pain. The recommendations are an educational tool based on the expert opinion of numerous physicians and other health care providers, medical/nursing boards, mental and public health officials, and law enforcement personnel in Oklahoma and throughout the United States. The guidelines are available at http://poison.health.ok.gov.

Opioid Treatment for Acute Pain

1. Opioids should only be used for treatment of acute pain when the severity of the pain warrants that choice and after determining that other non-opioid pain medications or therapies will not provide adequate pain relief.
2. Providers should query the Oklahoma Prescription Monitoring Program (PMP) for patients presenting with acute pain, prior to prescribing an opioid medication. In circumstances where a patient's pain is resulting from an objectively diagnosed disease process or injury, a provider may prudently opt not to review the Oklahoma PMP.
3. When opioids are prescribed for treatment of acute pain, the number of doses dispensed should be no more than the number of doses needed based on the usual duration of pain severe enough to require opioids for that condition.
4. When opioids are prescribed for treatment of acute pain, the patient should be counseled to store the medications securely and never to share with others. In order to prevent non-medical use of the medications, it is also recommended that patients dispose of medications when the pain has resolved.
5. Long duration-of-action opioids (e.g., methadone, buprenorphine, fentanyl, extended release oxycodone, and morphine) are rarely indicated for treatment of acute pain.
6. The use of opioids should be re-evaluated carefully, including assessing the potential for abuse, if persistent pain suggests the need to continue opioids beyond the anticipated time period of acute pain treatment for that condition. Health care providers should query the Oklahoma PMP as part of this re-evaluation process.
7. Health care providers should generally not provide replacement prescriptions for opioids that have been lost, stolen, or destroyed.

Opioid Treatment for Chronic Pain

1. Alternatives to opioid treatment should be tried, or previous attempts documented, before initiating opioid treatment.
2. A comprehensive evaluation should be performed before initiating opioid treatment for chronic pain. For chronic pain patients transferring their care to new health care providers, new opioid prescriptions should generally not be written until the previous provider's records have been reviewed or the previous health care provider has been notified of the transfer of care.
3. The health care provider should screen for risk of abuse or addiction before initiating opioid treatment.
4. Prior to the initial prescribing of opioid medications, health care providers should query the Oklahoma Prescription Monitoring Program (PMP).
5. When opioids are used for the treatment of chronic pain, a written treatment plan should be established that includes measurable goals for reduction of pain and improvement of function. One health care provider should coordinate a patient's comprehensive pain care plan and provide all opioid prescriptions required for the plan.

6. The patient should be informed of the risks, benefits, and terms for continuation of opioid treatment, ideally using a written and signed treatment agreement.
7. Opioids should be initiated as a short-term trial to assess the effects of opioid treatment on pain intensity, function, and quality of life. In most instances, the trial should begin with a short-acting opioid medication.
8. Regular visits for evaluation of progress toward goals should be scheduled during the period when the dose of opioids is being adjusted (titration period). During the titration period, and until the patient is clinically stable and judged to be compliant with therapy, it is recommended that the health care provider check the Oklahoma PMP more frequently.
9. Once a stable dose has been established (maintenance period), regular monitoring should be conducted at face-to-face visits during which treatment goals, analgesia, activity, adverse effects, and aberrant behaviors are monitored. The Oklahoma PMP should be queried at least once per year for patients receiving opioid treatment for chronic pain.
10. Continuing opioid treatment should be a deliberate decision that takes into consideration the risks and benefits o chronic opioid treatment for that patient. Patients and health care providers should periodically reassess the need for continued opioid treatment, weaning whenever possible, as part of the comprehensive pain care plan. A second opinion or consultation may be useful in making that decision.
11. Opioid treatment should be discontinued if adverse effects outweigh benefits or if aberrant, dangerous, or illegal behaviors are demonstrated.
12. Health care providers treating chronic pain patients with opioids should maintain records, in accordance with state and federal law, documenting patient evaluation, treatment plan, discussion of risks and benefits, informed consent, treatments prescribed, results of treatment, and any aberrant behavior observed.
13. Health care providers should consider consultation for patients with complex pain conditions, serious co-morbidities and mental illness, a history or evidence of current drug addiction or abuse, or when the provider is not confident of his/her ability to manage the treatment.
14. Health care providers should generally not provide replacement prescriptions for opioids that have been lost, stolen, or destroyed.
15. The administration of intravenous and intramuscular opioids for the relief of exacerbations of chronic pain is discouraged, except in special circumstances.
16. Long-acting opioids are associated with an increased risk of overdose death, and should only be prescribed by health care providers familiar with their indications, risks, and need for careful monitoring.
17. When opioids are prescribed for treatment of chronic pain, the patient should be counseled to store the medications securely and never to share with others. In order to prevent non-medical use of the medications, it is also recommended that patients dispose of medications when the pain has resolved.

Oklahoma Society of Interventional Pain Physicians

Background

Prescription drug abuse is Oklahoma's fastest growing drug problem. Of the nearly 3,200 unintentional poisoning deaths in Oklahoma from 2007-2011, 81% involved at least one prescription drug.[1] In 2010, Oklahoma had the fourth highest unintentional poisoning death rate in the nation (17.9 deaths per 100,000 population).[2] Prescription painkillers (opioids) are now the most common class of drug involved in overdose deaths in Oklahoma (involved in 87% of prescription drug-related deaths, with 417 opioid-involved overdose deaths in 2011).1 In a 2010 National Survey on Drug Use and Health report, Oklahoma led the nation in non-medical use of painkillers, with more than 8% of the population age 12 and older abusing/misusing painkillers.[3] Oklahoma is also one of the leading states in prescription painkiller sales per capita.[4]

These guidelines were primarily adapted from the Utah Clinical Guidelines on Prescribing Opioids.[5] The Opioid Prescribing Guidelines for Oklahoma Workgroup also studied other state and national recommendations in an effort to prepare guidelines most relevant to the practice of medicine in Oklahoma. The Workgroup created these guidelines in an effort to help reduce the misuse of prescription opioid analgesics while preserving patient access to needed medical treatment.

Guidelines for Acute Pain

1. Opioids should only be used for treatment of acute pain when the severity of the pain warrants that choice and after determining that other non-opioid pain medications or therapies will not provide adequate pain relief.[6]

Most acute pain is better treated with non-opioid medications [e.g., acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs)] or physical modalities such as therapeutic exercises or stretching. Opioid medications have less desirable adverse effect profiles in acute pain patients. Care should be taken to assure that opioid treatment does not interfere with early implementation of functional restoration programs such as exercise and physical therapy. Non-medical use of opioids is more common among younger people, and these risks should be considered when prescribing to an adolescent.

2. Providers should query the Oklahoma Prescription Monitoring Program (PMP) for patients presenting with acute pain, prior to prescribing an opioid medication. In circumstances where a patient's pain is resulting from an objectively diagnosed disease process or injury, a provider may prudently opt not to review the Oklahoma PMP.

The Oklahoma PMP is a real-time database of scheduled prescriptions written to persons who filled a prescription in Oklahoma. The Oklahoma PMP can be accessed at: http://www.ok.gov/obndd/Prescription_Monitoring_Program/.

Patients with a history of or current substance abuse are at increased risk of misusing opioids when prescribed.[7,8] Medical providers should ask the patient about a history of substance abuse prior to prescribing an opioid medication for the treatment of acute pain. A non-opioid regimen is preferred for patients presenting with a history of substance abuse who have acute pain. Although this should not exclude a patient from being prescribed opioids for acute pain, it should prompt a discussion with the patient about the potential for addiction. When a patient with a history of opioid addiction presents with acute pain due to an objectively diagnosed clinical or traumatic condition requiring the use of opioids for pain control, very close follow-up is indicated.

3. When opioids are prescribed for treatment of acute pain, the number of doses dispensed should be no more than the number of doses needed based on the usual duration of pain severe enough to require opioids for that condition.

Prescribing more medications than necessary can lead to non-medical use, abuse, and diversion of unused

medications. Opioid pain medications should be discontinued when the pain severity no longer requires opioid medications.

4. When opioids are prescribed for treatment of acute pain, the patient should be counseled to store the medications securely and never to share with others. In order to prevent non-medical use of the medications, it is also recommended that patients dispose of medications when the pain has resolved.

It is important that patients understand the need to store medications securely. Health care providers should encourage patients to keep medications in a locked environment rather than in easily accessible locations, such as the bathroom or kitchen cabinet, where medications are accessible to children and can be a target for theft. After recovery from pain, leftover medications should be properly disposed of immediately to help protect the medications from being diverted.

Tools to accompany *Recommendation 4:*

- United States Food and Drug Administration (FDA) Guidelines on Proper Disposal of Prescription Drugs http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm107163.pdf
- Oklahoma Bureau of Narcotics and Dangerous Drugs Take Back Container Locations http://www.ok.gov/obndd/documents/TakeBackBoxes.pdf

5. Long duration-of-action opioids (e.g., methadone, buprenorphine, fentanyl, extended release oxycodone, and morphine) are rarely indicated for treatment of acute pain.

Given the epidemiological data showing a significant increase in mortality associated with long-acting opioids, the inherent difficulty in titrating these medications, and the availability of alternative medications and/or treatment modalities, health care providers are advised to refrain from the routine use of long-acting opioids in the acute pain setting.[5,9]

6. The use of opioids should be re-evaluated carefully, including assessing the potential for abuse, if persistent pain suggests the need to continue opioids beyond the anticipated time period of acute pain treatment for that condition. Health care providers should query the Oklahoma PMP as part of this re-evaluation process.

Patients with acute pain who fail to recover in a usual timeframe or otherwise deviate from the expected clinical course for their diagnosis should be carefully re-evaluated. The continuation of opioid treatment for acute pain in this setting may represent the initiation of opioid treatment for a chronic pain condition without being recognized as such. At this time, the diagnosis and appropriateness of the treatment plan should be re-evaluated and the patient's medical history should be reviewed for factors that could interfere with treatment and pose a risk for complications during opioid treatment, including substance abuse or history of substance abuse.

Tools to accompany *Recommendation 6:*

- Oklahoma Prescription Monitoring Program http://www.ok.gov/obndd/Prescription_Monitoring_Program/

7. Health care providers should generally not provide replacement prescriptions for opioids that have been lost, stolen, or destroyed.

Patients misusing controlled substances frequently report their opioid medications as having been lost or stolen. Pain specialists routinely stipulate in pain agreements with patients that lost or stolen controlled substances will not be replaced. Most written agreements between chronic pain patients and pain management physicians, including the Health Resources and Services Administration (HRSA) toolkit sample pain agreement, state that prescriptions for opioids will not be replaced.[10]

The diversion of prescribed opioids is common. One study looked at completed patient surveys, and found that 45% of respondents reported some form of drug diversion at least once. Stolen medication was the most prevalent method of drug diversion, with 30% of respondents reporting at least one incident of stolen medication.[11] In another survey study, among persons 12 years and older who abused opioid pain medications (2009-2010), 71.2% came from friends or relatives; 55% were given to the abuser, 11.4% were purchased, and 4.8% were stolen.[12,13]

Guidelines for Chronic Pain

1. Alternatives to opioid treatment should be tried, or previous attempts documented, before initiating opioid treatment.[6,9,13,14,15]

Opioid medications are usually not the most appropriate first line of treatment for patients with chronic pain. Other measures, such as non-opioid pain medications, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, antiepileptic drugs, and non-pharmacologic therapies (e.g., therapeutic exercise, physical therapy), should be tried first and the outcomes of those therapies documented. Opioid therapy should be considered only when other potentially safer and more effective therapies prove inadequate. This approach is consistent with the World Health Organization's (WHO) *Pain Relief Ladder*.[16]

1.1 Clinicians should refer to disease-specific guidelines for recommendations for treatment of chronic pain related to specific diseases or conditions.

Tools to accompany *Recommendation 1:*

- Non-opioid Pain Management Tool
  http://health.utah.gov/prescription/tools.html (see *Informational Tools* on website)

2. A comprehensive evaluation should be performed before initiating opioid treatment for chronic pain. For chronic pain patients transferring their care to new health care providers, new opioid prescriptions should generally not be written until the previous provider's records have been reviewed or the previous health care provider has been notified of the transfer of care.[13,14,15,17]

There are many reasons to prescribe cautiously when initiating opioid therapy; therefore a comprehensive initial evaluation is necessary to identify patients at high risk for adverse outcomes. The major goal should be to provide the greatest functional benefit while minimizing the potential for harm to patients. The potential for serious harm, including death, exists due either to overdose or to dangerous behaviors that may occur while taking opioids. The patient may be directly harmed, but others may also be harmed through diversion or by acts performed by a person taking opioids.

Initiating opioid treatment often results in short-term relief, which may not be sustainable. Safe long-term use of opioid medications requires the commitment of adequate resources. Patients need to be monitored regularly to evaluate outcomes and identify aberrant behavior or adverse side effects.

The goal of the comprehensive evaluation is to determine the nature of the patient's pain, and to evaluate how the pain is affecting the patient's function and quality of life. The provider should attempt to identify other conditions or circumstances that could adversely affect the treatment plan or the approach to managing the patient's treatment plan. The provider should also re-assess and re-evaluate prior approaches to the patient's pain management to provide a basis for establishing an effective ongoing plan of care.

The evaluation should specifically assess:

A. The character and potential cause(s) of pain, as well as prior treatments.

- The duration of the pain should be considered.
- The character of the pain should be considered. Since certain types of pain, such as neuropathic pain,

might not be best treated with opioids. It is important for the clinician to consider the type and character of pain when prescribing a medication.

B. Social factors and medical or mental health conditions might influence treatment, especially those that might interfere with appropriate and safe use of opioid therapy.[14]

- Obtain a history of substance use, addiction, or dependence. (If present, refer to *Recommendations 13.2 and 13.3*.)
- Consider potential psychiatric conditions, including personality disorders that may affect pain or the treatment of pain. (If present, refer to *Recommendation 13.4*.)
- Identify use of alcohol and other medications that might interact with opioid medications used to treat pain. Particular attention and caution should be given to alcohol, benzodiazepines, and other sedative medications.
- Assess the presence of medical conditions that might complicate the treatment of pain, including medication allergy, cardiac or respiratory disease, and sleep apnea or risk factors for sleep apnea.
- Central sleep apnea is common among persons treated with methadone and other opioid medications, especially at higher dosages. Some experts recommend that all patients who are considered for long-term opioid treatment receive a sleep study prior to therapy or when higher dosages are considered.[14]

C. Effects of pain on the patient's life and function.

- Assess the patient's baseline severity of pain, functional status, and quality of life using a valid, reliable method/instrument that can be used later to evaluate treatment effectiveness.

Tools to accompany *Recommendation 2:*

- Sheehan Disability Tool
  http://health.utah.gov/prescription/pdf/guidelines/SheehanDisabilityScale.pdf
- Pain Management Evaluation Tool
  http://health.utah.gov/prescription/pdf/guidelines/PainManagementWorksheet.pdf

3. The health care provider should screen for risk of abuse or addiction before initiating opioid treatment.

3.1 Use a screening tool to assess the patient's risk of misuse prior to prescribing an opioid medication for chronic pain.[6]

A number of screening tools have been developed for assessing a patient's risk of misuse of medications. The screening tools are intended to assist the health care provider in determining whether opioid treatment is appropriate and in determining the level of monitoring appropriate for the patient's level of risk.

3.2 Consider performing drug screening before initiating long term opioid treatment for chronic pain.

Drug testing can identify problems, such as use of undisclosed medications, non-use of reported medications (i.e., potential diversion), undisclosed use of alcohol, or the use of illicit substances, not identified without testing.

Health care providers should use a urine drug screen or another laboratory test that can detect the presence of illegal drugs, unreported prescription medications, and/or unreported alcohol use. It is recommended that drug testing be strongly considered and conducted, especially when other factors suggest caution. When screening is limited to situations when there is suspicion of substance misuse, some opportunities may be missed. In one study, testing results upon first admission to a pain clinic did not correlate with reported medication use for nearly one-fourth of patients. Most discrepancies involved substances not reported by the patient; a small minority reported taking medications that were not found on testing.[18]

A positive drug screen indicates the need for caution, but does not preclude opioid use for the treatment of pain. However, consideration should be given to referral for substance abuse counseling and/or a pain management specialist. If an opioid medication is subsequently prescribed, the patient should be more carefully monitored and the conditions under which opioids are being prescribed should be well documented in the treatment plan. (See *Recommendations 5, 6, 8, 12*.)

Inexpensive immunoassays can be performed in the office. These tests can rapidly determine if opioids are present but they do not identify specific substances. When necessary, specific substances can be identified by ordering confirmatory laboratory testing. However, in many cases, candidly going over the results of the initial in-office test with the patient can eliminate the need for confirmatory testing. It is extremely important to keep in mind that immunoassays have both false-positive and false-negative results. Certain over-the-counter medications may cause a positive result. The prescriber should consider confirmatory gas chromatography or mass spectrometry testing or consultation with a certified Medical Review Officer if drug test results are unclear or confirmation is clinically necessary.[9]

Tools to accompany *Recommendation 3:*

- Urine Drug Testing Devices
  http://health.utah.gov/prescription/pdf/guidelines/CLIADrugTestlist.pdf
- Current Opioid Misuse Measure
  http://health.utah.gov/prescription/tools.html (see *Tools to Screen for Risk of Complications* on website)
- SOAPP-R
  http://health.utah.gov/prescription/tools.html (see *Tools to Screen for Risk of Complications* on website)
- Opioid Risk Tool
  http://health.utah.gov/prescription/pdf/guidelines/ORTwithout_scoring.pdf
- Signs of Substance Misuse
  http://health.utah.gov/prescription/pdf/guidelines/signs_substance_misuse.pdf
- Checklist for Adverse Effects, Function, and Opioid Dependence
  http://health.utah.gov/prescription/pdf/guidelines/checklist%20for%20adverse%20effects.pdf

4. Prior to the initial prescribing of opioid medications, health care providers should query the Oklahoma Prescription Monitoring Program (PMP).

Most patients who request treatment for pain are legitimately seeking relief of pain. However, subsets of patients seeking treatment for pain are seeking drugs for recreational use, to support an established addiction, or for profit. Information about past patterns of controlled substance prescriptions filled by the patient, such as obtaining medications from multiple providers or obtaining concurrent prescriptions, can alert the provider to potential problems.

The Oklahoma Bureau of Narcotics and Dangerous Drugs Control (OBNDDC) maintains the Oklahoma Prescription Monitoring Program, a real time, searchable database of all controlled substance prescriptions filled in the state. The PMP is used to track and collect data on the dispensing of Schedule II-V drugs by all retail, institutional, and outpatient hospital pharmacies, and in-state/out-of-state mail order pharmacies. Access to the data is provided to authorized individuals and used to identify potential cases of drug over-utilization, misuse, and potential abuse of controlled substances throughout the state. This database is accessible online to all controlled substance prescribers.

Tools to accompany *Recommendation 4:*

- Oklahoma Prescription Monitoring Program
  http://www.ok.gov/obndd/Prescription_Monitoring_Program/

5. When opioids are used for the treatment of chronic pain, a written treatment plan should be established that includes measurable goals for reduction of pain and improvement of function. One health care provider should coordinate a patient's comprehensive pain care plan and provide all opioid prescriptions required for the plan.

5.1 The treatment plan should be tailored to the patient's circumstances and the characteristics and pathophysiology of the pain. The pathophysiology helps to predict whether opioid medication is likely to help reduce pain or to improve function, and should be considered when establishing treatment goals. Non-opioid treatment modalities should be included in the treatment plan, whenever possible, to maximize the likelihood of achieving treatment goals.

5.2 Goals for the treatment of chronic pain should be measurable and should include improved function and quality of life as well as improved control of pain.[6,9,14]

For most chronic pain conditions, complete elimination of pain is an unreasonable goal. Goals for treatment of chronic pain should include improvement in the tolerability of pain and function.[15] The clinician should counsel the patient on reasonable expectations for treatment outcomes so that agreement is achieved on the goals of addressing pain, function, and quality of life.

The pathophysiologic basis of the pain can help establish a prognosis for future improvement (or worsening) in function and pain and should influence the goals of treatment. Goals for functional improvement and measures to track progress against those goals should be established and documented to serve as a basis of evaluating treatment outcomes.[6,14] These include:

- Objective physical findings obtained by the examining health care provider (e.g., improved strength, range of motion, aerobic capacity);
- Functional status at work (e.g., increase in physical output, endurance, or ability to perform job functions); and
- Functional status at home (e.g., increased ability to perform instrumental activities of daily living, and frequency and intensity of conditioning).

Targets for improved quality of life should also be identified and documented to serve as a basis for evaluating treatment outcomes. These may include:

- Patient rating of quality of life on a measurement scale;
- Psychosocial status (e.g., increased social engagement or decreased emotional distress);
- Familial status (e.g., improved relationships with, or decreased burden, on family members); and
- Physical status (e.g., increased ability to exercise, perform chores, or participate in hobbies).

Health care providers should consider cultural differences in assessing function, quality of life, and pain intensity (see http://prc.coh.org/culture.asp for examples). These measures of improvement could be reported by the patient, family members, and/or the employer. Permission to discuss the patient's condition with these persons should have been previously obtained and documented.

5.3 Treatment goals should be developed jointly by the patient and health care provider.[15]

Engage patients in their own health care. Health care providers have observed that when patients assume a significant portion of the responsibility for their rehabilitation they are more likely to improve and that when they participate in goal setting they are more likely to achieve the goals. As with any other chronic illness (such as diabetes or heart disease), the health care provider should focus not just on pain control, but also on treating the patient's underlying diseases and encouraging them to engage in ownership of their own health.

Tools to accompany *Recommendation 5:*

- Pain Management Evaluation Tool
  http://health.utah.gov/prescription/pdf/guidelines/PainManagementWorksheet.pdf
- Patient Pain and Medication Tracking Chart
  http://health.utah.gov/prescription/pdf/guidelines/PatientPain-FunctionTracking.pdf
- Sheehan Disability Scale
  http://health.utah.gov/prescription/pdf/guidelines/SheehanDisabilityScale.pdf
- Brief Pain Inventory Form
  http://health.utah.gov/prescription/pdf/guidelines/BriefPainInvNPEC.pdf
- Sample Treatment Plan for Prescription Opioids
  http://health.utah.gov/prescription/pdf/guidelines/treatment_plan.pdf
- Cultural considerations in assessing function, quality of life, and pain intensity
  http://prc.coh.org/culture.asp

6. The patient should be informed of the risks, benefits, and terms for continuation of opioid treatment, ideally using a written and signed treatment agreement.[13]

6.1 Patients should be informed not to expect complete relief from pain. The excitement and euphoria of initial pain relief that may occur with a potent opioid can lead the patient to expect long-term complete pain relief. Without careful guidance, this may lead the patient to disappointment and to seek excessive doses of opioids.

The patient should be counseled about the appropriate use of opioid medications, possible adverse effects, and the risks of developing tolerance, physical and/or psychological dependence, and withdrawal symptoms.[9,19] Adverse effects can include opioid-induced hyperalgesia, allodynia, abnormal pain sensitivity, and depression.[6,9,20]

Sedation and cognitive impairment may occur when patients are taking opioid medications. Therefore, discuss with patients the need for caution in operating motor vehicles or equipment or performing other tasks where impairment would put them or others at risk.[11]

Ensure the patient does not have any absolute contraindications, and review risks and benefits related to any relative contraindications with the patient.

Absolute contraindications for opioid prescribing:

- Allergy to an opioid agent (may be addressed by using an alternative agent);
- Co-administration of a drug capable of inducing life-threatening drug-drug interaction; and
- Active diversion of controlled substances (providing medication to someone for whom it was not prescribed).

More detail about absolute contraindications is contained in the *Guidelines Tools* section.

Consider co-prescribing naloxone for high risk patients, and providing training to family/caregivers to reverse potential life-threatening depression of the respiratory and central nervous system. Educate patients and family/caregivers about the danger signs of respiratory depression. Everyone in the household should know to summon medical help immediately if a person demonstrates any of the following signs while on opioids:

- Snoring heavily and cannot be awakened;
- Periods of ataxic (irregular) or other sleep disordered breathing;
- Trouble breathing;

- Exhibiting extreme drowsiness and slow breathing;
- Slow, shallow breathing with little chest movement;
- Increased or decreased heartbeat; and
- Feeling faint, very dizzy, confused or has heart palpitations.

6.2 The patient and, when applicable, the family or caregiver should be involved in the education process.[14]

Educational material should be provided in written form and discussed in person with the patient and, when applicable, the family or caregiver.[14] Educating the family or caregiver about the signs of opioid overdose may help detect problems before they lead to a serious complication.

It is important to act within the constraints of the Health Insurance Portability and Accountability Act (HIPAA). HIPAA regulates the conditions under which information about the patient can be disclosed to others, such as family members, and under what conditions discussions about the patient with others are allowed.

6.3 The treatment plan, which defines the responsibilities of both the patient and health care provider, should be documented.[6,9,13,14,15]

Patient responsibilities include properly obtaining, filling, and using prescriptions, and adherence to the treatment plan. Patient responsibilities also include instructions to keep a pain diary, a diary or log of daily activities and accomplishments, and/or instructions on how and when to give feedback to the prescriber.[14]

The prescribing health care provider may consider requiring that the treatment plan be documented in the form of a treatment agreement signed by the patient. Patients should be encouraged to store opioid medications in a secure location to keep the medication away from others who should not have access to them.

6.4 The treatment plan should contain goals of treatment, guidelines for prescription refills, agreement to submit to urine or serum screening upon request, and reasons for possible discontinuation of drug therapy.[9,13,14,15,17]

The treatment plan (sometimes referred to as a treatment agreement) should contain the items developed jointly by the patient and health care provider, such as follow-up appointments, the pharmacy and health care provider to be used, as well as any non-negotiable demands or limitations the health care provider wishes to make, such as the prohibition of sharing or trading the medication or getting refills early. Specific grounds for immediate termination of the agreement and cessation of prescribing may also be specified, such as forgery or selling of prescriptions or medications or obtaining them from multiple providers as documented by Oklahoma's Prescription Monitoring Program.[14,20]

Optional inclusions in the agreement:

- Pill counts may be required as a means to gauge proper medication use;[14,19]
- Prohibition of use with alcohol or certain other medications;[14]
- Documentation of counseling regarding driving or operating heavy machinery; and [6,14]
- Specific frequencies of urine testing.

Ideally, the patient should be receiving prescriptions from one prescriber only and filling those prescriptions at one pharmacy only.[14,17,19]

It is not necessary to include specific consequences for specific non-compliant behaviors, but it should be documented in the treatment agreement that continuing failure by the patient to adhere to the treatment plan will result in escalating consequences, up to and including termination of the clinician-patient relationship and of opioid prescribing by that clinician.

6.5 Discuss involvement of family members in the patient's care and request that the patient give written permission to talk with family members about the patient's care.

This is best done before starting to treat the patient because it can be more difficult to obtain consent after an issue occurs. Prior to initiating treatment with opioids, the health care provider may want to consider a family conference to help assess the patient's integrity.[19] Consultation with others, however, must be done within the constraints of HIPAA, as noted above. (See *Recommendation 6.2*.)

Tools to accompany *Recommendation 6:*

- Absolute Contraindications to Opioid Prescribing
  http://health.utah.gov/prescription/pdf/guidelines/absolute_contraindications.pdf
- Sample Treatment Plan for Prescribing Opioids
  http://health.utah.gov/prescription/pdf/guidelines/treatment_plan.pdf
- Signs of Substance Misuse
  http://health.utah.gov/prescription/pdf/guidelines/signs_substance_misuse.pdf
- Guidance on HIPAA
  http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/provider_ffg.pdf
- Prescription Drug Overdose in Oklahoma Brochure
  http://www.ok.gov/health2/documents/DrugOverDoseBrochure_2013.pdf

Initiating, Monitoring, and Discontinuing Opioid Treatment

7. Opioids should be initiated as a short-term trial to assess the effects of opioid treatment on pain intensity, function, and quality of life. In most instances, the trial should begin with a short-acting opioid medication.

7.1 The health care provider should clearly explain to the patient that initiation of opioid treatment is not a commitment to long-term opioid treatment and that treatment will be stopped if the trial is determined to be unsuccessful. The trial should be for a specific time period with pre-determined evaluation points. The decision to continue opioid medication treatment beyond the trial period should be based on the balance between benefits, including function and quality of life, and adverse effects experienced. Criteria for cessation should be considered before treatment begins. Refer to *Recommendation 11* for more information on discontinuation of treatment.

7.2 Short-acting opioid medications are, in general, safer and easier to titrate to an effective dose. If the treatment trial proves successful in achieving the goals established in the treatment plan, the health care provider may consider switching the patient to a long-acting or sustained-release formulation. The patient's individual situation should influence whether the patient is switched from a short-acting medication. Treatment with a long-acting opioid medication before a trial using a short-acting medication has been performed is an option that should be prescribed only by those with considerable expertise in chronic pain management.

Tools to accompany *Recommendation 7:*

- Dosing Guidelines
  http://health.utah.gov/prescription/pdf/guidelines/dosing_guidelines.pdf
- Current Opioid Misuse Measure (COMM)
  http://health.utah.gov/prescription/tools.html (see *Tools to Screen for Risk of Complications* on website)

Titration Phase of Opioid Treatment

8. Regular visits for evaluation of progress toward goals should be scheduled during the period when the dose of opioids is being adjusted (titration period). During the titration period, and until the patient is clinically stable and judged to be compliant with therapy, it is recommended that the health care provider check the Oklahoma PMP more frequently.[14]

8.1 Face-to-face follow-up visits should occur at least every 2-4 weeks during the titration period. More frequent follow-up visits may be advisable and caution should be used when prescribing an opioid medication if the patient has a known addiction problem, suspected drug-behavior problems, or co-existing psychiatric or medical problems. Frequency of visits should also be based on risk stratification (e.g., as determined by a screening tool) and the clinician's judgment (taking into account the volume of the drug being prescribed and how likely it is to be abused).[15]

8.2 When pain and function have not sufficiently improved on a current opioid dose, a trial of a slightly higher dose could be considered.[14,15]

The rate at which the dosing is increased should balance the risk of leaving the patient in a painful state longer than necessary by increasing too slowly with the risk of causing harm, including fatal overdose, by increasing too fast. Ideally, only one drug at a time should be titrated in an opioid-naïve patient.[14] Age, health, and severity of pain should be taken into consideration when deciding on increments and rates of titration. Particular caution should be used in titrating dosing of methadone.

Evidence and other guidelines are not in agreement regarding the risks and benefits of high daily doses of opioid measured in morphine milligram equivalents (MMEs). It is likely that the risk-benefit ratio is less favorable at higher doses. Clinical vigilance is needed at all dosage levels of opioids, but is even more important at higher doses. Health care providers who are not experienced in prescribing high doses of opioids should consider either referring the patient or obtaining a consultation from a qualified provider for patients receiving high dosages. No clear threshold for a high dose has been established based on evidence. The Washington State guidelines suggest a threshold of 120 MME per day. It is important to increase clinical vigilance at doses exceeding 120 MME per day. Patients receiving 100 MME or more per day had a 9-fold increase in overdose risk. Most overdoses were medically serious, 12% were fatal.[9]

During titration, all patients should be seen frequently until dosing requirements have stabilized. Patients should be instructed to use medication only as directed, that is, not to change doses or frequency of administration without specific instructions from the health care provider.

8.3 During the titration period, and until the patient is clinically stable and judged to be compliant with therapy, it is recommended that the health care provider check the Oklahoma Prescription Monitoring Program more frequently, such as monthly or quarterly.

Tools to accompany *Recommendation 8:*

- Dosing Guidelines
  http://health.utah.gov/prescription/pdf/guidelines/dosing_guidelines.pdf
- Electronic MME Dosing Calculator
  http://agencymeddirectors.wa.gov/mobile.html
- Prescription Monitoring Program
  http://www.ok.gov/obndd/Prescription_Monitoring_Program/

Maintenance of Opioid Treatment

9. Once a stable dose has been established (maintenance period), regular monitoring should be conducted at face-to-face visits during which treatment goals, analgesia, activity, adverse effects, and aberrant behaviors are monitored. The Oklahoma PMP should be queried at least once per year for patients receiving opioid treatment for chronic pain.[13,15]

9.1 The health care provider is advised to consider baseline drug testing at the initiation of opioid treatment, compliance monitoring one to three months later, and random monitoring every 6-12 months. In the event of unexpected drug screens or suspicious patient behavior, additional monitoring can be performed. Health care

providers may consider each of the following four areas of concern at each visit: Analgesia, Activity, Adverse effects, and Aberrant behavior. These assessments can be remembered as the "four A's": [21]

- Analgesia: inquire about level of pain (current, recent, trends, etc.)
- Activity: assess the patient's function and overall quality of life
- Adverse events: determine whether the patient is having medication side effects
- Aberrant behavior: evaluate for possible drug abuse-related behavior

9.2 During the maintenance period, the Oklahoma Prescription Monitoring Program should be checked at least annually.

After the titration period is complete and the maintenance period is underway, the frequency of checks of the Oklahoma PMP can be based on clinical judgment, but should be done no less than annually. The Oklahoma PMP should be checked more often for high risk patients and patients exhibiting aberrant behavior.

9.3 Continuation or modification of treatment should depend on the health care provider's evaluation of progress towards stated treatment goals.[13]

Treatment goals include reduction in a patient's pain scores and improved physical, psychological, and social function. If patient compliance with agreed-upon activity levels, are not being achieved despite medication adjustments, the health care provider should re-evaluate the appropriateness of continued treatment with the current medications.[9,17]

A frequent need for dose adjustments after a reasonable time interval of titration is an indication to re-evaluate the underlying condition and consider the possibility the patient has developed opioid hyperalgesia, substantial tolerance, or psychological/physical dependence.

9.4 Adjustments to previously stable maintenance treatment may be considered if the patient develops tolerance, a new pain-producing medical condition arises or an existing one worsens, or if a new adverse effect emerges or becomes more clinically significant.[14]

Options for adjustment include reducing the medication or rotating opioid medications. If it is documented that the patient is compliant with agreed-upon recommendations such as exercise, working, etc., the addition of supplemental short-acting medications for control of break-through pain (e.g., as related to an increase in activity, end-of-dose pain, weather-related pain exacerbation, or specific medical conditions) can be considered as well. If patients do not achieve effective pain relief with one opioid, rotation to another frequently produces greater success.[22] If rotating among different opioid medications, refer to a standard dosing equivalence table, taking into account the current drug's half-life and potency.

If the patient's situation has changed permanently and consideration is given to the increased risk of adverse events, it is reasonable to consider an ongoing increase in maintenance dosing. In general, if the patient's underlying medical condition is chronic and unchanging, and if opioid-associated problems (hyperalgesia, substantial tolerance, important adverse effects) have not developed, it is recommended that the effective dose achieved through titration not be lowered once the patient has reached a plateau of adequate pain relief and functional level.[14]

9.5 Dosing changes should generally be made during a clinic visit.[14]

If the patient's underlying, pain-producing, chronic medical condition improves, it is expected that the health care provider will begin tapering the patient off the opioid medication. (See *Recommendation 11* for guidelines on discontinuation.)

Tapering an opioid medication with or without the goal of discontinuation may be performed as described below (*Recommendation 11*) or as described in the *Strategies for Tapering and Weaning Tool*.

Tools to accompany *Recommendation 9:*

- Checklist for Adverse Effects, Function, and Opioid Dependence
  http://health.utah.gov/prescription/pdf/guidelines/checklist%20for%20adverse%20effects.pdf
- Signs of Substance Misuse
  http://health.utah.gov/prescription/pdf/guidelines/signs_substance_misuse.pdf
- Pain Management Evaluation Tool
  http://health.utah.gov/prescription/pdf/guidelines/PainManagementWorksheet.pdf
- Dosing Guidelines
  http://health.utah.gov/prescription/pdf/guidelines/dosing_guidelines.pdf
- Strategies for Tapering and Weaning
  http://health.utah.gov/prescription/pdf/guidelines/Strategies_tapering_weaning.pdf

Evaluating the Opioid Treatment Trial

10. Continuing opioid treatment should be a deliberate decision that takes into consideration the risks and benefits of chronic opioid treatment for that patient. Patients and health care providers should periodically reassess the need for continued opioid treatment, weaning whenever possible, as part of the comprehensive pain care plan. A second opinion or consultation may be useful in making that decision.

The health care provider should clearly explain to the patient that initiation of opioid treatment is not a commitment to long-term opioid treatment and that treatment will be stopped if the trial is determined to be unsuccessful. The trial should be for a specific time period with pre-determined evaluation points. The decision to continue opioid treatment beyond the trial period should be based on the balance between benefits, including function and quality of life, and adverse effects experienced. A second opinion or consult may be useful in making the decision to continue or discontinue opioids after the treatment trial.

Discontinuing Opioid Treatment

11. Opioid treatment should be discontinued if adverse effects outweigh benefits, or if aberrant, dangerous, or illegal behaviors are demonstrated.[9]

11.1 Discontinuation of opioid treatment is recommended if any of the following occurs:

- Dangerous or illegal behaviors are identified;
- Patient claims or exhibits a lack of effectiveness;
- Pain problem resolves;
- Patient expresses a desire to discontinue therapy; and
- Opioid treatment appears to be causing harm to the patient, particularly if harm exceeds benefit.[14]

The decision to discontinue opioid treatment should ideally be made jointly with the patient and, if appropriate, the family/caregiver.[17] This decision should include careful consideration of the outcomes of ongoing monitoring.

11.2 When possible, offer to assist patients in safely discontinuing medications, even if they have withdrawn from treatment or been discharged for agreement violations.[14]

The goal is to taper all patients off opioid medications safely. If the patient is discharged, the health care provider is obliged to offer continued monitoring for 30 days post-discharge. Possible complications of opioid

withdrawal should be taken into consideration when discontinuing or tapering opioid medications.

Tools to accompany *Recommendation 11:*

- Strategies for Tapering and Weaning
  http://health.utah.gov/prescription/pdf/guidelines/Strategies_tapering_weaning.pdf

Documentation and Medical Records

12. Health care providers treating chronic pain patients with opioids should maintain records, in accordance with state and federal law, documenting patient evaluation, treatment plan, discussion of risks and benefits, informed consent, treatments prescribed, results of treatment, and any aberrant behavior observed. [9,13,14,15,17]

12.1 A written treatment plan should document objectives that will be used to evaluate treatment success.[9,13,14,15,17]

12.2 Opioid prescriptions should be written on tamper-resistant prescription paper to help reduce the likelihood of prescription fraud or misuse.[15]

To reduce the chance of tampering with the prescription, write legibly, and keep a copy.[15]

12.3 Assessment of treatment effectiveness should be documented in the medical record.[9,13,15]

Both the underlying medical condition responsible for the pain, if known, and other medical conditions that may affect the efficacy of treatment or risks of adverse events should be assessed and documented at every visit.

Health care providers should consider utilizing a standardized approach such as "The Four A's" or "The SAFE Tool" for medical documentation. The Four A's considers four areas of concern: Analgesia, Activity, Adverse effects, and Aberrant behavior.[21] The SAFE Tool is a numerical five point scoring system that helps to guide the health care provider toward broader views of treatment options.[23] It considers four areas of concern: social functioning (S), analgesia (A), physical function (F), and emotional functioning (E).

The Four A's can be remembered as:

- Analgesia: inquire about level of pain (current, recent, trends, etc.);
- Activity: assess both the patient's function and overall quality of life;
- Adverse events: determine whether the patient is having medication side effects; and
- Aberrant behavior: regularly evaluate for possible drug abuse-related behavior.

The SAFE Tool can be remembered as:

- Social functioning: inquire about family and employment relationships;
- Analgesia: inquire about level of pain (current, recent, trends, etc.);
- Physical functioning: inquire about how well the patient is meeting goals; and
- Emotional functioning: ask about changes in the patient's mental health status.

12.4 Adherence to the treatment plan, including any evidence of aberrant behavior, should be documented in the medical record.[14]

Specific components of the treatment plan for which adherence should be assessed include:

- Use of opioid analgesics; and
- Follow-up referrals, tests, and other therapies.

Health care providers are encouraged to make use of resources designed to assist them in managing the care of patients with aberrant behavior. Serious non-adherence issues (e.g., illegal, criminal, or dangerous behaviors, including altering of prescriptions) may also warrant immediate discontinuation of opioid treatment.

Tools to accompany *Recommendation 12:*

- Checklist for Adverse Effects, Function, and Opioid Dependence
  http://health.utah.gov/prescription/pdf/guidelines/checklist%20for%20adverse%20effects.pdf
- Signs of Substance Misuse
  http://health.utah.gov/prescription/pdf/guidelines/signs_substance_misuse.pdf
- Federal Laws on Prescribing Controlled Substances (21 CFR 1306 et. seq.)
  http://www.deadiversion.usdoj.gov/21cfr/cfr/
- Osteopathic Rules on Prescribing for Intractable Pain (OAC 510:5-9-1 et. seq.)
  http://www.ok.gov/osboe/documents/RULES.pdf
- Medical Board Rules on Prescribing for Intractable Pain (OAC 435:10-7-11 et. seq.)
  http://www.okmedicalboard.org/download/457/MDRULES.pdf

Consultation and Management of Complex Patients

13. Health care providers should consider consultation for patients with complex pain conditions, serious co-morbidities and mental illness, a history or evidence of current drug addiction or abuse, or when the provider is not confident of his or her ability to manage the treatment.[9,13]

13.1 Prescribers may wish to consider referring patients if any of the following conditions or situations are present, or if other concerns arise during treatment:

- The patient has a complex pain condition and the clinician wishes verification of diagnosis;
- The patient has significant co-morbidities, including psychiatric illness;
- The patient is at high risk of aberrant behavior or addiction; or
- The clinician suspects the development of significant tolerance, particularly at higher doses.

The main goal of a consultation is for the prescribing clinician to receive recommendations for ongoing treatment.

13.2 Patients with a history of addiction or substance use disorder or who have positive drug screens indicative of a problem should be closely monitored (e.g., more frequent random drug screens, random pill counts) or considered for referral to an addiction specialist for evaluation of recurrent risk and for assistance with treatment.[9,13,14]

Although this is a desirable approach, it is recognized that following this recommendation may not be feasible in parts of Oklahoma where there is a shortage of readily available addiction specialists.

13.3 Pain patients addicted to medications/drugs should be referred to a pain management and/or mental health/substance use disorder specialist, if available, for recommendations on the treatment plan and assistance in management.

The health care provider may consider prescribing opioid medications for pain even if the patient has a self-reported or documented previous opioid abuse problem, as long as monitoring is performed during the titration and maintenance phase.

13.4 Patients with a coexisting psychiatric disorder should receive ongoing mental health support and treatment while receiving an opioid medication for pain control.

Management of patients with a coexisting psychiatric condition may require extra care, monitoring, or documentation.[17,19] Consultation can be obtained to assist in formulating the treatment plan and establishing a

plan for coordinated care of both the chronic pain and psychiatric condition(s).

Tools to accompany *Recommendation 13:*

- Strategies for Tapering and Weaning
  http://health.utah.gov/prescription/pdf/guidelines/Strategies_tapering_weaning.pdf

14. Health care providers should generally not provide replacement prescriptions for opioids that have been lost, stolen, or destroyed.

Patients misusing controlled substances frequently report their opioid medications as having been lost or stolen. Pain specialists routinely stipulate in pain agreements with patients that lost or stolen controlled substances will not be replaced. Most written agreements between chronic pain patients and pain management physicians, including the Health Resources and Services Administration (HRSA) toolkit sample pain agreement, state that prescriptions for opioids will not be replaced.[10]

The diversion of prescribed opioids is common. One study looked at completed patient surveys and determined that 45% of respondents reported some form of drug diversion at least once. Stolen medication was the most prevalent method of drug diversion, and 30% of respondents reported at least one incident of stolen medication.[11] Another survey study found that among persons 12 years and older who abused opioid pain medications (2009-2010), 71.2% came from friends or relatives; 55% were given to the abuser, while 11.4% were purchased, and 4.8% were stolen.[12,13]

15. The administration of intravenous and intramuscular opioids for the relief of exacerbations of chronic pain is discouraged, except in special circumstances.

Parenteral opioids should be generally avoided for the treatment of chronic pain because of their short duration and potential for addictive euphoria. For chronic pain, oral opioids are superior to parenteral opioids in duration of action and provide a gradual decrease in the level of pain control. When there is evidence or reasonable suspicion of an acute pathological process causing the acute exacerbation of chronic pain, parenteral opioids may be appropriate.

Tools to accompany *Recommendation 15:*

- Dosing Guidelines
  http://health.utah.gov/prescription/pdf/guidelines/dosing_guidelines.pdf
- Current Opioid Misuse Measure (COMM)
  http://health.utah.gov/prescription/tools.html (see *Tools to Screen for Risk of Complications*)

Methadone and Extended Release/Long-Acting Opioids

16. Long-acting opioids are associated with an increased risk of overdose death, and should only be prescribed by health care providers familiar with their indications, risks, and need for careful monitoring.

16.1 The prescription use of methadone remains controversial due to concerns about its efficacy and safety. During the past two decades methadone-related death rates increased in Oklahoma and the U.S. From 2007-2011, methadone was listed in the cause of death in 21% of prescription drug-related unintentional poisoning deaths in Oklahoma.[1]

The half-life of methadone is long and unpredictable, increasing the risk of inadvertent overdose. The peak respiratory depressant effect of methadone occurs later and lasts longer after treatment initiation or dosage change than does the peak analgesic effect. Conversion tables that have been established to assist with converting a patient from another opioid medication to methadone are considered by many experts to be unreliable.

Methadone metabolism is complicated and varies among individuals. Methadone interacts with several other medications that can alter its metabolism, changing the effects of a given dose on pain and on respiratory depression. Potential for interactions should be considered before starting methadone in a patient taking other medications, and before starting any medication in a patient taking methadone.

Methadone can prolong the rate-corrected QT interval (QTc), increase the risk of Torsades de Pointe, and sudden cardiac death. Caution should be used in prescribing methadone to any patient at risk for prolonged QTc interval, including those with structural cardiac disease, cardiac arrhythmias or cardiac conduction abnormalities and in patients taking another medication associated with QTc interval prolongation.[24] An online reference of such medications is available at: http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.

Health care providers should consider obtaining an electrocardiogram (ECG) to measure the QTc interval in patients treated with methadone, especially at higher doses. A recently published consensus guideline recommended that an ECG be performed before prescribing methadone, within the first 30 days, and annually. Additional ECG examinations were recommended if the methadone dose exceeds 100 mg per day or if a patient on methadone has unexplained syncope or seizure. Guidance was provided for actions to be taken at two levels of QTc prolongation (450-500 ms and greater than 500 ms).[25]

Methadone and other opioids have been associated with worsening obstructive sleep apnea and new onset of central sleep apnea. Clinicians should question patients about symptoms and signs of sleep apnea and consider obtaining a sleep study in patients treated with opioids if they develop any signs of sleep-disordered breathing or respiratory depression. This is particularly important for patients receiving higher doses of opioid medications. In a recent study, 92% of patients on opioid doses at or above 200 MMEs had developed ataxic or irregular breathing.[25]

16.2 If extended release/long-acting opioids are prescribed, consideration should be given to the increased risk of overdose with these medications. Prescribers should consider the current risk evaluation and implement mitigation strategies and close monitoring to reduce the possibility of adverse events.

Tools to accompany *Recommendation 16:*

- Dosing Guidelines
  http://health.utah.gov/prescription/pdf/guidelines/dosing_guidelines.pdf
- The Role of Methadone in the Management of Chronic Non-Malignant Pain
  http://health.utah.gov/prescription/pdf/guidelines/role_of_methadone.pdf
- Electronic MME Dosing Calculator
  http://agencymeddirectors.wa.gov/mobile.html

Education of Chronic Pain Patients on Using Opioids

17. When opioids are prescribed for treatment of chronic pain, the patient should be counseled to store the medications securely and never to share with others. In order to prevent non-medical use of the medications, it is also recommended that patients dispose of medications when the pain has resolved.

It is important that patients understand the need to store medications securely. Health care providers should encourage patients to keep medications in a locked environment rather than in easily accessible locations, such as the bathroom or kitchen cabinet, where they are accessible to unsuspecting children, curious teenagers, and can be a target for theft. Tell the patient that if they have leftover medications after they have recovered, they should dispose of their medications immediately to help protect them from being a target for theft as well as protect others from getting into the medications.

Tools to accompany *Recommendation 17:*

- United States Food and Drug Administration (FDA) Guidelines on Proper Disposal of Prescription Drugs http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm107163.pdf
- Oklahoma Bureau of Narcotics and Dangerous Drugs Take Back Container Locations http://www.ok.gov/obndd/documents/TakeBackBoxes.pdf

Guidelines Tools

Tools to use in evaluation and monitoring:

- Pain Management Evaluation Tool
  http://health.utah.gov/prescription/pdf/guidelines/PainManagementWorksheet.pdf
- Patient Pain and Medication Tracking
  http://health.utah.gov/prescription/pdf/guidelines/PatientPain-FunctionTracking.pdf
- Sheehan Disability Scale
  http://health.utah.gov/prescription/pdf/guidelines/SheehanDisabilityScale.pdf
- Brief Pain Inventory Form
  http://health.utah.gov/prescription/pdf/guidelines/BriefPainInvNPEC.pdf
- Treatment Plan for Prescribing
  http://health.utah.gov/prescription/pdf/guidelines/treatment_plan.pdf
- SF-12
  http://health.utah.gov/prescription/pdf/guidelines/SF-12v2Standard-Sample.pdf

Tools to screen for risk of complications:

- Oklahoma Prescription Monitoring Program
  http://www.ok.gov/obndd/Prescription_Monitoring_Program/
- Current Opioid Misuse Measure (COMM)
  http://health.utah.gov/prescription/tools.html
- SOAPP-R
  http://health.utah.gov/prescription/tools.html
- Opioid Risk Tool
  http://health.utah.gov/prescription/pdf/guidelines/ORTwithout_scoring.pdf
- Urine Drug Testing Devices
  http://health.utah.gov/prescription/pdf/guidelines/CLIADrugTestlist.pdf
- Signs of Substance Misuse
  http://health.utah.gov/prescription/pdf/guidelines/signs_substance_misuse.pdf
- Checklist for Adverse Effects, Function, and Opioid Dependence
  http://health.utah.gov/prescription/pdf/guidelines/checklist%20for%20adverse%20effects.pdf

Informational tools:

- United States Food and Drug Administration (FDA) Guidelines on Proper Disposal of Prescription Drugs
  http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm107163.pdf
- Non-opioid Pain Management Tool
  http://health.utah.gov/prescription/tools.html
- Absolute Contraindications to Opioid Prescribing
  http://health.utah.gov/prescription/pdf/guidelines/absolute_contraindications.pdf
- Strategies for Tapering and Weaning
  http://health.utah.gov/prescription/pdf/guidelines/Strategies_tapering_weaning.pdf
- Information for Patients-Opioid Analgesics for Non-cancer Pain
  http://health.utah.gov/prescription/pdf/guidelines/Information_for_patients.Opioid_analgesics_for_non-cancer_pain.pdf
- The Role of Methadone in the Management of Chronic Non-Malignant Pain
  http://health.utah.gov/prescription/pdf/guidelines/role_of_methadone.pdf
- Dosing Guidelines
  http://health.utah.gov/prescription/pdf/guidelines/dosing_guidelines.pdf

- Prescription Drug Overdose in Oklahoma Brochure
  http://www.ok.gov/health2/documents/DrugOverDoseBrochure_2013.pdf
- Oklahoma Bureau of Narcotics and Dangerous Drugs Take Back Container Locations
  http://www.ok.gov/obndd/documents/TakeBackBoxes.pdf
- Electronic MME Dosing Calculator
  http://agencymeddirectors.wa.gov/mobile.html
- Federal Laws on Prescribing Controlled Substances (21 CFR 1306 et. seq.)
  http://www.deadiversion.usdoj.gov/21cfr/cfr/
- Osteopathic Rules on Prescribing for Intractable Pain (OAC 510:5-9-1 et. seq.)
  http://www.ok.gov/osboe/documents/RULES.pdf
- Medical Board Rules on Prescribing for Intractable Pain (OAC 435:10-7-11 et. seq.)
  http://www.okmedicalboard.org/download/457/MDRULES.pdf

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Disclaimer: *This document should not be used to establish any standard of care. No legal proceeding, including medical malpractice proceedings or disciplinary hearings, should reference a deviation from any part of this document as constituting a breach of professional conduct. These guidelines are only an educational tool. Clinicians should use their own clinical judgment and not base clinical decisions solely on this document. The recommendations are based on evidence-based research, promising interventions, and expert opinion. Additional research is needed to understand the impact of these interventions on decreasing unintentional drug poisoning and on health care costs. These guidelines should be considered by clinicians, hospitals, administrators, public health entities, and other relevant stakeholders.*

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CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

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Centers for Disease Control and Prevention

CONTENTS

Disclosure of Relationship

The Core Expert Group (CEG) members disclose that they have no financial conflicts of interest. Experts disclose the following activities related to the content of this guideline: Pam Archer discloses authorship of the Oklahoma Emergency Department and Urgent Care Clinic Opioid Prescribing Guidelines and the Opioid Prescribing Guidelines for Oklahoma Health Care Providers in the Office Based Setting; Bonnie Burman discloses authorship of the Ohio Guidelines for Prescribing Opioids for the Treatment of Chronic, Non-Terminal Pain; Jane Ballantyne discloses that she has served as a paid consultant to Cohen Milstein Sellers & Toll, PLLC, and has special advisory committee responsibilities on the Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategies committee; Phillip Coffin discloses that in 2012 he provided expert testimony to the California State Assembly regarding a bill to expand naloxone access and reports that he is the principal investigator on a research study of methamphetamine dependence that receives donated injectable naltrexone from Alkermes, Inc.; Gary Franklin discloses authorship of the AMDG Interagency Guideline on Prescribing Opioids for Pain; Erin Krebs discloses that she represented the American College of Physicians at a 2014 Food and Drug Administration meeting on Abuse Deterrent Opioid Formulations; Lewis Nelson discloses his ad-hoc membership on the FDA Drug Safety and Risk Management Advisory Committee; Trupti Patel discloses authorship of the Arizona Opioid Prescribing Guidelines; Robert "Chuck" Rich discloses that he was an author of the 2013 American Academy of Family Physicians position paper on opioids and pain management; Joanna Starrels discloses that she received honoraria from the Betty Ford Institute; Thomas Tape discloses that he was an author of the 2013 American College of Physicians policy position paper on prescription drug abuse. CDC provided 100% of the funding for the supplemental evidence review tasks and meeting support. No foundation or industry support was accepted.

The Opioid Guideline Workgroup (OGW) members disclose that they have no financial conflicts of interest. Experts disclose the following activities related to the content of this guideline: Anne Burns discloses that she participated in a congressional briefing sponsored by Reps. Carter and DeSaulnier on the pharmacist's role of furnishing Naloxone and that she participates on the National Advisory Board for the Prescription Drug Abuse and Heroin Summit. Chinazo Cunningham discloses that her husband is employed by Quest Diagnostics and Dr. Cunningham was recused from any discussion related to urine drug testing. Traci Green discloses that she was previously employed by Inflexxion, a small business that conducts Small Business Innovation Research on behavioral interventions for behavioral health and chronic pain and created several psychometric tools for conducting risk assessment for prescription opioid abuse potential. Dr. Green also discloses that while at the hospital where she is employed, she provided consultation to Purdue Pharma Ltd to design overdose prevention brochures for persons who use diverted prescription opioids non-medically with an emphasis on persons who inject prescription drugs, and not for patients using opioid therapy for pain. Dr. Green was recused from any discussion related to risk assessment tools and patient education materials. Erin Krebs discloses that she served on the CDC Opioid Prescribing Guideline CEG. Christina Porucznik discloses that she served on the CDC Opioid Prescribing Guideline CEG. Greg Terman discloses that he serves as the President of the American Pain Society. Mark Wallace discloses that he served on a Kempharma advisory panel for an abuse-deterrent hydrocodone formulation to treat acute postoperative pain and Dr. Wallace was recused form any discussion related to abuse-deterrent drugs.

The NCIPC Board of Scientific Counselors (BSC) members disclose that they have no financial conflicts of interest. Two BSC members, Traci Green and Christina Porucznik, served on the Opioid Guideline Workgroup. Traci Green discloses that she was previously employed by Inflexxion, a small business that conducts Small Business Innovation Research on behavioral interventions for behavioral health and chronic pain and created several psychometric tools for conducting risk assessment for prescription opioid abuse potential. Dr. Green also discloses that while at the hospital where she is employed, she provided consultation to Purdue Pharma Ltd to design overdose prevention brochures for persons who use diverted prescription opioids non-medically with an emphasis on persons who inject prescription drugs, and not for patients using opioid therapy for pain. Dr. Green was recused from any discussion related to risk assessment tools and patient education materials. Christina Porucznik discloses that she served on the CDC Opioid Prescribing Guideline CEG.

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CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

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Summary

This guideline provides recommendations for primary care clinicians who are prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses 1) when to initiate or continue opioids for chronic pain; 2) opioid selection, dosage, duration, follow-up, and discontinuation; and 3) assessing risk and addressing harms of opioid use. CDC developed the guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and recommendations are made on the basis of a systematic review of the scientific evidence while considering benefits and harms, values and preferences, and resource allocation. CDC obtained input from experts, stakeholders, the public, peer reviewers, and a federally chartered advisory committee. It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. This guideline is intended to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death. CDC has provided a checklist for prescribing opioids for chronic pain (http://stacks.cdc.gov/view/cdc/38025) as well as a website (http://www.cdc.gov/drugoverdose/prescribingresources.html) with additional tools to guide clinicians in implementing the recommendations.

Introduction

Background

Opioids are commonly prescribed for pain. An estimated 20% of patients presenting to physician offices with noncancer pain symptoms or pain-related diagnoses (including acute and chronic pain) receive an opioid prescription (*1*). In 2012, health care providers wrote 259 million prescriptions for opioid pain medication, enough for every adult in the United States to have a bottle of pills (*2*). Opioid prescriptions per capita increased 7.3% from 2007 to 2012, with opioid prescribing rates increasing more for family practice, general practice, and internal medicine compared with other specialties (*3*). Rates of opioid prescribing vary greatly across states in ways that cannot be explained by the underlying health status of the population, highlighting the lack of consensus among clinicians on how to use opioid pain medication (*2*).

Prevention, assessment, and treatment of chronic pain are challenges for health providers and systems. Pain might go unrecognized, and patients, particularly members of racial and ethnic minority groups, women, the elderly, persons with cognitive impairment, and those with cancer and at the end of life, can be at risk for inadequate pain treatment (*4*). Patients can experience persistent pain that is not well controlled. There are clinical, psychological, and social consequences associated with chronic pain including limitations in complex activities, lost work productivity, reduced quality of life, and stigma, emphasizing the importance of appropriate and compassionate patient care (*4*). Patients should receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options.

Chronic pain has been variably defined but is defined within this guideline as pain that typically lasts >3 months or past the time of normal tissue healing (*5*). Chronic pain can be the result of an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause (*4*). Estimates of the prevalence of chronic pain vary, but it is clear that the number of persons experiencing chronic pain in the United States is substantial. The 1999–2002 National Health and Nutrition Examination Survey estimated that 14.6% of adults have current widespread or localized pain lasting at least 3 months (*6*). Based on a survey conducted during 2001–2003 (*7*), the overall prevalence of common, predominantly musculoskeletal pain conditions (e.g., arthritis, rheumatism, chronic back or neck problems, and frequent severe headaches) was estimated at 43% among adults in the

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United States, although minimum duration of symptoms was not specified. Most recently, analysis of data from the 2012 National Health Interview Study showed that 11.2% of adults report having daily pain (*8*). Clinicians should consider the full range of therapeutic options for the treatment of chronic pain. However, it is hard to estimate the number of persons who could potentially benefit from opioid pain medication long term. Evidence supports short-term efficacy of opioids for reducing pain and improving function in noncancer nociceptive and neuropathic pain in randomized clinical trials lasting primarily ≤12 weeks (*9*,*10*), and patients receiving opioid therapy for chronic pain report some pain relief when surveyed (*11*–*13*). However, few studies have been conducted to rigorously assess the long-term benefits of opioids for chronic pain (pain lasting >3 months) with outcomes examined at least 1 year later (*14*). On the basis of data available from health systems, researchers estimate that 9.6–11.5 million adults, or approximately 3%–4% of the adult U.S. population, were prescribed long-term opioid therapy in 2005 (*15*).

Opioid pain medication use presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, more than 165,000 persons died from overdose related to opioid pain medication in the United States (*16*). In the past decade, while the death rates for the top leading causes of death such as heart disease and cancer have decreased substantially, the death rate associated with opioid pain medication has increased markedly (*17*). Sales of opioid pain medication have increased in parallel with opioid-related overdose deaths (*18*). The Drug Abuse Warning Network estimated that >420,000 emergency department visits were related to the misuse or abuse of narcotic pain relievers in 2011, the most recent year for which data are available (*19*). Although clinical criteria have varied over time, opioid use disorder is a problematic pattern of opioid use leading to clinically significant impairment or distress. This disorder is manifested by specific criteria such as unsuccessful efforts to cut down or control use and use resulting in social problems and a failure to fulfill major role obligations at work, school, or home (*20*). This diagnosis has also been referred to as "abuse or dependence" and "addiction" in the literature, and is different from tolerance (diminished response to a drug with repeated use) and physical dependence (adaptation to a drug that produces symptoms of withdrawal when the drug is stopped), both of which can exist without a diagnosed disorder. In 2013, on the basis of DSM-IV diagnosis criteria, an estimated 1.9 million persons abused or were dependent on prescription opioid pain medication (*21*). Having a history of a prescription for an opioid pain medication increases the risk for overdose and opioid use disorder (*22*–*24*), highlighting the value of guidance on safer prescribing practices for clinicians. For example, a recent study of patients aged 15–64 years receiving opioids for chronic noncancer pain and followed for up to 13 years revealed that one in 550 patients died from opioid-related overdose at a median of 2.6 years from their first opioid prescription, and one in 32 patients who escalated to opioid dosages >200 morphine milligram equivalents (MME) died from opioid-related overdose (*25*).

This guideline provides recommendations for the prescribing of opioid pain medication by primary care clinicians for chronic pain (i.e., pain conditions that typically last >3 months or past the time of normal tissue healing) in outpatient settings outside of active cancer treatment, palliative care, and end-of-life care. Although the guideline does not focus broadly on pain management, appropriate use of long-term opioid therapy must be considered within the context of all pain management strategies (including nonopioid pain medications and nonpharmacologic treatments). CDC's recommendations are made on the basis of a systematic review of the best available evidence, along with input from experts, and further review and deliberation by a federally chartered advisory committee. The guideline is intended to ensure that clinicians and patients consider safer and more effective treatment, improve patient outcomes such as reduced pain and improved function, and reduce the number of persons who develop opioid use disorder, overdose, or experience other adverse events related to these drugs. Clinical decision making should be based on a relationship between the clinician and patient, and an understanding of the patient's clinical situation, functioning, and life context. The recommendations in the guideline are voluntary, rather than prescriptive standards. They are based on emerging evidence, including observational studies or randomized clinical trials with notable limitations. Clinicians should consider the circumstances and unique needs of each patient when providing care.

Rationale

Primary care clinicians report having concerns about opioid pain medication misuse, find managing patients with chronic pain stressful, express concern about patient addiction, and report insufficient training in prescribing opioids (*26*). Across specialties, physicians believe that opioid pain medication can be effective in controlling pain, that addiction is a common consequence of prolonged use, and that long-term opioid therapy often is overprescribed for patients with chronic noncancer pain (*27*). These attitudes and beliefs, combined with increasing trends in opioid-related overdose, underscore the need for better clinician guidance on opioid prescribing. Clinical practice guidelines focused on prescribing can improve clinician knowledge, change prescribing practices (*28*), and ultimately benefit patient health.

Professional organizations, states, and federal agencies (e.g., the American Pain Society/American Academy of Pain Medicine, 2009; the Washington Agency Medical Directors Group, 2015; and the U.S. Department of Veterans Affairs/Department of Defense, 2010) have developed guidelines for opioid prescribing (*29–31*). Existing guidelines share some common elements, including dosing thresholds, cautious titration, and risk mitigation strategies such as using risk assessment tools, treatment agreements, and urine drug testing. However, there is considerable variability in the specific recommendations (e.g., range of dosing thresholds of 90 MME/day to 200 MME/day), audience (e.g., primary care clinicians versus specialists), use of evidence (e.g., systematic review, grading of evidence and recommendations, and role of expert opinion), and rigor of methods for addressing conflict of interest (*32*). Most guidelines, especially those that are not based on evidence from scientific studies published in 2010 or later, also do not reflect the most recent scientific evidence about risks related to opioid dosage.

This CDC guideline offers clarity on recommendations based on the most recent scientific evidence, informed by expert opinion and stakeholder and public input. Scientific research has identified high-risk prescribing practices that have contributed to the overdose epidemic (e.g., high-dose prescribing, overlapping opioid and benzodiazepine prescriptions, and extended-release/long-acting [ER/LA] opioids for acute pain) (*24*,*33*,*34*). Using guidelines to address problematic prescribing has the potential to optimize care and improve patient safety based on evidence-based practice (*28*), as well as reverse the cycle of opioid pain medication misuse that contributes to the opioid overdose epidemic.

Scope and Audience

This guideline is intended for primary care clinicians (e.g., family physicians and internists) who are treating patients with chronic pain (i.e., pain lasting >3 months or past the time of normal tissue healing) in outpatient settings. Prescriptions by primary care clinicians account for nearly half of all dispensed opioid prescriptions, and the growth in prescribing rates among these clinicians has been above average (*3*). Primary care clinicians include physicians as well as nurse practitioners and physician assistants. Although the focus is on primary care clinicians, because clinicians work within team-based care, the recommendations refer to and promote integrated pain management and collaborative working relationships with other providers (e.g., behavioral health providers, pharmacists, and pain management specialists). Although the transition from use of opioid therapy for acute pain to use for chronic pain is hard to predict and identify, the guideline is intended to inform clinicians who are considering prescribing opioid pain medication for painful conditions that can or have become chronic.

This guideline is intended to apply to patients aged ≥18 years with chronic pain outside of palliative and end-of-life care. For this guideline, palliative care is defined in a manner consistent with that of the Institute of Medicine as care that provides relief from pain and other symptoms, supports quality of life, and is focused on patients with serious advanced illness. Palliative care can begin early in the course of treatment for any serious illness that requires excellent management of pain or other distressing symptoms (*35*). End-of-life care is defined as care for persons with a terminal illness or at high risk for dying in the near future in hospice care, hospitals, long-term care settings, or at home. Patients within the scope of this guideline include cancer survivors with chronic pain who have completed cancer treatment, are in clinical remission, and are under cancer surveillance only. The guideline is not intended for patients undergoing active cancer treatment, palliative care, or end-of-life care because of the unique therapeutic goals, ethical considerations, opportunities for medical supervision, and balance of risks and benefits with opioid therapy in such care.

The recommendations address the use of opioid pain medication in certain special populations (e.g., older adults and pregnant women) and in populations with conditions posing special risks (e.g., a history of substance use disorder). The recommendations do not address the use of opioid pain medication in children or adolescents aged <18 years. The available evidence concerning the benefits and harms of long-term opioid therapy in children and adolescents is limited, and few opioid medications provide information on the label regarding safety and effectiveness in pediatric patients. However, observational research shows significant increases in opioid prescriptions for pediatric populations from 2001 to 2010 (*36*), and a large proportion of adolescents are commonly prescribed opioid pain medications for conditions such as headache and sports injuries (e.g., in one study, 50% of adolescents presenting with headache received a prescription for an opioid pain medication [*37*,*38*]). Adolescents who misuse opioid pain medication often misuse medications from their own previous prescriptions (*39*), with an estimated 20% of adolescents with currently prescribed opioid medications reporting using them intentionally to get high or increase the effects of alcohol or other drugs (*40*). Use of prescribed opioid pain medication before high school graduation is associated with a 33% increase in the risk of later opioid misuse (*41*). Misuse of opioid pain medications in adolescence strongly predicts later onset of heroin use (*42*). Thus, risk of opioid medication use in pediatric populations is of great concern. Additional clinical trial and observational research is needed,

and encouraged, to inform development of future guidelines for this critical population.

The recommendations are not intended to provide guidance on use of opioids as part of medication-assisted treatment for opioid use disorder. Some of the recommendations might be relevant for acute care settings or other specialists, such as emergency physicians or dentists, but use in these settings or by other specialists is not the focus of this guideline. Readers are referred to other sources for prescribing recommendations within acute care settings and in dental practice, such as the American College of Emergency Physicians' guideline for prescribing of opioids in the emergency department (*43*); the American Society of Anesthesiologists' guideline for acute pain management in the perioperative setting (*44*); the Washington Agency Medical Directors' Group Interagency Guideline on Prescribing Opioids for Pain, Part II: Prescribing Opioids in the Acute and Subacute Phase (*30*); and the Pennsylvania Guidelines on the Use of Opioids in Dental Practice (*45*). In addition, given the challenges of managing the painful complications of sickle cell disease, readers are referred to the NIH National Heart, Lung, and Blood Institute's Evidence Based Management of Sickle Cell Disease Expert Panel Report for management of sickle cell disease (*46*).

Guideline Development Methods

Guideline Development Using the Grading of Recommendations Assessment, Development, and Evaluation Method

CDC developed this guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (http://www.gradeworkinggroup.org). This method specifies the systematic review of scientific evidence and offers a transparent approach to grading quality of evidence and strength of recommendations. The method has been adapted by the CDC Advisory Committee on Immunization Practices (ACIP) (*47*). CDC has applied the ACIP translation of the GRADE framework in this guideline. Within the ACIP GRADE framework, the body of evidence is categorized in a hierarchy. This hierarchy reflects degree of confidence in the effect of a clinical action on health outcomes. The categories include type 1 evidence (randomized clinical trials or overwhelming evidence from observational studies), type 2 evidence (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies), type 3 evidence (observational studies or randomized clinical trials with notable limitations), and type 4 evidence (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations). Type of evidence is categorized by study design as well as limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and a constellation of plausible biases that could change observations of effects. Type 1 evidence indicates that one can be very confident that the true effect lies close to that of the estimate of the effect; type 2 evidence means that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; type 3 evidence means that confidence in the effect estimate is limited and the true effect might be substantially different from the estimate of the effect; and type 4 evidence indicates that one has very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of the effect (*47*,*48*). When no studies are present, evidence is considered to be insufficient. The ACIP GRADE framework places recommendations in two categories, Category A and Category B. Four major factors determine the category of the recommendation: the quality of evidence, the balance between desirable and undesirable effects, values and preferences, and resource allocation (cost). Category A recommendations apply to all persons in a specified group and indicate that most patients should receive the recommended course of action. Category B recommendations indicate that there should be individual decision making; different choices will be appropriate for different patients, so clinicians must help patients arrive at a decision consistent with patient values and preferences, and specific clinical situations (*47*). According to the GRADE methodology, a particular quality of evidence does not necessarily imply a particular strength of recommendation (*48*–*50*). Category A recommendations can be made based on type 3 or type 4 evidence when the advantages of a clinical action greatly outweigh the disadvantages based on a consideration of benefits and harms, values and preferences, and costs. Category B recommendations are made when the advantages and disadvantages of a clinical action are more balanced. GRADE methodology is discussed extensively elsewhere (*47*,*51*). The U.S. Preventive Services Task Force (USPSTF) follows different methods for developing and categorizing recommendations (http://www.uspreventiveservicestaskforce.org). USPSTF recommendations focus on preventive services and are categorized as A, B, C, D, and I. Under the Affordable Care Act, all "nongrandfathered" health plans (that is, those health plans not in existence prior to March 23, 2010 or those with significant changes to their coverage) and expanded Medicaid plans are required to cover

preventive services recommended by USPSTF with a category A or B rating with no cost sharing. The coverage requirements went into effect September 23, 2010. Similar requirements are in place for vaccinations recommended by ACIP, but do not exist for other recommendations made by CDC, including recommendations within this guideline.

A previously published systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) on the effectiveness and risks of long-term opioid treatment of chronic pain (*14*,*52*) initially served to directly inform the recommendation statements. This systematic clinical evidence review addressed the effectiveness of long-term opioid therapy for outcomes related to pain, function, and quality of life; the comparative effectiveness of different methods for initiating and titrating opioids; the harms and adverse events associated with opioids; and the accuracy of risk-prediction instruments and effectiveness of risk mitigation strategies on outcomes related to overdose, addiction, abuse, or misuse. For the current guideline development, CDC conducted additional literature searches to update the evidence review to include more recently available publications and to answer an additional clinical question about the effect of opioid therapy for acute pain on long-term use. More details about the literature search strategies and GRADE methods applied are provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026). CDC developed GRADE evidence tables to illustrate the quality of the evidence for each clinical question.

As identified in the AHRQ-sponsored clinical evidence review, the overall evidence base for the effectiveness and risks of long-term opioid therapy is low in quality per the GRADE criteria. Thus, contextual evidence is needed to provide information about the benefits and harms of nonpharmacologic and nonopioid pharmacologic therapy and the epidemiology of opioid pain medication overdose and inform the recommendations. Further, as elucidated by the GRADE Working Group, supplemental information on clinician and patient values and preferences and resource allocation can inform judgments of benefits and harms and be helpful for translating the evidence into recommendations. CDC conducted a contextual evidence review to supplement the clinical evidence review based on systematic searches of the literature. The review focused on the following four areas: effectiveness of nonpharmacologic and nonopioid pharmacologic treatments; benefits and harms related to opioid therapy (including additional studies not included in the clinical evidence review such as studies that evaluated outcomes at any duration or used observational study designs related to specific opioid pain medications, high-dose opioid therapy, co-prescription of opioids with other controlled substances, duration of opioid use, special populations, risk stratification/mitigation approaches, and effectiveness of treatments for addressing potential harms of opioid therapy); clinician and patient values and preferences; and resource allocation. CDC constructed narrative summaries of this contextual evidence and used the information to support the clinical recommendations. More details on methods for the contextual evidence review are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027).

On the basis of a review of the clinical and contextual evidence (review methods are described in more detail in subsequent sections of this report), CDC drafted recommendation statements focused on determining when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. To help assure the draft guideline's integrity and credibility, CDC then began a multistep review process to obtain input from experts, stakeholders, and the public to help refine the recommendations.

Solicitation of Expert Opinion

CDC sought the input of experts to assist in reviewing the evidence and providing perspective on how CDC used the evidence to develop the draft recommendations. These experts, referred to as the "Core Expert Group" (CEG) included subject matter experts, representatives of primary care professional societies and state agencies, and an expert in guideline development methodology.* CDC identified subject matter experts with high scientific standing; appropriate academic and clinical training and relevant clinical experience; and proven scientific excellence in opioid prescribing, substance use disorder treatment, and pain management. CDC identified representatives from leading primary care professional organizations to represent the audience for this guideline. Finally, CDC identified state agency officials and representatives based on their experience with state guidelines for opioid prescribing that were developed with multiple agency stakeholders and informed by scientific literature and existing evidence-based guidelines.

Prior to their participation, CDC asked potential experts to reveal possible conflicts of interest such as financial relationships with industry, intellectual preconceptions, or previously stated public positions. Experts could not serve if they had conflicts that might have a direct and predictable effect on the recommendations. CDC excluded experts who had a financial or promotional relationship with a company

* A list of the members appears at the end of this report. The recommendations and all statements included in this guideline are those of CDC and do not necessarily represent the official position of any persons or organizations providing comments on the draft guideline.

that makes a product that might be affected by the guideline. CDC reviewed potential nonfinancial conflicts carefully (e.g., intellectual property, travel, public statements or positions such as congressional testimony) to determine if the activities would have a direct and predictable effect on the recommendations. CDC determined the risk of these types of activities to be minimal for the identified experts. All experts completed a statement certifying that there was no potential or actual conflict of interest. Activities that did not pose a conflict (e.g., participation in Food and Drug Administration [FDA] activities or other guideline efforts) are disclosed.

CDC provided to each expert written summaries of the scientific evidence (both the clinical and contextual evidence reviews conducted for this guideline) and CDC's draft recommendation statements. Experts provided individual ratings for each draft recommendation statement based on the balance of benefits and harms, evidence strength, certainty of values and preferences, cost, recommendation strength, rationale, importance, clarity, and ease of implementation. CDC hosted an in-person meeting of the experts that was held on June 23–24, 2015, in Atlanta, Georgia, to seek their views on the evidence and draft recommendations and to better understand their premeeting ratings. CDC sought the experts' individual opinions at the meeting. Although there was widespread agreement on some of the recommendations, there was disagreement on others. Experts did not vote on the recommendations or seek to come to a consensus. Decisions about recommendations to be included in the guideline, and their rationale, were made by CDC. After revising the guideline, CDC sent written copies of it to each of the experts for review and asked for any additional comments; CDC reviewed these written comments and considered them when making further revisions to the draft guideline. The experts have not reviewed the final version of the guideline.

Federal Partner Engagement

Given the scope of this guideline and the interest of agencies across the federal government in appropriate pain management, opioid prescribing, and related outcomes, CDC invited its National Institute of Occupational Safety and Health and CDC's federal partners to observe the expert meeting, provide written comments on the full draft guideline after the meeting, and review the guideline through an agency clearance process; CDC reviewed comments and incorporated changes. Interagency collaboration will be critical for translating these recommendations into clinical practice. Federal partners included representatives from the Substance Abuse and Mental Health Services Administration, the National Institute on Drug Abuse, FDA, the U.S. Department of Veterans Affairs, the U.S. Department of Defense, the Office of the National Coordinator for Health Information Technology, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, AHRQ, and the Office of National Drug Control Policy.

Stakeholder Comment

Given the importance of the guideline for a wide variety of stakeholders, CDC also invited review from a Stakeholder Review Group (SRG) to provide comment so that CDC could consider modifications that would improve the recommendations' specificity, applicability, and ease of implementation. The SRG included representatives from professional organizations that represent specialties that commonly prescribe opioids (e.g., pain medicine, physical medicine and rehabilitation), delivery systems within which opioid prescribing occurs (e.g., hospitals), and representation from community organizations with interests in pain management and opioid prescribing.* Representatives from each of the SRG organizations were provided a copy of the guideline for comment. Each of these representatives provided written comments. Once input was received from the full SRG, CDC reviewed all comments and carefully considered them when revising the draft guideline.

Constituent Engagement

To obtain initial perspectives from constituents on the recommendation statements, including clinicians and prospective patients, CDC convened a constituent engagement webinar and circulated information about the webinar in advance through announcements to partners. CDC hosted the webinar on September 16 and 17, 2015, provided information about the methodology for developing the guideline, and presented the key recommendations. A fact sheet was posted on the CDC Injury Center website (http://www.cdc.gov/injury) summarizing the guideline development process and clinical practice areas addressed in the guideline; instructions were included on how to submit comments via email. CDC received comments during and for 2 days following the first webinar. Over 1,200 constituent comments were received. Comments were reviewed and carefully considered when revising the draft guideline.

Peer Review

Per the final information quality bulletin for peer review (https://www.whitehouse.gov/sites/default/files/omb/memoranda/fy2005/m05-03.pdf), peer review requirements applied to this guideline because it provides influential

scientific information that could have a clear and substantial impact on public- and private-sector decisions. Three experts independently reviewed the guideline to determine the reasonableness and strength of recommendations; the clarity with which scientific uncertainties were clearly identified; and the rationale, importance, clarity, and ease of implementation of the recommendations.* CDC selected peer reviewers based on expertise, diversity of scientific viewpoints, and independence from the guideline development process. CDC assessed and managed potential conflicts of interest using a process similar to the one as described for solicitation of expert opinion. No financial interests were identified in the disclosure and review process, and nonfinancial activities were determined to be of minimal risk; thus, no significant conflict of interest concerns were identified. CDC placed the names of peer reviewers on the CDC and the National Center for Injury Prevention and Control Peer Review Agenda websites that are used to provide information about the peer review of influential documents. CDC reviewed peer review comments and revised the draft guideline accordingly.

Public Comment

To obtain comments from the public on the full guideline, CDC published a notice in the *Federal Register* (80 FR 77351) announcing the availability of the guideline and the supporting clinical and contextual evidence reviews for public comment. The comment period closed January 13, 2016. CDC received more than 4,350 comments from the general public, including patients with chronic pain, clinicians, families who have lost loved ones to overdose, medical associations, professional organizations, academic institutions, state and local governments, and industry. CDC reviewed each of the comments and carefully considered them when revising the draft guideline.

Federal Advisory Committee Review and Recommendation

The National Center for Injury Prevention and Control (NCIPC) Board of Scientific Counselors (BSC) is a federal advisory committee that advises and makes recommendations to the Secretary of the Department of Health and Human Services, the Director of CDC, and the Director of NCIPC.* The BSC makes recommendations regarding policies, strategies, objectives, and priorities, and reviews progress toward injury and violence prevention. CDC sought the BSC's advice on the draft guideline. BSC members are special government employees appointed as CDC advisory committee members; as such, all members completed an OGE Form 450 to disclose relevant interests. BSC members also reported on their disclosures during meetings. Disclosures for the BSC are reported in the guideline.

To assist in guideline review, on December 14, 2015, via Federal Register notice, CDC announced the intent to form an Opioid Guideline Workgroup (OGW) to provide observations on the draft guideline to the BSC. CDC provided the BSC with the draft guideline as well as summaries of comments provided to CDC by stakeholders, constituents, and peer reviewers, and edits made to the draft guideline in response. During an open meeting held on January 7, 2016, the BSC recommended the formation of the OGW. The OGW included a balance of perspectives from audiences directly affected by the guideline, audiences that would be directly involved with implementing the recommendations, and audiences qualified to provide representation. The OGW comprised clinicians, subject matter experts, and a patient representative, with the following perspectives represented: primary care, pain medicine, public health, behavioral health, substance abuse treatment, pharmacy, patients, and research.* Additional sought-after attributes were appropriate academic and clinical training and relevant clinical experience; high scientific standing; and knowledge of the patient, clinician, and caregiver perspectives. In accordance with CDC policy, two BSC committee members also served as OGW members, with one serving as the OGW Chair. The professional credentials and interests of OGW members were carefully reviewed to identify possible conflicts of interest such as financial relationships with industry, intellectual preconceptions, or previously stated public positions. Only OGW members whose interests were determined to be minimal were selected. When an activity was perceived as having the potential to affect a specific aspect of the recommendations, the activity was disclosed, and the OGW member was recused from discussions related to that specific aspect of the recommendations (e.g., urine drug testing and abuse-deterrent formulations). Disclosures for the OGW are reported. CDC and the OGW identified ad-hoc consultants to supplement the workgroup expertise, when needed, in the areas of pediatrics, occupational medicine, obstetrics and gynecology, medical ethics, addiction psychiatry, physical medicine and rehabilitation, guideline development methodology, and the perspective of a family member who lost a loved one to opioid use disorder or overdose.

The BSC charged the OGW with reviewing the quality of the clinical and contextual evidence reviews and reviewing each of the recommendation statements and accompanying rationales. For each recommendation statement, the OGW considered the quality of the evidence, the balance of benefits and risks, the values and preferences of clinicians and patients, the cost feasibility, and the category designation

of the recommendation (A or B). The OGW also reviewed supplementary documents, including input provided by the CEG, SRG, peer reviewers, and the public. OGW members discussed the guideline accordingly during virtual meetings and drafted a summary report of members' observations, including points of agreement and disagreement, and delivered the report to the BSC.

NCIPC announced an open meeting of the NCIPC BSC in the Federal Register on January 11, 2015. The BSC met on January 28, 2016, to discuss the OGW report and deliberate on the draft guideline itself. Members of the public provided comments at this meeting. After discussing the OGW report, deliberating on specific issues about the draft guideline identified at the meeting, and hearing public comment, the BSC voted unanimously: to support the observations made by the OGW; that CDC adopt the guideline recommendations that, according to the workgroup's report, had unanimous or majority support; and that CDC further consider the guideline recommendations for which the group had mixed opinions. CDC carefully considered the OGW observations, public comments, and BSC recommendations, and revised the guideline in response.

Summary of the Clinical Evidence Review

Primary Clinical Questions

CDC conducted a clinical systematic review of the scientific evidence to identify the effectiveness, benefits, and harms of long-term opioid therapy for chronic pain, consistent with the GRADE approach (*47*,*48*). Long-term opioid therapy is defined as use of opioids on most days for >3 months. A previously published AHRQ-funded systematic review on the effectiveness and risks of long-term opioid therapy for chronic pain comprehensively addressed four clinical questions (*14*,*52*). CDC, with the assistance of a methodology expert, searched the literature to identify newly published studies on these four original questions. Because long-term opioid use might be affected by use of opioids for acute pain, CDC subsequently developed a fifth clinical question (last in the series below), and in collaboration with a methodologist conducted a systematic review of the scientific evidence to address it. In brief, five clinical questions were addressed:

- The effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for long term (≥1 year) outcomes related to pain, function, and quality of life, and how effectiveness varies according to the type/cause of pain, patient demographics, and patient comorbidities (Key Question [KQ] 1).
- The risks of opioids versus placebo or no opioids on abuse, addiction, overdose, and other harms, and how harms vary according to the type/cause of pain, patient demographics, patient comorbidities, and dose (KQ2).
- The comparative effectiveness of opioid dosing strategies (different methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations of chronic pain; decreasing opioid doses or tapering off versus continuation; and different tapering protocols and strategies) (KQ3).
- The accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse; the effectiveness of risk mitigation strategies (use of risk prediction instruments); effectiveness of risk mitigation strategies including opioid management plans, patient education, urine drug testing, prescription drug monitoring program (PDMP) data, monitoring instruments, monitoring intervals, pill counts, and abuse-deterrent formulations for reducing risk for opioid overdose, addiction, abuse, or misuse; and the comparative effectiveness of treatment strategies for managing patients with addiction (KQ4).
- The effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on long-term use (KQ5).

The review was focused on the effectiveness of long-term opioid therapy on long-term (>1 year) outcomes related to pain, function, and quality of life to ensure that findings are relevant to patients with chronic pain and long-term opioid prescribing. The effectiveness of short-term opioid therapy has already been established (*10*). However, opioids have unique effects such as tolerance and physical dependence that might influence assessments of benefit over time. These effects raise questions about whether findings on short-term effectiveness of opioid therapy can be extrapolated to estimate benefits of long-term therapy for chronic pain. Thus, it is important to consider studies that provide data on long-term benefit. For certain opioid-related harms (overdose, fractures, falls, motor vehicle crashes), observational studies were included with outcomes measured at shorter intervals because such outcomes can occur early during opioid therapy, and such harms are not captured well in short-term clinical trials. A detailed listing of the key questions is provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026).

Clinical Evidence Systematic Review Methods

Complete methods and data for the 2014 AHRQ report, upon which this updated systematic review is based, have been published previously (*14*,*52*). Study authors developed the protocol using a standardized process (*53*) with input from experts and the public and registered the protocol in the PROSPERO database (*54*). For the 2014 AHRQ report, a research librarian searched MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsycINFO, and CINAHL for English-language articles published January 2008 through August 2014, using search terms for opioid therapy, specific opioids, chronic pain, and comparative study designs. Also included were relevant studies from an earlier review (*10*) in which searches were conducted without a date restriction, reference lists were reviewed, and ClinicalTrials.gov was searched. CDC updated the AHRQ literature search using the same search strategies as in the original review including studies published before April, 2015. Seven additional studies met inclusion criteria and were added to the review. CDC used the GRADE approach outlined in the ACIP Handbook for Developing Evidence-Based Recommendations (*47*) to rate the quality of evidence for the full body of evidence (evidence from the 2014 AHRQ review plus the update) for each clinical question. Evidence was categorized into the following types: type 1 (randomized clinical trials or overwhelming evidence from observational studies), type 2 (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies), type 3 (observational studies, or randomized clinical trials with notable limitations), or type 4 (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations). When no studies were present, evidence was considered to be insufficient. Per GRADE methods, type of evidence was categorized by study design as well as a function of limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and constellation of plausible biases that could change effects. Results were synthesized qualitatively, highlighting new evidence identified during the update process. Meta-analysis was not attempted due to the small numbers of studies, variability in study designs and clinical heterogeneity, and methodological shortcomings of the studies. More detailed information about data sources and searches, study selection, data extraction and quality assessment, data synthesis, and update search yield and new evidence for the current review is provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026).

Summary of Findings for Clinical Questions

The main findings of this updated review are consistent with the findings of the 2014 AHRQ report (*14*). In summary, evidence on long-term opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits versus no opioid therapy, though evidence suggests risk for serious harms that appears to be dose-dependent. These findings supplement findings from a previous review of the effectiveness of opioids for adults with chronic noncancer pain. In this previous review, based on randomized trials predominantly ≤12 weeks in duration, opioids were found to be moderately effective for pain relief, with small benefits for functional outcomes; although estimates vary, based on uncontrolled studies, a high percentage of patients discontinued long-term opioid use because of lack of efficacy and because of adverse events (*10*).

The GRADE evidence summary with type of evidence ratings for the five clinical questions for the current evidence review are outlined (Table 1). This summary is based on studies included in the AHRQ 2014 review (35 studies) plus additional studies identified in the updated search (seven studies). Additional details on findings from the original review are provided in the full 2014 AHRQ report (*14*,*52*). Full details on the clinical evidence review findings supporting this guideline are provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026).

Effectiveness

For KQ1, no study of opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for chronic pain evaluated long-term (≥1 year) outcomes related to pain, function, or quality of life. Most placebo-controlled randomized clinical trials were ≤6 weeks in duration. Thus, the body of evidence for KQ1 is rated as insufficient (0 studies contributing) (*14*).

Harms

For KQ2, the body of evidence is rated as type 3 (12 studies contributing; 11 from the original review plus one new study). One fair-quality cohort study found that long-term opioid therapy is associated with increased risk for an opioid abuse or dependence diagnosis (as defined by ICD-9-CM codes) versus no opioid prescription (*22*). Rates of opioid abuse or dependence diagnosis ranged from 0.7% with lower-dose (≤36 MME) chronic therapy to 6.1% with higher-dose (≥120 MME) chronic therapy, versus 0.004% with no opioids prescribed. Ten fair-quality uncontrolled studies reported estimates of opioid abuse, addiction, and related outcomes (*55*–*65*). In primary care settings, prevalence of opioid dependence

(using DSM-IV criteria) ranged from 3% to 26% (*55*,*56*,*59*). In pain clinic settings, prevalence of addiction ranged from 2% to 14% (*57*,*58*,*60*,*61*,*63–65*).

Factors associated with increased risk for misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications (*55*,*62*). Two studies reported on the association between opioid use and risk for overdose (*66*,*67*). One large fair-quality retrospective cohort study found that recent opioid use was associated with increased risk for any overdose events and serious overdose events versus nonuse (*66*). It also found higher doses associated with increased risk. Relative to 1–19 MME/day, the adjusted hazard ratio (HR) for any overdose event (consisting of mostly nonfatal overdose) was 1.44 for 20 to 49 MME/day, 3.73 for 50–99 MME/day, and 8.87 for ≥100 MME/day. A similar pattern was observed for serious overdose. A good-quality population-based, nested case-control study also found a dose-dependent association with risk for overdose death (*67*). Relative to 1–19 MME/day, the adjusted odds ratio (OR) was 1.32 for 20–49 MME/day, 1.92 for 50–99 MME/day, 2.04 for 100–199 MME/day, and 2.88 for ≥200 MME/day.

Findings of increased fracture risk for current opioid use, versus nonuse, were mixed in two studies (*68*,*69*). Two studies found an association between opioid use and increased risk for cardiovascular events (*70*,*71*). Indirect evidence was found for endocrinologic harms (increased use of medications for erectile dysfunction or testosterone from one previously included study; laboratory-defined androgen deficiency from one newly reviewed study) (*72*,*73*). One study found that opioid dosages ≥20 MME/day were associated with increased odds of road trauma among drivers (*74*).

Opioid Dosing Strategies

For KQ3, the body of evidence is rated as type 4 (14 studies contributing; 12 from the original review plus two new studies). For initiation and titration of opioids, the 2014 AHRQ report found insufficient evidence from three fair-quality, open-label trials to determine comparative effectiveness of ER/LA versus immediate-release opioids for titrating patients to stable pain control (*75*,*76*). One new fair-quality cohort study of Veterans Affairs patients found initiation of therapy with an ER/LA opioid associated with greater risk for nonfatal overdose than initiation with an immediate-release opioid, with risk greatest in the first 2 weeks after initiation of treatment (*77*).

For comparative effectiveness and harms of ER/LA opioids, the 2014 AHRQ report included three randomized, head-to-head trials of various ER/LA opioids that found no clear differences in 1-year outcomes related to pain or function (*78–80*) but had methodological shortcomings. A fair-quality retrospective cohort study based on national Veterans Health Administration system pharmacy data found that methadone was associated with lower overall risk for all-cause mortality versus morphine (*81*), and a fair-quality retrospective cohort study based on Oregon Medicaid data found no statistically significant differences between methadone and long-acting morphine in risk for death or overdose symptoms (*82*). However, a new observational study (*83*) found methadone associated with increased risk for overdose versus sustained-release morphine among Tennessee Medicaid patients. The observed inconsistency in study findings suggests that risks of methadone might vary in different settings as a function of different monitoring and management protocols, though more research is needed to understand factors associated with safer methadone prescribing.

For dose escalation, the 2014 AHRQ report included one fair-quality randomized trial that found no differences between more liberal dose escalation and maintenance of current doses after 12 months in pain, function, all-cause withdrawals, or withdrawals due to opioid misuse (*84*). However, the difference in opioid dosages prescribed at the end of the trial was relatively small (mean 52 MME/day with more liberal dosing versus 40 MME/day). Evidence on other comparisons related to opioid dosing strategies (ER/LA versus immediate-release opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled continuous dosing versus as-needed dosing; or opioid rotation versus maintenance of current therapy; long-term effects of strategies for treating acute exacerbations of chronic pain) was not available or too limited to determine effects on long-term clinical outcomes. For example, evidence on the comparative effectiveness of opioid tapering or discontinuation versus maintenance, and of different opioid tapering strategies, was limited to small, poor-quality studies (*85–87*).

Risk Assessment and Mitigation

For KQ4, the body of evidence is rated as type 3 for the accuracy of risk assessment tools and insufficient for the effectiveness of use of risk assessment tools and mitigation strategies in reducing harms (six studies contributing; four from the original review plus two new studies). The 2014 AHRQ report included four studies (*88–91*) on the accuracy of risk assessment instruments, administered prior to opioid therapy initiation, for predicting opioid abuse or misuse. Results for the Opioid Risk Tool (ORT) (*89–91*) were extremely inconsistent; evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings. One additional fair-quality (*92*) and one poor-quality (*93*) study identified for this update compared the predictive accuracy of the ORT, the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), and the Brief Risk Interview.

For the ORT, sensitivity was 0.58 and 0.75 and specificity 0.54 and 0.86; for the SOAPP-R, sensitivity was 0.53 and 0.25 and specificity 0.62 and 0.73; and for the Brief Risk Interview, sensitivity was 0.73 and 0.83 and specificity 0.43 and 0.88. For the ORT, positive likelihood ratios ranged from noninformative (positive likelihood ratio close to 1) to moderately useful (positive likelihood ratio >5). The SOAPP-R was associated with noninformative likelihood ratios (estimates close to 1) in both studies.

No study evaluated the effectiveness of risk mitigation strategies (use of risk assessment instruments, opioid management plans, patient education, urine drug testing, use of PDMP data, use of monitoring instruments, more frequent monitoring intervals, pill counts, or use of abuse-deterrent formulations) for improving outcomes related to overdose, addiction, abuse, or misuse.

Effects of Opioid Therapy for Acute Pain on Long-Term Use

For KQ5, the body of evidence is rated as type 3 (two new studies contributing). Two fair-quality retrospective cohort studies found opioid therapy prescribed for acute pain associated with greater likelihood of long-term use. One study evaluated opioid-naïve patients who had undergone low-risk surgery, such as cataract surgery and varicose vein stripping (*94*). Use of opioids within 7 days of surgery was associated with increased risk for use at 1 year. The other study found that among patients with a workers' compensation claim for acute low back pain, compared to patients who did not receive opioids early after injury (defined as use within 15 days following onset of pain), patients who did receive early opioids had an increased likelihood of receiving five or more opioid prescriptions 30–730 days following onset that increased with greater early exposure. Versus no early opioid use, the adjusted OR was 2.08 (95% CI = 1.55–2.78) for 1–140 MME/day and increased to 6.14 (95% confidence interval [CI] = 4.92–7.66) for ≥450 MME/day (*95*).

Summary of the Contextual Evidence Review

Primary Areas of Focus

Contextual evidence is complementary information that assists in translating the clinical research findings into recommendations. CDC conducted contextual evidence reviews on four topics to supplement the clinical evidence review findings:

- Effectiveness of nonpharmacologic (e.g., cognitive behavioral therapy [CBT], exercise therapy, interventional treatments, and multimodal pain treatment) and nonopioid pharmacologic treatments (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants, and anticonvulsants), including studies of any duration.
- Benefits and harms of opioid therapy (including additional studies not included in the clinical evidence review, such as studies that were not restricted to patients with chronic pain, evaluated outcomes at any duration, performed ecological analyses, or used observational study designs other than cohort and case-cohort control studies) related to specific opioids, high-dose therapy, co-prescription with other controlled substances, duration of use, special populations, and potential usefulness of risk stratification/mitigation approaches, in addition to effectiveness of treatments associated with addressing potential harms of opioid therapy (opioid use disorder).
- Clinician and patient values and preferences related to opioids and medication risks, benefits, and use.
- Resource allocation including costs and economic efficiency of opioid therapy and risk mitigation strategies.

CDC also reviewed clinical guidelines that were relevant to opioid prescribing and could inform or complement the CDC recommendations under development (e.g., guidelines on nonpharmacologic and nonopioid pharmacologic treatments and guidelines with recommendations related to specific clinician actions such as urine drug testing or opioid tapering protocols).

Contextual Evidence Review Methods

CDC conducted a contextual evidence review to assist in developing the recommendations by providing an assessment of the balance of benefits and harms, values and preferences, and cost, consistent with the GRADE approach. Given the public health urgency for developing opioid prescribing recommendations, a rapid review was required for the contextual evidence review for the current guideline. Rapid reviews are used when there is a need to streamline the systematic review process to obtain evidence quickly (*96*). Methods used to streamline the process include limiting searches by databases, years, and languages considered, and truncating quality assessment and data abstraction protocols. CDC conducted "rapid reviews" of the contextual evidence on nonpharmacologic and nonopioid pharmacologic treatments, benefits and harms, values and preferences, and resource allocation.

Detailed information about contextual evidence data sources and searches, inclusion criteria, study selection, and

data extraction and synthesis are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027). In brief, CDC conducted systematic literature searches to identify original studies, systematic reviews, and clinical guidelines, depending on the topic being searched. CDC also solicited publication referrals from subject matter experts. Given the need for a rapid review process, grey literature (e.g., literature by academia, organizations, or government in the forms of reports, documents, or proceedings not published by commercial publishers) was not systematically searched. Database sources, including MEDLINE, PsycINFO, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, varied by topic. Multiple reviewers scanned study abstracts identified through the database searches and extracted relevant studies for review. CDC constructed narrative summaries and tables based on relevant articles that met inclusion criteria, which are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027).

Findings from the contextual reviews provide indirect evidence and should be interpreted accordingly. CDC did not formally rate the quality of evidence for the studies included in the contextual evidence review using the GRADE method. The studies that addressed benefits and harms, values and preferences, and resource allocation most often employed observational methods, used short follow-up periods, and evaluated selected samples. Therefore the strength of the evidence from these contextual review areas was considered to be low, comparable to type 3 or type 4 evidence. The quality of evidence for nonopioid pharmacologic and nonpharmacologic pain treatments was generally rated as moderate, comparable to type 2 evidence, in systematic reviews and clinical guidelines (e.g., for treatment of chronic neuropathic pain, low back pain, osteoarthritis, and fibromyalgia). Similarly, the quality of evidence on pharmacologic and psychosocial opioid use disorder treatment was generally rated as moderate, comparable to type 2 evidence, in systematic reviews and clinical guidelines.

Summary of Findings for Contextual Areas

Full narrative reviews and tables that summarize key findings from the contextual evidence review are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027).

Effectiveness of Nonpharmacologic and Nonopioid Pharmacologic Treatments

Several nonpharmacologic and nonopioid pharmacologic treatments have been shown to be effective in managing chronic pain in studies ranging in duration from 2 weeks to 6 months. For example, CBT that trains patients in behavioral techniques and helps patients modify situational factors and cognitive processes that exacerbate pain has small positive effects on disability and catastrophic thinking (*97*). Exercise therapy can help reduce pain and improve function in chronic low back pain (*98*), improve function and reduce pain in osteoarthritis of the knee (*99*) and hip (*100*), and improve well-being, fibromyalgia symptoms, and physical function in fibromyalgia (*101*). Multimodal and multidisciplinary therapies (e.g., therapies that combine exercise and related therapies with psychologically based approaches) can help reduce pain and improve function more effectively than single modalities (*102*,*103*). Nonopioid pharmacologic approaches used for pain include analgesics such as acetaminophen, NSAIDs, and cyclooxygenase 2 (COX-2) inhibitors; selected anticonvulsants; and selected antidepressants (particularly tricyclics and serotonin and norepinephrine reuptake inhibitors [SNRIs]). Multiple guidelines recommend acetaminophen as first-line pharmacotherapy for osteoarthritis (*104*–*109*) or for low back pain (*110*) but note that it should be avoided in liver failure and that dosage should be reduced in patients with hepatic insufficiency or a history of alcohol abuse (*109*). Although guidelines also recommend NSAIDs as first-line treatment for osteoarthritis or low back pain (*106*,*110*), NSAIDs and COX-2 inhibitors do have risks, including gastrointestinal bleeding or perforation as well as renal and cardiovascular risks (*111*). FDA has recently strengthened existing label warnings that NSAIDs increase risks for heart attack and stroke, including that these risks might increase with longer use or at higher doses (*112*). Several guidelines agree that first- and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin), tricyclic antidepressants, and SNRIs (*113*–*116*). Interventional approaches such as epidural injection for certain conditions (e.g., lumbar radiculopathy) can provide short-term improvement in pain (*117*–*119*). Epidural injection has been associated with rare but serious adverse events, including loss of vision, stroke, paralysis, and death (*120*).

Benefits and Harms of Opioid Therapy

Balance between benefits and harms is a critical factor influencing the strength of clinical recommendations. In particular, CDC considered what is known from the epidemiology research about benefits and harms related to specific opioids and formulations, high dose therapy, co-prescription with other controlled substances, duration of use, special populations, and risk stratification and mitigation approaches. Additional information on benefits and harms of long-term opioid therapy from studies meeting rigorous selection criteria is provided in the clinical evidence review (e.g., see KQ2). CDC also considered the number of persons experiencing chronic pain, numbers potentially benefiting

from opioids, and numbers affected by opioid-related harms. A review of these data is presented in the background section of this document, with detailed information provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027). Finally, CDC considered the effectiveness of treatments that addressed potential harms of opioid therapy (opioid use disorder).

Regarding specific opioids and formulations, as noted by FDA, there are serious risks of ER/LA opioids, and the indication for this class of medications is for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment in patients for whom other treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain (*121*). Time-scheduled opioid use was associated with substantially higher average daily opioid dosage than as-needed opioid use in one study (*122*). Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain. Methadone has been found to account for as much as a third of opioid-related overdose deaths involving single or multiple drugs in states that participated in the Drug Abuse Warning Network, which was more than any opioid other than oxycodone, despite representing <2% of opioid prescriptions outside of opioid treatment programs in the United States; further, methadone was involved in twice as many single-drug deaths as any other prescription opioid (*123*).

Regarding high-dose therapy, several epidemiologic studies that were excluded from the clinical evidence review because patient samples were not restricted to patients with chronic pain also examined the association between opioid dosage and overdose risk (*23*,*24*,*124*–*126*). Consistent with the clinical evidence review, the contextual review found that opioid-related overdose risk is dose-dependent, with higher opioid dosages associated with increased overdose risk. Two of these studies (*23*,*24*), as well as the two studies in the clinical evidence review (*66*,*67*), evaluated similar MME/day dose ranges for association with overdose risk. In these four studies, compared with opioids prescribed at <20 MME/day, the odds of overdose among patients prescribed opioids for chronic nonmalignant pain were between 1.3 (*67*) and 1.9 (*24*) for dosages of 20 to <50 MME/day, between 1.9 (*67*) and 4.6 (*24*) for dosages of 50 to <100 MME/day, and between 2.0 (*67*) and 8.9 (*66*) for dosages of ≥100 MME/day. Compared with dosages of 1–<20 MME/day, absolute risk difference approximation for 50–<100 MME/day was 0.15% for fatal overdose (*24*) and 1.40% for any overdose (*66*), and for ≥100 MME/day was 0.25% for fatal overdose (*24*) and 4.04% for any overdose (*66*). A recent study of Veterans Health Administration patients with chronic pain found that patients who died of overdoses related to opioids were prescribed higher opioid dosages (mean: 98 MME/day; median: 60 MME/day) than controls (mean: 48 MME/day, median: 25 MME/day) (*127*). Finally, another recent study of overdose deaths among state residents with and without opioid prescriptions revealed that prescription opioid-related overdose mortality rates rose rapidly up to prescribed doses of 200 MME/day, after which the mortality rates continued to increase but grew more gradually (*128*). A listing of common opioid medications and their MME equivalents is provided (Table 2).

Regarding coprescription of opioids with benzodiazepines, epidemiologic studies suggest that concurrent use of benzodiazepines and opioids might put patients at greater risk for potentially fatal overdose. Three studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 31%–61% of decedents (*67*,*128*,*129*). In one of these studies (*67*), among decedents who received an opioid prescription, those whose deaths were related to opioids were more likely to have obtained opioids from multiple physicians and pharmacies than decedents whose deaths were not related to opioids.

Regarding duration of use, patients can experience tolerance and loss of effectiveness of opioids over time (*130*). Patients who do not experience clinically meaningful pain relief early in treatment (i.e., within 1 month) are unlikely to experience pain relief with longer-term use (*131*).

Regarding populations potentially at greater risk for harm, risk is greater for patients with sleep apnea or other causes of sleep-disordered breathing, patients with renal or hepatic insufficiency, older adults, pregnant women, patients with depression or other mental health conditions, and patients with alcohol or other substance use disorders. Interpretation of clinical data on the effects of opioids on sleep-disordered breathing is difficult because of the types of study designs and methods employed, and there is no clear consensus regarding association with risk for developing obstructive sleep apnea syndrome (*132*). However, opioid therapy can decrease respiratory drive, a high percentage of patients on long-term opioid therapy have been reported to have an abnormal apnea-hypopnea index (*133*), opioid therapy can worsen central sleep apnea in obstructive sleep apnea patients, and it can cause further desaturation in obstructive sleep apnea patients not on continuous positive airway pressure (CPAP) (*31*). Reduced renal or hepatic function can result in greater peak effect and longer duration of action and reduce the dose at which respiratory depression and overdose occurs (*134*). Age-related changes in patients aged ≥65 years, such as reduced renal function and medication clearance, even in the absence of renal disease (*135*), result in a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose. Older adults might also be at increased risk for falls and fractures related to opioids (*136*–*138*). Opioids used

in pregnancy can be associated with additional risks to both mother and fetus. Some studies have shown an association of opioid use in pregnancy with birth defects, including neural tube defects (*139*,*140*), congenital heart defects (*140*), and gastroschisis (*140*); preterm delivery (*141*), poor fetal growth (*141*), and stillbirth (*141*). Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome (*142*). Patients with mental health comorbidities and patients with histories of substance use disorders might be at higher risk than other patients for opioid use disorder (*62*,*143*,*144*). Recent analyses found that depressed patients were at higher risk for drug overdose than patients without depression, particularly at higher opioid dosages, although investigators were unable to distinguish unintentional overdose from suicide attempts (*145*). In case-control and case-cohort studies, substance abuse/dependence was more prevalent among patients experiencing overdose than among patients not experiencing overdose (12% versus 6% [*66*], 40% versus 10% [*24*], and 26% versus 9% [*23*]).

Regarding risk stratification approaches, limited evidence was found regarding benefits and harms. Potential benefits of PDMPs and urine drug testing include the ability to identify patients who might be at higher risk for opioid overdose or opioid use disorder, and help determine which patients will benefit from greater caution and increased monitoring or interventions when risk factors are present. For example, one study found that most fatal overdoses could be identified retrospectively on the basis of two pieces of information, multiple prescribers and high total daily opioid dosage, both important risk factors for overdose (*124*,*146*) that are available to prescribers in the PDMP (*124*). However, limited evaluation of PDMPs at the state level has revealed mixed effects on changes in prescribing and mortality outcomes (*28*). Potential harms of risk stratification include underestimation of risks of opioid therapy when screening tools are not adequately sensitive, as well as potential overestimation of risk, which could lead to inappropriate clinical decisions.

Regarding risk mitigation approaches, limited evidence was found regarding benefits and harms. Although no studies were found to examine prescribing of naloxone with opioid pain medication in primary care settings, naloxone distribution through community-based programs providing prevention services for substance users has been demonstrated to be associated with decreased risk for opioid overdose death at the community level (*147*).

Concerns have been raised that prescribing changes such as dose reduction might be associated with unintended negative consequences, such as patients seeking heroin or other illicitly obtained opioids (*148*) or interference with appropriate pain treatment (*149*). With the exception of a study noting an association between an abuse-deterrent formulation of OxyContin and heroin use, showing that some patients in qualitative interviews reported switching to another opioid, including heroin, for many reasons, including cost and availability as well as ease of use (*150*), CDC did not identify studies evaluating these potential outcomes.

Finally, regarding the effectiveness of opioid use disorder treatments, methadone and buprenorphine for opioid use disorder have been found to increase retention in treatment and to decrease illicit opioid use among patients with opioid use disorder involving heroin (*151*–*153*). Although findings are mixed, some studies suggest that effectiveness is enhanced when psychosocial treatments (e.g., contingency management, community reinforcement, psychotherapeutic counseling, and family therapy) are used in conjunction with medication-assisted therapy; for example, by reducing opioid misuse and increasing retention during maintenance therapy, and improving compliance after detoxification (*154*,*155*).

Clinician and Patient Values and Preferences

Clinician and patient values and preferences can inform how benefits and harms of long-term opioid therapy are weighted and estimate the effort and resources required to effectively provide implementation support. Many physicians lack confidence in their ability to prescribe opioids safely (*156*), to predict (*157*) or detect (*158*) prescription drug abuse, and to discuss abuse with their patients (*158*). Although clinicians have reported favorable beliefs and attitudes about improvements in pain and quality of life attributed to opioids (*159*), most consider prescription drug abuse to be a "moderate" or "big" problem in their community, and large proportions are "very" concerned about opioid addiction (55%) and death (48%) (*160*). Clinicians do not consistently use practices intended to decrease the risk for misuse, such as PDMPs (*161*,*162*), urine drug testing (*163*), and opioid treatment agreements (*164*). This is likely due in part to challenges related to registering for PDMP access and logging into the PDMP (which can interrupt normal clinical workflow if data are not integrated into electronic health record systems) (*165*), competing clinical demands, perceived inadequate time to discuss the rationale for urine drug testing and to order confirmatory testing, and feeling unprepared to interpret and address results (*166*).

Many patients do not have an opinion about "opioids" or know what this term means (*167*). Most are familiar with the term "narcotics." About a third associated "narcotics" with addiction or abuse, and about half feared "addiction" from long-term "narcotic" use (*168*). Most patients taking opioids experience side effects (73% of patients taking hydrocodone for noncancer pain [*11*], 96% of patients taking opioids for chronic pain [*12*]), and side effects, rather than pain relief,

have been found to explain most of the variation in patients' preferences related to taking opioids (*12*). For example, patients taking hydrocodone for noncancer pain commonly reported side effects including dizziness, headache, fatigue, drowsiness, nausea, vomiting, and constipation (*11*). Patients with chronic pain in focus groups emphasized effectiveness of goal setting for increasing motivation and functioning (*168*). Patients taking high dosages report reliance on opioids despite ambivalence about their benefits (*169*) and regardless of pain reduction, reported problems, concerns, side effects, or perceived helpfulness (*13*).

Resource Allocation

Resource allocation (cost) is an important consideration in understanding the feasibility of clinical recommendations. CDC searched for evidence on opioid therapy compared with other treatments; costs of misuse, abuse, and overdose from prescription opioids; and costs of specific risk mitigation strategies (e.g., urine drug testing). Yearly direct and indirect costs related to prescription opioids have been estimated (based on studies published since 2010) to be $53.4 billion for nonmedical use of prescription opioids (*170*); $55.7 billion for abuse, dependence (i.e., opioid use disorder), and misuse of prescription opioids (*171*); and $20.4 billion for direct and indirect costs related to opioid-related overdose alone (*172*). In 2012, total expenses for outpatient prescription opioids were estimated at $9.0 billion, an increase of 120% from 2002 (*173*). Although there are perceptions that opioid therapy for chronic pain is less expensive than more time-intensive nonpharmacologic management approaches, many pain treatments, including acetaminophen, NSAIDs, tricyclic antidepressants, and massage therapy, are associated with lower mean and median annual costs compared with opioid therapy (*174*). COX-2 inhibitors, SNRIs, anticonvulsants, topical analgesics, physical therapy, and CBT are also associated with lower median annual costs compared with opioid therapy (*174*). Limited information was found on costs of strategies to decrease risks associated with opioid therapy; however, urine drug testing, including screening and confirmatory tests, has been estimated to cost $211–$363 per test (*175*).

Recommendations

The recommendations are grouped into three areas for consideration:

- Determining when to initiate or continue opioids for chronic pain.
- Opioid selection, dosage, duration, follow-up, and discontinuation.
- Assessing risk and addressing harms of opioid use.

There are 12 recommendations (Box 1). Each recommendation is followed by a rationale for the recommendation, with considerations for implementation noted. In accordance with the ACIP GRADE process, CDC based the recommendations on consideration of the clinical evidence, contextual evidence (including benefits and harms, values and preferences, resource allocation), and expert opinion. For each recommendation statement, CDC notes the recommendation category (A or B) and the type of the evidence (1, 2, 3, or 4) supporting the statement (Box 2). Expert opinion is reflected within each of the recommendation rationales. While there was not an attempt to reach consensus among experts, experts from the Core Expert Group and from the Opioid Guideline Workgroup ("experts") expressed overall, general support for all recommendations. Where differences in expert opinion emerged for detailed actions within the clinical recommendations or for implementation considerations, CDC notes the differences of opinion in the supporting rationale statements.

Category A recommendations indicate that most patients should receive the recommended course of action; category B recommendations indicate that different choices will be appropriate for different patients, requiring clinicians to help patients arrive at a decision consistent with patient values and preferences and specific clinical situations. Consistent with the ACIP (*47*) and GRADE process (*48*), category A recommendations were made, even with type 3 and 4 evidence, when there was broad agreement that the advantages of a clinical action greatly outweighed the disadvantages based on a consideration of benefits and harms, values and preferences, and resource allocation. Category B recommendations were made when there was broad agreement that the advantages and disadvantages of a clinical action were more balanced, but advantages were significant enough to warrant a recommendation. All recommendations are category A recommendations, with the exception of recommendation 10, which is rated as category B. Recommendations were associated with a range of evidence types, from type 2 to type 4.

In summary, the categorization of recommendations was based on the following assessment:

- No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials ≤6 weeks in duration).
- Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury).
- Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic treatments compared with long-term opioid therapy, with less harm.

BOX 1. CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

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

* All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required); see full guideline for evidence ratings.

BOX 2. Interpretation of recommendation categories and evidence type

Recommendation Categories

Based on evidence type, balance between desirable and undesirable effects, values and preferences, and resource allocation (cost).

Category A recommendation: Applies to all persons; most patients should receive the recommended course of action.

Category B recommendation: Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type

Based on study design as well as a function of limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and constellation of plausible biases that could change effects.

Type 1 evidence: Randomized clinical trials or overwhelming evidence from observational studies.

Type 2 evidence: Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.

Type 3 evidence: Observational studies or randomized clinical trials with notable limitations.

Type 4 evidence: Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

Determining When to Initiate or Continue Opioids for Chronic Pain

1. **Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (recommendation category: A, evidence type: 3).**

Patients with pain should receive treatment that provides the greatest benefits relative to risks. The contextual evidence review found that many nonpharmacologic therapies, including physical therapy, weight loss for knee osteoarthritis, psychological therapies such as CBT, and certain interventional procedures can ameliorate chronic pain. There is high-quality evidence that exercise therapy (a prominent modality in physical therapy) for hip (*100*) or knee (*99*) osteoarthritis reduces pain and improves function immediately after treatment and that the improvements are sustained for at least 2–6 months. Previous guidelines have strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of the knee or hip (*176*). Exercise therapy also can help reduce pain and improve function in low back pain and can improve global well-being and physical function in fibromyalgia (*98*,*101*). Multimodal therapies and multidisciplinary biopsychosocial rehabilitation-combining approaches (e.g., psychological therapies with exercise) can reduce long-term pain and disability compared with usual care and compared with physical treatments (e.g., exercise) alone. Multimodal therapies are not always available or reimbursed by insurance and can be time-consuming and costly for patients. Interventional approaches such as arthrocentesis and intraarticular glucocorticoid injection for pain associated with rheumatoid arthritis (*117*) or osteoarthritis (*118*) and subacromial corticosteroid injection for rotator cuff disease (*119*) can provide short-term improvement in pain and function. Evidence is insufficient to determine the extent to which repeated glucocorticoid injection increases potential risks such as articular cartilage changes (in osteoarthritis) and sepsis (*118*). Serious adverse events are rare but have been reported with epidural injection (*120*).

Several nonopioid pharmacologic therapies (including acetaminophen, NSAIDs, and selected antidepressants and anticonvulsants) are effective for chronic pain. In particular, acetaminophen and NSAIDs can be useful for arthritis and low back pain. Selected anticonvulsants such as pregabalin and gabapentin can improve pain in diabetic neuropathy and post-herpetic neuralgia (contextual evidence review). Pregabalin, gabapentin, and carbamazepine are FDA-approved for treatment of certain neuropathic pain conditions, and pregabalin is FDA approved for fibromyalgia management. In patients with or without depression, tricyclic antidepressants and SNRIs provide effective analgesia for neuropathic pain conditions including diabetic neuropathy and post-herpetic neuralgia, often at lower dosages and with a shorter time to onset of effect than for treatment of depression (see contextual evidence review). Tricyclics and SNRIs can also relieve fibromyalgia symptoms. The SNRI duloxetine is FDA-approved for the treatment of diabetic neuropathy and fibromyalgia. Because patients with chronic pain often suffer from concurrent depression (*144*), and depression can exacerbate physical symptoms including pain (*177*), patients with co-occurring pain and depression are especially likely to benefit from antidepressant medication (see Recommendation 8). Nonopioid pharmacologic therapies

are not generally associated with substance use disorder, and the numbers of fatal overdoses associated with nonopioid medications are a fraction of those associated with opioid medications (contextual evidence review). For example, acetaminophen, NSAIDs, and opioid pain medication were involved in 881, 228, and 16,651 pharmaceutical overdose deaths in the United States in 2010 (*178*). However, nonopioid pharmacologic therapies are associated with certain risks, particularly in older patients, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, gastrointestinal, and liver disease (see contextual evidence review). For example, acetaminophen can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic alcohol use or liver disease (*109*). NSAID use has been associated with gastritis, peptic ulcer disease, cardiovascular events (*111*,*112*), and fluid retention, and most NSAIDs (choline magnesium trilisate and selective COX-2 inhibitors are exceptions) interfere with platelet aggregation (*179*). Clinicians should review FDA-approved labeling including boxed warnings before initiating treatment with any pharmacologic therapy.

Although opioids can reduce pain during short-term use, the clinical evidence review found insufficient evidence to determine whether pain relief is sustained and whether function or quality of life improves with long-term opioid therapy (KQ1). While benefits for pain relief, function, and quality of life with long-term opioid use for chronic pain are uncertain, risks associated with long-term opioid use are clearer and significant. Based on the clinical evidence review, long-term opioid use for chronic pain is associated with serious risks including increased risk for opioid use disorder, overdose, myocardial infarction, and motor vehicle injury (KQ2). At a population level, more than 165,000 persons in the United States have died from opioid pain-medication-related overdoses since 1999 (see Contextual Evidence Review).

Integrated pain management requires coordination of medical, psychological, and social aspects of health care and includes primary care, mental health care, and specialist services when needed (*180*). Nonpharmacologic physical and psychological treatments such as exercise and CBT are approaches that encourage active patient participation in the care plan, address the effects of pain in the patient's life, and can result in sustained improvements in pain and function without apparent risks. Despite this, these therapies are not always or fully covered by insurance, and access and cost can be barriers for patients. For many patients, aspects of these approaches can be used even when there is limited access to specialty care. For example, previous guidelines have strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of the knee or hip (*176*) and maintenance of activity for patients with low back pain (*110*). A randomized trial found no difference in reduced chronic low back pain intensity, frequency or disability between patients assigned to relatively low-cost group aerobics and individual physiotherapy or muscle reconditioning sessions (*181*). Low-cost options to integrate exercise include brisk walking in public spaces or use of public recreation facilities for group exercise. CBT addresses psychosocial contributors to pain and improves function (*97*). Primary care clinicians can integrate elements of a cognitive behavioral approach into their practice by encouraging patients to take an active role in the care plan, by supporting patients in engaging in beneficial but potentially anxiety-provoking activities, such as exercise (*179*), or by providing education in relaxation techniques and coping strategies. In many locations, there are free or low-cost patient support, self-help, and educational community-based programs that can provide stress reduction and other mental health benefits. Patients with more entrenched anxiety or fear related to pain, or other significant psychological distress, can be referred for formal therapy with a mental health specialist (e.g., psychologist, psychiatrist, clinical social worker). Multimodal therapies should be considered for patients not responding to single-modality therapy, and combinations should be tailored depending on patient needs, cost, and convenience.

To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis. Detailed recommendations on diagnosis are provided in other guidelines (*110*,*179*), but evaluation should generally include a focused history, including history and characteristics of pain and potentially contributing factors (e.g., function, psychosocial stressors, sleep) and physical exam, with imaging or other diagnostic testing only if indicated (e.g., if severe or progressive neurologic deficits are present or if serious underlying conditions are suspected) (*110*,*179*). For complex pain syndromes, pain specialty consultation can be considered to assist with diagnosis as well as management. Diagnosis can help identify disease-specific interventions to reverse or ameliorate pain; for example, improving glucose control to prevent progression of diabetic neuropathy; immune-modulating agents for rheumatoid arthritis; physical or occupational therapy to address posture, muscle weakness, or repetitive occupational motions that contribute to musculoskeletal pain; or surgical intervention to relieve mechanical/compressive pain (*179*). The underlying mechanism for most pain syndromes can be categorized as neuropathic (e.g., diabetic neuropathy, postherpetic neuralgia, fibromyalgia), or nociceptive (e.g., osteoarthritis, muscular back pain). The diagnosis and pathophysiologic mechanism of pain have implications for symptomatic pain treatment with medication. For example, evidence is limited or insufficient

for improved pain or function with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as low back pain (*182*), headache (*183*), and fibromyalgia (*184*). Although NSAIDs can be used for exacerbations of nociceptive pain, other medications (e.g., tricyclics, selected anticonvulsants, or transdermal lidocaine) generally are recommended for neuropathic pain. In addition, improvement of neuropathic pain can begin weeks or longer after symptomatic treatment is initiated (*179*). Medications should be used only after assessment and determination that expected benefits outweigh risks given patient-specific factors. For example, clinicians should consider falls risk when selecting and dosing potentially sedating medications such as tricyclics, anticonvulsants, or opioids, and should weigh risks and benefits of use, dose, and duration of NSAIDs when treating older adults as well as patients with hypertension, renal insufficiency, or heart failure, or those with risk for peptic ulcer disease or cardiovascular disease. Some guidelines recommend topical NSAIDs for localized osteoarthritis (e.g., knee osteoarthritis) over oral NSAIDs in patients aged ≥75 years to minimize systemic effects (*176*).

Experts agreed that opioids should not be considered first-line or routine therapy for chronic pain (i.e., pain continuing or expected to continue >3 months or past the time of normal tissue healing) outside of active cancer, palliative, and end-of-life care, given small to moderate short-term benefits, uncertain long-term benefits, and potential for serious harms; although evidence on long-term benefits of nonopioid therapies is also limited, these therapies are also associated with short-term benefits, and risks are much lower. This does not mean that patients should be required to sequentially "fail" nonpharmacologic and nonopioid pharmacologic therapy before proceeding to opioid therapy. Rather, expected benefits specific to the clinical context should be weighed against risks before initiating therapy. In some clinical contexts (e.g., headache or fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used. In other situations (e.g., serious illness in a patient with poor prognosis for return to previous level of function, contraindications to other therapies, and clinician and patient agreement that the overriding goal is patient comfort), opioids might be appropriate regardless of previous therapies used. In addition, when opioid pain medication is used, it is more likely to be effective if integrated with nonpharmacologic therapy. Nonpharmacologic approaches such as exercise and CBT should be used to reduce pain and improve function in patients with chronic pain. Nonopioid pharmacologic therapy should be used when benefits outweigh risks and should be combined with nonpharmacologic therapy to reduce pain and improve function. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate, to provide greater benefits to patients in improving pain and function.

2. **Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (recommendation category: A, evidence type: 4).**

The clinical evidence review found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent. In addition, studies on currently available risk assessment instruments were sparse and showed inconsistent results (KQ4). The clinical evidence review for the current guideline considered studies with outcomes examined at ≥1 year that compared opioid use versus nonuse or placebo. Studies of opioid therapy for chronic pain that did not have a nonopioid control group have found that although many patients discontinue opioid therapy for chronic noncancer pain due to adverse effects or insufficient pain relief, there is weak evidence that patients who are able to continue opioid therapy for at least 6 months can experience clinically significant pain relief and insufficient evidence that function or quality of life improves (*185*). These findings suggest that it is very difficult for clinicians to predict whether benefits of opioids for chronic pain will outweigh risks of ongoing treatment for individual patients. Opioid therapy should not be initiated without consideration of an "exit strategy" to be used if the therapy is unsuccessful.

Experts agreed that before opioid therapy is initiated for chronic pain outside of active cancer, palliative, and end-of-life care, clinicians should determine how effectiveness will be evaluated and should establish treatment goals with patients. Because the line between acute pain and initial chronic pain is not always clear, it might be difficult for clinicians to determine when they are initiating opioids for chronic pain rather than treating acute pain. Pain lasting longer than 3 months or past the time of normal tissue healing (which could be substantially shorter than 3 months, depending on the condition) is generally no longer considered acute. However, establishing treatment goals with a patient who has already received opioid therapy for 3 months would defer this discussion well past the point of

initiation of opioid therapy for chronic pain. Clinicians often write prescriptions for long-term use in 30-day increments, and opioid prescriptions written for ≥30 days are likely to represent initiation or continuation of long-term opioid therapy. Before writing an opioid prescription for ≥30 days, clinicians should establish treatment goals with patients. Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy. Although the clinical evidence review did not find studies evaluating the effectiveness of written agreements or treatment plans (KQ4), clinicians and patients who set a plan in advance will clarify expectations regarding how opioids will be prescribed and monitored, as well as situations in which opioids will be discontinued or doses tapered (e.g., if treatment goals are not met, opioids are no longer needed, or adverse events put the patient at risk) to improve patient safety.

Experts thought that goals should include improvement in both pain relief and function (and therefore in quality of life). However, there are some clinical circumstances under which reductions in pain without improvement in physical function might be a more realistic goal (e.g., diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma). Experts noted that function can include emotional and social as well as physical dimensions. In addition, experts emphasized that mood has important interactions with pain and function. Experts agreed that clinicians may use validated instruments such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (*186*) to track patient outcomes. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function (*187*). Monitoring progress toward patient-centered functional goals (e.g., walking the dog or walking around the block, returning to part-time work, attending family sports or recreational activities) can also contribute to the assessment of functional improvement. Clinicians should use these goals in assessing benefits of opioid therapy for individual patients and in weighing benefits against risks of continued opioid therapy (see Recommendation 7, including recommended intervals for follow-up). Because depression, anxiety, and other psychological co-morbidities often coexist with and can interfere with resolution of pain, clinicians should use validated instruments to assess for these conditions (see Recommendation 8) and ensure that treatment for these conditions is optimized. If patients receiving opioid therapy for chronic pain do not experience meaningful improvements in both pain and function compared with prior to initiation of opioid therapy, clinicians should consider working with patients to taper and discontinue opioids (see Recommendation 7) and should use nonpharmacologic and nonopioid pharmacologic approaches to pain management (see Recommendation 1).

3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (recommendation category: A, evidence type: 3).

The clinical evidence review did not find studies evaluating effectiveness of patient education or opioid treatment plans as risk-mitigation strategies (KQ4). However, the contextual evidence review found that many patients lack information about opioids and identified concerns that some clinicians miss opportunities to effectively communicate about safety. Given the substantial evidence gaps on opioids, uncertain benefits of long-term use, and potential for serious harms, patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions. Experts agreed that essential elements to communicate to patients before starting and periodically during opioid therapy include realistic expected benefits, common and serious harms, and expectations for clinician and patient responsibilities to mitigate risks of opioid therapy.

Clinicians should involve patients in decisions about whether to start or continue opioid therapy. Given potentially serious risks of long-term opioid therapy, clinicians should ensure that patients are aware of potential benefits of, harms of, and alternatives to opioids before starting or continuing opioid therapy. Clinicians are encouraged to have open and honest discussions with patients to inform mutual decisions about whether to start or continue opioid therapy. Important considerations include the following:

- Be explicit and realistic about expected benefits of opioids, explaining that while opioids can reduce pain during short-term use, there is no good evidence that opioids improve pain or function with long-term use, and that complete relief of pain is unlikely (clinical evidence review, KQ1).
- Emphasize improvement in function as a primary goal and that function can improve even when pain is still present.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder that can cause distress and inability to fulfill major role obligations.
- Advise patients about common effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids. To prevent constipation associated with opioid use, advise patients to increase

hydration and fiber intake and to maintain or increase physical activity. Stool softeners or laxatives might be needed.
- Discuss effects that opioids might have on ability to safely operate a vehicle, particularly when opioids are initiated, when dosages are increased, or when other central nervous system depressants, such as benzodiazepines or alcohol, are used concurrently.
- Discuss increased risks for opioid use disorder, respiratory depression, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not taking more opioids or taking them more often.
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.
- Discuss risks to household members and other individuals if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient, and that young children are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (*188*).
- Discuss the importance of periodic reassessment to ensure that opioids are helping to meet patient goals and to allow opportunities for opioid discontinuation and consideration of additional nonpharmacologic or nonopioid pharmacologic treatment options if opioids are not effective or are harmful.
- Discuss planned use of precautions to reduce risks, including use of prescription drug monitoring program information (see Recommendation 9) and urine drug testing (see Recommendation 10). Consider including discussion of naloxone use for overdose reversal (see Recommendation 8).
- Consider whether cognitive limitations might interfere with management of opioid therapy (for older adults in particular) and, if so, determine whether a caregiver can responsibly co-manage medication therapy. Discuss the importance of reassessing safer medication use with both the patient and caregiver.

Given the possibility that benefits of opioid therapy might diminish or that risks might become more prominent over time, it is important that clinicians review expected benefits and risks of continued opioid therapy with patients periodically, at least every 3 months (see Recommendation 7).

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids (recommendation category: A, evidence type: 4).

ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of opioids such as oxycodone, oxymorphone, hydrocodone, and morphine. The clinical evidence review found a fair-quality study showing a higher risk for overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with immediate-release opioids (*77*). The clinical evidence review did not find evidence that continuous, time-scheduled use of ER/LA opioids is more effective or safer than intermittent use of immediate-release opioids or that time-scheduled use of ER/LA opioids reduces risks for opioid misuse or addiction (KQ3).

In 2014, the FDA modified the labeling for ER/LA opioid pain medications, noting serious risks and recommending that ER/LA opioids be reserved for "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment" when "alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain" and not used as "as needed" pain relievers (*121*). FDA has also noted that some ER/LA opioids are only appropriate for opioid-tolerant patients, defined as patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) for at least 1 week (*189*). Time-scheduled opioid use can be associated with greater total average daily opioid dosage compared with intermittent, as-needed opioid use (contextual evidence review). In addition, experts indicated that there was not enough evidence to determine the safety of using immediate-release opioids for breakthrough pain when ER/LA opioids are used for chronic pain outside of active cancer pain, palliative care, or end-of-life care, and that this practice might be associated with dose escalation.

Abuse-deterrent technologies have been employed to prevent manipulation intended to defeat extended-release properties of ER/LA opioids and to prevent opioid use by unintended routes of administration, such as injection of oral opioids. As indicated in FDA guidance for industry on evaluation and labeling of abuse-deterrent opioids (*190*), although abuse-deterrent technologies are expected to make manipulation of opioids more difficult or less rewarding, they do not prevent

opioid abuse through oral intake, the most common route of opioid abuse, and can still be abused by nonoral routes. The "abuse-deterrent" label does not indicate that there is no risk for abuse. No studies were found in the clinical evidence review assessing the effectiveness of abuse-deterrent technologies as a risk mitigation strategy for deterring or preventing abuse. In addition, abuse-deterrent technologies do not prevent unintentional overdose through oral intake. Experts agreed that recommendations could not be offered at this time related to use of abuse-deterrent formulations.

In comparing different ER/LA formulations, the clinical evidence review found inconsistent results for overdose risk with methadone versus other ER/LA opioids used for chronic pain (KQ3). The contextual evidence review found that methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for chronic pain. In addition, methadone is associated with cardiac arrhythmias along with QT prolongation on the electrocardiogram, and it has complicated pharmacokinetics and pharmacodynamics, including a long and variable half-life and peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect. Experts noted that the pharmacodynamics of methadone are subject to more inter-individual variability than other opioids. In regard to other ER/LA opioid formulations, experts noted that the absorption and pharmacodynamics of transdermal fentanyl are complex, with gradually increasing serum concentration during the first part of the 72-hour dosing interval, as well as variable absorption based on factors such as external heat. In addition, the dosing of transdermal fentanyl in mcg/hour, which is not typical for a drug used by outpatients, can be confusing. Experts thought that these complexities might increase the risk for fatal overdose when methadone or transdermal fentanyl is prescribed to a patient who has not used it previously or by clinicians who are not familiar with its effects.

Experts agreed that for patients not already receiving opioids, clinicians should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week. When changing to an ER/LA opioid for a patient previously receiving a different immediate-release opioid, clinicians should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance. Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction because decreased clearance of drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations. Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given potentially increased risk and diminishing returns of such an approach for chronic pain.

When an ER/LA opioid is prescribed, using one with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk. In particular, unusual characteristics of methadone and of transdermal fentanyl make safe prescribing of these medications for pain especially challenging.

- Methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients, including risk assessment for QT prolongation and consideration of electrocardiographic monitoring, should consider prescribing methadone for pain. A clinical practice guideline that contains further guidance regarding methadone prescribing for pain has been published previously (*191*).
- Because dosing effects of transdermal fentanyl are often misunderstood by both clinicians and patients, only clinicians who are familiar with the dosing and absorption properties of transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day (recommendation category: A, evidence type: 3).

Benefits of high-dose opioids for chronic pain are not established. The clinical evidence review found only one study (*84*) addressing effectiveness of dose titration for outcomes related to pain control, function, and quality of life (KQ3). This randomized trial found no difference in pain or function between a more liberal opioid dose escalation strategy and maintenance of current dosage. (These groups were prescribed average dosages of 52 and 40 MME/day, respectively, at the end of the trial.) At the same time, risks for serious harms

related to opioid therapy increase at higher opioid dosage. The clinical evidence review found that higher opioid dosages are associated with increased risks for motor vehicle injury, opioid use disorder, and overdose (KQ2). The clinical and contextual evidence reviews found that opioid overdose risk increases in a dose-response manner, that dosages of 50–<100 MME/day have been found to increase risks for opioid overdose by factors of 1.9 to 4.6 compared with dosages of 1–<20 MME/day, and that dosages ≥100 MME/day are associated with increased risks of overdose 2.0–8.9 times the risk at 1–<20 MME/day. In a national sample of Veterans Health Administration patients with chronic pain who were prescribed opioids, mean prescribed opioid dosage among patients who died from opioid overdose was 98 MME (median 60 MME) compared with mean prescribed opioid dosage of 48 MME (median 25 MME) among patients not experiencing fatal overdose (*127*).

The contextual evidence review found that although there is not a single dosage threshold below which overdose risk is eliminated, holding dosages <50 MME/day would likely reduce risk among a large proportion of patients who would experience fatal overdose at higher prescribed dosages. Experts agreed that lower dosages of opioids reduce the risk for overdose, but that a single dosage threshold for safe opioid use could not be identified. Experts noted that daily opioid dosages close to or greater than 100 MME/day are associated with significant risks, that dosages <50 MME/day are safer than dosages of 50–100 MME/day, and that dosages <20 MME/day are safer than dosages of 20–50 MME/day. One expert thought that a specific dosage at which the benefit/risk ratio of opioid therapy decreases could not be identified. Most experts agreed that, in general, increasing dosages to 50 or more MME/day increases overdose risk without necessarily adding benefits for pain control or function and that clinicians should carefully reassess evidence of individual benefits and risks when considering increasing opioid dosages to ≥50 MME/day. Most experts also agreed that opioid dosages should not be increased to ≥90 MME/day without careful justification based on diagnosis and on individualized assessment of benefits and risks.

When opioids are used for chronic pain outside of active cancer, palliative, and end-of-life care, clinicians should start opioids at the lowest possible effective dosage (the lowest starting dosage on product labeling for patients not already taking opioids and according to product labeling guidance regarding tolerance for patients already taking opioids). Clinicians should use additional caution when initiating opioids for patients aged ≥65 years and for patients with renal or hepatic insufficiency because decreased clearance of drugs in these patients can result in accumulation of drugs to toxic levels. Clinicians should use caution when increasing opioid dosages and increase dosage by the smallest practical amount because overdose risk increases with increases in opioid dosage. Although there is limited evidence to recommend specific intervals for dosage titration, a previous guideline recommended waiting at least five half-lives before increasing dosage and waiting at least a week before increasing dosage of methadone to make sure that full effects of the previous dosage are evident (*31*). Clinicians should re-evaluate patients after increasing dosage for changes in pain, function, and risk for harm (see Recommendation 7). Before increasing total opioid dosage to ≥50 MME/day, clinicians should reassess whether opioid treatment is meeting the patient's treatment goals (see Recommendation 2). If a patient's opioid dosage for all sources of opioids combined reaches or exceeds 50 MME/day, clinicians should implement additional precautions, including increased frequency of follow-up (see Recommendation 7) and considering offering naloxone and overdose prevention education to both patients and the patients' household members (see Recommendation 8). Clinicians should avoid increasing opioid dosages to ≥90 MME/day or should carefully justify a decision to increase dosage to ≥90 MME/day based on individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to harms as dosages approach 90 MME/day, other treatments and effectiveness, and recommendations based on consultation with pain specialists. If patients do not experience improvement in pain and function at ≥90 MME/day, or if there are escalating dosage requirements, clinicians should discuss other approaches to pain management with the patient, consider working with patients to taper opioids to a lower dosage or to taper and discontinue opioids (see Recommendation 7), and consider consulting a pain specialist. Some states require clinicians to implement clinical protocols at specific dosage levels. For example, before increasing long-term opioid therapy dosage to >120 MME/day, clinicians in Washington state must obtain consultation from a pain specialist who agrees that this is indicated and appropriate (*30*). Clinicians should be aware of rules related to MME thresholds and associated clinical protocols established by their states.

Established patients already taking high dosages of opioids, as well as patients transferring from other clinicians, might consider the possibility of opioid dosage reduction to be anxiety-provoking, and tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence. However, these patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk. Clinicians should explain in a nonjudgmental manner to patients already taking high opioid dosages (≥90 MME/day) that there is

now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages. Clinicians should empathically review benefits and risks of continued high-dosage opioid therapy and should offer to work with the patient to taper opioids to safer dosages. For patients who agree to taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan (see Recommendation 7). Experts noted that patients tapering opioids after taking them for years might require very slow opioid tapers as well as pauses in the taper to allow gradual accommodation to lower opioid dosages. Clinicians should remain alert to signs of anxiety, depression, and opioid use disorder (see Recommendations 8 and 12) that might be unmasked by an opioid taper and arrange for management of these co-morbidities. For patients agreeing to taper to lower opioid dosages as well as for those remaining on high opioid dosages, clinicians should establish goals with the patient for continued opioid therapy (see Recommendation 2), maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1), and consider consulting a pain specialist as needed to assist with pain management.

6. **Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (recommendation category: A, evidence type: 4).**

The clinical evidence review found that opioid use for acute pain (i.e., pain with abrupt onset and caused by an injury or other process that is not ongoing) is associated with long-term opioid use, and that a greater amount of early opioid exposure is associated with greater risk for long-term use (KQ5). Several guidelines on opioid prescribing for acute pain from emergency departments (*192*–*194*) and other settings (*195*,*196*) have recommended prescribing ≤3 days of opioids in most cases, whereas others have recommended ≤7 days (*197*) or <14 days (*30*). Because physical dependence on opioids is an expected physiologic response in patients exposed to opioids for more than a few days (contextual evidence review), limiting days of opioids prescribed also should minimize the need to taper opioids to prevent distressing or unpleasant withdrawal symptoms. Experts noted that more than a few days of exposure to opioids significantly increases hazards, that each day of unnecessary opioid use increases likelihood of physical dependence without adding benefit, and that prescriptions with fewer days' supply will minimize the number of pills available for unintentional or intentional diversion.

Experts agreed that when opioids are needed for acute pain, clinicians should prescribe opioids at the lowest effective dose and for no longer than the expected duration of pain severe enough to require opioids to minimize unintentional initiation of long-term opioid use. The lowest effective dose can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8). Experts thought, based on clinical experience regarding anticipated duration of pain severe enough to require an opioid, that in most cases of acute pain not related to surgery or trauma, a ≤3 days' supply of opioids will be sufficient. For example, in one study of the course of acute low back pain (not associated with malignancies, infections, spondylarthropathies, fractures, or neurological signs) in a primary care setting, there was a large decrease in pain until the fourth day after treatment with paracetamol, with smaller decreases thereafter (*198*). Some experts thought that because some types of acute pain might require more than 3 days of opioid treatment, it would be appropriate to recommend a range of ≤3–5 days or ≤3–7 days when opioids are needed. Some experts thought that a range including 7 days was too long given the expected course of severe acute pain for most acute pain syndromes seen in primary care.

Acute pain can often be managed without opioids. It is important to evaluate the patient for reversible causes of pain, for underlying etiologies with potentially serious sequelae, and to determine appropriate treatment. When the diagnosis and severity of nontraumatic, nonsurgical acute pain are reasonably assumed to warrant the use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids, often 3 days or less, unless circumstances clearly warrant additional opioid therapy. More than 7 days will rarely be needed. Opioid treatment for post-surgical pain is outside the scope of this guideline but has been addressed elsewhere (*30*). Clinicians should not prescribe additional opioids to patients "just in case" pain continues longer than expected. Clinicians should re-evaluate the subset of patients who experience severe acute pain that continues longer than the expected duration to confirm or revise the initial diagnosis and to adjust management accordingly. Given longer half-lives and longer duration of effects (e.g., respiratory depression) with ER/LA opioids such as methadone, fentanyl patches, or extended release versions of opioids such as oxycodone, oxymorphone, or morphine, clinicians should not prescribe ER/LA opioids for the treatment of acute pain.

7. **Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (recommendation category: A, evidence type: 4).**

Although the clinical evidence review did not find studies evaluating the effectiveness of more frequent monitoring intervals (KQ4), it did find that continuing opioid therapy for 3 months substantially increases risk for opioid use disorder (KQ2); therefore, follow-up earlier than 3 months might be necessary to provide the greatest opportunity to prevent the development of opioid use disorder. In addition, risk for overdose associated with ER/LA opioids might be particularly high during the first 2 weeks of treatment (KQ3). The contextual evidence review found that patients who do not have pain relief with opioids at 1 month are unlikely to experience pain relief with opioids at 6 months. Although evidence is insufficient to determine at what point within the first 3 months of opioid therapy the risks for opioid use disorder increase, reassessment of pain and function within 1 month of initiating opioids provides an opportunity to minimize risks of long-term opioid use by discontinuing opioids among patients not receiving a clear benefit from these medications. Experts noted that risks for opioid overdose are greatest during the first 3–7 days after opioid initiation or increase in dosage, particularly when methadone or transdermal fentanyl are prescribed; that follow-up within 3 days is appropriate when initiating or increasing the dosage of methadone; and that follow-up within 1 week might be appropriate when initiating or increasing the dosage of other ER/LA opioids.

Clinicians should evaluate patients to assess benefits and harms of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation. Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased or when total daily opioid dosage is ≥50 MME/day. Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone. At follow up, clinicians should assess benefits in function, pain control, and quality of life using tools such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (*186*) and/or asking patients about progress toward functional goals that have meaning for them (see Recommendation 2). Clinicians should also ask patients about common adverse effects such as constipation and drowsiness (see Recommendation 3), as well as asking about and assessing for effects that might be early warning signs for more serious problems such as overdose (e.g., sedation or slurred speech) or opioid use disorder (e.g., craving, wanting to take opioids in greater quantities or more frequently than prescribed, or difficulty controlling use). Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced.

Because of potential changes in the balance of benefits and risks of opioid therapy over time, clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, at least every 3 months. At reassessment, clinicians should determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function, whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events, signs of opioid use disorder (e.g., difficulty controlling use, work or family problems related to opioid use), whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued. Ideally, these reassessments would take place in person and be conducted by the prescribing clinician. In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other issues make follow-up visits challenging), follow-up assessments that allow the clinician to communicate with and observe the patient through video and audio could be conducted, with in-person visits occurring at least once per year. Clinicians should re-evaluate patients who are exposed to greater risk of opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a history of overdose, taking ≥50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months. If clinically meaningful improvements in pain and function are not sustained, if patients are taking high-risk regimens (e.g., dosages ≥50 MME/day or opioids combined with benzodiazepines) without evidence of benefit, if patients believe benefits no longer outweigh risks or if they request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events (e.g., an event leading to hospitalization or disability) or warning signs of serious adverse events, clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible. Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to assist with pain management.

Considerations for Tapering Opioids

Although the clinical evidence review did not find high-quality studies comparing the effectiveness of different tapering protocols for use when opioid dosage is reduced or opioids are discontinued (KQ3), tapers reducing weekly dosage by 10%–50% of the original dosage have been recommended by other clinical guidelines (*199*), and a rapid taper over 2–3 weeks has been recommended in the case of a severe adverse event such as overdose (*30*). Experts noted that tapers slower than 10% per week (e.g., 10% per month) also might be appropriate and better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for years). Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor.

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used. A decrease of 10% of the original dose per week is a reasonable starting point; experts agreed that tapering plans may be individualized based on patient goals and concerns. Experts noted that at times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages. Tapers may be considered successful as long as the patient is making progress. Once the smallest available dose is reached, the interval between doses can be extended. Opioids may be stopped when taken less frequently than once a day. More rapid tapers might be needed for patient safety under certain circumstances (e.g., for patients who have experienced overdose on their current dosage). Ultrarapid detoxification under anesthesia is associated with substantial risks, including death, and should not be used (*200*). Clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal. Patients who are not taking opioids (including patients who are diverting all opioids they obtain) do not require tapers. Clinicians should discuss with patients undergoing tapering the increased risk for overdose on abrupt return to a previously prescribed higher dose. Primary care clinicians should collaborate with mental health providers and with other specialists as needed to optimize nonopioid pain management (see Recommendation 1), as well as psychosocial support for anxiety related to the taper. More detailed guidance on tapering, including management of withdrawal symptoms has been published previously (*30*,*201*). If a patient exhibits signs of opioid use disorder, clinicians should offer or arrange for treatment of opioid use disorder (see Recommendation 12) and consider offering naloxone for overdose prevention (see Recommendation 8).

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present (recommendation category: A, evidence type: 4).

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on patient demographics or patient comorbidities (KQ2). However, based on the contextual evidence review and expert opinion, certain risk factors are likely to increase susceptibility to opioid-associated harms and warrant incorporation of additional strategies into the management plan to mitigate risk. Clinicians should assess these risk factors periodically, with frequency varying by risk factor and patient characteristics. For example, factors that vary more frequently over time, such as alcohol use, require more frequent follow up. In addition, clinicians should consider offering naloxone, re-evaluating patients more frequently (see Recommendation 7), and referring to pain and/or behavioral health specialists when factors that increase risk for harm, such as history of overdose, history of substance use disorder, higher dosages of opioids (≥50 MME/day), and concurrent use of benzodiazepines with opioids, are present.

Patients with Sleep-Disordered Breathing, Including Sleep Apnea

Risk factors for sleep-disordered breathing include congestive heart failure, and obesity. Experts noted that careful monitoring and cautious dose titration should be used if opioids are prescribed for patients with mild sleep-disordered breathing. Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing whenever possible to minimize risks for opioid overdose (contextual evidence review).

Pregnant Women

Opioids used in pregnancy might be associated with additional risks to both mother and fetus. Some studies have shown an association of opioid use in pregnancy with stillbirth, poor fetal growth, pre-term delivery, and birth defects (contextual evidence review). Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome. Clinicians and patients together should carefully weigh risks and benefits when making decisions

about whether to initiate opioid therapy for chronic pain during pregnancy. In addition, before initiating opioid therapy for chronic pain for reproductive-age women, clinicians should discuss family planning and how long-term opioid use might affect any future pregnancy. For pregnant women already receiving opioids, clinicians should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 7). For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered (*202*) (see Recommendation 12). Clinicians caring for pregnant women receiving opioids for pain or receiving buprenorphine or methadone for opioid use disorder should arrange for delivery at a facility prepared to monitor, evaluate for, and treat neonatal opioid withdrawal syndrome. In instances when travel to such a facility would present an undue burden on the pregnant woman, it is appropriate to deliver locally, monitor and evaluate the newborn for neonatal opioid withdrawal syndrome, and transfer the newborn for additional treatment if needed. Neonatal toxicity and death have been reported in breast-feeding infants whose mothers are taking codeine (contextual evidence review); previous guidelines have recommended that codeine be avoided whenever possible among mothers who are breast feeding and, if used, should be limited to the lowest possible dose and to a 4-day supply (*203*).

Patients with Renal or Hepatic Insufficiency

Clinicians should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency, given their decreased ability to process and excrete drugs, susceptibility to accumulation of opioids, and reduced therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review; see Recommendations 4, 5, and 7).

Patients Aged ≥65 Years

Inadequate pain treatment among persons aged ≥65 years has been documented (*204*). Pain management for older patients can be challenging given increased risks of both nonopioid pharmacologic therapies (see Recommendation 1) and opioid therapy in this population. Given reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review). Some older adults suffer from cognitive impairment, which can increase risk for medication errors and make opioid-related confusion more dangerous. In addition, older adults are more likely than younger adults to experience co-morbid medical conditions and more likely to receive multiple medications, some of which might interact with opioids (such as benzodiazepines). Clinicians should use additional caution and increased monitoring (see Recommendations 4, 5, and 7) to minimize risks of opioids prescribed for patients aged ≥65 years. Experts suggested that clinicians educate older adults receiving opioids to avoid risky medication-related behaviors such as obtaining controlled medications from multiple prescribers and saving unused medications. Clinicians should also implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Patients with Mental Health Conditions

Because psychological distress frequently interferes with improvement of pain and function in patients with chronic pain, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ)-9 or the PHQ-4 to assess for anxiety, post-traumatic stress disorder, and/or depression (*205*), might help clinicians improve overall pain treatment outcomes. Experts noted that clinicians should use additional caution and increased monitoring (see Recommendation 7) to lessen the increased risk for opioid use disorder among patients with mental health conditions (including depression, anxiety disorders, and PTSD), as well as increased risk for drug overdose among patients with depression. Previous guidelines have noted that opioid therapy should not be initiated during acute psychiatric instability or uncontrolled suicide risk, and that clinicians should consider behavioral health specialist consultation for any patient with a history of suicide attempt or psychiatric disorder (*31*). In addition, patients with anxiety disorders and other mental health conditions are more likely to receive benzodiazepines, which can exacerbate opioid-induced respiratory depression and increase risk for overdose (see Recommendation 11). Clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed. Treatment for depression can improve pain symptoms as well as depression and might decrease overdose risk (contextual evidence review). For treatment of chronic pain in patients with depression, clinicians should strongly consider using tricyclic or SNRI antidepressants for analgesic as well as antidepressant effects if these medications are not otherwise contraindicated (see Recommendation 1).

Patients with Substance Use Disorder

Illicit drugs and alcohol are listed as contributory factors on a substantial proportion of death certificates for opioid-related overdose deaths (contextual evidence review). Previous guidelines have recommended screening or risk assessment tools to identify patients at higher risk for misuse or abuse of opioids. However, the clinical evidence review found that currently available risk-stratification tools (e.g., Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain Version 1, SOAPP-R, and Brief Risk Interview) show insufficient accuracy for classification of patients as at low or high risk for abuse or misuse (KQ4). Clinicians should always exercise caution when considering or prescribing opioids for any patient with chronic pain outside of active cancer, palliative, and end-of-life care and should not overestimate the ability of these tools to rule out risks from long-term opioid therapy.

Clinicians should ask patients about their drug and alcohol use. Single screening questions can be used (*206*). For example, the question "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" (with an answer of one or more considered positive) was found in a primary care setting to be 100% sensitive and 73.5% specific for the detection of a drug use disorder compared with a standardized diagnostic interview (*207*). Validated screening tools such as the Drug Abuse Screening Test (DAST) (*208*) and the Alcohol Use Disorders Identification Test (AUDIT) (*209*) can also be used. Clinicians should use PDMP data (see Recommendation 9) and drug testing (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose. Clinicians should also provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 3) and ensure that patients receive effective treatment for substance use disorders when needed (see Recommendation 12).

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on past or current substance use disorder (KQ2), although a history of substance use disorder was associated with misuse. Similarly, based on contextual evidence, patients with drug or alcohol use disorders are likely to experience greater risks for opioid use disorder and overdose than persons without these conditions. If clinicians consider opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care for patients with drug or alcohol use disorders, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed. Because pain management in patients with substance use disorder can be complex, clinicians should consider consulting substance use disorder specialists and pain specialists regarding pain management for persons with active or recent past history of substance abuse. Experts also noted that clinicians should communicate with patients' substance use disorder treatment providers if opioids are prescribed.

Patients with Prior Nonfatal Overdose

Although studies were not identified that directly addressed the risk for overdose among patients with prior nonfatal overdose who are prescribed opioids, based on clinical experience, experts thought that prior nonfatal overdose would substantially increase risk for future nonfatal or fatal opioid overdose. If patients experience nonfatal opioid overdose, clinicians should work with them to reduce opioid dosage and to discontinue opioids when possible (see Recommendation 7). If clinicians continue opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed.

Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present

Naloxone is an opioid antagonist that can reverse severe respiratory depression; its administration by lay persons, such as friends and family of persons who experience opioid overdose, can save lives. Naloxone precipitates acute withdrawal among patients physically dependent on opioids. Serious adverse effects, such as pulmonary edema, cardiovascular instability, and seizures, have been reported but are rare at doses consistent with labeled use for opioid overdose (*210*). The contextual evidence review did not find any studies on effectiveness of prescribing naloxone for overdose prevention among patients prescribed opioids for chronic pain. However, there is evidence for effectiveness of naloxone provision in preventing opioid-related overdose death at the community level through community-based distribution (e.g., through overdose education and naloxone distribution programs in community service agencies) to persons at risk for overdose

(mostly due to illicit opiate use), and it is plausible that effectiveness would be observed when naloxone is provided in the clinical setting as well. Experts agreed that it is preferable not to initiate opioid treatment when factors that increase risk for opioid-related harms are present. Opinions diverged about the likelihood of naloxone being useful to patients and the circumstances under which it should be offered. However, most experts agreed that clinicians should consider offering naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids (see Recommendation 11), patients at risk for returning to a high dose to which they are no longer tolerant (e.g., patients recently released from prison), and patients taking higher dosages of opioids (≥50 MME/day). Practices should provide education on overdose prevention and naloxone use to patients receiving naloxone prescriptions and to members of their households. Experts noted that naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists. Resources for prescribing naloxone in primary care settings can be found through Prescribe to Prevent at http://prescribetoprevent.org.

9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (recommendation category: A, evidence type: 4).

PDMPs are state-based databases that collect information on controlled prescription drugs dispensed by pharmacies in most states and, in select states, by dispensing physicians as well. In addition, some clinicians employed by the federal government, including some clinicians in the Indian Health Care Delivery System, are not licensed in the states where they practice, and do not have access to PDMP data. Certain states require clinicians to review PDMP data prior to writing each opioid prescription (see state-level PDMP-related policies on the National Alliance for Model State Drug Laws website at http://www.namsdl.org/prescription-monitoring-programs.cfm). The clinical evidence review did not find studies evaluating the effectiveness of PDMPs on outcomes related to overdose, addiction, abuse, or misuse (KQ4). However, even though evidence is limited on the effectiveness of PDMP implementation at the state level on prescribing and mortality outcomes (*28*), the contextual evidence review found that most fatal overdoses were associated with patients receiving opioids from multiple prescribers and/or with patients receiving high total daily opioid dosages; information on both of these risk factors for overdose are available to prescribers in the PDMP. PDMP data also can be helpful when patient medication history is not otherwise available (e.g., for patients from other locales) and when patients transition care to a new clinician. The contextual evidence review also found that PDMP information could be used in a way that is harmful to patients. For example, it has been used to dismiss patients from clinician practices (*211*), which might adversely affect patient safety.

The contextual review found variation in state policies that affect timeliness of PDMP data (and therefore benefits of reviewing PDMP data) as well as time and workload for clinicians in accessing PDMP data. In states that permit delegating access to other members of the health care team, workload for prescribers can be reduced. These differences might result in a different balance of benefits to clinician workload in different states. Experts agreed that PDMPs are useful tools that should be consulted when starting a patient on opioid therapy and periodically during long-term opioid therapy. However, experts disagreed on how frequently clinicians should check the PDMP during long-term opioid therapy, given PDMP access issues and the lag time in reporting in some states. Most experts agreed that PDMP data should be reviewed every 3 months or more frequently during long-term opioid therapy. A minority of experts noted that, given the current burden of accessing PDMP data in some states and the lack of evidence surrounding the most effective interval for PDMP review to improve patient outcomes, annual review of PDMP data during long-term opioid therapy would be reasonable when factors that increase risk for opioid-related harms are not present.

Clinicians should review PDMP data for opioids and other controlled medications patients might have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or dangerous combinations (e.g., opioids combined with benzodiazepines) that put him or her at high risk for overdose. Ideally, PDMP data should be reviewed before every opioid prescription. This is recommended in all states with well-functioning PDMPs and where PDMP access policies make this practicable (e.g., clinician and delegate access permitted), but it is not currently possible in states without functional PDMPs or in those that do not permit certain prescribers to access them. As vendors and practices facilitate integration of PDMP information into regular clinical workflow (e.g., data made available in electronic health records), clinicians' ease of access in reviewing PDMP data is expected to improve.

In addition, improved timeliness of PDMP data will improve their value in identifying patient risks.

If patients are found to have high opioid dosages, dangerous combinations of medications, or multiple controlled substance prescriptions written by different clinicians, several actions can be taken to augment clinicians' abilities to improve patient safety:

- Clinicians should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).
- Clinicians should discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving opioids from more than one prescriber or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines) and consider offering naloxone (see Recommendation 8).
- Clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. Clinicians should communicate with others managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care (see Recommendation 11).
- Clinicians should calculate the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 5). If patients are found to be receiving high total daily dosages of opioids, clinicians should discuss their safety concerns with the patient, consider tapering to a safer dosage (see Recommendations 5 and 7), and consider offering naloxone (see Recommendation 8).
- Clinicians should discuss safety concerns with other clinicians who are prescribing controlled substances for their patient. Ideally clinicians should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other prescribers to improve the patient's safety.
- Clinicians should consider the possibility of a substance use disorder and discuss concerns with their patient (see Recommendation 12).
- If clinicians suspect their patient might be sharing or selling opioids and not taking them, clinicians should consider urine drug testing to assist in determining whether opioids can be discontinued without causing withdrawal (see Recommendations 7 and 10). A negative drug test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result (see Recommendation 10).

Experts agreed that clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendation 1], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendation 12]).

10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (recommendation category: B, evidence type: 4).

Concurrent use of opioid pain medications with other opioid pain medications, benzodiazepines, or heroin can increase patients' risk for overdose. Urine drug tests can provide information about drug use that is not reported by the patient. In addition, urine drug tests can assist clinicians in identifying when patients are not taking opioids prescribed for them, which might in some cases indicate diversion or other clinically important issues such as difficulties with adverse effects. Urine drug tests do not provide accurate information about how much or what dose of opioids or other drugs a patient took. The clinical evidence review did not find studies evaluating the effectiveness of urine drug screening for risk mitigation during opioid prescribing for pain (KQ4). The contextual evidence review found that urine drug testing can provide useful information about patients assumed not to be using unreported drugs. Urine drug testing results can be subject to misinterpretation and might sometimes be associated with practices that might harm patients (e.g., stigmatization, inappropriate termination from care). Routine use of urine drug tests with standardized policies at the practice or clinic level might destigmatize their use. Although random drug testing also might destigmatize urine drug testing, experts thought that truly random testing was not feasible in clinical practice. Some clinics obtain a urine specimen at every visit, but only send it for testing on a random schedule. Experts noted that in addition to direct costs of urine drug testing, which often are not covered fully by insurance and can be a burden for patients, clinician time is needed to interpret, confirm, and communicate results.

Experts agreed that prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should

use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin. There was some difference of opinion among experts as to whether this recommendation should apply to all patients, or whether this recommendation should entail individual decision making with different choices for different patients based on values, preferences, and clinical situations. While experts agreed that clinicians should use urine drug testing before initiating opioid therapy for chronic pain, they disagreed on how frequently urine drug testing should be conducted during long-term opioid therapy. Most experts agreed that urine drug testing at least annually for all patients was reasonable. Some experts noted that this interval might be too long in some cases and too short in others, and that the follow-up interval should be left to the discretion of the clinician. Previous guidelines have recommended more frequent urine drug testing in patients thought to be at higher risk for substance use disorder (*30*). However, experts thought that predicting risk prior to urine drug testing is challenging and that currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use disorder.

In most situations, initial urine drug testing can be performed with a relatively inexpensive immunoassay panel for commonly prescribed opioids and illicit drugs. Patients prescribed less commonly used opioids might require specific testing for those agents. The use of confirmatory testing adds substantial costs and should be based on the need to detect specific opioids that cannot be identified on standard immunoassays or on the presence of unexpected urine drug test results. Clinicians should be familiar with the drugs included in urine drug testing panels used in their practice and should understand how to interpret results for these drugs. For example, a positive "opiates" immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but this immunoassay does not detect synthetic opioids (e.g., fentanyl or methadone) and might not detect semisynthetic opioids (e.g., oxycodone). However, many laboratories use an oxycodone immunoassay that detects oxycodone and oxymorphone. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive. For example, hydromorphone is a metabolite of hydrocodone, and oxymorphone is a metabolite of oxycodone. Detailed guidance on interpretation of urine drug test results, including which tests to order and expected results, drug detection time in urine, drug metabolism, and other considerations has been published previously (*30*). Clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might be uncertainty about the clinical implications of a positive urine drug test for tetrahyrdocannabinol (THC). In addition, restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of urine drug testing, given the substantial costs associated with confirmatory testing methods. Before ordering urine drug testing, clinicians should have a plan for responding to unexpected results. Clinicians should explain to patients that urine drug testing is intended to improve their safety and should also explain expected results (e.g., presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient). Clinicians should ask patients about use of prescribed and other drugs and ask whether there might be unexpected results. This will provide an opportunity for patients to provide information about changes in their use of prescribed opioids or other drugs. Clinicians should discuss unexpected results with the local laboratory or toxicologist and with the patient. Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted to clarify the situation.

Clinicians should use unexpected results to improve patient safety (e.g., change in pain management strategy [see Recommendation 1], tapering or discontinuation of opioids [see Recommendation 7], more frequent re-evaluation [see Recommendation 7], offering naloxone [see Recommendation 8], or referral for treatment for substance use disorder [see Recommendation 12], all as appropriate). If tests for prescribed opioids are repeatedly negative, confirming that the patient is not taking the prescribed opioid, clinicians can discontinue the prescription without a taper. Clinicians should not dismiss patients from care based on a urine drug test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.

11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently

whenever possible (recommendation category: A, evidence type: 3).

Benzodiazepines and opioids both cause central nervous system depression and can decrease respiratory drive. Concurrent use is likely to put patients at greater risk for potentially fatal overdose. The clinical evidence review did not address risks of benzodiazepine co-prescription among patients prescribed opioids. However, the contextual evidence review found evidence in epidemiologic series of concurrent benzodiazepine use in large proportions of opioid-related overdose deaths, and a case-cohort study found concurrent benzodiazepine prescription with opioid prescription to be associated with a near quadrupling of risk for overdose death compared with opioid prescription alone (*212*). Experts agreed that although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. In addition, given that other central nervous system depressants (e.g., muscle relaxants, hypnotics) can potentiate central nervous system depression associated with opioids, clinicians should consider whether benefits outweigh risks of concurrent use of these drugs. Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation 9) and should consider involving pharmacists and pain specialists as part of the management team when opioids are co-prescribed with other central nervous system depressants. Because of greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and because tapering opioids can be associated with anxiety, when patients receiving both benzodiazepines and opioids require tapering to reduce risk for fatal respiratory depression, it might be safer and more practical to taper opioids first (see Recommendation 7). Clinicians should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death (contextual evidence review). A commonly used tapering schedule that has been used safely and with moderate success is a reduction of the benzodiazepine dose by 25% every 1–2 weeks (*213*,*214*). CBT increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper (*213*). If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific anti-depressants or other nonbenzodiazepine medications approved for anxiety should be offered. Experts emphasized that clinicians should communicate with mental health professionals managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (recommendation category: A, evidence type: 2).

Opioid use disorder (previously classified as opioid abuse or opioid dependence) is defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) as a problematic pattern of opioid use leading to clinically significant impairment or distress, manifested by at least two defined criteria occurring within a year (http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf) (*20*).

The clinical evidence review found prevalence of opioid dependence (using DSM-IV diagnosis criteria) in primary care settings among patients with chronic pain on opioid therapy to be 3%–26% (KQ2). As found in the contextual evidence review and supported by moderate quality evidence, opioid agonist or partial agonist treatment with methadone maintenance therapy or buprenorphine has been shown to be more effective in preventing relapse among patients with opioid use disorder (*151–153*). Some studies suggest that using behavioral therapies in combination with these treatments can reduce opioid misuse and increase retention during maintenance therapy and improve compliance after detoxification (*154*,*155*); behavioral therapies are also recommended by clinical practice guidelines (*215*). The cited studies primarily evaluated patients with a history of illicit opioid use, rather than prescription opioid use for chronic pain. Recent studies among patients with prescription opioid dependence (based on DSM-IV criteria) have found maintenance therapy with buprenorphine and buprenorphine-naloxone effective in preventing relapse (*216*,*217*). Treatment need in a community is often not met by capacity to provide buprenorphine or methadone maintenance therapy (*218*), and patient cost can be a barrier to buprenorphine treatment because insurance coverage of buprenorphine for opioid use disorder is often limited (*219*). Oral or long-acting injectable formulations of naltrexone can also be used as medication-assisted treatment for opioid use disorder in nonpregnant adults, particularly for highly motivated persons (*220*,*221*). Experts agreed that clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community and should work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.

If clinicians suspect opioid use disorder based on patient concerns or behaviors or on findings in prescription drug monitoring program data (see Recommendation 9) or from urine drug testing (see Recommendation 10), they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems. Clinicians should assess for the presence of opioid use disorder using DSM-5 criteria (*20*). Alternatively, clinicians can arrange for a substance use disorder treatment specialist to assess for the presence of opioid use disorder. For patients meeting criteria for opioid use disorder, clinicians should offer or arrange for patients to receive evidence-based treatment, usually medication-assisted treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies. Oral or long-acting injectable naltrexone, a long-acting opioid antagonist, can also be used in nonpregnant adults. Naltrexone blocks the effects of opioids if they are used but requires adherence to daily oral therapy or monthly injections. For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine (without naloxone) or methadone has been associated with improved maternal outcomes and should be offered (see Recommendation 8). Clinicians should also consider offering naloxone for overdose prevention to patients with opioid use disorder (see Recommendation 8). For patients with problematic opioid use that does not meet criteria for opioid use disorder, experts noted that clinicians can offer to taper and discontinue opioids (see Recommendation 7). For patients who choose to but are unable to taper, clinicians may reassess for opioid use disorder and offer opioid agonist therapy if criteria are met.

Physicians not already certified to provide buprenorphine in an office-based setting can undergo training to receive a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) that allows them to prescribe buprenorphine to treat patients with opioid use disorder. Physicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder should strongly consider obtaining this waiver. Information about qualifications and the process to obtain a waiver are available from SAMHSA (*222*). Clinicians do not need a waiver to offer naltrexone for opioid use disorder as part of their practice.

Additional guidance has been published previously (*215*) on induction, use, and monitoring of buprenorphine treatment (see Part 5) and naltrexone treatment (see Part 6) for opioid use disorder and on goals, components of, and types of effective psychosocial treatment that are recommended in conjunction with pharmacological treatment of opioid use disorder (see Part 7). Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office-based buprenorphine or naltrexone treatment provider, or from an opioid treatment program certified by SAMHSA to provide supervised medication-assisted treatment for patients with opioid use disorder. Clinicians should assist patients in finding qualified treatment providers and should arrange for patients to follow up with these providers, as well as arranging for ongoing coordination of care. Clinicians should not dismiss patients from their practice because of a substance use disorder because this can adversely affect patient safety and could represent patient abandonment. Identification of substance use disorder represents an opportunity for a clinician to initiate potentially life-saving interventions, and it is important for the clinician to collaborate with the patient regarding their safety to increase the likelihood of successful treatment. In addition, although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should continue to use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to provide optimal pain management.

Resources to help with arranging for treatment include SAMHSA's buprenorphine physician locator (http://buprenorphine.samhsa.gov/bwns_locator); SAMHSA's Opioid Treatment Program Directory (http://dpt2.samhsa.gov/treatment/directory.aspx); SAMHSA's Provider Clinical Support System for Opioid Therapies (http://pcss-o.org), which offers extensive experience in the treatment of substance use disorders and specifically of opioid use disorder, as well as expertise on the interface of pain and opioid misuse; and SAMHSA's Provider's Clinical Support System for Medication-Assisted Treatment (http://pcssmat.org), which offers expert physician mentors to answer questions about assessment for and treatment of substance use disorders.

Conclusions and Future Directions

Clinical guidelines represent one strategy for improving prescribing practices and health outcomes. Efforts are required to disseminate the guideline and achieve widespread adoption and implementation of the recommendations in clinical settings. CDC will translate this guideline into user-friendly materials for distribution and use by health systems, medical professional societies, insurers, public health departments, health information technology developers, and clinicians and engage in dissemination efforts. CDC has provided a

checklist for prescribing opioids for chronic pain (http://stacks.cdc.gov/view/cdc/38025), additional resources such as fact sheets (http://www.cdc.gov/drugoverdose/prescribing/resources.html), and will provide a mobile application to guide clinicians in implementing the recommendations. CDC will also work with partners to support clinician education on pain management options, opioid therapy, and risk mitigation strategies (e.g., urine drug testing). Activities such as development of clinical decision support in electronic health records to assist clinicians' treatment decisions at the point of care; identification of mechanisms that insurers and pharmacy benefit plan managers can use to promote safer prescribing within plans; and development of clinical quality improvement measures and initiatives to improve prescribing and patient care within health systems have promise for increasing guideline adoption and improving practice. In addition, policy initiatives that address barriers to implementation of the guidelines, such as increasing accessibility of PDMP data within and across states, e-prescribing, and availability of clinicians who can offer medication-assisted treatment for opioid use disorder, are strategies to consider to enhance implementation of the recommended practices. CDC will work with federal partners and payers to evaluate strategies such as payment reform and health care delivery models that could improve patient health and safety. For example, strategies might include strengthened coverage for nonpharmacologic treatments, appropriate urine drug testing, and medication-assisted treatment; reimbursable time for patient counseling; and payment models that improve access to interdisciplinary, coordinated care.

As highlighted in the forthcoming report on the National Pain Strategy, an overarching federal effort that outlines a comprehensive population-level health strategy for addressing pain as a public health problem, clinical guidelines complement other strategies aimed at preventing illnesses and injuries that lead to pain. A draft of the National Pain Strategy has been published previously (*180*). These strategies include strengthening the evidence base for pain prevention and treatment strategies, reducing disparities in pain treatment, improving service delivery and reimbursement, supporting professional education and training, and providing public education. It is important that overall improvements be made in developing the workforce to address pain management in general, in addition to opioid prescribing specifically. This guideline also complements other federal efforts focused on addressing the opioid overdose epidemic including prescriber training and education, improving access to treatment for opioid use disorder, safe storage and disposal programs, utilization management mechanisms, naloxone distribution programs, law enforcement and supply reduction efforts, prescription drug monitoring program improvements, and support for community coalitions and state prevention programs.

This guideline provides recommendations that are based on the best available evidence that was interpreted and informed by expert opinion. The clinical scientific evidence informing the recommendations is low in quality. To inform future guideline development, more research is necessary to fill in critical evidence gaps. The evidence reviews forming the basis of this guideline clearly illustrate that there is much yet to be learned about the effectiveness, safety, and economic efficiency of long-term opioid therapy. As highlighted by an expert panel in a recent workshop sponsored by the National Institutes of Health on the role of opioid pain medications in the treatment of chronic pain, "evidence is insufficient for every clinical decision that a provider needs to make about the use of opioids for chronic pain" (*223*). The National Institutes of Health panel recommended that research is needed to improve our understanding of which types of pain, specific diseases, and patients are most likely to be associated with benefit and harm from opioid pain medications; evaluate multidisciplinary pain interventions; estimate cost-benefit; develop and validate tools for identification of patient risk and outcomes; assess the effectiveness and harms of opioid pain medications with alternative study designs; and investigate risk identification and mitigation strategies and their effects on patient and public health outcomes. It is also important to obtain data to inform the cost feasibility and cost-effectiveness of recommended actions, such as use of nonpharmacologic therapy and urine drug testing. Research that contributes to safer and more effective pain treatment can be implemented across public health entities and federal agencies (*4*). Additional research can inform the development of future guidelines for special populations that could not be adequately addressed in this guideline, such as children and adolescents, where evidence and guidance is needed but currently lacking. CDC is committed to working with partners to identify the highest priority research areas to build the evidence base. Yet, given that chronic pain is recognized as a significant public health problem, the risks associated with long-term opioid therapy, the availability of effective nonpharmacological and nonopioid pharmacologic treatment options for pain, and the potential for improvement in the quality of health care with the implementation of recommended practices, a guideline for prescribing is warranted with the evidence that is currently available. The balance between the benefits and the risks of long-term opioid therapy for chronic pain based on both clinical and contextual evidence is strong enough to support the issuance of category A recommendations in most cases.

CDC will revisit this guideline as new evidence becomes available to determine when evidence gaps have been sufficiently closed to warrant an update of the guideline. Until this research is conducted, clinical practice guidelines will have to be based on the best available evidence and expert opinion. This guideline is intended to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder, overdose, and death. CDC is committed to evaluating the guideline to identify the impact of the recommendations on clinician and patient outcomes, both intended and unintended, and revising the recommendations in future updates when warranted.

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TABLE 1. Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Effectiveness and comparative effectiveness (KQ1)							
Effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥1 year) outcomes							
Pain, function, and quality of life	None	—[†]	—	—	Insufficient	—	No evidence
Harms and adverse events (KQ2)							
Risks of opioids versus placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found long-term use of prescribed opioids associated with an increased risk of abuse or dependence diagnosis versus no opioid use (adjusted OR ranged from 14.9 to 122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (n = 3,780)	Very serious limitations	Very serious inconsistency	No imprecision	4	None identified	In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence from 3% to 26%. In pain clinic settings, prevalence of misuse ranged from 8% to 16% and addiction from 2% to 14%. Prevalence of aberrant drug-related behaviors ranged from 6% to 37%.
Overdose	1 cohort study (n = 9,940)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Current opioid use associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI = 2.1–12) and serious overdose events (adjusted HR 8.4, 95% CI = 2.5–28) versus current nonuse.
Fractures	1 cohort study (n = 2,341) and 1 case–control study (n = 21,739 case patients)	Serious limitations	No inconsistency	No imprecision	3	None identified	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI = 0.99–1.64) and 1 case-control study (adjusted OR 1.27, 95% CI = 1.21–1.33).
Myocardial infarction	1 cohort study (n = 426,124) and 1 case–control study (n = 11,693 case patients)	No limitations	No inconsistency	No imprecision	3	None identified	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI = 1.19–1.37 and incidence rate ratio 2.66, 95% CI = 2.30–3.08).
Endocrinologic harms	1 cross-sectional study (n = 11,327)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI = 1.1–1.9).
How do harms vary depending on the opioid dose used?							
Abuse or addiction	1 cohort study (n = 568,640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95% CI = 10–21) for 1 to 36 MME/day, 29 (95 % CI = 20–41) for 36 to120 MME/day, and 122 (95 % CI = 73–205) for ≥120 MME/day.
Overdose	1 cohort study (n = 9,940) and 1 case–control study (n = 593 case patients in primary analysis)	Serious limitations	No inconsistency	No imprecision	3	Magnitude of effect, dose response relationship	Versus 1 to <20 MME/day, one cohort study found an adjusted HR for an overdose event of 1.44 (95% CI = 0.57–3.62) for 20 to <50 MME/day that increased to 8.87 (95% CI = 3.99–19.72) at ≥100 MME/day; one case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI = 0.94–1.84) for 20 to 49 MME/day that increased to 2.88 (95% CI = 1.79–4.63) at ≥200 MME/day.
Fractures	1 cohort study (n = 2,341)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Risk of fracture increased from an adjusted HR of 1.20 (95% CI = 0.92–1.56) at 1 to <20 MME/day to 2.00 (95% CI = 1.24–3.24) at ≥50 MME/day; the trend was of borderline statistical significance.

See table footnotes on page 47.

TABLE 1. (*Continued*) Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Myocardial infarction	1 cohort study (n = 426,124)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Relative to a cumulative dose of 0 to 1,350 MME during a 90-day period, the incidence rate ratio for myocardial infarction for 1350 to <2700 MME was 1.21 (95% CI = 1.02–1.45), for 2,700 to <8,100 MME was 1.42 (95% CI = 1.21–1.67), for 8,100 to <18,000 MME was 1.89 (95% CI = 1.54–2.33), and for ≥18,000 MME was 1.73 (95% CI = 1.32–2.26).
Motor vehicle crash injuries	1 case–control study (n = 5,300 case patients)	No limitations	Unknown (1 study)	No imprecision	3	None identified	No association between opioid dose and risk of motor vehicle crash injuries even though opioid doses >20 MME/day were associated with increased odds of road trauma among drivers.
Endocrinologic harms	1 cross-sectional study (n = 11,327) New for update: 1 additional cross-sectional study (n=1,585)	Serious limitations	Consistent	No imprecision	3	None identified	Relative to 0 to <20 MME/day, the adjusted OR for ≥120 MME/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI = 1.0–2.4). One new cross-sectional study found higher-dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving immediate-release opioids (adjusted OR per 10 MME/day 1.16, 95% CI = 1.09–1.23), but the dose response was very weak among men receiving ER/LA opioids.
Dosing strategies (KQ3)							
Comparative effectiveness of different methods for initiating opioid therapy and titrating doses							
Pain	3 randomized trials (n = 93)	Serious limitations	Serious inconsistency	Very serious imprecision	4	None identified	Trials on effects of titration with immediate-release versus ER/LA opioids reported inconsistent results and had additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used.
Overdose	New for update: 1 cohort study (n = 840,606)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose versus initiation with an immediate-release opioid (adjusted HR 2.33, 95% CI = 1.26–4.32).
Comparative effectiveness of different ER/LA opioids							
Pain and function	3 randomized trials (n = 1,850)	Serious limitations	No inconsistency	No imprecision	3	None identified	No differences
All-cause mortality	1 cohort study (n = 108,492) New for update: 1 cohort study (n = 38,756)	Serious limitations	Serious inconsistency	No imprecision	4	None identified	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity-adjusted analysis (adjusted HR 0.56, 95% CI = 0.51–0.62) and one cohort study among Tennessee Medicaid patients found methadone to be associated with higher risk of all-cause mortality than sustained-release morphine (adjusted HR 1.46, 95% CI = 1.17–1.73).
Abuse and related outcomes	1 cohort study (n = 5,684)	Serious limitations	Unknown (1 study)	Serious imprecision	4	None identified	One cohort study found some differences between ER/LA opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.
ER/LA versus immediate-release opioids							
Endocrinologic harms	New for update: 1 cross-sectional study (n = 1,585)	Serious limitations	Unknown (1 study)	No imprecision	4	None identified	One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency versus immediate-release opioids (adjusted OR 3.39, 95% CI = 2.39–4.77).

See table footnotes on page 47.

TABLE 1. (*Continued*) Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Dose escalation versus dose maintenance or use of dose thresholds							
Pain, function, or withdrawal due to opioid misuse	1 randomized trial (n = 140)	Serious limitations	Unknown (1 study)	Very serious imprecision	3	None identified	No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 versus 40 MME/day at the end of the trial).
Immediate-release versus ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled and continuous versus as-needed dosing of opioids; or opioid rotation versus maintenance of current therapy							
Pain, function, quality of life, and outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effects of decreasing or tapering opioid doses versus continuation of opioid therapy							
Pain and function	1 randomized trial (n = 10)	Very serious limitations	Unknown (1 study)	Very serious imprecision	4	None identified	Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.
Comparative effectiveness of different tapering protocols and strategies							
Opioid abstinence	2 nonrandomized trials (n = 150)	Very serious limitations	No inconsistency	Very serious imprecision	4	None identified	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3–6 months
Risk assessment and risk mitigation strategies (KQ4)							
Diagnostic accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse among patients with chronic pain being considered for long-term opioid therapy							
Opioid risk tool	3 studies of diagnostic accuracy (n = 496) New for update: 2 studies of diagnostic accuracy (n = 320)	Serious limitations	Very serious inconsistency	Serious imprecision	4	None identified	Based on a cutoff score of >4 (or unspecified), five studies (two fair-quality, three poor-quality) reported sensitivity that ranged from 0.20 to 0.99 and specificity that ranged from 0.16 to 0.88.
Screener and Opioid Assessment for Patients with Pain, Version 1	2 studies of diagnostic accuracy (n = 203)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38 in one study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in one study.
Screener and Opioid Assessment for Patients with Pain-Revised	New for update: 2 studies of diagnostic accuracy (n = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a cutoff score of >3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in two studies, for likelihood ratios close to 1.
Brief Risk Interview	New for update: 2 studies of diagnostic accuracy (n = 320)	Very serious limitations	No inconsistency	Serious imprecision	3	None identified	Based on a "high risk" assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in two studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.

See table footnotes on page 47.

TABLE 1. (*Continued*) Grading of Recommendations Assessment, Development and Evaluation (GRADE) clinical evidence review ratings of the evidence for the key clinical questions regarding effectiveness and risks of long-term opioid therapy for chronic pain

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of evidence	Other factors	Estimates of effect/findings
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse in patients with chronic pain							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids							
Outcomes related to abuse	None	—	—	—	Insufficient	—	No evidence
Effects of opioid therapy for acute pain on long-term use (KQ5)							
Long-term opioid use	New for update: 2 cohort studies (n = 399,852)	Serious limitations	No inconsistency	No imprecision	3	None identified	One study found use of opioids within 7 days of low-risk surgery associated with increased likelihood of opioid use at 1 year (adjusted OR 1.44, 95% CI = 1.39–1.50), and one study found use of opioids within 15 days of onset of low back pain among workers with a compensation claim associated with increased risk of late opioid use (adjusted OR 2.08, 95% CI = 1.55–2.78 for 1 to 140 MME/day and OR 6.14, 95% CI = 4.92–7.66 for ≥450 MME/day).

Abbreviations: CI = confidence interval; ER/LA = extended release/long-acting; HR = hazard ratio; MME = morphine milligram equivalents; OR = odds ratio.
* Ratings were made per GRADE quality assessment criteria; "no limitations" indicates that limitations assessed through the GRADE method were not identified.
† Not applicable as no evidence was available for rating.

TABLE 2. Morphine milligram equivalent (MME) doses for commonly prescribed opioids

Opioid	Conversion factor*
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1–20 mg/day	4
21–40 mg/day	8
41–60 mg/day	10
≥61–80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol†	0.4

Source: Adapted from Von Korff M, Saunders K, Ray GT, et al. Clin J Pain 2008;24:521–7 and Washington State Interagency Guideline on Prescribing Opioids for Pain (http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf).

* Multiply the dose for each opioid by the conversion factor to determine the dose in MMEs. For example, tablets containing hydrocodone 5 mg and acetaminophen 300 mg taken four times a day would contain a total of 20 mg of hydrocodone daily, equivalent to 20 MME daily; extended-release tablets containing oxycodone 10mg and taken twice a day would contain a total of 20mg of oxycodone daily, equivalent to 30 MME daily. The following cautions should be noted: 1) All doses are in mg/day except for fentanyl, which is mcg/hr. 2) Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics. 3) Do not use the calculated dose in MMEs to determine the doses to use when converting opioid to another; when converting opioids the new opioid is typically dosed at substantially lower than the calculated MME dose to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics. 4) Use particular caution with methadone dose conversions because the conversion factor increases at higher doses. 5) Use particular caution with fentanyl since it is dosed in mcg/hr instead of mg/day, and its absorption is affected by heat and other factors.

† Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. MMEs are based on degree of mu-receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely mu receptor agonists.

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IV: Practice Tools

A. Pain Assessment and Documentation Tool

B. Care Plan

C. Substance Use Risk Assessment Tool

D. Behavioral Health Screening

E. Prescription Monitoring Program Information

F. Patient-Provider Agreement

G. Patient Education Handouts / Opioid Side Effects

H. Non-Opioid Options

I. Naloxone Resources

J. Monitoring Options

K. Opioid Statistics

Progress Note
Pain Assessment and Documentation Tool (PADT™)

Patient Name: _____ **Record #:**_____

Assessment Date: _____

Patient Stamp Here

Current Analgesic Regimen

Drug Name	Strength (eg, mg)	Frequency	Maximum Total Daily Dose

The PADT is a clinician-directed interview; that is, the clinician asks the questions, and the clinician records the responses. The Analgesia, Activities of Daily Living, and Adverse Events sections may be completed by the physician, nurse practitioner, physician assistant, or nurse. The Potential Aberrant Drug-Related Behavior and Assessment sections must be completed by the physician. Ask the patient the questions below, except as noted.

Analgesia

If zero indicates "no pain" and ten indicates "pain as bad as it can be," on a scale of 0 to 10, what is your level of pain for the following questions?

1. What was your pain level on average during the past week? (Please circle the appropriate number)

No Pain 0 1 2 3 4 5 6 7 8 9 10 Pain as bad as it can be

2. What was your pain level at its worst during the past week?

No Pain 0 1 2 3 4 5 6 7 8 9 10 Pain as bad as it can be

3. What percentage of your pain has been relieved during the past week? (Write in a percentage between 0% and 100%.)

_____

4. Is the amount of pain relief you are now obtaining from your current pain reliever(s) enough to make a real difference in your life?

☐ **Yes** ☐ **No**

5. Query to clinician: Is the patient's pain relief clinically significant?

☐ **Yes** ☐ **No** ☐ **Unsure**

Activities of Daily Living

Please indicate whether the patient's functioning with the current pain reliever(s) is Better, the Same, or Worse since the patient's last assessment with the PADT.* (Please check the box for Better, Same, or Worse for each item below.)

	Better	Same	Worse
1. Physical functioning	☐	☐	☐
2. Family relationships	☐	☐	☐
3. Social relationships	☐	☐	☐
4. Mood	☐	☐	☐
5. Sleep patterns	☐	☐	☐
6. Overall functioning	☐	☐	☐

***If the patient is receiving his or her first PADT assessment, the clinician should compare the patient's functional status with other reports from the last office visit.**

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(Continued on reverse side)

Progress Note

Pain Assessment and Documentation Tool (PADT™)

Adverse Events

1. Is patient experiencing any side effects from current pain reliever? ☐ Yes ☐ No

Ask patient about potential side effects:

	None	Mild	Moderate	Severe
a. Nausea	☐	☐	☐	☐
b. Vomiting	☐	☐	☐	☐
c. Constipation	☐	☐	☐	☐
d. Itching	☐	☐	☐	☐
e. Mental cloudiness	☐	☐	☐	☐
f. Sweating	☐	☐	☐	☐
g. Fatigue	☐	☐	☐	☐
h. Drowsiness	☐	☐	☐	☐
i. Other_____	☐	☐	☐	
j. Other_____	☐	☐	☐	

Potential Aberrant Drug-Related Behavior

This section must be completed by the physician

Please check any of the following items that you discovered during your interactions with the patient. Please note that some of these are directly observable (eg, appears intoxicated), while others may require more active listening and/or probing. Use the "Assessment" section below to note additional details.

- ☐ Purposeful over-sedation
- ☐ Negative mood change
- ☐ Appears intoxicated
- ☐ Increasingly unkempt or impaired
- ☐ Involvement in car or other accident
- ☐ Requests frequent early renewals
- ☐ Increased dose without authorization
- ☐ Reports lost or stolen prescriptions
- ☐ Attempts to obtain prescriptions from other doctors
- ☐ Changes route of administration
- ☐ Uses pain medication in response to situational stressor
- ☐ Insists on certain medications by name
- ☐ Contact with street drug culture
- ☐ Abusing alcohol or illicit drugs
- ☐ Hoarding (ie, stockpiling) of medication
- ☐ Arrested by police
- ☐ Victim of abuse
- ☐ Other: _____

_____

_____

2. Patients overall severity of side effects?

☐ None ☐ Mild ☐ Moderate ☐ Severe

Assessment: (This section must be completed by the physician.)

Is your overall impression that this patient is benefiting (eg, benefits, such as pain relief, outweigh side effects) from opioid therapy? ☐ Yes ☐ No ☐ Unsure

Comments: _____

_____

Specific Analgesic Plan:

- ☐ Continue present regimen
- ☐ Adjust dose of present analgesic
- ☐ Switch analgesics
- ☐ Add/Adjust concomitant therapy
- ☐ Discontinue/taper off opioid therapy

Comments:_____

_____

_____

_____

_____

Date:_____ Physicians Signature: _____

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Functional Ability Assessment

For use with the Personal Care Plan

Instructions: For each assessment, circle the number that best describes your ability.

_____ Self-care ability assessment

1. Requires total care for bathing, toileting, dressing, moving, and eating
2. Requires frequent assistance
3. Requires occasional assistance
4. Independent with self-care

_____ Family and social ability assessment

1. Unable to perform any chores, hobbies, driving, sex and social activities
2. Able to perform some chores, hobbies, driving, sex and social activities
3. Able to perform many chores, hobbies, driving, sex and social activities
4. Able to perform all chores, hobbies, driving, sex and social activities

_____ Movement ability assessment

1. Able to get up and walk with assistance, unable to climb stairs
2. Able to get up and walk independently, able to climb one (1) flight of stairs
3. Able to walk short distances and climb more than one (1) flight of stairs
4. Able to walk long distances and climb stairs without difficulty

_____ Lifting ability assessment

1. Able to lift up to 10 pounds occasionally
2. Able to lift up to 20 pounds occasionally
3. Able to lift up to 50 pounds occasionally
4. Able to lift over 50 pounds occasionally

_____ Work ability assessment

1. Unable to do any work
2. Able to work part time **and** with physical limitations
3. Able to work part time **or** with physical limitations
4. Able to perform normal work

Add the numbers together: _____ x 5 = _____/100 **(Functional Ability Score)**

Adapted from: Institute for Clinical Systems Improvement, *Assessment and Management of Chronic Pain*; 6th Ed, Nov. 2013 (pg87)

Example

Patient name _____ Date _____

Personal Care Plan for Chronic Pain

1. Set personal goals

- ☐ Improve Functional Ability Score by _____ points by: Date _____
- ☐ Return to specific activities, tasks, hobbies, sports, etc. by: Date _____
  1. _____
  2. _____
  3. _____
- ☐ Return to ☐ Limited work/or ☐ Normal work by: Date _____

2. Improve sleep (Goal: _____ hours/night, Current: _____ hours/night)

- ☐ Follow a basic sleep plan
  1. Eliminate caffeine and naps, relax before bed, and go to bed at this time: _____
- ☐ Take nighttime medications
  1. _____
  2. _____
  3. _____

3. Increase physical activity

- ☐ Attend physical therapy (days/week _____)
- ☐ Complete daily stretching (_____ times/day, for _____ minutes)
- ☐ Complete aerobic exercise/endurance exercise
  1. Walking (____ times/day, for _____ minutes) or pedometer (____ steps/day)
  2. Treadmill, bike, rower, elliptical trainer (____ times/week, for ____ minutes)
  3. Target heart rate goal with exercise _____ bpm

  Strengthening
  1. Elastic bands, hand weights, weight machines (____ minutes/day, ____ days/week)

4. Manage stress – List main stressors _____

- ☐ Formal interventions (counseling or classes, support group or therapy group)
  1. _____
- ☐ Daily practice of relaxation techniques, meditation, yoga, creative activity, service activity, etc.
  1. _____
  2. _____
- ☐ Medications
  1. _____
  2. _____

Example

5. **Decrease pain** (best pain level in the past week: ____/10, worst pain level in the past week: ____/10)

   - ☐ Non-medication treatments (ice, heat, etc.)
     1. _____
     2. _____
   - ☐ Medication
     1. _____
     2. _____
     3. _____
     4. _____
   - ☐ Other treatments _____

Provider name: _____ Date:_____

Example

Date _____

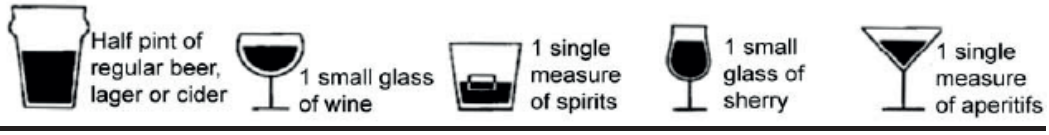
Patient Name _____

OPIOID RISK TOOL

		Mark each box that applies	Item Score If Female	Item Score If Male
1. Family History of Substance Abuse	Alcohol	[ ]	1	3
	Illegal Drugs	[ ]	2	3
	Prescription Drugs	[ ]	4	4
2. Personal History of Substance Abuse	Alcohol	[ ]	3	3
	Illegal Drugs	[ ]	4	4
	Prescription Drugs	[ ]	5	5
3. Age (Mark box if 16 – 45)		[ ]	1	1
4. History of Preadolescent Sexual Abuse		[ ]	3	0
5. Psychological Disease	Attention Deficit Disorder Obsessive Compulsive Disorder Bipolar Schizophrenia	[ ]	2	2
	Depression	[ ]	1	1
TOTAL		**[ ]**		

Total Score Risk Category Low Risk 0 – 3 Moderate Risk 4 – 7 High Risk $\geq$ 8

This is one unit of alcohol…



…and each of these is more than one unit

AUDIT – C

Questions	Scoring system					Your score
	0	1	2	3	4	
How often do you have a drink containing alcohol?	Never	Monthly or less	2 - 4 times per month	2 - 3 times per week	4+ times per week	
How many units of alcohol do you drink on a typical day when you are drinking?	1 -2	3 - 4	5 - 6	7 - 9	10+	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	

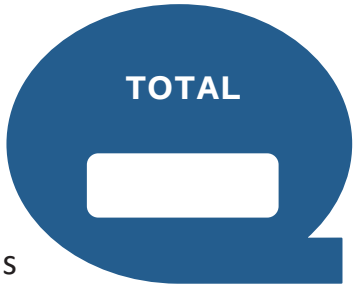
Scoring:
A total of 5+ indicates increasing or higher risk drinking.
An overall total score of 5 or above is AUDIT-C positive.

Score from AUDIT- C (other side)

Remaining AUDIT questions

Questions	Scoring system					Your score
	0	1	2	3	4	
How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you failed to do what was normally expected from you because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you needed an alcoholic drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
Have you or somebody else been injured as a result of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested that you cut down?	No		Yes, but not in the last year		Yes, during the last year	

Scoring: 0 – 7 Lower risk, 8 – 15 Increasing risk,
16 – 19 Higher risk, 20+ Possible dependence



TOTAL Score equals
AUDIT C Score (above) +
Score of remaining questions

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last *2 weeks,* how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
add columns		+	+	

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

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PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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Oklahoma Prescription Monitoring Program

(This document was created on 08/04/2016)

63 O.S. § 2-309D (OSCN 2015) – Effective November 1, 2015:

1. A mandatory PMP check is required on new patients and after 180 days has elapsed since it was last checked for a patient.
2. A medical provider must perform step 1 prior to prescribing one of the following: Opiates, Synthetic opiates, Semi-synthetic opiates, benzodiazepines, or carisoprodol (The exclusions are: Hospice, End-of-Life, or Nursing Home residents).
3. A medical provider may designate a staff member to run the patient's PMP on their behalf.
4. Medical providers may include a copy of the patient's PMP in that patient's medical record.

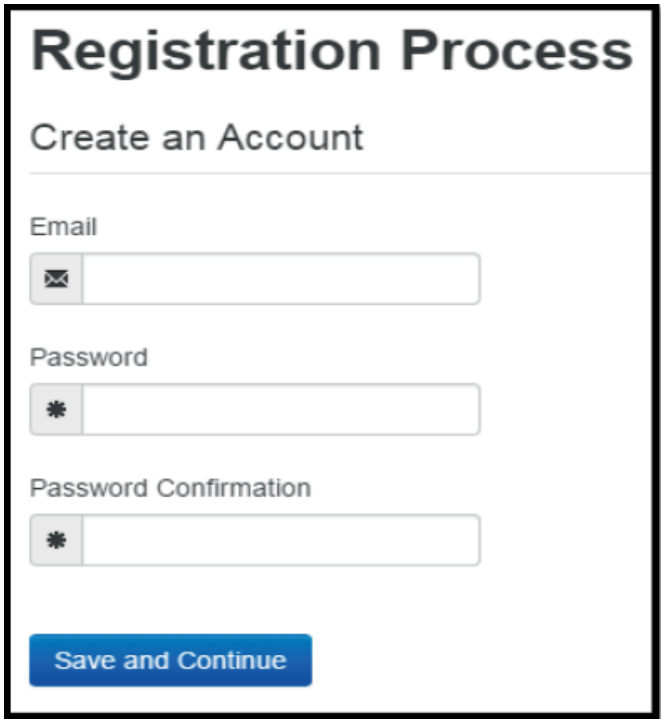
http://www.ok.gov/obndd/documents/HB1948%20ENR.pdf

To sign in to the Prescription Monitoring Program (If Registered):

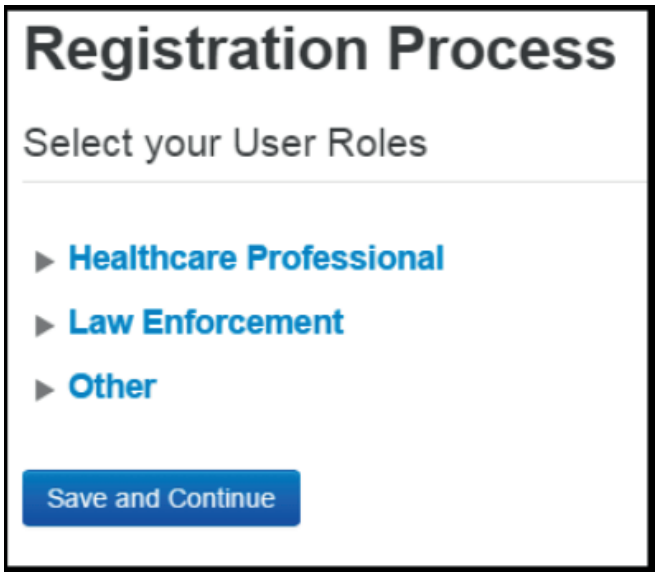
1. https://oklahoma.pmpaware.net/login

To sign in to the Prescription Monitoring Program (<u>If Not Registered</u>):

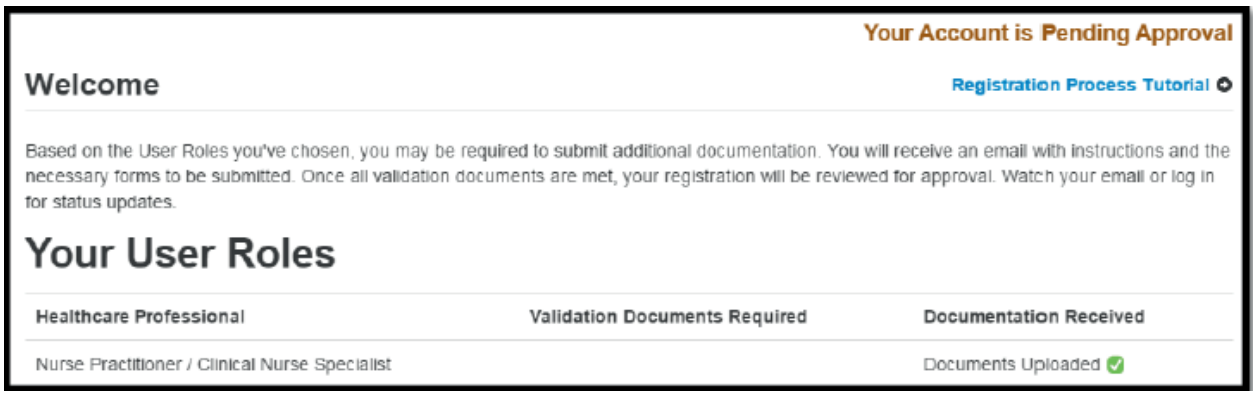
1. https://oklahoma.pmpaware.net/login
2. Once at the login screen, you will click on **Create an Account**
3. This screen will come up:



4. Fill out your email and password and click **Save and Continue**
5. This screen will come up:



6. After you select your User Role, click **Save and Continue**
7. You will receive a message requesting you to verify your email address and the directions on how to do that
8. After verifying your email address, the final screen will have you enter your demographics
9. After all the required information has been entered, you will click **Submit Your Registration** to complete the process
10. You will be redirected to the Welcome page:



To Register as a Delegate:

1. You will register using the same steps outlined above
2. You will create an account
3. Select your User Role – when selecting your User Role, you will choose one of the delegate roles available
4. In the final section, on the demographics screen, you will enter your supervisor's email address. Your supervisor must already be registered in the system.

Patient & Provider(s) Agreements

www.sempguidelines.org

West Virginia
Safe & Effective Management of Pain
(SEMP) Guidelines

Patient & Provider(s) Agreements Items to Include

- Emphasis of Goal to improve daily function more so than reduce pain
- Adverse effects of opioids especially with higher doses and/or concurrent use with other sedatives such as alcohol, other opioids, benzodiazepines, muscle relaxers, hypnotics, etc.
  - Serious adverse effects
    - Opioid use disorder, respiratory depression, etc.
  - Common adverse effects
    - Constipation, drowsiness, withdrawal symptoms, hyperalgesia, etc.
- Reduced ability to safely operate any vehicle.
- Periodic reassessment of function, pain, risk, & psychological state
- Prescription Drug Monitor Program (PDMP) verification
- Urine drug screening & testing
- Naloxone (need assessment & administration)
- Discuss risks to other individuals if opioids are shared with them
- Safe and secure storage of opioids
- Disposal of unused opioids
- Co-manager of medication therapy if cognitive limitations are present

OPIOID INFORMED CONSENT

YOUR SAFETY RISKS WHILE WORKING UNDER THE INFLUENCE OF OPIOIDS:

You should be aware of potential side effects of opioids such as decreased reaction time, clouded judgment, drowsiness and tolerance. Also, you should know the possible danger associated with the use of opioids while operating heavy equipment or driving.

POSSIBLE SIDE EFFECTS OF OPIOIDS:

- Confusion or other change in thinking abilities
- Nausea/Vomiting
- Constipation
- Problems with coordination or balance that may make it unsafe to operate dangerous equipment or motor vehicles
- Breathing too slowly – overdose can stop your breathing and lead to death
- Aggravation of depression
- Sleepiness or drowsiness
- Dry mouth

THESE SIDE EFECTS MAY BE MADE WORSE IF YOU MIX OPIOIDS WITH OTHER DRUGS INCLUDING ALCOHOL AND BENZODIAZEPINES

RISKS:

- Physical dependence. This means that abrupt stopping of the drug may lead to withdrawal symptoms characterized by one or more of the following:

Runny nose	*Difficulty sleeping for several days*
Diarrhea	*Abdominal cramping*
Sweating	*'Goose bumps'*
Rapid heart rate	*Nervousness*

- Psychological dependence. This means it is possible that stopping the drug will cause you to miss or crave it.
- Tolerance. This means you may need more and more drug to get the same effect.
- Addiction. A small percentage of patients may develop addiction problems based on genetic or other factors. This means you may develop a chronic compulsive craving for opioid medication despite it causing more harmful effects and less pain relief.
- Problems with pregnancy. If you are pregnant or contemplating pregnancy, discuss with your physician.

RECOMMENDATIONS TO MANAGE YOUR MEDICATIONS:

- Use of a lockbox that you can purchase at Walmart, your pharmacy or other locations
- When leaving home take along only the amount of medicine you need so there is less risk of losing all your medication at the same time.
- For expired or medications you no longer need, dispose of properly by taking to a take-back facility, flush down the toilet or place in a plastic bag with undesirable substance such as kitty litter or used coffee grounds, seal and put in a trash container.

Patient Signature Date

Sample Treatment Plan for Prescribing Opioids

Treatment Plan Using Prescription Opioids

Patient name: _____

Prescriber name: _____

THE PURPOSE OF THIS AGREEMENT IS TO STRUCTURE OUR PLAN TO WORK TOGETHER TO TREAT YOUR CHRONIC PAIN. THIS WILL PROTECT YOUR ACCESS TO CONTROLLED SUBSTANCES AND OUR ABILITY TO PRESCRIBE THEM TO YOU.

I (patient) understand the following (initial each):

_____Opioids have been prescribed to me on a trial basis. One of the goals of this treatment is to improve my ability to perform various functions, including return to work. If significant demonstrable improvement in my functional capabilities does not result from this trial of treatment, my prescriber may determine to end the trial.

Goal for improved function: _____

_____Opioids are being prescribed to make my pain tolerable but may not cause it to disappear entirely. If that goal is not reached, my physician may end the trial.

Goal for reduction of pain: _____

_____Drowsiness and slowed reflexes can be a temporary side effect of opioids, especially during dosage adjustments. If I am experiencing drowsiness while taking opioids, I agree not to drive a vehicle nor perform other tasks that could involve danger to myself or others.

_____Using opioids to treat chronic pain will result in the development of a physical dependence on this medication, and sudden decreases or discontinuation of the medication will lead to symptoms of opioid withdrawal. These symptoms can include: runny nose, yawning, large pupils, goose bumps, abdominal pain and cramping, diarrhea, vomiting, irritability, aches and flu-like symptoms. I understand that opioid withdrawal is uncomfortable but not physically life threatening.

_____There is a risk that opioid addiction can occur. Almost always, this occurs in patients with a personal or family history of other drug or alcohol abuse. If it appears that I may be developing addiction, my physician may determine to end the trial.

Continued on other side.

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Sample Treatment Plan for Prescribing Opioids

I agree to the following (initial each):

_____I agree not to take more medication than prescribed and not to take doses more frequently than prescribed.

_____I agree to keep the prescribed medication in a safe and secure place, and that lost, damaged, or stolen medication will not be replaced.

_____I agree not to share, sell, or in any way provide my medication to any other person.

_____I agree to obtain prescription medication from one designated licensed pharmacist. I understand that my doctor may check the Utah Controlled Substance Database at any time to check my compliance.

_____I agree not to seek or obtain **ANY** mood-modifying medication, including pain relievers or tranquilizers from **ANY** other prescriber without first discussing this with my prescriber. If a situation arises in which I have no alternative but to obtain my necessary prescription from another prescriber, I will advise that prescriber of this agreement. I will then immediately advise my prescriber that I obtained a prescription from another prescriber.

_____I agree to refrain from the use of **ALL** other mood-modifying drugs, including alcohol, unless agreed to by my prescriber. The moderate use of nicotine and caffeine are an exception to this restriction.

_____I agree to submit to random urine, blood or saliva testing, at my prescriber's request, to verify compliance with this, and to be seen by an addiction specialist if requested.

_____I agree to attend and participate fully in any other assessments of pain treatment programs which may be recommended by the prescriber at any time.

I understand that ANY deviation from the above agreement may be grounds for the prescriber to stop prescribing opioid therapy at any time.

_____ _____
Patient Signature Date

_____ _____
Prescriber Signature Date

Produced by Utah Department of Health, Prescription Pain Medication Program, 2008

Eight Opioid Safety Principles for Patients and Caregivers

1. Never take an opioid pain medication that is not prescribed to you

2. Never adjust your own doses

3. Never mix with alcohol

4. Taking sleep aids or anti-anxiety medications together with opioid pain medication can be dangerous

5. Always tell your prescriber about all medications you are taking from any prescriber

6. Keep track of when you take all medications

7. Keep your medications locked in a safe place

8. Dispose of any unused medications properly

The American Academy of Pain Medicine
www.painmed.org

UW Medicine

Benefits and Risks of Treatment with Opioids

This handout explains the benefits and risks of using opioid pain medicines.

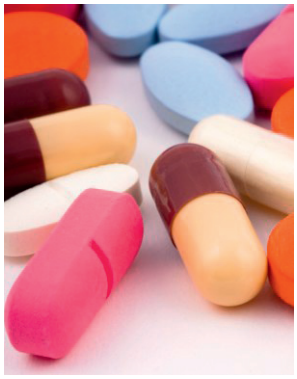
What are opioids?

Opioids are medicines that are used for pain control. They are similar to morphine. Laws control how these medicines are used.

You and your health care team can safely manage your opioid treatment. Please talk with your provider if you have any questions after reading this handout.

What are the benefits of opioids?

- You may have less pain.
- You may be able to be more active physically.
- Your emotional health may improve.



Like many medicines, opioids have both benefits and risks.

What are the possible side effects and risks of opioids?

The most dangerous side effect of opioids is that they may cause your breathing to slow down. This slowing of your breathing increases the risk that your breathing and heart could stop.

Special Warning: It is very dangerous to drink alcohol or use sleeping pills, illegal drugs (cocaine, heroin, methamphetamines) or pain medicines that your provider did not prescribe while you are taking your prescribed pain medicine. If you do, your breathing and heart could stop.

Other side effects are:

- The medicine may make you very sleepy.
- You may have nausea and vomiting.

UWMC Patient Care Services
1959 N.E. Pacific St., Seattle, WA 98195

- You may become constipated.
- You may feel itchy.
- You may have an allergic reaction that causes shortness of breath, wheezing, and a rash.
- Your brain will become dependent on the pain medicine. This means you will have symptoms of withdrawal if you suddenly stop taking it. Some symptoms of withdrawal are nausea, vomiting, and sweating. These are not life-threatening.
- The medicine may not work as well over time.
- You may become addicted to the medicine, or it may be hard to control how often you take it or how much you take.
- You may have more pain.
- If you have depression, it may get worse.
- You may gain weight.
- You may lose sexual desire and have trouble getting aroused.
- You may become infertile while you are taking opioids.
- Your immune system will become weaker and less able to fight infection. You may not be able to fight off colds or other viruses well. Wounds might take a long time to heal.
- You may have trouble thinking.
- Your judgment may be impaired. This can cause you to make poor decisions.
- It may be unsafe to drive or use machinery.

Questions?

Your questions are important. Call your doctor or health care provider if you have questions or concerns.

Clinic Name and Phone Number:

_____

_____

_____

_____

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Published PFES: 05/2012
Clinician Review: 05/2012
Reprints on Health Online: https://healthonline.washington.edu

UWMC Patient Care Services
1959 N.E. Pacific St., Seattle, WA 98195

Treatment of chronic pain at home

You have been prescribed pain medication to take at home. Taking care of your pain is important to your health. We cannot promise to make all of your pain go away. We are able to tell you some ways to help keep you comfortable and take care of your pain safely at home.

Taking your pain medicine:

- Take your pain medicine on time if you have pain most of the day
- Do not skip doses of your pain medicine **or** take more than your prescriber tells you to take
- Take only the medicine that your prescriber tells you to
- Take pain medicine with some food to keep from having an upset stomach
- Do not drink alcohol (beer, wine or liquor) while using pain medicine

Special instructions: _____

_____

Types of pain medicine:

Opioids (hydrocodone, oxycodone, dilaudid, morphine, etc.)

- These are strong medicines used for bad to very bad pain
- You must have a prescription to get these medicines
- These medicines may cause side effects such as:
    - dizziness
    - nausea (feeling sick to your stomach)
    - vomiting
    - itching

  **You should tell your prescriber if you have any of these side effects and they do not get better.
- Take these medicines with a snack and plenty of water
- You will probably get constipation (bowel movements that are small, hard, and dry, plus hurt to pass) if you take these medicines for more than 2 – 3 days. You may need to take a laxative or a stool softener while you are taking these pain medicines.
    - It also helps if you eat food high in fiber such as fruits, vegetables, and cereals
    - You should drink plenty of water

Adapted from: IH-IV-168 Taking Care Of Your Pain At Home; W.D. 8/04; pg1-3

Non-opioids (acetaminophen [Tylenol], ibuprofen, etc.)

- Ask your prescriber before using these medications
- These medicines may be used alone for mild to moderate pain, or they may be taken along with opioids to boost pain relief
- Some decrease swelling
- Do not take more than the dose listed on the label
- Take these medicines with a snack and plenty of water
- These medicines may cause you to have an upset stomach and sticky, black stools

Pain problems to report:

Call 911 if you have:

- trouble breathing
- really bad itching
- a rash after taking your pain medicine

Call your prescriber if you have:

- pain that does not get better after taking your pain medicine as your prescriber has told you to do so
- nausea (feeling sick to your stomach) and vomiting, diarrhea, stomach cramps or dry, hard bowel movements that hurt to pass
- dizziness or are over-tired after taking your pain medicine

Adapted from: IH-IV-168 Taking Care Of Your Pain At Home; W.D. 8/04; pg1-3

Other ways to decrease pain

You may try some of these helpful ways to decrease your pain and stress. These examples may help your pain medicine work better.

Ice or heat

- Ask your prescriber before using ice or heat to help your pain
- Put an ice pack (or bag of frozen peas), wrapped in a thin cloth, on the painful area
- Put a warm, moist towel (not too hot) covered in plastic, on the painful area
- Leave either the ice or heat on for 20 minutes, then take off for 20 minutes, to see if this helps the pain

Deep breathing

- Deep breathing will help relax your entire body
- Breathe in slowly and deeply through your nose as you count to five (5). Hold your breath for two (2) seconds, then breathe out slowly through your nose as you count to 10.

Distraction (doing something else)

- Take your mind off of your pain by doing something you enjoy. Talk with friends and family, listen to music, watch a movie, do handiwork, read, meditate or pray.

Total body relaxation

- Close your eyes, tighten your foot muscles, and hold for three (3) seconds. Relax the foot muscles. Now tighten the muscles in your legs and hold for three (3) seconds. Relax the leg muscles. Do this, working the muscles in your body, up to your shoulders.

Imagery

- Close your eyes, breathe deeply, and picture yourself in a quiet, peaceful place. Imagine how you feel in that place. Keep all other thoughts out of your mind during this time.

Exercise

- When your prescriber tells you it is okay, you may begin to exercise and stretch your muscles. Exercise helps decrease the risk of getting a blood clot and keeps your muscles loose and strong.

Adapted from: IH-IV-168 Taking Care Of Your Pain At Home; W.D. 8/04; pg1-3

United States Environmental Protection Agency

How to Dispose of Medicines Properly

DON'T: Flush expired or unwanted prescription and over-the-counter drugs down the toilet or drain unless the label or accompanying patient information specifically instructs you to do so.

DO: Return unwanted or expired prescription and over-the-counter drugs to a drug take-back program or follow the steps for household disposal below.

1ST CHOICE: DRUG TAKE-BACK EVENTS

To dispose of prescription and over-the-counter drugs, call your city or county government's household trash and recycling service and ask if a drug take-back program is available in your community. Some counties hold household hazardous waste collection days, where prescription and over-the-counter drugs are accepted at a central location for proper disposal.

Courtesy: Upper Watauga Riverkeeper and Appalachian Voices

Drug Take-Back Event

2ND CHOICE: HOUSEHOLD DISPOSAL STEPS*

1. Take your prescription drugs out of their original containers.

2. Mix drugs with an undesirable substance, such as cat litter or used coffee grounds.

3. Put the mixture into a disposable container with a lid, such as an empty margarine tub, or into a sealable bag.

4. Conceal or remove any personal information, including Rx number, on the empty containers by covering it with permanent marker or duct tape, or by scratching it off.

5. The sealed container with the drug mixture, and the empty drug containers, can now be placed in the trash.

* Drug Disposal Guidelines, Office of National Drug Control Policy, October 2009

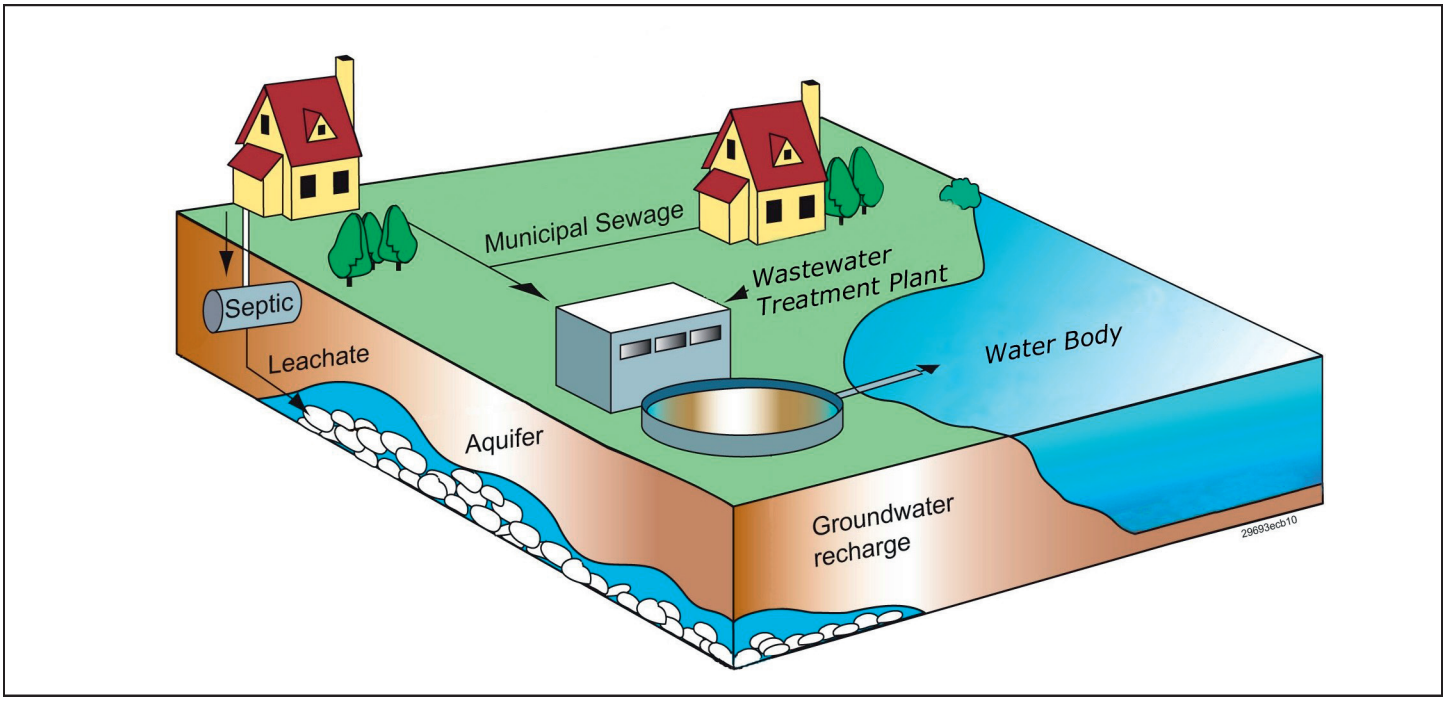
How Proper Disposal of Medicines Protects You and the Earth:

- Prevents poisoning of children and pets
- Deters misuse by teenagers and adults
- Avoids health problems from accidentally taking the wrong medicine, too much of the same medicine, or a medicine that is too old to work well
- Keeps medicines from entering streams and rivers when poured down the drain or flushed down the toilet

How Improper Disposal of Medicines May End Up in Our Drinking Water Sources

In homes that use septic tanks, prescription and over-the-counter drugs flushed down the toilet can leach into the ground and seep into ground water.

In cities and towns where residences are connected to wastewater treatment plants, prescription and over-the-counter drugs poured down the sink or flushed down the toilet can pass through the treatment system and enter rivers and lakes. They may flow downstream to serve as sources for community drinking water supplies. Water treatment plants are generally not equipped to routinely remove medicines.



For more information, go to www.epa.gov/ppcp/
Or call the Safe Drinking Water Hotline at 800-426-4791

Office of Water EPA 816-F-11-003 April 2011

Managing Side Effects and Complications of Opioid Therapy for Chronic Pain

This fact sheet accompanies the 2017 VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain and was created to aid with treatment of adult populations. Department of Veterans Affairs (VA) and Department of Defense (DoD) employees who use this information are responsible for considering all applicable regulations and policies throughout the course of care and patient education. The goal of this factsheet is to explain how to properly manage side effects of opioid therapy (OT) in DoD and VA primary care settings. Co-occurring conditions and side effects are common consequences of OT, and may occur during both short-term and long-term opioid therapy (LOT).

Risk Mitigation

The greatest risk factors for the development of opioid-related adverse events are the duration and dose of opioid analgesic use.[1] Many other factors also increase the risk of adverse outcomes and must be considered when prescribing opioid medications (see Significant risk factors).

Providers should consider and implement risk mitigation strategies before prescribing opioid medications. The provider should discuss the potential risks and benefits as well as alternative therapies with the patient and if possible, obtain the patient's informed consent regarding the patient care plan, including risk mitigation strategies. Risk mitigation strategies may include:

- Ongoing random urine drug testing and appropriate confirmatory testing
- Frequent face-to-face follow-up appointments to assess for co-occurring conditions and side effects
- Monitoring for overdose potential and suicidality
- Providing overdose education, including prescribing of naloxone rescue
- Checking state prescription drug monitoring programs

Evaluation of the benefits of continued opioid therapy and risk for opioid-related adverse events every three months (at a minimum) is recommended.

Significant risk factors

- Duration and dose of OT
- Severe respiratory instability
- Sleep disordered breathing (e.g., sleep apnea)
- Acute psychiatric instability or intermediate to high acute suicide risk (suicidality)
- Traumatic brain injury
- Mental disorders
  - Current or history of substance use disorder (SUD) (untreated SUD confers additional risk)
  - Depression or history of depression[2]
  - Generalized anxiety disorder
  - Borderline personality disorder
  - Antisocial personality disorder
  - Posttraumatic stress disorder (PTSD)
- History of drug overdose
- Under 30 years of age
- Evidence for or history of diversion of controlled substances
- Intolerance, serious adverse effects, or a history of inadequate beneficial response to opioids
- Impaired bowel motility unresponsive to therapy
- Pain conditions worsened by opioids (e.g., fibromyalgia, headache)
- True allergy to opioid agents (that cannot be resolved by switching agents)
- Co-administration of a drug capable of inducing fatal drug-drug interactions

Clinical reminders:

- Evaluate risk factors for opioid-related harms
- Conduct a suicide risk assessment and intervene when necessary
- Check the Prescription Drug Monitoring Program (PDMP) for high dosages and prescriptions from other providers
- Use urine drug testing to identify prescribed substances and undisclosed use
- Refer for opioid use disorder treatment if indicated

STOP Avoid prescribing concurrent benzodiazepines and opioids

Spectrum of Side Effects

Carefully consider side effects (e.g., depression, weight gain, headaches, nightmares, problems with intimacy, paresthesias) during monitoring and adjust treatment in order to minimize the side effects pursuant to individual patient preferences. Slower initiation and titration improves tolerability.

Managing Adverse Effects

It is imperative that providers discuss possible adverse effects of OT with patients and family members. If adverse effects are unmanageable and therapy is a greater detriment than benefit as determined by discussion with the patient and family, OT should be discontinued. See the chart below for more information on some of the potential adverse effects.

Adverse Effects	Symptoms	Protocol for Management
Respiratory depression	▪ Drowsiness ▪ Slow or shallow breathing ▪ Difficulty staying awake ▪ Difficulty awakening ▪ Loud or unusual snoring	▪ Administer the lowest effective opioid dose necessary to achieve satisfactory pain control – start low and go slow STOP Avoid other central nervous system (CNS) depressants, especially benzodiazepines because this combination has been identified in opioid-related deaths ▪ Alert family members or caretakers of the important warning signs to watch for that may indicate that the opioid should be decreased or stopped: — Difficult or slow breathing — Difficulty staying awake — Loud or unusual snoring — Difficulty being awakened
Mental status changes	▪ Confusion ▪ Bad dreams ▪ Hallucinations ▪ Restlessness ▪ Agitation ▪ Dysphoria ▪ Significantly depressed level of consciousness ▪ Seizures	▪ Evaluate underlying cause; consider role of primary therapy – hallucinations can be due to a variety of causes, including change in surroundings and sleep deprivation ▪ Evaluation of hallucinations is often performed by "trial and error" techniques – eliminate nonessential CNS-acting medications (e.g., steroids) ▪ Re-evaluate and treat underlying process if appropriate ▪ Dysphoria is more common with mixed opioid agonists/antagonists and antidopaminergic medications ▪ If hallucinations persist: — Consider a trial of an antipsychotic in consultation with behavioral health specialty, or — Switch to another opioid
Opioid-induced endocrinopathy	▪ Loss of libido ▪ Impotence ▪ Fatigue ▪ Mood alterations ▪ Loss of muscle mass and strength ▪ Abnormal menses ▪ Infertility	▪ Ask all patients on opioids about symptoms of opioid-induced endocrinopathy (e.g., hypogonadism) ▪ Determine cause of symptoms through lab work and/or consultation with an endocrinologist ▪ For males, consider testosterone patch therapy, as research indicates it may improve androgen deficiency symptoms, sexual function, mood, depression and hematocrit levels ▪ NOTE: There is insufficient data to recommend routine laboratory screening for endocrinopathy in asymptomatic patients on OT
Severe respiratory instability or sleep disordered breathing (sleep apnea or COPD)	▪ Loud snoring ▪ Excessive daytime sleepiness ▪ Fatigue ▪ Morning headaches (cerebral vasodilation) ▪ Depression and/or emotional instability ▪ Short-term memory loss ▪ Impaired concentration ▪ Irregular pauses in breathing	▪ Strongly consider discontinuing OT and obtain sleep studies ▪ The type of sleep apnea should be evaluated to determine if it is obstructive or central ▪ Central sleep apnea is a relative contraindication to OT, and discontinuation of OT should be considered if sleep apnea is severe or life-threatening ▪ Instruct patients to avoid alcohol and medications that cause drowsiness

References

1 Opioid Therapy for Chronic Pain Working Group, Department of Veterans Affairs & Department of Defense. (2017). VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. Version 3.0. Retrieved from https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPG022717.pdf

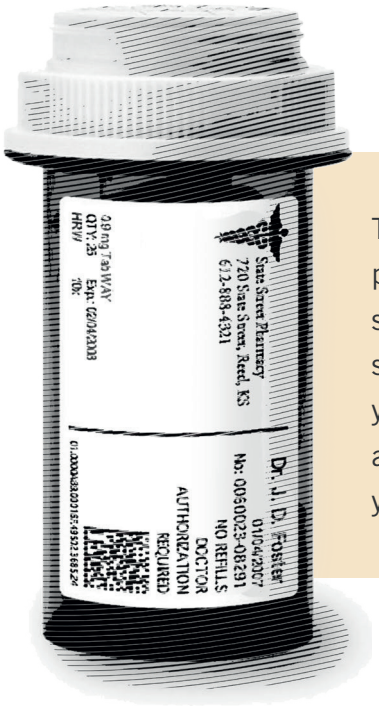
2 Management of Major Depressive Disorder Working Group, Department of Veterans Affairs & Department of Defense. (2016). VA/DoD Clinical Practice Guideline for the Management of Depressive Disorder. Version 3.0. Retrieved from http://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFINAL1.pdf

Updated June 2017 by Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury

PUID 4316

PREGNANCY AND OPIOID PAIN MEDICATIONS

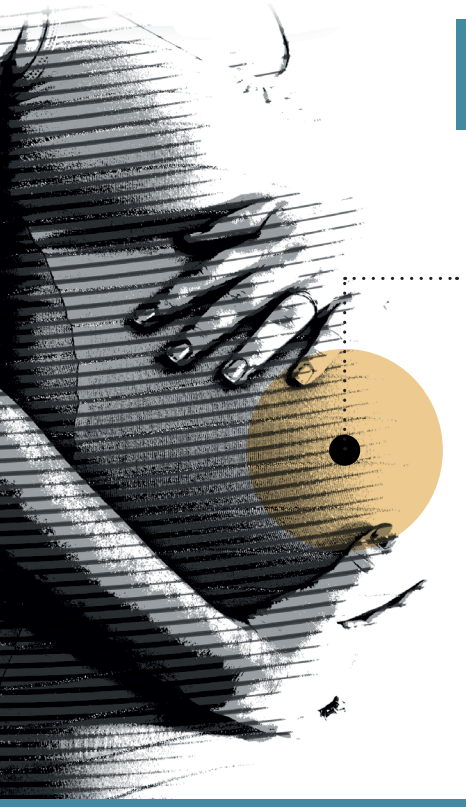
Women who take opioid pain medications should be aware of the possible risks during pregnancy.



Talk to your provider before starting or stopping any medications to help you understand all of the risks and make the safest choice for you and your pregnancy.

WHAT ARE OPIOID PAIN MEDICATIONS?

Opioid pain medications are prescribed by doctors to treat moderate to severe pain. Common types are codeine, oxycodone, hydrocodone, and morphine.



ARE OPIOID PAIN MEDICATIONS SAFE FOR WOMEN WHO ARE PREGNANT OR PLANNING TO BECOME PREGNANT?

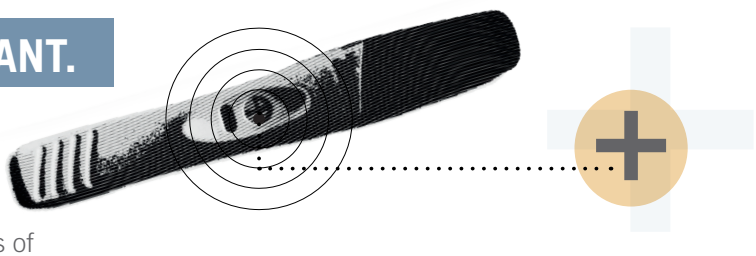
Possible risks to your pregnancy include[1,2]:

- **Neonatal Opioid Withdrawal Syndrome (NOWS):** withdrawal symptoms (irritability, seizures, vomiting, diarrhea, fever, and poor feeding) in newborns[3]
- **Neural tube defects:** serious problems in the development (or formation) of the fetus' brain or spine
- **Congenital heart defects:** problems affecting how the fetus' heart develops or how it works
- **Gastroschisis:** birth defect of developing baby's abdomen (belly) or where the intestines stick outside of the body through a hole beside the belly button
- **Stillbirth:** the loss of a pregnancy after 20 or more weeks
- **Preterm delivery:** a birth before 37 weeks

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline.html

I JUST FOUND OUT THAT I'M PREGNANT.



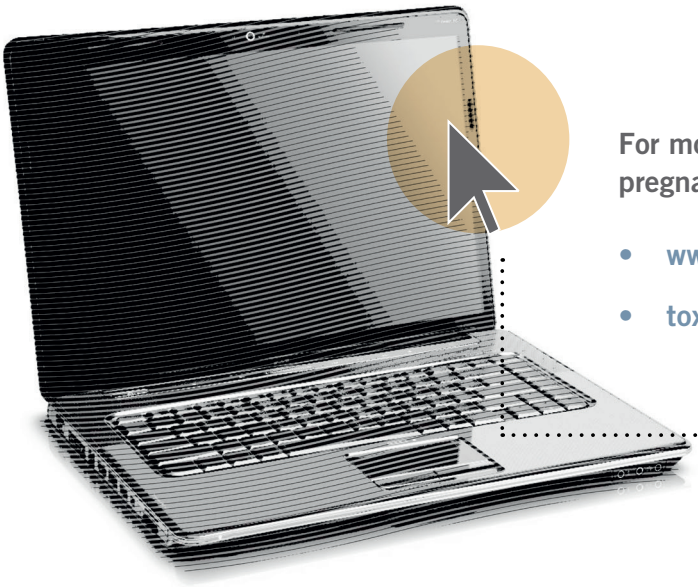
Should I stop taking my opioid pain medication? What are the risks?

- First, talk to your provider. Discuss all risks and benefits of continuing any medication use during pregnancy.
- Some women need to take opioid pain medication during pregnancy and quickly stopping your medication can have serious consequences.
- In some cases, avoiding or stopping medication use during pregnancy may be more harmful than taking it.

WHAT ABOUT BREASTFEEDING?

- Women without HIV who are already taking opioid pain medications regularly (and not using illicit drugs) are generally encouraged to breastfeed.
- Be sure to ask your doctor about breastfeeding if you are taking any other medications.
- During breastfeeding, avoid codeine whenever possible, and if used, ask your doctor for the lowest possible dose due to possible risk of newborn illness and death[4].

The information provided here applies to the use of opioid medication for pain. Opioid medications may also be used in medication assisted therapy (MAT) for treatment of substance use disorders. There are unique benefits and risks associated with MAT. To learn more about opioid medication use for substance use disorder treatment and considerations in pregnancy, visit **www.samhsa.gov/medication-assisted-treatment/treatment.**



For more information on opioid and other medication use in pregnancy or breastfeeding, go to:

- **www.cdc.gov/treatingfortwo**
- **toxnet.nlm.nih.gov/newtoxnet/lactmed.htm**

[1] Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011; 204:314:e1–11.

[2] Kellogg A, Rose CH, Harms RH, Watson WJ. Current trends in narcotic use in pregnancy and neonatal outcomes. Am J Obstet Gynecol 2011; 204:259:e124.

[3] Hudak ML, Tan RC, Committee On Drugs, Committee On Fetus and Newborn, American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics 2012;129:e540–60.

[4] National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic non-cancer pain; 2010. Available at: http://nationalpaincentre.mcmaster.ca/opioid/documents.html.

Opioid Use Disorder and Pregnancy

Taking helpful steps for a healthy pregnancy

Introduction

If you have an opioid use disorder (OUD) and are pregnant, you can take helpful steps now to ensure you have a healthy pregnancy and a healthy baby. During pregnancy, OUD should be treated with medicines, counseling, and recovery support. Good prenatal care is also very important. Ongoing contact between the healthcare professionals treating your OUD and those supporting your pregnancy is very important.

The actions you take or don't take play a vital role during your pregnancy. Below are some important things to know, about OUD and pregnancy, as well as the Do's and Don'ts for making sure you have a healthy pregnancy and a healthy baby.

Things to know

- OUD is a treatable illness like diabetes or high blood pressure.
- You should not try to stop opioid use on your own. Suddenly stopping the use of opioids can lead to withdrawal for you and your baby. You may be more likely to start using drugs again and even experience overdoses.
- For pregnant women, OUD is best treated with the medicines called methadone or buprenorphine along with counseling and recovery support services. Both of these medicines stop and prevent withdrawal and reduce opioid cravings, allowing you to focus on your recovery and caring for your baby.
- Tobacco, alcohol, and benzodiazepines may harm your baby, so make sure your treatment includes steps to stop using these substances.
- Depression and anxiety are common in women with OUD, and new mothers may also experience depression and anxiety after giving birth. Your healthcare professionals should check for these conditions regularly and, if you have them, help you get treatment for them.
- Mothers with OUD are at risk for hepatitis and HIV. Your healthcare professionals should do regular lab tests to make sure you are not infected and, if you are infected, provide treatment.
- Babies exposed to opioids and other substances before birth may develop neonatal abstinence syndrome (NAS) after birth. NAS is a group of withdrawal signs. Babies need to be watched for NAS in the hospital and may need treatment for a little while to help them sleep and eat.

About OUD

People with OUD typically feel a **strong craving for opioids** and find it hard to cut back or stop using them. Over time, many people **build up a tolerance** to opioids and need larger amounts. They also spend more time looking for and using opioids and less time on everyday tasks and relationships. Those who suddenly reduce or stop opioid use may suffer **withdrawal symptoms** such as nausea or vomiting, muscle aches, diarrhea, fever, and trouble sleeping.

If you are concerned about your opioid use or have any of these symptoms, please check with your **healthcare professionals** about treatment or tapering or find a provider at this website: www.samhsa.gov/find-help.

Do

Do talk with your healthcare professionals about the right treatment plan for you.

Do begin good prenatal care and continue it throughout your pregnancy. These two websites give helpful information on planning for your pregnancy: http://bit.ly/ACOGprenatal and http://bit.ly/CDCprenatal.

Do stop tobacco and alcohol use. Call your state's Tobacco Quit Line at 800-QUIT-NOW (800-784-8669).

Do talk to your healthcare professionals before starting or stopping any medicines.

Do get tested for hepatitis B and C and for HIV.

Do ask your healthcare professionals to talk to each other on a regular basis.

Don't

Don't hide your substance use or pregnancy from healthcare professionals.

Don't attempt to stop using opioids or other substances on your own.

Don't let fear or feeling embarrassed keep you from getting the care and help you need.

What to expect when you meet with healthcare professionals about OUD treatment and your pregnancy

The healthcare professionals who are treating your OUD and providing your prenatal care need a complete picture of your overall health. Together, they will make sure you are tested for hepatitis B and C and for HIV. They will ask you about any symptoms of depression or other feelings. You should be ready to answer questions about all substances you have used. They need this information to plan the best possible treatment for you and to help you prepare for your baby. These issues may be hard to talk about, but do the best you can to answer their questions completely and honestly. Expect them to treat you with respect and to answer any questions you may have.

Remember: Pregnancy is a time for you to feel **engaged** and **supported**. Work with your healthcare professionals to gain a better understanding of what you need for a healthy future for you and your baby.

Do you have questions for your healthcare professionals? If so, write them down and take them to your next visit.

_____

_____

_____

_____

Next Appointment Date: _____ Time: _____ Location: _____

SAMHSA's mission is to reduce the impact of substance abuse and mental illness on America's communities.

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HHS Publication No. SMA-18-5071FS1

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Choosing Wisely®

An initiative of the ABIM Foundation

American Society of Anesthesiologists (ASA) releases Choosing Wisely® list for pain medicine

January 21, 2014

Patients suffering from chronic pain should question certain tests and treatments

CHICAGO – January 21, 2014 – Not prescribing opioids first or as a long-term therapy for chronic, non-cancer pain and avoiding MRIs, CTs and X-rays for low-back pain are among the tests and treatments identified by ASA that are commonly ordered but not always necessary. As part of the ABIM Foundation's *Choosing Wisely* campaign, ASA today released its second list of five targeted, evidence-based recommendations that can support conversations between patients and physician anesthesiologists about what care is really necessary.

ASA's list identified the following recommendations:

1. **Don't prescribe opioid analgesics as first-line therapy to treat chronic non-cancer pain.**

Physicians should consider multimodal therapy, including non-drug treatments such as behavioral and physical therapies prior to pharmacological intervention. If drug therapy appears indicated, non-opioid medication (e.g., NSAIDs, anticonvulsants, etc.) should be trialed prior to commencing opioids.

2. **Don't prescribe opioid analgesics as long-term therapy to treat chronic non-cancer pain until the risks are considered and discussed with the patient.**

Patients should be informed of the risks of such treatment, including the potential for addiction. Physicians and patients should review and sign a written agreement that identifies the responsibilities of each party (e.g., urine drug testing) and the consequences of non-compliance with the agreement. Physicians should be cautious in co-prescribing opioids and benzodiazepines. Physicians should proactively evaluate and treat, if indicated, the nearly universal side effects of constipation and low testosterone or estrogen.

3. **Avoid imaging studies (MRI, CT or X-rays) for acute low-back pain without specific indications.**

Imaging for low-back pain in the first six weeks after pain begins should be avoided in the absence of specific clinical indications (e.g., history of cancer with potential metastases, known aortic aneurysm, progressive neurologic deficit, etc.). Most low back pain does not need imaging and doing so may reveal incidental findings that divert attention and increase the risk of having unhelpful surgery.

4. **Don't use intravenous sedation for diagnostic and therapeutic nerve blocks, or joint injections as a default practice. ***

Intravenous sedation, such as with propofol, midazolam, or ultrashort-acting opioid infusions for diagnostic and therapeutic nerve blocks, or joint injections, should not be used as the default practice. Ideally, diagnostic procedures should be performed with local anesthetic alone. Intravenous sedation can be used after evaluation and discussion of risks, including interference with assessing the acute pain-relieving effects of the procedure and the potential for false positive responses ASA Standards for Basic Anesthetic Monitoring should be followed in cases where moderate or deep sedation is provided or anticipated.

5. **Avoid irreversible interventions for non-cancer pain that carry significant costs and/or risks.**

Irreversible interventions for non-cancer pain, such as peripheral chemical neurolytic blocks or peripheral radiofrequency ablation, should be avoided because they may carry significant long-term risks of weakness, numbness or increased pain.

**This recommendation does not apply to pediatric patients.*

"As leaders in patient safety, physician anesthesiologists want the most effective tests and treatments for our patients and we want them to be used appropriately," said ASA President Jane C. K. Fitch, M.D. "ASA has taken the lead in improving patient safety related to anesthesiology

and pain medicine. This *Choosing Wisely* list can make a positive and significant impact on patient care and quality."

The ASA Committee on Pain Medicine was charged with developing the *Choosing Wisely* list on pain medicine. Committee members submitted recommendations for the campaign, and from this list voted on which should be included in the *Choosing Wisely* list. The literature was then searched to provide supporting evidence. Once approved by the committee, the *Choosing Wisely* list was reviewed by ASA's Chair of the Section on Subspecialties, Vice President for Scientific Affairs, Executive Committee, and Administrative Council. The American Pain Society (APS) has endorsed ASA's *Choosing Wisely* list on pain medicine.

"ASA has shown tremendous leadership by releasing its list of tests and treatments they say are commonly done in pain medicine, but aren't always necessary," said Richard J. Baron, M.D., president and CEO of the ABIM Foundation. "The content of this list and all of the others developed through this effort are helping physicians and patients across the country engage in conversations about what care they need, and what we can do to reduce waste and overuse in our health care system."

To date, nearly 100 national and state medical specialty societies, regional health collaboratives and consumer partners have joined the conversations about appropriate care. With the release of these new lists, the campaign will have covered more than 250 tests and procedures that the specialty society partners say are overused and inappropriate, and that physicians and patients should discuss. ASA published its first *Choosing Wisely* list in October, 2013 regarding anesthesiology.

The campaign also continues to reach millions of consumers nationwide through a stable of consumer and advocacy partners, led by Consumer Reports—the world's largest independent product-testing organization—which has worked with the ABIM Foundation to distribute patient-friendly resources for consumers and physicians to engage in these important conversations. *Choosing Wisely* consumer partners include:

- AARP
- Alliance Health Networks
- Midwest Business Group on Health
- Minnesota Health Action Group
- National Business Coalition on Health
- National Business Group on Health
- National Center for Farmworker Health
- National Hospice and Palliative Care Organization
- National Partnership for Women & Families
- Pacific Business Group on Health
- SEIU
- The Leapfrog Group
- Union Plus
- Wikipedia

To learn more about *Choosing Wisely* and to view the complete lists and additional detail about the recommendations and evidence supporting them, visit ChoosingWisely.org.

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http://www.choosingwisely.org/american-society-of-anesthesiologists-asa-releases-choosing-wisely-list-for-pain-medicine/

Non-opioid pain management options

*Options that SoonerCare pays for as of 01/02/2018. Contact OHCA Provider Services for the most current covered options.

1. **Physical therapy** – Up to age 20 with a prior authorization (PA); Ages 21 and over limited to 15 visits per year at outpatient, hospital-based facilities, no PA required
2. **Epidurals/Blocks** – PA required
3. **Cognitive behavioral therapy** – All ages with prior authorization
4. **TENS** – All ages, no PA required
5. **Medications**
    a. Acetaminophen
    b. NSAIDs - http://www.okhca.org
    c. Muscle relaxers - http://www.okhca.org
    d. Antidepressants - http://www.okhca.org
    e. Anti-migraine - http://www.okhca.org

To see a more extensive list of non-opioid pain management options:

Katz, Nathaniel, MD. Tufts University School of Medicine, Analgesic Research. (2006). *Opioid Prescribing Tool Kit*

Utah Department of Health (2009). *Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain*

Anti-Migraine

Prior Authorization (PA) Criteria:

Tier-1 products are covered with no authorization necessary.

Tier-2 authorization requires:

- trial of all available Tier-1 products with inadequate response; **OR**
- documented adverse effect to all Tier-1 products; **OR**
- previous success with a Tier-2 product within the last 60 days.

Tier-3 authorization requires:

- trial of all available Tier-1 and Tier-2 products with inadequate response; **OR**
- documented adverse effect to all Tier-1 and Tier-2 products; **OR**
- previous success with a Tier-3 medication within the last 60 days; **AND**
- Use of any non-oral formulation requires a patient-specific, clinically significant reason why member cannot use the oral tablet formulation.

Anti-migraine Medication Special PA Approval Criteria:

- Use of any non-oral sumatriptan formulation requires a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation or lower-tiered triptan products.
- Use of Onzetra® Xsail®, and Zembrace™ SymTouch™ requires a patient-specific, clinically significant reason why the member cannot use all available generic formulations of sumatriptan (tablets, nasal spray and injection) or lower-tiered triptan products.
- Use of Treximet® (sumatriptan/naproxen) requires a patient-specific, clinically significant reason why the member cannot use the individual ingredients separately or lower-tiered triptan products.
- Use of dihydroergotamine injection (D.H.E. 45®) requires a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan products.
- Use of dihydroergotamine nasal spray (Migranal®) requires a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan products and dihydroergotamine injection (D.H.E. 45®).
- Use of ergotamine sublingual tablets (Ergomar®) requires a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan medications.

Tier 1	Tier 2	Tier 3	Special PA
• Eletriptan (Relpax®) • Rizatriptan (Maxalt®, Maxalt MLT®) • Sumatriptan (Imitrex®)	• Naratriptan (Amerg) • Zolmitriptan tablets & ODTs (Zomig®, Zomig ZMT®)	• Almotriptan (Axert®) • Frovatriptan (Frova®) • Zolmitriptan nasal spray (Zomig®)	• Dihydroergotamine injection (D.H.E. 45®) • Dihydroergotamine nasal spray (Migranal®) • Ergotamine sublingual tablets (Ergomar®) • Sumatriptan injection (Imitrex®) • Sumatriptan injection (Zembrace™ SymTouch™)* • Sumatriptan nasal powder (Onzetra® Xsail®)* • Sumatriptan nasal spray (Imitrex®) • Sumatriptan (Sumavel DosePro®) • Sumatriptan/naproxen (Treximet®)
*Requires a clinically significant reason why member cannot use all other available formulations of sumatriptan.			

Butalbital Products
Approval criteria for the butalbital medications (Dolgic Plus® [butalbital-acetaminophen-caffeine 50-750-40 mg], Phrenilin Forte® [butalbital-acetaminophen 50-650 mg], Orbivan® [butalbital- acetaminophen-caffeine 50-300-40 mg], Orbivan® CF [butalbital-acetaminophen 50-300 mg], Esgic-Plus® [butalbital-acetaminophen-caffeine 50-500-40 mg], and Allzital® [butalbital-acetaminophen 25mg-325mg]): • an FDA-approved indication for the treatment of tension-type headache; **AND** • member must be aged 12 or older; **AND** • failure within the previous 60 days of the following:

- all available formulations of butalbital-acetaminophen medications that do not require a PA[1]; **AND**
- trials of at least two nonsteroidal anti-inflammatory drugs (NSAIDs), unless contraindicated.

[1]medications available without a PA contain butalbital-acetaminophen-caffeine in the standard 50-325-40mg dose

Esgic® capsules (butalbital-acetaminophen-caffeine 50-325-40mg) approval criteria:

- A patient-specific, clinically significant reason why the member cannot use Fioricet® tablets (butalbital-acetaminophen-caffeine 50-325-40mg).

Fibromyalgia

PA Criteria:

Tier-1 products are covered with no authorization necessary.

Tier-2 authorization requires:

- a documented, recent (within the last six months) trial of two Tier-1 medications (must include one trial with duloxetine) at least three weeks in duration that did not provide an adequate response or resulted in intolerable adverse effects; **OR**
- contraindication(s) to all available lower-tiered medications; **OR**
- current stabilization on a Tier-2 medication.

Pregabalin (Lyrica®) Approval Criteria (Diabetic Neuropathy Diagnosis):

- For the diagnosis of diabetic neuropathy, a trial of duloxetine and a trial of gabapentin or a patient-specific, clinically significant reason why duloxetine or gabapentin cannot be used must be provided.
- Other criteria for Lyrica® (pregabalin) will continue to apply.
- Clinical exceptions for Lyrica® (pregabalin) include:
  - diagnosis of seizures or postherpetic neuralgia

Tier-3 authorization requires:

- a documented, recent (within the last six months) trial of two Tier-1 medications (must include one trial with duloxetine) and all available Tier-2 medications at least three weeks in duration that did not provide an adequate response **OR** resulted in intolerable adverse effects; **OR**
- contraindication(s) to all available lower-tiered medications; **OR**
- current stabilization on a Tier-3 medication.

Tier 1	Tier 2	Tier 3
• Amitriptyline • Cyclobenzaprine • Duloxetine HCl (Cymbalta ®) • Fluoxetine • Tramadol	• Milnacipran (Savella ®)	• Pregabalin (Lyrica®)

NSAIDs

PA Criteria:

Tier-1 products are covered with no authorization necessary.

Tier-2 authorization requires:

- previous use of at least two Tier-1 NSAIDs (from different product lines) plus a proton-pump inhibitor (PPI) within the last 120 days; **OR**
- for those with a prior gastrointestinal (GI) bleed who must have an NSAID, a Tier-2 product may be approved (Celebrex® should also be taken with a PPI).

Special PA Approval Criteria:

- A unique indication for which a Tier-1 or Tier-2 medication is not appropriate, such as the diagnosis of gout for indomethacin; **OR**
- Previous use of at least two Tier-1 NSAID products (from different product lines); **AND**
- A patient-specific, clinically significant reason why a special formulation is needed in lieu of a Tier-1 product.

- Additionally, use of Tivorbex™ requires a patient-specific, clinically significant reason why member cannot use other available generic indomethacin products.

Meloxicam suspension for members older than 7 years of age requires a PA. The PA request should include a reason why the member needs the liquid formulation and cannot use the oral tablet formulation.

NOTE: *The member's NSAID therapy must have been continuous in order for previously utilized Tier-1 medications to count as trials toward a Tier-2 authorization. Dates and dosing information for Tier-1 trials must be included on the petition for authorization. Trials with OTC formulations of Tier-1 products must be dosed at full prescription strength.*

Tier 1	Tier 2	Special PA
• Diclofenac sodium (Voltaren®) • Diclofenac potassium (Cataflam®) • Diclofenac ER (Voltaren XR®) • Etodolac (Lodine®) 400mg and 500mg tabs • Flurbiprofen (Ansaid®) • Ibuprofen (Motrin®) • Ketoprofen (Orudis®) • Meloxicam (Mobic®) • Nabumetone (Relafen®) • Naproxen (Naprosyn®) • Naproxen EC (Naprosyn EC®) • Sulindac (Clinoril®)	• Celecoxib (Celebrex®) • Diclofenac sodium/misoprostol (Arthrotec®) • Etodolac (Lodine®) 200mg and 300mg cap • Etodolac ER (Lodine XL®) • Fenoprofen (Nalfon®) • Meclofenamate (Meclomen®) • Naproxen sodium (Anaprox®) 275mg and 550mg tabs • Oxaprozin (Daypro®) • Piroxicam (Feldene®) • Tolmetin (Tolectin®)	• Diclofenac (Zorvolex™) • Diclofenac epolamine (Flector®) • Diclofenac potassium (Zipsor®, Cambia®) • Diclofenac injection (Dyloject™) • Diclofenac sodium gel (Voltaren Gel®) • Diclofenac sodium drops (Pennsaid®) • Ibuprofen/famotidine (Duexis®) • Indomethacin (Tivorbex™) • Ketoprofen ER (Oruvail®) • Mefanamic acid (Ponstel®) • Meloxicam capsules (Vivlodex™) • Naproxen sodium (Naprelan®) • Naproxen/esomeprazole (Vimovo®)

Skeletal Muscle Relaxants

PA Criteria:

Tier-1 products are covered with no authorization necessary.

Tier-2 authorization requires:

- Documented trial of two Tier-1 medications within the last 90 days with no beneficial response after a minimum of two weeks of continuous therapy, during which time the medication has been titrated to the recommended dose.

Tier 1	Tier 2	Special PA
• Cyclobenzaprine (Flexeril®) • Baclofen (Lioresal®) • Orphenadrine (Norflex®) • Chlorzoxazone (Parafon Forte, Paraflex®) • Methocarbamol (Robaxin®) • Tizanidine (Zanaflex®)	• Metaxolone (Skelaxin®)	• Carisoprodol 350mg w/aspirin • Carisoprodol 350mg, ASA, codeine • Cyclobenzaprine ER (Amrix®) Caps • Cyclobenzaprine 7.5mg (Fexmid®) Tabs • Chlorzoxazone (Lorzone™) • Carisoprodol (Soma®) 250mg, 350mg • Tizanidine (Zanaflex®) Caps

Soma

PA Criteria:

- A cumulative 90-day therapy window per 365 days is in place for these products with further approval based on the following:
  - Granting of an additional 1-month approval to allow titration or change to a Tier-1 muscle relaxant (further authorizations will not be granted).
  - Clinical exceptions may be made for members with the following diagnosis, and approvals will be granted for the duration of one year:

- Multiple Sclerosis
- Cerebral Palsy
- Muscular Dystrophy
- Paralysis

- A quantity limit of 120 pills per 30 days applies for carisoprodol and carisoprodol combination products.

Soma 250 approval for coverage is based on the following criteria:

- Documentation regarding member's inability to use other skeletal muscle relaxants including carisoprodol 350 mg, and specific reason member cannot be drowsy for even a short time period (member must not have other sedating medications in current claims history).
- A diagnosis of *acute* musculoskeletal pain, in which case the approval will be for 14 days per 365 day period; conditions requiring chronic use will not be approved.

Amrix and Fexmid

PA criteria:

- Approval requires FDA-approved indication and clinical documentation of inability to take other generically available forms of cyclobenzaprine hydrochloride.
- A quantity limit of 30 capsules for 30 days placed on Amrix.
- A quantity limit of 90 tablets for 30 days placed on Fexmid.

Zanaflex

PA Criteria:

- Tizanidine tablets must be tried prior to consideration of the capsules.
- Capsules may be considered for approval if there is supporting information as to why the member cannot take the tablets.

Lorzone

PA Criteria:

- Generic chlorzoxazone 500mg tablets must be tried prior to consideration of Lorzone™; **AND**
- A patient-specific, clinically significant reason why the member cannot use generic chlorzoxazone 500mg tablets must be

provided; **AND**

- The following quantity limits apply:
  - Lorzone™ 375mg tablets: 120 tablets for 30 days
  - Lorzone™ 750mg tablets: 120 tablets for 30 days

Antidepressants

PA Criteria:

Tier-1 products available with no authorization necessary

Tier-2 authorization requires:

- A documented, recent (within six months) trial of two Tier-1 medications at least four weeks in duration and titrated to recommended dosing that did not provide an adequate response.
  - Tier-1 selection must include at least one medication from the SSRI category and one trial with duloxetine; **OR**
- Prior stabilization on the Tier-2 medication documented within the last 100 days (a past history of success on the Tier-2 medication will also be considered with adequate documentation); **OR**
- A unique, FDA-approved indication not covered by Tier-1 products or other products from a different therapeutic class; **OR**
- A petition may be submitted for consideration whenever a unique, patient-specific situation exists.

Tier-3 authorization requires:

- A documented, recent (within six months) trial with two Tier-1 medications (one medication from the SSRI category and one trial with duloxetine) and a Tier-2 medication at least four weeks in duration and titrated to recommended dose that did not provide an adequate response; **OR**
- Prior stabilization on the Tier-3 medication documented within the last 100 days (a past history of success on the Tier-3 medication will also be considered with adequate documentation); **OR**
- A unique, FDA-approved indication not covered by a lower-tiered product or other products from a different therapeutic class; **OR**
- A petition may be submitted for consideration whenever a unique, patient-specific situation exists.

Special Criteria:

- Use of any special PA product requires a patient-specific, clinically significant reason why the member cannot use other

available generic Tier-1 products; **OR**

- A petition may be submitted for consideration whenever a unique, patient-specific situation exists.
- Tier structure rules still apply.
- When Irenka™ (duloxetine 40mg) is requested for non-depression related diagnoses, the criteria below will apply:
  - An FDA-approved diagnosis of diabetic peripheral neuropathy or chronic musculoskeletal pain; **AND**
  - A patient-specific, clinically significant reason why the member cannot use two duloxetine 20mg capsules in place of Irenka™ 40mg capsules; **AND**
  - A quantity limit of 30 capsules per 30 days applies.
- Marplan® (isocarboxazid) Approval Criteria:
  - A patient-specific, clinically significant reason why the member cannot use any of the Tier-3 monoamine oxidase inhibitors (MAOIs) or other cost-effective, lower-tiered alternatives in place of Marplan®.
  - Tier structure rules still apply.
- Desyrel® (trazodone 300mg tablets) Approval Criteria:
  - A patient-specific, clinically significant reason why the member cannot use other available generic Tier-1 products including two trazodone 150mg tablets or three trazodone 100mg tablets to achieve a 300mg dose.
- Fluoxetine capsules are preferred over fluoxetine tablets.
  - Fluoxetine capsules are available without a PA.
  - Tablet formulation requires a PA and reasoning why it is required in place of the capsule formulation.

Approval Criteria for Atypical Antipsychotics as Adjunctive Treatment for Major Depression Disorder (MDD):

Authorization of Rexulti® (brexipiprazole) or Symbyax® (olanzapine/fluoxetine) for a diagnosis of major depression disorder requires current use of an antidepressant, previous trials with at least two other antidepressants from both categories (an SSRI and duloxetine) and a trial of aripiprazole tablets that did not yield adequate response. Tier structure rules still apply (the member must have tried the Tier-2 atypical antipsychotics indicated for adjunctive treatment of MDD before trying a Tier-3).

**Irenka™ for musculoskeletal conditions requires a patient-specific, clinically significant reason why the member cannot use two duloxetine 20mg capsules in place of the 40mg capsules.

Tier 1	Tier 2	Tier 3	Special PA
Selective Serotonin Reuptake Inhibitors (SSRIs)			
• Citalopram			• Fluvoxamine (Luvox

(Celexa®) • Escitalopram (Lexapro®) • Fluoxetine (Prozac®, Sarafem®) • Fluvoxamine (Luvox®) • Paroxetine (Paxil®) • Sertraline (Zoloft®)			CR®) • Fluoxetine 10mg, 20mg, & 60mg tablets • Fluoxetine DR (Prozac weekly®) • Paroxetine CR (Paxil CR®) • Paroxetine (Pexeva®)
Dual Acting Antidepressants			
• Bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®) • Duloxetine HCl (Cymbalta ®) • Mirtazapine (Remeron®, Remeron SolTab®) • Trazodone (Desyrel®) • Venlafaxine (Effexor®, Effexor XR® capsules)	• Desvenlafaxine (Pristiq®) • Vilazodone (Viibryd®)	• Desvenlafaxine (Khedezla®) • Levomilnacipran (Fetzima®) • Nefazodone (Serzone®)	• Bupropion ER (Aplenzin®, Forfivo®) • Duloxetine (Irenka™)** • Trazodone 300mg tablet (Desyrel®) • Trazodone ER (Oleptro®) • Venlafaxine extended release tablets
Monoamine Oxidase Inhibitors			
		• Phenelzine (Nardil®) • Selegiline transderm (Emsam®) • Tranylcypromine(Parnate®)	• Isocarboxazid (Marplan®)

Unique Mechanisms of Action			
		• Vortioxetine (Trintellix®)	

Insomnia Medications
Tier-1 products are available without a PA for members aged 19 or older. PA is required for all products for members younger than age 19. Tier-2 authorization requires: • Minimum 30-day trial with at least two Tier-1 products and clinical documentation of attempts to correct any primary cause for insomnia. • An FDA-approved diagnosis. • Approvals granted for 6 months. • No current anxiolytic benzodiazepine therapy greater than three times per day (TID). Tier-3 authorization requires: • Minimum 30-day trial with all available Tier-2 products and clinical documentation of attempts to correct any primary cause for insomnia. • An FDA-approved diagnosis. • Approvals granted for 6 months. • No current anxiolytic benzodiazepine therapy greater than TID. **Tasimelteon (Hetlioz®) Approval Criteria**: • An FDA-approved diagnosis of Non-24-Hour Sleep-Wake Disorder (Non-24) confirmed by a sleep specialist; **AND** • Member must be aged 18 or older; **AND**

- Member must be totally blind; **AND**
- A failed trial of appropriately-timed doses of melatonin; **AND**
- A failed trial of Rozerem® (ramelteon); **AND**
- Initial approvals will be for the duration of 12 weeks.
    - For continuation, the prescriber must include information regarding improved response/effectiveness of this medication.
- A quantity limit of 30 capsules for 30 days applies.

Tier 1	Tier 2	Tier 3	Special PA*
• Zolpidem tartrate (Ambien®) • Flurazepam (Dalmane®) • Triazolam (Halcion®) • Eszopiclone (Lunesta®) • Estazolam (ProSom®) • Temazepam (Restoril®) 15mg & 30mg • Ramelteon (Rozerem®) • Zaleplon (Sonata®)	• Zolpidem tartrate (Ambien CR®)	• Suvorexant (Belsomra®)	• Zolpidem SL tabs (Edluar®) • Tasimelteon (Hetlioz®)+ • Zolpidem SL tabs (Intermezzo®) • Temazepam (Restoril®) 7.5mg & 22.5mg • Doxepin (Silenor®) • Zolpidem Oral Spray (Zolpimist®)

*Unique dosage formulations require a special reason for use in place of Tier-1 formulations.

+ Individual criteria specific to tasimelteon.

SoonerCare
Oklahoma Health Care Authority

Pharmacy Services
(800) 522-0114, option 4

October 1, 2018

Dear SoonerCare Provider,

SB1446, Regulation of opioid drugs; providing limitations on quantities of certain prescriptions.

SB1446, an act relating to the regulation of opioid drugs, which will **limit the *initial prescription* for all opioids to a seven-day (7) supply,** was signed in to law and will take effect November 1, 2018. Signed by the Governor on May 2, 2018, the new law addresses opioid abuse by establishing prescribing limits, requiring continuing education on controlled substance prescribing, and expanding required use of the prescription monitoring program by prescribers.

Pharmacists are affected by the changes in this law in the following ways:

- Pharmacists will need to educate themselves regarding the changes to prescribing limits on controlled substances, including any opioid drug.
- The new law establishes guidelines to be adopted by prescribers that limit the number of days supply and number of prescriptions for the treatment of acute pain.

Opioid drugs quantity limit

Coinciding with SB1446 **SoonerCare will allow a quantity of eight (8) units per day for acute opioid therapy up to a seven-day (7) supply**. Prescriptions written for opioid therapy greater than or equal to an eight-day (8) supply will be limited to a quantity of four (4) units per day.

Fycompa™ (perampanel)

Recently criteria was modified for the reimbursement of Fycompa™ (perampanel). Effective October 01, 2018, **Fycompa™ (perampanel) tablets and oral suspension will no longer require prior authorization**. Claims for Fycompa™ (perampanel) will process without a prior authorization. Please refer to the SoonerCare pharmacy website (www.okhca.org/pa) for prior authorization criteria for other products in the anticonvulsant class.

For additional coverage information, please call the SoonerCare Pharmacy helpdesk at (800) 522-0114, option 4.

Thank you for your continued service to Oklahoma's SoonerCare members.

Naloxone for High Risk Patients

Who to prescribe to and when?

- Patients released after emergency medical care involving opioid intoxication or poisoning
- Patients with suspected history of substance abuse, dependence or nonmedical use of opioids
- Patients participating in methadone or buprenorphine detox/maintenance programs
- Patients receiving an opioid prescription for pain who also have any of the following characteristics:
    - High dose (> 50mg of morphine equivalent dose/day) opioid for long term management of chronic pain
    - Rotate from one opioid to another, when there may be incomplete cross- tolerance
    - Smokes, has COPD, emphysema, asthma, sleep apnea, respiratory infection, or any additional respiratory illness or potential obstruction
    - Renal dysfunction, hepatic disease (including hepatitis), cardiac illness, HIV/AIDS
    - Is known or suspected of having concurrent heavy alcohol use, concurrent benzodiazepine or other sedative prescription, and/or concurrent antidepressant prescription
- Patients who may have difficulty accessing emergency medical services i.e. due to distance
- Patients or caregivers who voluntarily request it

Adapted from: Power in a Bottle: Expanding Naloxone Access; naloxoneinfo.org

Naloxone

A Guide for Overdose Prevention

What is naloxone?

- Naloxone is a prescription medication that reverses heroin and prescription opioid overdoses.
- Naloxone is safe and effective, and has no effect on non-opioid overdoses.

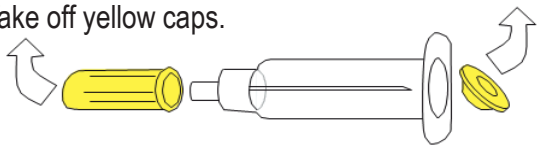
In case of overdose:

- **Call 911 and give naloxone**
  If no reaction in 3 minutes, give second naloxone dose.
- **Do rescue breathing or chest compressions**
  Follow 911 dispatcher instructions.
- **After naloxone**
  Stay with the person until help arrives; naloxone does wear off.

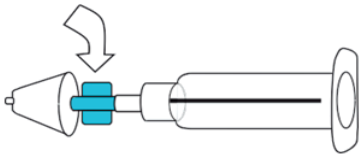
There are 3 ways to give naloxone. Follow the instructions for the type you have.

Nasal spray naloxone

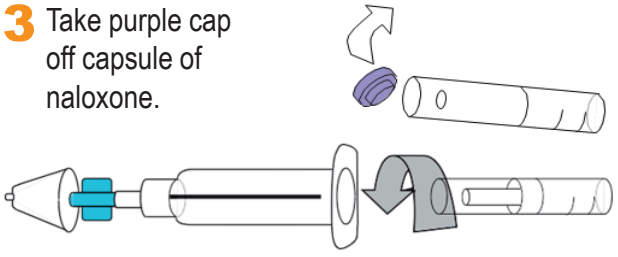
1 Take off yellow caps.



2 Screw on white cone.

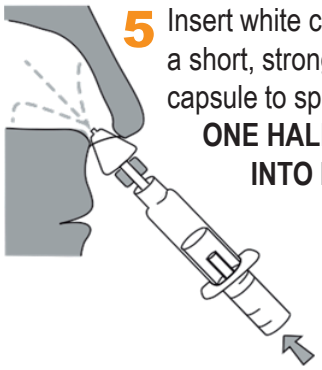


3 Take purple cap off capsule of naloxone.



4 Gently screw capsule of naloxone into barrel of syringe.

5 Insert white cone into nostril; give a short, strong push on end of capsule to spray naloxone into nose: **ONE HALF OF THE CAPSULE INTO EACH NOSTRIL.**

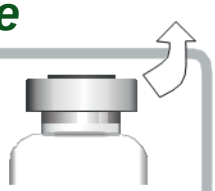


Push to spray.

6 If no reaction in 3 minutes, give second dose.

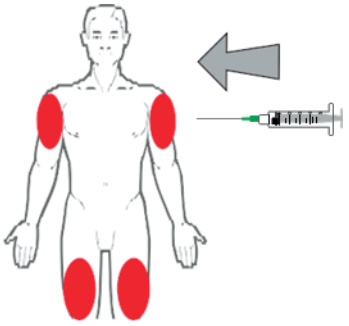
Injectable naloxone

1 Remove cap from naloxone vial and uncover the needle.



2 Insert needle through rubber plug with vial upside down. Pull back on plunger and take up 1 ml.

3 Inject 1 ml of naloxone into an upper arm or thigh muscle.



4 If no reaction in 3 minutes, give second dose.

The ***naloxone auto-injector*** is FDA approved for use by anyone in the community. It contains a speaker that provides instructions to inject naloxone into the outer thigh, through clothing if needed.

What is an opioid overdose?

Opioids affect the part of the brain that regulates breathing; in high doses, they can cause breathing to slow or even stop. This can happen when opioids are misused, which includes taking the wrong dosage or using excessively.

Look for these common signs:

- The person will not wake up even if you shake them or say their name
- Breathing slows or even stops
- Lips and fingernails turn blue or gray
- Skin gets pale, clammy

Generic	Brand Name
Hydrocodone	Vicodin, Lorcet, Lortab, Norco, Zohydro
Oxycodone	Percocet, OxyContin, Roxicodone, Percodan
Morphine	MSContin, Kadian, Embeda, Avinza
Codeine	Tylenol with Codeine, TyCo, Tylenol #3
Fentanyl	Duragesic
Hydromorphone	Dilaudid
Oxymorphone	Opana
Meperidine	Demerol
Methadone	Dolophine, Methadose
Buprenorphine	Suboxone, Subutex, Zubsolv, Bunavail, Butrans
Heroin is also an opioid.	

To avoid an opioid overdose:

- Tell your healthcare provider about ALL medications and supplements you are taking; opioids in combination with other depressants such as sleep aids, anti-anxiety medications, or cold medicine can be dangerous.
- Be extra careful if you miss or change doses, feel ill, or start new medications.

Naloxone can reverse an opioid overdose

Naloxone is now available at select pharmacies without a prescription.

For more information about where to get a naloxone kit, please visit **www.TakeAsPrescribed.org**

Now that you have naloxone…

Tell someone where it is and how to use it.

Injury Prevention Service
Oklahoma State Department of Health
1000 NE 10th Street
Oklahoma City, OK 73117
(405) 271-3430
http://poison.health.ok.gov

Adapted with permission from the San Francisco Department of Public Health

WHAT ARE OPIOIDS?

Opioids include illicit drugs such as heroin and prescription medications used to treat pain such as morphine, codeine, methadone, oxycodone (OxyContin®, Percodan®, Percocet®), hydrocodone (Vicodin®, Lortab®, Norco®), fentany (Duragesic®, Fentora®), hydromorphone (Dilaudid, Exalgo), and buprenorphine (Suboxone®).

Opioids work by binding to specific receptors in the brain, spinal cord and gastrointestinal tract. In doing so, they minimize the body's perception of pain. However, stimulating the opioid receptors or "reward centers" in the brain also can trigger other systems of the body, such as those responsible for regulating mood, breathing, and blood pressure.

A variety of effects can occur after a person takes opioids, ranging from pleasure to nausea, vomiting, severe allergic reactions (anaphylaxis) to overdose, in which breathing and heartbeat slow or even stop.

Opioid overdose can occur when a patient misunderstands the directions for use, accidentally takes an extra dose, or deliberately misuses a prescription opioid or an illicit drug such as heroin.

Also at risk is the person who takes opioid medications prescribed for someone else, as is the individual who combines opioids — prescribed or illicit — with alcohol, certain other medications, and even some over-the-counter products that depress breathing, heart rate, and other functions of the central nervous system [4].

PREVENTING OVERDOSE

If you are concerned about your own use of opioids, don't wait! Talk with the health care professional/s who prescribed the medications for you. If you are concerned about a family member or friend, urge him or her to do so as well.

Effective treatment of opioid use disorders can reduce the risk of overdose and help a person who is misusing or addicted to opioid medications attain a healthier life. An evidence-based practice for treating opioid addiction is the use of FDA-approved medications, along with counseling and other supportive services. These services are available at SAMHSA-certified and DEA-registered opioid treatment programs (OTPs) [19-20]. In addition, physicians who are trained to provide treatment for opioid addiction in office-based and other settings with medications such as buprenor-phine/naloxone and naltrexone may be available in your community [21].

IF YOU SUSPECT AN OVERDOSE

An opioid overdose requires immediate medical attention. An essential first step is to get help from someone with medical expertise as soon as possible.

Call 911 immediately if you or someone you know exhibits any of the symptoms listed below. All you have to say: "Someone is unresponsive and not breathing." Give a clear address and/or description of your location.

Signs of **OVERDOSE**, which is a life- threatening emergency, include:

- Face is extremely pale and/or clammy to the touch
- Body is limp
- Fingernails or lips have a blue or purple cast
- The patient is vomiting or making gurgling noises
- He or she cannot be awakened from sleep or is unable to speak
- Breathing is very slow or stopped
- Heartbeat is very slow or stopped.

Signs of **OVERMEDICATION**, which may progress to overdose, include:

- Unusual sleepiness or drowsiness
- Mental confusion, slurred speech, intoxicated behavior
- Slow or shallow breathing
- Pinpoint pupils
- Slow heartbeat, low blood pressure
- Difficulty waking the person from sleep.

SAFETY ADVICE FOR PATIENTS & FAMILY MEMBERS

WHAT IS NALOXONE?

Naloxone is an antidote to opioid overdose. It is an opioid antagonist that is used to reverse the effects of opioids. Naloxone works by blocking opiate receptor sites. It is not effective in treating overdoses of benzodiazepines (such as Valium®, Xanax®, or Klonopin®), barbiturates (Seconal® or Fiorinal®), clonidine, Elavil®, GHB, or ketamine. It also is not effective in treating overdoses of stimulants such as cocaine and amphetamines (including methamphetamine and Ecstasy). However, if opioids are taken in combination with other sedatives or stimulants, naloxone may be helpful.

IMPORTANT SAFETY INFORMATION. Naloxone may cause dizziness, drowsiness, or fainting. These effects may be worse if it is taken with alcohol or certain medicines. Use naloxone with caution. Do not drive or perform other possibly unsafe tasks until you know how you react to it.

If you experience a return of symptoms (such as drowsiness or difficulty breathing), *get help immediately*.

REPORT ANY SIDE EFFECTS

Get emergency medical help if you have any signs of an allergic reaction after taking naloxone, such as hives, difficulty breathing, or swelling of your face, lips, tongue, or throat.

Call your doctor or 911 at once if you have a serious side effect such as:

- Chest pain, or fast or irregular heartbeats;
- Dry cough, wheezing, or feeling short of breath;
- Sweating, severe nausea, or vomiting;
- Severe headache, agitation, anxiety, confusion, or ringing in your ears;
- Seizures (convulsions);
- Feeling that you might pass out; or
- Slow heart rate, weak pulse, fainting, or slowed breathing.

If you are being treated for dependence on opioid drugs (either an illicit drug like heroin or a medication prescribed for pain), you may experience the following symptoms of opioid withdrawal after taking naloxone:

- Feeling nervous, restless, or irritable;
- Body aches;
- Dizziness or weakness;
- Diarrhea, stomach pain, or mild nausea;
- Fever, chills, or goosebumps; or
- Sneezing or runny nose in the absence of a cold.

This is not a complete list of side effects, and others may occur. Talk to your doctor about side effects and how to deal with them.

STORE NALOXONE IN A SAFE PLACE

Naloxone is usually handled and stored by a health care provider. If you are using naloxone at home, store it in a locked cabinet or other space that is out of the reach of children or pets.

SUMMARY: HOW TO AVOID OPIOID OVERDOSE

1. Take medicine only if it has been prescribed to you by your doctor.
2. Do not take more medicine or take it more often than instructed.
3. Call a doctor if your pain gets worse.
4. Never mix pain medicines with alcohol, sleeping pills, or any illicit substance.
5. Store your medicine in a safe place where children or pets cannot reach it.
6. Learn the signs of overdose and how to use naloxone to keep it from becoming fatal.
7. Teach your family and friends how to respond to an overdose.
8. Dispose of unused medication properly.

READ MORE AT http://www.drugs.com/cdi/naloxone.html.

Opioid Use in Chronic Pain

Substance Use Risk Screening Tool

Options Include:

Opioid Risk Tool, DIRE Score, ABC Checklist, DAST, SOAPP, COMM, PMQ, AUDIT-C

Low Risk

- PMP: every 6 months
- UDS: once per year
- Prescribe > 50mg MED* if needed
- Aberrant Behaviors: If these are demonstrated, counseling must be initiated to address these behaviors. If they are unchanged, opioid use must be seriously reconsidered.

Medium Risk

- PMP: every 4 months
- UDS: every 6-12 months
- Prescribe > 50mg MED* occasionally
- Aberrant Behaviors: If these are demonstrated, counseling must be initiated to address these behaviors. If they are unchanged, opioid use must be seriously reconsidered.

High Risk

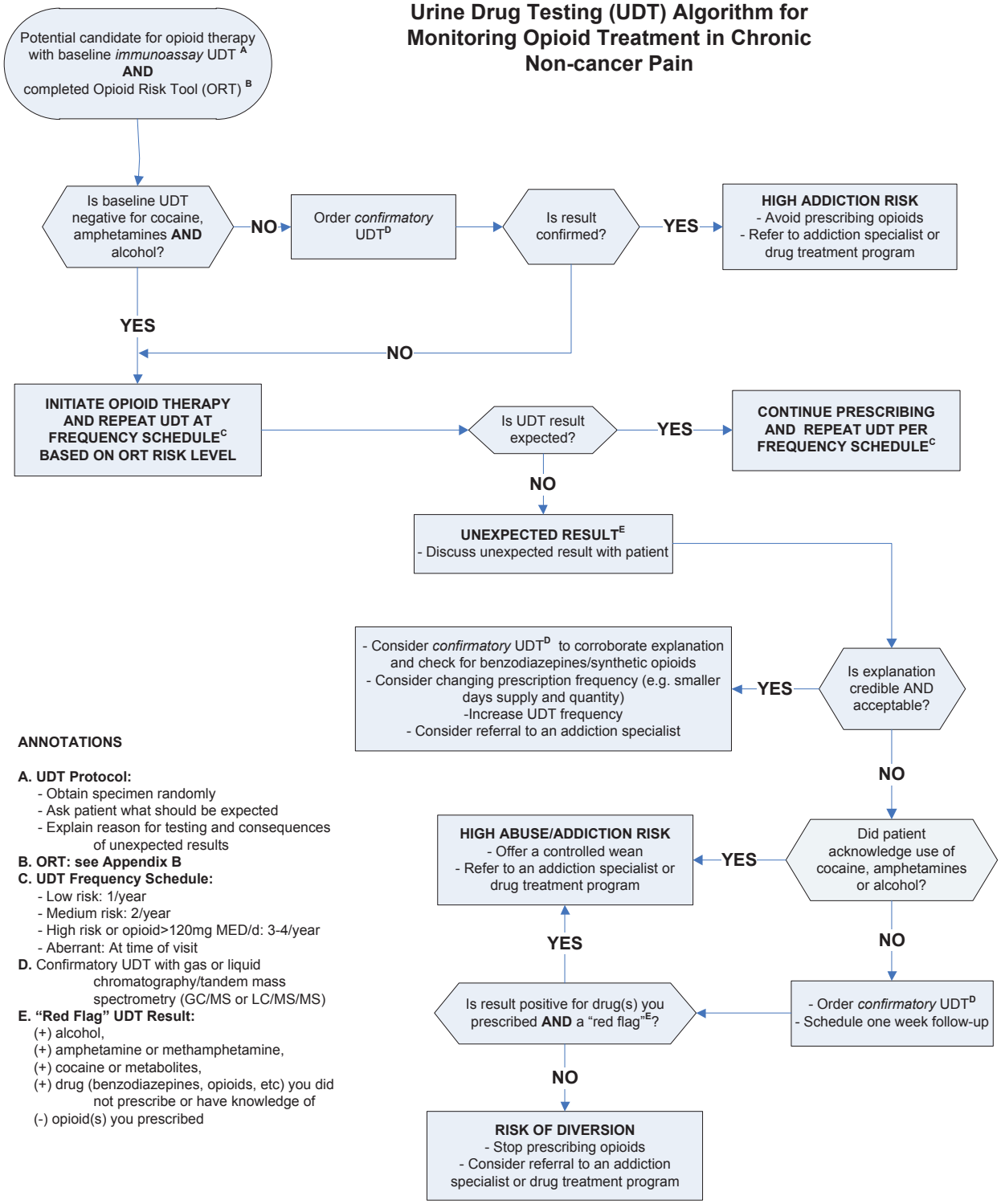
- PMP: every 3 months
- UDS: every 3-6 months
- Avoid Opioids or use a very low dose (10mg MED*)
- Avoid dose increases
- Aberrant Behaviors: Patients displaying these behaviors should be weaned off opioids

*MED – Morphine Equivalent Dose

Adapted from: Pain Physician, *Prevention of Opioid Abuse in Chronic Non-Cancer Pain;* 2012; 15:ES177-ES189

ii. UDT Algorithm for Monitoring Opioid Therapy

Figure E: UDT Algorithm for Monitoring COAT for CNCP



Urine Drug Screenings & Tests

www.sempguidelines.org

West Virginia Safe & Effective Management of Pain (SEMP) Guidelines

Urine Drug Screening (UDS)	Urine Drug Testing (UDT)
Immunoassay screen (i.e. Cup)	GC-MS or LC-MS/MS
In-office, point-of-care, or lab-based	Laboratory, highly specific and sensitive
Results within minutes	Results in hours or days
Detects a few legal & illicit medications by structural class	Measures concentrations of all medications, illicit substances, & metabolites
Guidance for preliminary treatment decisions	Definitive identification & analysis
Cross-reactivity common: more false positives	False-positive results are rare
Higher cutoff levels: more false negatives	False-negative results are rare
$	$$$

Target Drug Test	Cross-Reactant
Cannabinoids	NSAIDs, dronabinol, promethazine, & pantoprazole
Opioids	Poppy seeds, chlorpromazine, rifampin, dextromethorphan, quinolones, diphenhydramine, & quinine
Amphetamines	Methylphenidate, trazodone, bupropion, amantadine, propranolol, labetalol, ranitidine, & menthol
PCP	Ibuprofen, tramadol, chlorpromazine, venlafaxine, thioridazine, meperidine, dextromethorphan, diphenhydramine, & doxylamine
Benzodiazepines	Oxaprozin, sertraline, & some herbals
Alcohol	Asthma inhalers
Methadone	Quetiapine

Opioid	Opioids Expected in Testing Results (Based on Metabolites)
Morphine	Morphine & hydromorphone*
Hydromorphone	Hydromorphone
Hydrocodone	Hydrocodone & hydromorphone
Codeine	Codeine, hydrocodone*, morphine, & hydromorphone
Oxycodone	Oxycodone & oxymorphone
Oxymorphone	Oxymorphone
Fentanyl	Fentanyl
Tramadol	Tramadol
Methadone	Methadone
Heroin	Heroin, morphine, & hydromorphone

*Minor

iv. UDT Frequently Asked Questions (FAQ)

Q Drug screening implies that I don't trust my patients. How do I get around this?

A Self-report of drug use has limited validity, and monitoring behavior alone can fail to detect problems revealed by UDTs. Creating a UDT policy in advance and applying it consistently to all patients on opioids may help de-stigmatize the testing. Inform patients that drug testing is a routine procedure for all patients starting or maintained on opioid therapy and it is an important tool for monitoring the safety of opioid therapy. Possible language for explaining to patient includes:

- "Ensures my capacity to provide treatment for your pain while balancing the need for safety."
- "Provides critical information needed to assess the success of your therapy."
- "Prescription medications are a common form of treatment for chronic pain. However, each person reacts differently to them. UDT enables us to identify individual risks related to your medications and avoid problems."
- "Our clinic uses 'universal precautions' in opioid prescribing, which includes UDT. This is the same as wearing gloves on all patients when drawing blood."

Q Can I tell whether my patient has taken the dose of opioid(s) I prescribed?

A No. It is very difficult to correlate urine drug concentration with a patient's dose. UDT can detect the parent drug and/or its metabolite(s) and demonstrate recent use of prescribed drugs and illegal substances. However, it CANNOT determine the amount of drug used and when the last dose was taken, nor can it identify the source of the drug.

Q My patient says he is a "high metabolizer" and that is why the expected drug is not found in the urine. Is this possible?

A A small percentage of persons are ultrarapid metabolizers. They metabolize specific drugs more rapidly than typical patients. It would be rare to take an opioid as prescribed and have a totally negative UDT. It is important that you use testing that is specific to the medication of interest and with cutoff thresholds that are extremely low.

Q How do I deal with marijuana?

A This is a complex issue. Marijuana is currently classified as a Schedule I drug by the DEA. For that reason, many providers will not prescribe opioids to patients using cannabis. Other providers reference State "Medical Marijuana" laws (**http://apps.leg.wa.gov/RCW/default.aspx?cite=69.51A&full=true**) and feel comfortable prescribing opioids to cannabis users. Some providers adopt a "don't ask, don't tell" policy, and request the lab to remove marijuana from the UDT so that positive results are not seen. Do your homework and create an office policy. Then disclose this policy to your patients.

Q Would short-acting opioids show up in UDT?

A Urine testing typically has a 1 to 3-day window of detection for most drugs depending on dose and individual differences in drug metabolism. Short-acting opioids can be detected if the lab removes the cutoff concentration so that the presence of lower concentrations is detected. If the laboratory uses LC/MS/MS, then it will have a lower limit of detection (LOD) with less interference.

Q Why confirm results?

A Immunoassays used in drug screening can cross-react with other drugs and vary in sensitivity and specificity. Thus, confirmation with a more accurate method may be required for clinical decision making. Confirmatory drug testing (GC/MS or LC/MS/MS) of the original specimen is recommended for unexpected results, or in cases where patients are known to be high risk. However, on occasion, even confirmatory testing requires expert assistance for interpretation. Consider consultation with the lab before discussing/confronting the patient with unexpected test results and discontinuing opioid therapy.

Q Should I use temperature and adulteration strips?

A It depends. Drug testing for clinical compliance, unlike employment testing, does not require a strict "chain-of-custody". However, if tampering is a concern, the specimen should be monitored for temperature and/or adulterants. Normal human urine should have a temperature between 90°F – 100°F, pH between 4.5 – 8.5 and creatinine >20mg/dL. Be aware that there are multiple websites and devices devoted to getting a "clean" urine drug screen.

Q Should I perform a drug screen on every visit for patients using opioids for chronic pain?

A No. Random screening based on the frequency recommended in the guideline should suffice for most patients. Those patients who you feel require drug screening on every visit, are perhaps not candidates for chronic opioid therapy.

Indications for Consultation and Referral during Opioid Therapy

This factsheet accompanies the 2010 VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. It was created to aid with treatment of adult populations. Department of Veterans Affairs (VA) and Department of Defense (DoD) employees who use this information are responsible for considering all applicable regulations and policies throughout the course of care and patient education.

This factsheet serves as a guide in the management of opioid therapy (OT) in the DoD and VA when consultation and referral to specialty care are necessary. For most patients who adhere to their treatment agreements, OT may be managed in the primary care setting. Patients who manage chronic pain with OT should have **one designated primary care provider** who accepts primary responsibility for their overall medical care. This provider should coordinate consultation and communication among all providers involved in the patient's care. However, some patients may present with complicated medical or pain conditions which may require integrated care with specialists outside of the primary care setting. REMINDER: Document **ALL** of the patient's information from **ALL** clinicians involved in the patient's treatment.

Pain Medicine Specialty Care

Consultation and/or referral to ***an advanced pain provider*** should be considered:

- For patients with complex pain or polytrauma
- For patients with significant medical comorbidities that may negatively impact OT
- When opioid-induced hyperalgesia or opioid tolerance is suspected
- When high doses of medication provide no further improvement in function
- When a patient requires management beyond the expertise of the primary care provider
- When a patient is unable to tolerate increased pain or physical withdrawal symptoms that arise from opioid tapering when OT is discontinued

Addiction Specialty Care

Consultation and/or referral to an ***addiction specialist*** should be considered when a patient:

- Has an uncontrolled substance use disorder (excluding nicotine)
- Has difficulty tolerating opioids or is unable to tolerate taper with discontinuation of OT
- Presents with behaviors suggestive of opioid abuse or addiction to either opioids or other drugs. These include:
  - Rapidly escalating demands for dose increases or unusual increase in doses
  - Observed or reported intoxication or unexplained withdrawal symptoms
  - Frequent reports that opioid medication was lost, stolen or destroyed
  - Ingestion of opioids in ways other than prescribed (e.g., snorting, injecting)
  - Threat or harassment of staff
  - Repeatedly seeking prescriptions from other providers or emergency departments
  - Alteration, theft, sales of prescriptions or use of someone else's prescription

Special attention should be given to those patients who display moderate- to high-risk behavior and misuse their medications or those whose living arrangements may create a risk for medication misuse or diversion.

Behavioral Health Care

If a patient presents with suicidal ideation, refer to a behavioral health provider immediately, in accordance with your crisis plan. When significant psychosocial, emotional, behavioral, cognitive or occupational health factors complicate chronic pain treatment, referral to or consultation with interdisciplinary pain care that involves behavioral health specialists is appropriate.

Consider referral to or consultation with a ***behavioral health provider*** for evaluation and treatment if the patient exhibits or has any of the following behaviors or conditions:

- Exacerbation of an underlying psychotic disorder
- Uncontrolled, severe psychiatric disorder or emotional instability
- Demonstration of high-risk behaviors suggestive of suicidal ideation or verbalization of suicidal thoughts
- Psychosocial problems or comorbidities that may benefit from case management
- Adverse behavioral or cognitive effects of OT
- Co-occurring trauma related conditions (e.g., traumatic brain injury, posttraumatic stress disorder)
- Expressed interest in alternative approaches

Note: Refer patients with significant headache to a neurologist for evaluation and treatment. Also, consider consultation with occupational health specialty if the patient's occupation requires a high level of cognitive function.

Table: Risks for Opioid Misuse and Preferred Treatment Settings		
Risk of Misuse	**Condition/Situation**	**Treatment Setting for Therapy**
Low	■ No history of substance use disorder ■ No co-occurring psychiatric disorder ■ Prior good adherence to treatments with the primary care provider ■ Existence of social support system	■ Provide OT in primary care setting
Moderate	■ History of substance use ■ History of co-occurring psychiatric disorder ■ History of suicide attempt ■ Any positive urine drug test ■ Any history of legal problems ■ Young age (less than 25)	■ Primary care with escalated monitoring and caution ■ Consider consultation with addiction specialist or behavioral health specialty
High	■ Unstable or untreated substance use or behavioral health disorder ■ Persistent troublesome aberrant behavior or history of aberrant drug-related behavior	■ Consider an advanced structured pain clinic/program ■ Co-manage with substance use disorder or behavioral health specialty

Illegal, Dangerous and Criminal Behaviors

Illegal, dangerous and criminal behaviors have an impact beyond the patient and provider. These behaviors must be addressed at the time the action becomes apparent to the treatment team or provider. Behaviors that jeopardize the safety of the patient or society, or are illegal, may require immediate consultation and/or referral to a specialist. Providers should consider notifying law enforcement after consulting with legal counsel to clarify current confidentiality laws and regulations (e.g., VA/military police, risk manager, regional counsel). Remember, documentation is mandatory. These types of behaviors include:

Illegal or Criminal Behavior	Other Dangerous Behaviors
■ Active diversion (selling or provision of drugs to others) ■ Prescription forgery ■ Theft or use of someone else's prescription	■ Motor vehicle crash/arrest related to opioid or illicit drug or alcohol intoxication or effects ■ Intentional or unintentional overdose or suicide attempt ■ Assaultive, aggressive, threatening or belligerent behavior inside or outside of the clinic

Conclusion

Contact a specialist if you have any questions about OT treatment. The patient should be referred to a specialist if any of the issues addressed in this factsheet are discovered. Due to the seriousness, or potential seriousness, of opioid use and abuse, do not hesitate to consult with a specialist. If your facility does not have a substance use disorder or addiction specialist available, please refer to and/or consult with a behavioral health provider who can assess addiction. For further education on OT for chronic pain, direct patients to the VA/DoD Patient Education Tool, "Taking Opioids Responsibly."

Neonatal Abstinence Syndrome: Information for the Primary Care Provider and Guidelines for Referral

NATIONWIDE CHILDREN'S
*When your child needs a hospital, everything matters.*SM

The Growing Problem of Neonatal Abstinence Syndrome

Neonatal Abstinence Syndrome (NAS) is a drug withdrawal syndrome that occurs in infants who were exposed to prescription or illicit drugs in utero. These drugs include heroin, prescription opiates, buprenorphine, morphine, cocaine, methamphetamine and anxiolytics. NAS affects infants of all ethnicities and socioeconomic statuses.

The syndrome has been a problem for as long as these drugs have existed, but it has become a growing concern in recent years. The incidence of NAS tripled in the United States between 2000 and 2009, then increased again between 2009 and 2012 from 3.4 to 5.8 per 1,000 live births. In Ohio alone, the incidence increased from 2 per 1,000 births in 2006 to 15.5 per 1,000 births in 2015.

While these infants receive specialty care in the hospital, primary care providers play a key role in identifying ongoing concerns once they leave the neonatal intensive care unit (NICU).

Presentation and Outcomes

Early symptoms are transient and may include inconsolable crying, tremors, hypertonia, diarrhea, sneezing, diaper rash, temperature instability, mottling and (less frequently) seizures. Infants with NAS are more likely to have low birth weight, exposure to poor prenatal care and later feeding difficulties.

The long-term neurodevelopmental impact of NAS remains uncertain; current literature suggests higher risks of communication and behavioral problems for babies with NAS well into adolescence. For these reasons, it is essential that these children are followed in their transition period after discharge from the NICU. They may also need services through a standardized developmental follow-up program.

Key Reasons for Referral to a Specialized NAS Clinic

- **Phenobarbital weaning**
- **Neurodevelopmental concerns**
  - > Language delays
  - > Motor delays
  - > Atypical behaviors
  - > Difficulties interacting with caregivers
  - > Sensory sensitivity in the home environment

The Nationwide Children's NAS Clinic

NAS patients who are discharged from a Nationwide Children's-affiliated NICU are seen within the following two weeks in the Nationwide Children's NAS Clinic. The initial appointment includes a thorough social assessment, explanation of care coordination and a discussion of developmental risks.

The clinic also works to carefully wean babies who have been treated with pharmacological methods in the hospital and were discharged home still on neuro-active medications. These infants often experience lasting withdrawal symptoms that can complicate their relationships with caregivers. They can be irritable, difficult to console, often act hungry and have difficulty sleeping, and this behavior can be exacerbated by a suboptimal home environment.

Of note, patients who are discharged on phenobarbital need to be weaned using a standardized protocol. The following protocol is an example of one that has been successfully utilized in the Nationwide Children's NAS Clinic, but there are no evidence-based protocols for phenobarbital weaning in the outpatient setting for patients diagnosed with NAS.

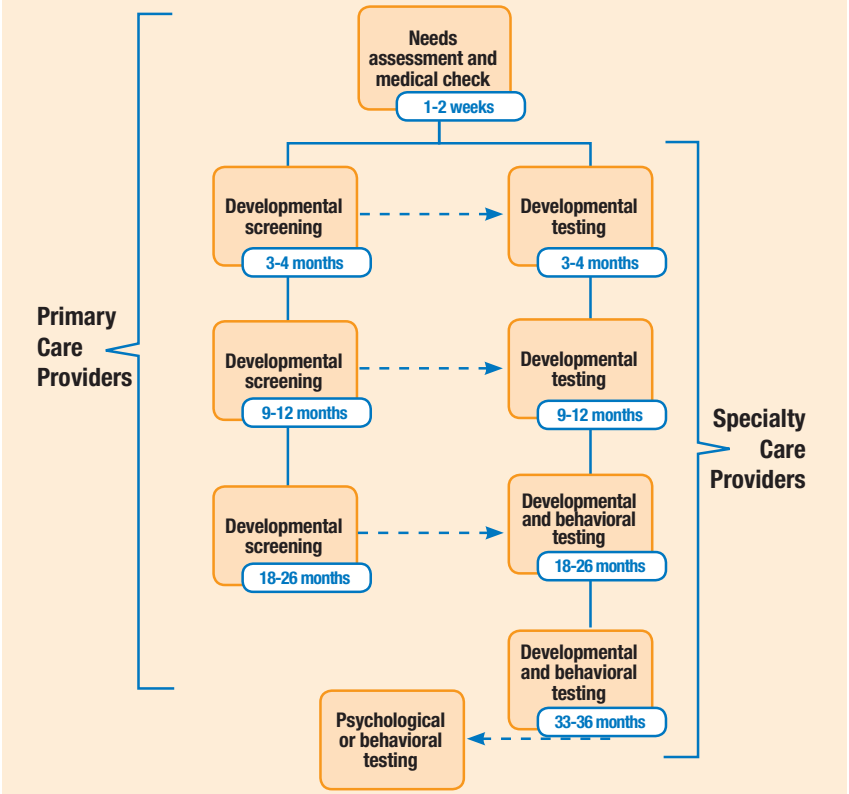
Phenobarbital Weaning Protocol for Outpatient Infants with NAS

If > 5mg/kg dosing twice per day then change to 5mg/kg at night and have patients return in 2-4 weeks for remainder of wean.
If ≤ 5mg/kg once per day or at night, follow these steps:

1.	If symptomatic with excessive neurologic symptoms (irritability, jitteriness/tremors, shrill cry and inability to calm interrupting sleep) then continue same dosing to outgrow without weight adjustment and return in 2-4 weeks. Sneezing, yawning and liquid stools are not reasons to stop wean.
2.	If asymptomatic, start to wean with a reduction of 25-30% per week for 2-4 weeks with convenient home dosing. (i.e. 4ml x 7 days, 3ml x 7days, 2ml x 7days, 1ml x 7 days.)
3.	If increased symptoms occur during wean, have caregivers go back to the previous week's dose and call for further instruction. Have patient return for follow-up medication check and assessment.
4.	After follow-up, attempt again to decrease dose by 25-30% per week over 3-4 weeks.
5.	Provider can use individual judgement and assessment to shorten or prolong wean. An infant no longer sleeping as well or no longer sleeping through the night are NOT reasons to stop the wean.

Transition From the NAS Clinic to Early Developmental Follow-up

The Timing of Screenings and Tests for Patients With NAS



Patients will be scheduled for an appointment in the Early Developmental Follow-up Clinic at Nationwide Children's if they demonstrate hypertonia outside of what is typically seen in this patient population, were exposed to barbiturates in utero or have any other developmental concerns. This appointment, at 3 to 4 months of age, includes a standardized neurological examination and a Test of Infant Motor Performance. The visits can take 60 to 90 minutes and involve a multidisciplinary team, including a medical provider, nurse, therapist and social worker.

A primary pediatric provider concerned about an infant's development can make a referral to the Early Developmental Follow-up Clinic at any point. The infant will enter the developmental follow-up pathway and stay until reaching the age of 3.

The Early Developmental Follow-up Clinic does not provide primary care and relies on the pediatric provider to remain the sole medical home for his or her patients. Even if there are no developmental concerns after referral, the patient will still be seen in the clinic at 22-26 months of age and at 30-36 months for a full neurological exam and standardized assessment of cognition, expressive/receptive language and fine/gross motor skills on the Bayley Scales of Infant and Toddler Development. The clinic can easily make necessary referrals to Nationwide Children's behavioral health providers who will follow and treat problems into childhood and adolescence.

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Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *Journal of Perinatology*. 2015 Aug; 35(8): 650-5.
The Ohio Department of Health. Neonatal Abstinence in Ohio: 2006-2015 Report.

Referrals and Consultations

Online: **NationwideChildrens.org/Neonatology**
Phone: **(614) 722-6200** or **(877) 722-6220** | Fax: **(614) 722-4000**
Physician Direct Connect Line for 24-hour urgent physician consultations:
(614) 355-0221 or **(877) 355-0221**.

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT HONOR ROLL 2017-18

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT NEONATOLOGY 2017-18

Duty to Report

Oklahoma State Statute (HB3104) was amended this month to change reporting requirements for substance exposed newborns. Here is what you need to know:

Why was this changed?

On July 22, 2016 the President signed into law Public Law 114-198, the Comprehensive Addiction and Recovery Act (CARA) of 2016. This law amended certain sections of the Child Abuse Prevention and Treatment Act (CAPTA). CAPTA is the key federal legislation that provides guidance and funding to state child welfare agencies in support of prevention, assessment, and investigation, prosecution, and treatment activities. Previous to CARA, states were required by CAPTA to have policies and procedures relating to "infants born and identified as being affected by illegal substance abuse or withdrawal symptoms resulting from prenatal drug exposure." In 2010, the provision was amended by Congress to also include infants affected by Fetal Alcohol Spectrum Disorder. The 2016 CARA required that states remove the term "illegal" as applied to substance abuse affecting infants and to specifically require that plans of safe care address the needs of both infants and their families or caretakers. As a result, Oklahoma State Statute had to be amended in order to come into compliance with federal law.

What was changed?

In the previous Oklahoma statute, the definition of "Drug-endangered child" included the sentence, "The term also includes newborns that test positive for a controlled dangerous substance, with the exception of those substances administered under the care of a physician." That sentence has been removed from the definition, removing the exception.

Newborns that test positive for a controlled dangerous substance should be reported to the Department of Human Services, regardless of if the substance had been prescribed to mother. **Infants who are diagnosed with Neonatal Abstinence Syndrome or Fetal Alcohol Spectrum Disorder** should also be reported.

Who should report an infant that tests positive?

The description of who should report has been broadened. With, the following description is included: "Every physician, surgeon, or other health care professional including doctors of medicine, licensed osteopathic physicians, residents and interns, or any other health care professional or midwife involved in the prenatal care of expectant mothers or the delivery or care of infants shall promptly report to the Department instances in which an infant tests positive for alcohol or a controlled dangerous substance . This shall include infants who are diagnosed with Neonatal Abstinence Syndrome or Fetal Alcohol Spectrum Disorder."

Read the entire Enrolled HB3104 to view all revisions.

Documentation in the Hospital

Providing a thorough discharge summary for a newborn that has tested positive is of utmost importance. Including details on follow-up appointments and treatment plans in the discharge instructions will greatly assist in the follow-up of these cases.

How does one make a report?

The preferred method of reporting is by calling the Department of Human Services' Statewide 24-hour Child Abuse Hotline at 1-800-522-3511. The following information will be asked:

- The names, addresses, ages and whereabouts of the child and the child's parents, or other persons responsible for the child's welfare

- Information pertaining to support systems for the family, other individuals who may be aware of the abuse or neglect, or any safety-related issues child welfare may need to be aware of prior to making contact with the family, such as domestic violence, presence of weapons, or use of illegal substances;

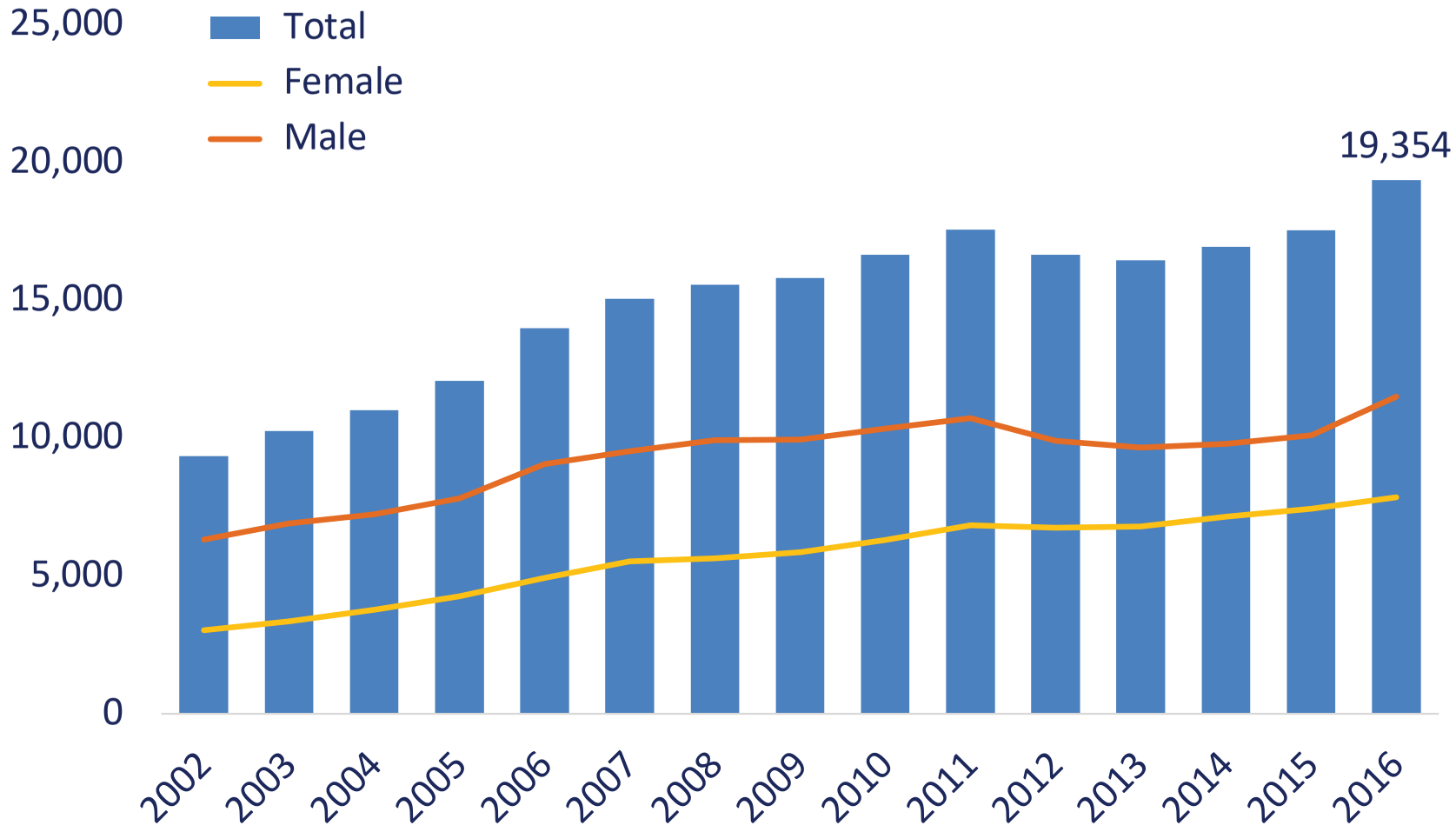
- Any other information that might be helpful in establishing the cause of the injuries and the identity of the person responsible. Such as discharge orders/plan of care from reported in medical records.

National Institute on Drug Abuse

National Overdose Deaths

Number of Deaths Involving

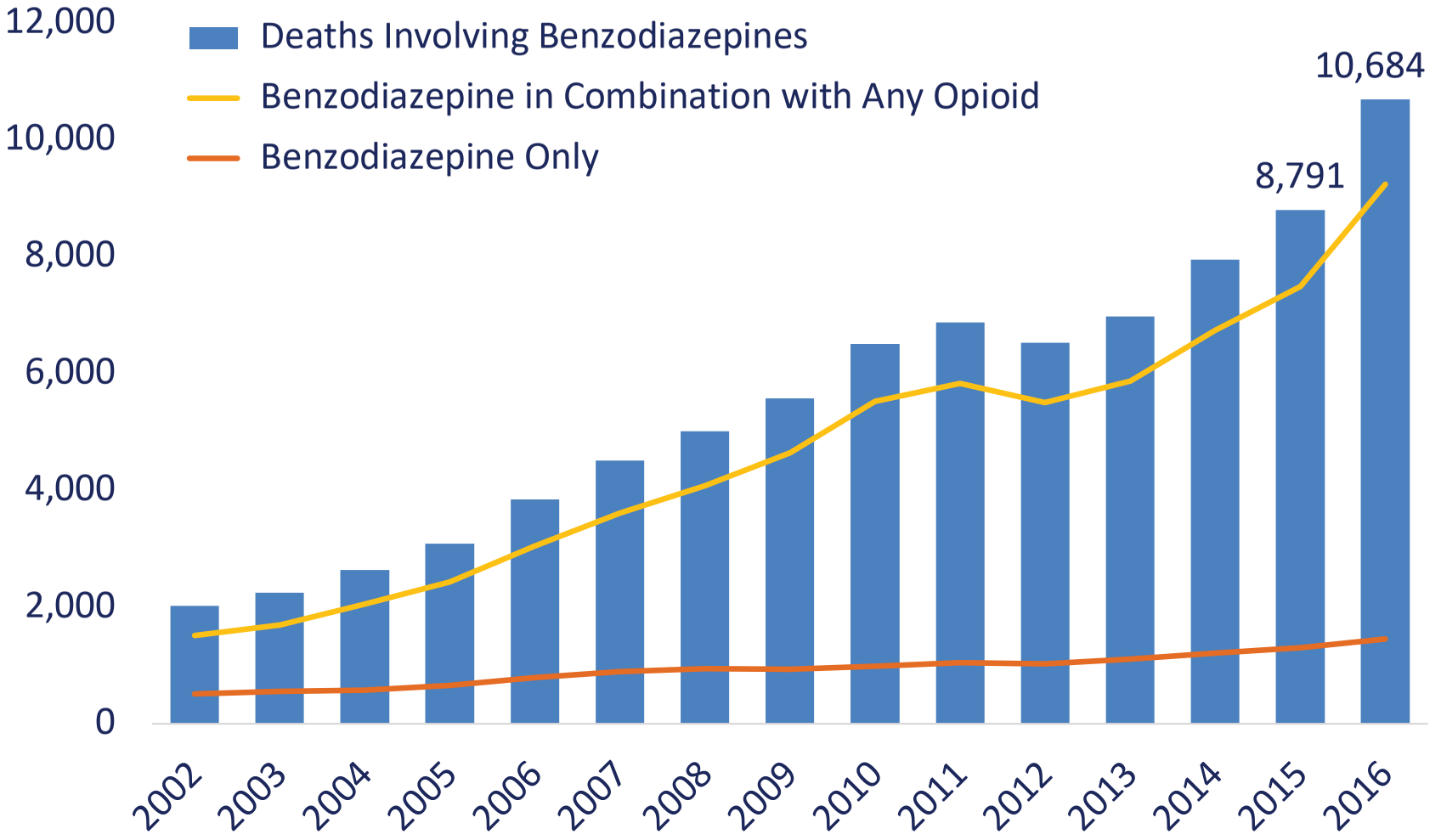
Opioid Pain Relievers (excluding non-methadone synthetics)



Source: National Center for Health Statistics, CDC Wonder

National Institute on Drug Abuse

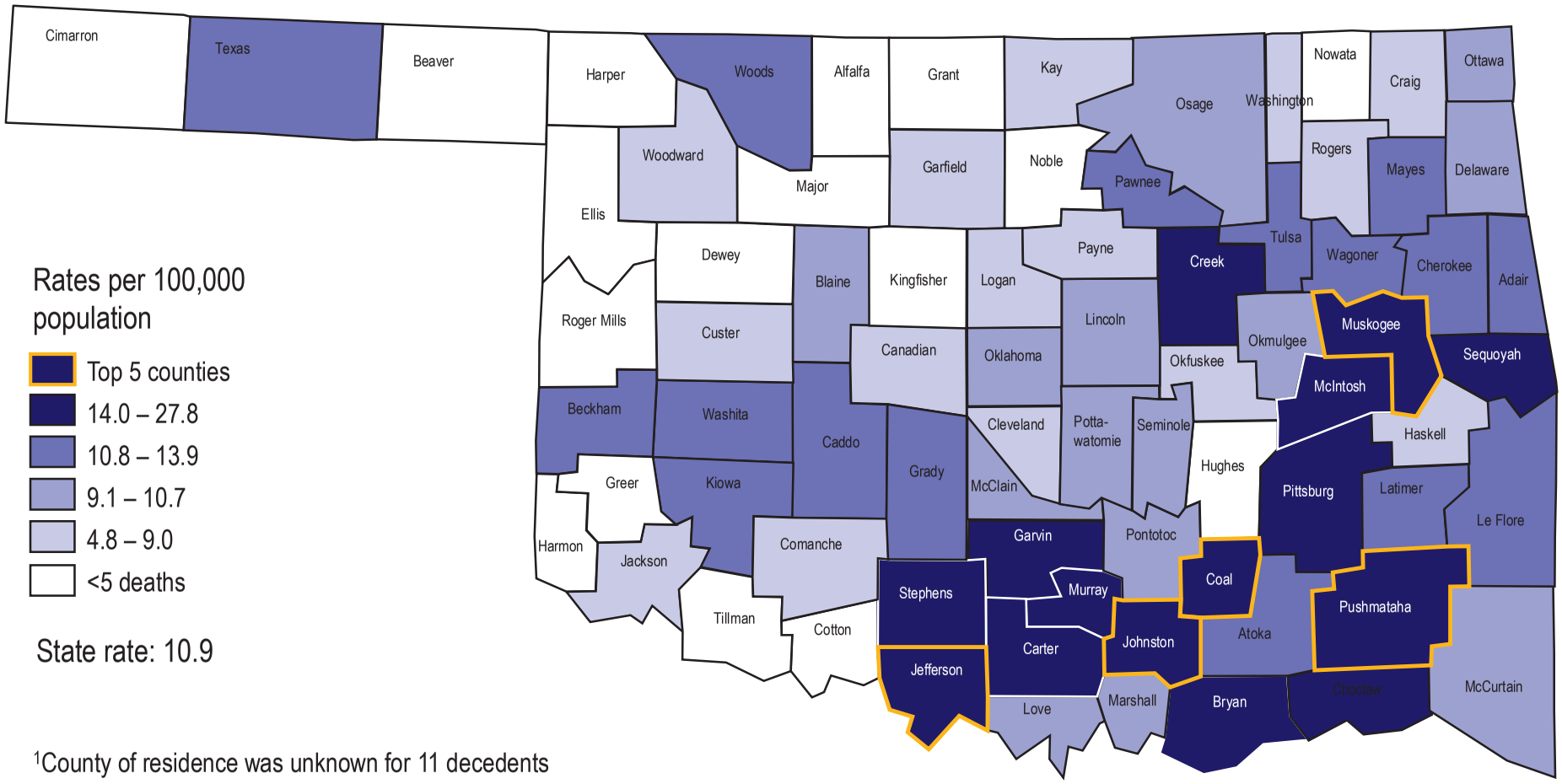
Opioid Involvement in Benzodiazepine Overdose



Source: National Center for Health Statistics, CDC Wonder

Source: National Center for Health Statistics, CDC Wonder

Unintentional Poisoning Death Rates Involving at Least One Prescription Opioid by County of Residence[1], Oklahoma, 2012-2016



Rates per 100,000 population

- Top 5 counties
- 14.0 – 27.8
- 10.8 – 13.9
- 9.1 – 10.7
- 4.8 – 9.0
- <5 deaths

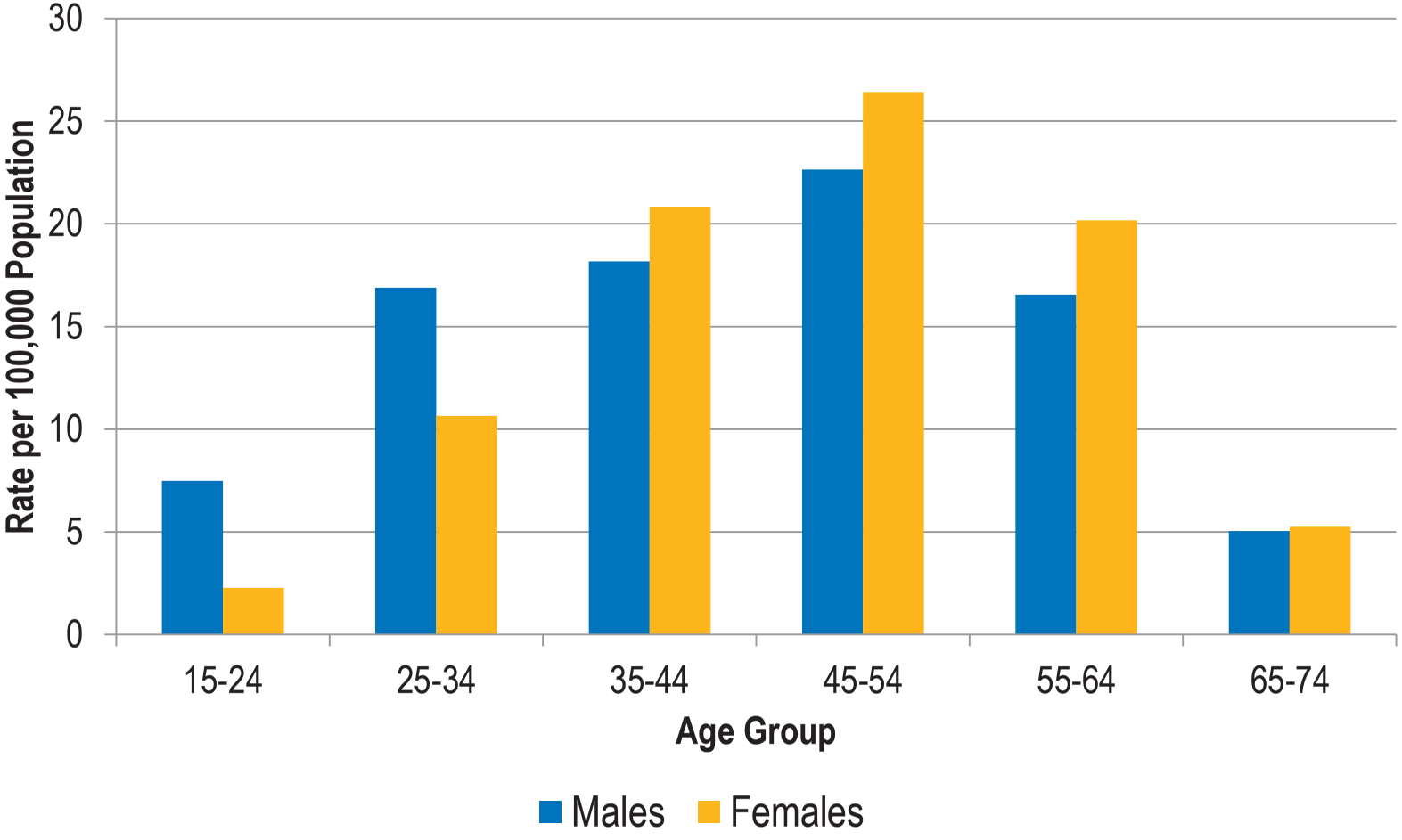
State rate: 10.9

[1]County of residence was unknown for 11 decedents

Source: OSDH, Injury Prevention Service, Unintentional Poisonings Database
(Abstracted from Medical Examiner reports)

Injury Prevention Service
Oklahoma State Department of Health

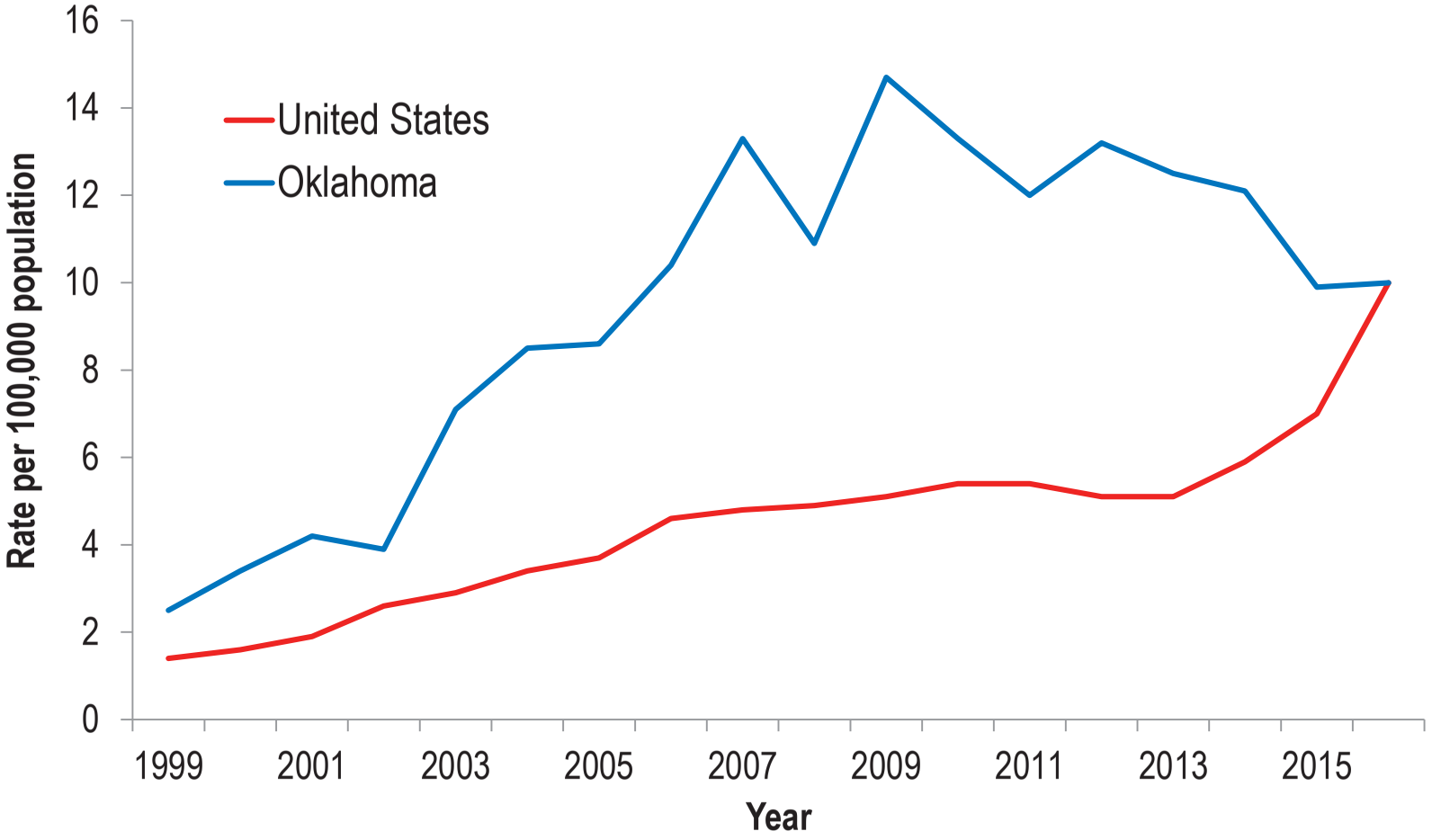
Unintentional Prescription Opioid Overdose Death Rates by Age Group* and Gender, Oklahoma, 2012-2016



*Decedents under age 15 and over age 74 were excluded due to small number of cases (<1% of all UP deaths)

Source: OSDH, Injury Prevention Service, Unintentional Poisonings Database (Abstracted from Medical Examiner reports)

Age-adjusted Prescription Opioid Overdose Death Rates, Oklahoma and the United States, 1999-2016



Source: CDC, National Center for Health Statistics, WONDER Multiple Cause of Death File

Injury Prevention Service
Oklahoma State Department of Health

Tapering and Discontinuing Opioids

This factsheet accompanies the 2010 VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. It was created to aid with treatment of adult populations. Department of Veterans Affairs (VA) and Department of Defense (DoD) employees who utilize this information are responsible for considering all applicable regulations and policies throughout the course of care and patient education.

This factsheet informs DoD and VA providers of approved strategies to successfully taper opioid medications. The decision to taper and/or discontinue opioid treatment should be made after a discussion with the patient. Once a decision is made to discontinue therapy, providers need to decide how fast the taper should be to prevent precipitating opioid withdrawal symptoms in physically dependent patients. There is no single tapering strategy to fit all patients; however, treatment should not be stopped abruptly unless there is an urgent need to stop therapy (e.g., an allergic reaction).

Reasons to discontinue opioids include, but are not limited to:

- Existence of severe unmanageable adverse effects
- Serious non-adherence to the treatment plan
- Evidence of illegal or unsafe behaviors
- Misuse suggestive of addiction to prescribed medication
- Lack of therapy effectiveness
- A desire on the part of the patient to discontinue therapy
- Decreased level of pain in stable patients
- Goals of treatment are not met

Remember: Tapering is generally not life threatening for patients without significant co-occurring conditions, but it can be quite uncomfortable.

Recommendations for Discontinuing and Tapering:

- Decisions regarding tapering schedule should be made on an individual basis, faster or slower tapering may be warranted.
- Complete evaluation of the current treatment plan, co-occurring psychological conditions and other relevant factors should be completed prior to initiation of the taper.
- Clear written and verbal instructions should be given to patients and their families to educate them about the slow taper protocol to minimize withdrawal symptoms.
- For patients who are at high risk to engage in aberrant behaviors (e.g., parasuicidal acts, dealing/selling medications, those with severe impulse control disorders), tapering opioids in a primary care setting is not appropriate. Those patients should be referred to an addiction or pain specialist.
- Patients with complicated withdrawal symptoms should be referred to a pain specialist or a center specializing in withdrawal treatment.
- Patients who develop an opioid addiction should be referred for substance use disorder treatment. While opioid prescribing should stop and withdrawal assessed if illicit drug use is clear, opioid agonist therapy, tapering, or discontinuation of opioid therapy should be decided after the consultation.

Withdrawal

Opioid withdrawal can develop within hours of drug cessation. While the effects of withdrawal are unlikely to be life threatening in patients without significant comorbidities, it can be quite uncomfortable. Signs and symptoms of withdrawal may include gastrointestinal symptoms (e.g., abdominal cramping, nausea, vomiting, diarrhea), musculoskeletal symptoms (e.g., myalgias, arthralgias, muscle spasms), anorexia, yawning, lacrimation, salivation, rhinorrhea, piloerection, insomnia, anxiety, irritability, dysphoria and manifestations of sympathetic hyperactivity such as diaphoresis, tachycardia, fever, mydriasis or mildly elevated blood pressures. In patients with significant comorbidities, withdrawal should be medically managed.

According to Mattick & Hall (1996), medically managed withdrawal is successful to the degree that the patient:

- Is physiologically stable
- Avoids hazardous medical consequences of withdrawal
- Experiences minimal discomfort
- Reports being treated with dignity and respect
- Completes the tapering protocol (e.g., no longer requires medication for withdrawal symptom management)
- Engages in continuing care for substance use disorder

Patient Education	Patient education is essential to successfully taper opioids. Clear written and verbal instructions should be given to patients and families to educate them about the rapid and slow taper protocols that will minimize withdrawal symptoms, as well as the proper way to dispose of opioids. From the outset of treatment, providers should reassure patients that they will work with them to manage their pain.

Tapering Factors and Protocol

One objective of opioid tapering is to maintain patient safety and comfort during initial and successive phases of the taper. This includes patient preparation to discontinue opioids in order to minimize withdrawal symptoms (e.g., muscle and joint aches, nausea, anxiety, runny nose).

Remember the following patient-specific factors as you begin a new taper:

- In general, the longer the patient has been on opioids, the slower the taper should be.
- Do not treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids. More information available at: *agencymeddirectors.wa.gov/Files/OpioidGdline.pdf*
- Consider tapering opioids in patients who have received regularly scheduled opioids at greater than the recommended starting doses for more than a few days.
- Patients taking opioids on a non-daily, as-needed basis can typically have their medication discontinued without tapering.
- Take into consideration patient-specific factors when deciding whether the patient needs to taper and at what rate. Consider risk of precipitating withdrawal, patient's level of anxiety about discontinuing opioids, duration of opioid therapy, medical and psychological comorbidities, and clinical need for rapid taper.
- Patients who develop a true allergic hypersensitivity reaction to their opioid should have therapy discontinued immediately.
- Taper by 20-50 percent per week (of original dose) for patients who are not addicted. The goal is to minimize adverse/withdrawal effects.
- The rapid detoxification literature indicates that a patient needs 20 percent of the previous day's dose to prevent withdrawal symptoms.
- Consider using adjuvant agents such as antidepressants to manage irritability and sleep disturbance, or antiepileptics for neuropathic pain. More information available at: *agencymeddirectors.wa.gov/Files/OpioidGdline.pdf*
- The patient on fentanyl should be rotated to a different opioid, either long-acting morphine or methadone. Once the patient is converted, the same guidelines will apply.
- Alternately, with the availability of transdermal fentanyl 12 mcg/hr patches, some patients may be tapered down on fentanyl patches and then given a brief supply of oral short-acting opioids to complete the taper.
- Clonidine 0.1 mg two or three times daily may be used to control many withdrawal symptoms if there are no contraindications. Supplemental medications will often be required as clonidine will not address all withdrawal symptoms (e.g., muscle and joint aches, nausea, diarrhea, anxiety).

*More information is available in the **Consultation and Referral** fact sheet for patients who are unable to tolerate the taper as described.*

Remember: If the primary care provider anticipates the need to contact a provider outside the DoD or VA regarding the patient's medical care, they must obtain the patient's permission in advance.

Suggested Tapers for...

- Methadone:
  - Decrease dose by 20-50 percent per day until you reach 30 mg/day
  - Then decrease by 5 mg/day every three to five days to 10 mg/day
  - Then decrease by 2.5 mg/day every three to five days
- Morphine SR/CR:
  - Decrease dose by 20-50 percent per day until you reach 45 mg/day
  - Then decrease by 15 mg/day every two to five days
- Oxycodone CR:
  - Decrease dose by 20-50 percent per day until you reach 30 mg/day
  - Then decrease by 10 mg/day every two to five days

Mattick RP, Hall W., *Are detoxification programmes effective?* Lancet, 1996 Jan, 13;347(8994):97-100

Indications for Medication-Assisted Treatment (MAT)

MAT should be considered in a patient with:

- Opioid use disorder or physical dependence
- 1 year history of addiction (*required by some programs*)
- Prior history of narcotic dependence who was previously in a MAT program
- Released from penal institutions with a history of narcotic dependence
- Injection of drugs, such as heroin

- Vermont Department of Health: Medication Assisted Therapy for Opioid Dependence Rules

- Aberrant behaviors, such as:
  - Early refill requests
  - Multiple reports of lost or stolen medications
  - Taking more of the medication than prescribed
  - Use of a relative or friend's opioids
  - Inconsistent urine drug screens
  - Multiple providers
- Concurrent use of opioids with benzodiazepines

- Indiana Prescription Drug Abuse Task Force

Indiana Prescription Drug Abuse Task Force. (Version 1.0). *First Do No Harm: The Indiana Healthcare Providers Guide to the Safe, Effective Management of Chronic Non-Terminal Pain.*

Vermont Department of Health. *Medication Assisted Therapy for Opioid Dependence Rules*. www.healthvermont.gov/regs/documents/opioid_dependence_rule.pdf. Accessed 10/13/2015.

Risk Factors for Suicide among People with Chronic Pain

Current evidence suggests that people who experience chronic pain are at increased risk for a number of adverse health outcomes, including opioid overdose and suicide.[1,2,3] Among this population, researchers have identified a variety of factors that can increase suicide risk among this group. Understanding these factors can help prevention practitioners and health care providers identify individuals experiencing chronic pain who may be at risk for suicide and implement interventions to address it.

FACTORS THAT MAY INCREASE THE RISK OF SUICIDAL BEHAVIOR AMONG PEOPLE WITH CHRONIC PAIN

Desire to escape from pain. Some individuals with chronic pain may wish to escape both the physical pain and its associated emotional pain.[4]

Duration of pain. People who have pain that lasts 6 to 12 months—namely, patients with chronic pain—are at increased risk for suicide compared to those who experience acute pain.[5,6]

Helplessness, hopelessness. Individuals who feel that nothing can help with their pain and believe that positive outcomes aren't possible may be at increased risk for suicide.[4]

Insomnia, common among patients with pain, is associated with increased risk of suicide.[7]

Passive coping strategies, such as hoping for the pain to go away, increased the risk of suicide.[8]

Pain catastrophizing. Cross-sectional studies have found that pain catastrophizing described as thinking the worst about one's pain, feeling helpless over it, or magnifying it, is associated with intentional overdose and suicidal ideation.[7,9]

Pain interference. A cross-sectional study of approximately 1,500 patients with chronic pain found that high pain interference (that is, the degree to which an individual's pain prevents them from engaging in everyday life) is associated with suicidal ideation after controlling for depression and other key risk factors.[8]

Pain severity. Although evidence is mixed, longitudinal data suggests a link between severe pain and both suicide attempts and deaths.[10] A cross-sectional study found mixed evidence after controlling for factors like depression.[11]

Perceived burdensomeness and/or thwarted belongingness. Distress in interpersonal relationships and self-perceived burden, such as feeling like a burden on someone and feelings of not belonging, are associated with suicidal ideation.[7,12]

Prescription pain medication access, when other factors are present. Several factors, including prescription pain medication dose, taking pain medications and anxiety medication (like in addition to benzodiazepines) concurrently, and having an alcohol use disorder or mood disorder while on prescription pain medication can increase suicide in chronic pain patients.[13,14]

Specific pain diagnoses. A Department of Veterans Affairs' study of more than five million veterans found that back pain, psychogenic pain (that is, pain with medically unexplained physical symptoms) and migraines were all associated with an increased risk for suicide, after taking into consideration other factors that could increase these individuals risk of suicide.[15]

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SoonerCare
Oklahoma Health Care Authority

Behavioral health referral

When a provider determines that a behavioral health referral is appropriate for a SoonerCare member with substance use disorder (or another behavioral health need regarding opioids), the following options should be considered:

1. Counseling only
2. Counseling and treatment
3. Co-management with addiction treatment or pain management consultation
4. Referral to pain management specialist
5. Referral for medication-assisted therapy (e.g. Suboxone or Methadone)

This referral is a phone call or fax away. Please call 405-522-7266 or 405-522-7253 or fax 405-530-3411 to communicate with a SoonerCare Pain Management Program substance use resource specialist.

Oklahoma Health Care Authority
4345 N. Lincoln Blvd.
Oklahoma City, OK 73105

FAX

To: Pain Management Program community resource specialist

Fax: 405-530-3411

Phone: 405-522-7266

From:

Fax:

Phone:

Subject:

Message: If including protected health information (PHI) on this form, use a fax cover sheet. If you would like a call back to communicate more information, please indicate the best day and time to reach you. Thank you.

This transmission and any documents or files accompanying it may contain confidential information. This may include patient medical information that is protected under state and federal laws. The information in this transmission is intended only for the delivery to the individual or entity named above. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this transmission is strictly prohibited and may be in violation of law. If you have received this transmission in error, please notify the sender immediately, to arrange for the return of the documents or deletion of the transmission.

SoonerCare
Oklahoma Health Care Authority

Pain Management Program
Behavioral Health
Referral Form

Practice phone:	**Practice Fax:**

Referral source

Name of clinic or practice:
_____

Provider name:
_____

Contact name: _____ **Contact phone:**
_____

Member information

Member name: _____ **Member ID:**
_____

Member DOB: _____ **Member phone:**
_____

Please use the attached cover sheet when faxing this form.

Upon receipt of this referral, our substance use resource specialist will get in touch with the contact listed above for additional member information.

• **Referral date:**	• **Date referral received:**
• **Received by:**	

Telligen®
Healthcare Intelligence

Opioid Use Disorder

Diagnostic Criteria:

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of a opioid.

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

11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome.
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

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

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Focused Review

Prevention of Opioid Abuse in Chronic Non-Cancer Pain: An Algorithmic, Evidence Based Approach

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Background: The use of opioids for chronic non-cancer pain has grown exponentially in the last 15 years. Associated with that, dramatic increases in abuse and overdose deaths from opioid use have been noted.

Objectives: Most opioid abuse stems from legitimate prescriptions, putting the onus on prescribers to use opioids responsibly for chronic pain. Very little evidence-based guidance exists for those who wish to prescribe opioids for legitimate chronic pain and at the same time prevent opioid abuse.

Methods: A review of literature was performed for articles focused on guidelines for opioid use when prescribed for chronic pain, opioid abuse, and overdose, strategies to detect and prevent abuse of opioids, urine drug screens (UDS) in chronic pain settings, prescription monitoring programs (PMP), and the relationship between opioid dosing and abuse.

Results: Based on the existing literature, an evidence-based algorithmic approach was developed to decrease opioid abuse in the chronic pain environment. The pillars of prevention are the screening of patients into high, medium, and low risk categories using screening tools; monitoring patients using UDS, PMP, and pill counts, and lastly, dose limitations.

Conclusion: This algorithmic approach may enable physicians to prescribe opioids for patients with chronic pain and also to reduce opioid abuse.

Key words: Opioids, chronic pain, abuse, prescription, overdose, deaths, overdose deaths, urine drug screens, prescription monitoring programs, opioid dose, screening, monitoring

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The use of opioids has gained universal acceptance in the treatment of acute pain and cancer pain. The use of opioids for chronic non-cancer pain, however, remains controversial. In the last 15 years, there has been a dramatic upsurge in the use of opioids for chronic pain, even though the evidence in support of this practice has not kept up with the increase in the number of prescriptions. Although the use of opioids for chronic non-cancer pain has resulted in an increase in the quality of life and decrease in pain for some, there has been an unacceptable increase in opioid abuse and opioid-related deaths. Most of the abuse and deaths are from legally prescribed opioids. This predicament calls for responsible prescribing by the physician community, and the need for serious and earnest effort to decrease abuse. Prescribers need do this, however, without compromising availability of opioids to those who benefit from them.

Scope of the Problem

The abuse of prescription opioids has escalated at such an alarming rate that many now consider it an epidemic. It has been reported that the United States consumes 83% of the global supply of oxycodone, and 99% of the hydrocodone supply, despite the fact its population is only 4.6% of the world's population (1-13). In 2010, enough opioids were sold to medicate every American adult with an equivalent dose of 5 mg of hydrocodone every 4 hours for one month (14). In 2008, 2.17 million Americans used pain relievers in an illicit manner; a number close to those using marijuana (2.20 million) and much higher than those using cocaine (722,000) (14). Since 2003, deaths in the United States from drug overdose for whites have exceeded age-adjusted deaths among African Americans. In 2007, the number of deaths involving prescription opioids was 9.3 times the number involving cocaine and 5.38 times the number involving heroin (1). These deaths were more than those from cocaine and heroin combined. It has been shown that from 1997 through 2007, there was a seven fold increase in the number of prescriptions for opioids. This paralleled closely with the increase in deaths due to opioid overdose (15). There were 14,800 opioid overdose deaths in 2008, as compared to less than 2,000, in 1997. In 2008, deaths attributable solely to prescription opioids constituted approximately 73% of all deaths associated with drug-related overdoses (2). This increase in unintentional drug overdose deaths has been directly credited to the increased use of prescription opioids (1,14,15). We must be cognizant that each death represents just the tip of the iceberg and that there is ample abuse lurking beneath it. For every unintentional overdose death related to an opioid analgesic, 9 patients are admitted for substance abuse treatment, 35 visit emergency departments, 161 report drug abuse or dependence, and as many as 461 patients report the nonmedical use of opioid analgesics (2). During the years 1999–2008, prescription opioid sales, emergency department admissions for substance abuse treatment related to prescription opioids, and mortality rates due to opioid overdose all increased at similar rates (14). Sales of prescription opioids in 2010 were 4 times those in 1999 (14). The Treatment Episode Data Set Report (16) found that substance abuse treatment admissions that reported any opioid abuse increased more than fourfold between 1998 and 2008, from 2.2 to 9.8%. A separate report indicated that the substance abuse treatment admission rate in 2009 was almost 6 times the rate in 1999 (14). The nonmedical use of opioids costs insurance companies up to $72.5 billion annually in health care costs (17). According to another report, total US societal costs of prescription opioid abuse were estimated at $55.7 billion in 2007. Workplace costs accounted for $25.6 billion (46%), health care costs accounted for $25 billion (45%), and criminal justice costs accounted for $5.1 billion (9%) (18).

Source of Opioids Used Illicitly

More than half of those who used opioids illicitly obtained them free of cost either from a relative or a friend; 14% bought the drugs from them and 5% stole the drugs from them. Only 18% got prescriptions from a physician. In other words, about 83% of those who used opioids in an illicit manner had access to them because of a legitimately written prescription. Moreover, 81% of those who obtained the opioids free of cost revealed that their sources had obtained these drugs through a single prescriber. Only 4% paid a drug dealer or a stranger for the medication. Only 5% obtained them by writing a fake prescription, stealing from a doctor's office/clinic/hospital/pharmacy or described their source as "some other way" (1). According to a report by the Centers for Disease Control and Prevention, 76% of nonmedical users report getting drugs that had been prescribed to someone else, while only 20% report that they acquired the drug from their own doctor (2). Furthermore, among persons who died of opioid overdoses, a significant proportion did not have a prescription in their records for the opioid that killed them. In West Virginia, Utah, and Ohio, 25%–66% of those who died of pharmaceutical overdoses used opioids originally prescribed to someone else (2). Hall et al (19) reported that 63% of overdose deaths were from pharmaceutical diversion and 21% were from doctor shopping, meaning that at least 84% of the deaths were from legally prescribed opioids. This data implies that not only is personal abuse a major concern, but that diversion of prescribed opioids deserves equal attention. Drug dealers are no longer the primary source of illicit drugs. It appears that the greatest enemy is now the diversion of drugs from family and friends -- drugs procured from one physician and not from doctor shopping (20).

How Did It Become An Epidemic?

In the late nineteenth- and early twentieth-century, opioids were used extensively in medicine, even for non-pain conditions such as respiratory problems, anxiety, gynecological conditions, bloating, and many

others. This led to the widespread abuse of opioids and resulted in a public health emergency. Congress in 1912 passed a law severely limiting the use of opioids. Following that, opioids were used very conservatively (21) and perhaps even too cautiously. This changed in the late 1990s with the introduction of long-acting opioid formulations (22). The pharmaceutical industry aggressively marketed long-acting opioids (20-24) for chronic pain relying on 2 erroneous facts:

- That medical management with opioids is the recommended solution for undertreated chronic pain
- That the use of long-acting formulations decreases incidences of prescription opioid abuse.

Aggressive marketing by pharmaceutical companies using "paid consultant" physicians (some of whom did not have formal chronic pain management training and some of whom were non physicians), along with the endorsements of major pain societies, resulted in a reconsideration of then current practices by the state medical boards. The principles of opioid management in acute pain and cancer pain were transferred to the chronic pain arena. This culminated in the embracing of this class of drugs by practicing physicians who wanted to provide relief to their chronic pain patients. According to one study, data from 1990 to 1996 (a phase before the aggressive push for use of opioids for chronic pain), show that during this time period, there was a 22% increase in the medical use of oxycodone and interestingly, a 29% decrease in oxycodone-related emergency department visits (25). The authors concluded that increased opioid use is not associated with deleterious health consequences. The article, in fact, was published in 2000 (during the onset of the epidemic), thus giving the false impression that increased opioid use was not associated with increased abuse. But when similar data were examined by the same group for 1997-2002, there was a 402% increase in the medical use of oxycodone and a 226% increase in fentanyl (26). It is to be noted that during this period, physicians had undergone a significant change in their outlook regarding pain management and were aggressively treating chronic non-cancer pain using opioids. Correspondingly, there was a 1000% and 381% increase in opioid-related emergency department visits; 1,000% for fentanyl and 381% for oxycodone. This group concluded that even though there was an increase in abuse, it did not interfere with legitimate practice (26)! As reported by the Milwaukee Journal Sentinel, this group received funding from the pharmaceutical industry. Approximately two-thirds of the panel responsible for writing guidelines for the use of opioids for chronic pain for the American Academy of Pain Medicine (AAPM) and American Pain Society (APS) had conflicts of interest with the opioid pharmaceutical industry (27-31). These guidelines, while addressing issues like dose escalations, high dose opioid therapy, breakthrough pain, and upward titration of opioids, do not address the issues of dramatic increases in overdoses, deaths, addiction, and costs associated with the increased use of opioids. The investigation announced by the Senate in reference to conflicts of interest in preparation of opioid guidelines and promotion of opioid usage, have resulted in abandonment of the American Pain Foundation on May 10, 2012, which was a pivotal organization in promoting opioid use (32).

Effectiveness of Opioids in Chronic Pain

The long-term improvement of pain scores and functionality with the use of opioids for chronic pain has been scrutinized by many organizations. A recent review of the literature by Manchikanti et al (33) suggested that, based on the lack of literature supporting the use of opioids for chronic pain, opioids should be used with great restraint and caution. A review of the literature by Kuijpers et al (34) showed that there was poor evidence that opioids were better than a placebo in relieving pain and improving function. They also reported that there was poor evidence that opioids were not superior to nonsteroidal anti-inflammatory drugs (NSAIDS) in relieving pain and improving function. Guidelines by APS and AAPM (27) also suggest that the evidence of effectiveness of opioids for chronic pain is limited, and yet a consensus is provided for the use of opioids. Chou et al (35) also expressed concern that the review of the literature used to formulate the clinical practice guideline for APS and AAPM revealed a lack of effective studies on the long-term benefits and harm of opioids for chronic pain. A Cochrane review (36) of the long-term use of opioids for chronic non-cancer pain showed that there is weak evidence that those who use them long-term experience clinically significant pain relief, and that there was inconclusive evidence that the quality of life or functioning improves. Pinto et al (37) have evaluated the efficacy of opioids for patients with sciatica and concluded that the clinical trials were of low quality and the efficacy and tolerability of these drugs were unclear. An analysis of the literature regarding pharmacological management for low back pain by White et al (38) concluded that opioids have

similar efficacy as NSAIDS, but have more side effects. Franklin et al (39) followed injured workers for one year. They found that despite a 62% increase in opioid doses over a 12 month period (from 26 mg morphine equivalent dose [MED] in the first quarter to 42 mg in the fourth quarter), improvement in pain and function was seen only in 27% and 16% of the patients. In concurrence with Franklin et al (39), multiple other authors have illustrated deleterious consequences of early or continued opioid use for chronic pain, including adverse consequences of dependence, hyperalgesia, and an association between opioid prescribing and overall health status, with increased disability, medical costs, subsequent surgery, and continued or late opioid use (1,39-56).

Call For Responsible Prescribing

The annual US expenditures related to pain (including direct medical costs and lost wages) are higher than those for cancer, heart disease, and diabetes combined (20). The improvements in the emotional and economic impact of untreated chronic pain are often the criteria by which pain management physicians measure the success of a treatment modality. But the notion that aggressive use of opioids in trying to alleviate chronic non-cancer pain would result in improvement of function (let alone improvement in pain) has been proven erroneous. Despite a cavalier approach to the prescription of opioids in the last decade, numerous studies have shown a consistent lack of evidence that opioids decreased pain, improved function, or decreased health care costs (27,33-39). On the contrary, there is now an abundance of evidence that this aggressive approach has harmed individuals and society and has had a negative economic impact (1,14-18,23,57-87). Gomes et al's study (57) reports that the overall death rate for patients receiving opioids was 10 times higher than those not on opioids, suggesting possible harm. Eriksen et al (23) have shown that patients on opioids report higher pain scores, poor self-rated health, not being engaged in employment, higher use of the health care system, and a negative influence on quality of life. Although pharmacists, state medical boards, and other agencies and professionals play a role in curbing abuse, the primary onus is on the prescribing physician. Since the vast majority of opioid overdose deaths from opioids stem from legitimate prescriptions, calls for responsible prescribing by physicians have been made (88-94). Given that 3% of physicians accounted for 62% of the opioids prescribed in one study (61), the proliferation of high-volume prescribers can have a large impact on the use of opioids and overdose death rates (14).

For controlling acute pain and cancer pain, opioids have been shown to be quite effective. Most of the evidence for prescribing opioids comes from studies of their use in these settings. In such scenarios, other medications, namely NSAIDs, muscle relaxants, antidepressants, and anticonvulsants are not as effective and are used, if at all, in a supplementary role. However, extrapolating these results from acute pain studies to guide managing chronic non-cancer pain may not be a wise step. Opioids have a very important role in chronic pain management and their value should not be underestimated. Unlike other analgesics, opioids do not result in organ toxicity, nor is there any ceiling dose associated with their use. Opioids have, thus, become the mainstay and play a vital role but they are not a panacea for chronic pain. In order to maximize their efficacy, opioids should be used with great restraint and caution and in carefully selected patients as recommended by American Society of Interventional Pain Physicians guidelines (62). According to one study, there is evidence that opioids are being used with the wrong patients (63). We concur with Manchikanti et al (20) that the most underappreciated issue in modern medicine is the adverse consequences of appropriately prescribed opioids, with all the blame diverted to abuses and overuses.

There are 3 types of patients that we should be cautious about: the first is the abuser; the second is the one who is involved in diversion; and, the third is the patient who is a combination of the two. The cornerstones for responsible opioid use for balancing pain relief along with curbing abuse and diversion are:

- Careful patient screening to stratify patients into different risk groups for opioid abuse/diversion
- Monitoring patients to ensure compliance for the responsible use of opioids
- Establishing and adhering to dose limitations.

Screening Patients

The need for effective screening tools was expressed as early as 2001 (64,65). A decade later we are still looking for a tool that is universally acceptable. Guidelines from AAPM and APS (27) state that risk stratification is an undeveloped skill for many physicians prescribing opioids and that these physicians should be more knowledgeable in this area. There are many screening tools that currently exist which are specifically designed for prescription opioid abuse. Solanki et al (66) reviewed all the available screening tools and con-

cluded that there was no single screening tool that can be applied universally. Chou et al (35) analyzed tools that were specific for prescription opioids and based on their criteria found that most of the studies evaluating the screening tools had methodological flaws. However, screening tools may play an important role in curbing abuse. The failure to utilize existing tools so as to find the perfect tool seems counterproductive in this environment. The question remains: Which is the best existing tool? The tools we find useful are the Screener and Opioid Assessment for Patients with Pain (SOAPP) (67), Pain Medication Questionnaire (PMQ) (68,69), Prescription Drug Use Questionnaire patient version (PDUQP) (70), Addiction Behaviors Checklist (ABC) (71), Diagnosis, Intractability, Risk, Efficacy (DIRE) score (72) and the one by Atluri and Sudarshan (73). The screening tool Current Opioid Misuse Measure (COMM) (74) and Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) (75) were not considered because many of the questions were not related to abuse/diversion and fell under the category of psychological queries. The Pain Assessment and Documentation Tool (PADT) (76) is not a screening tool as it addresses the level of analgesia, adverse events, and activities of daily living along with aberrant drug-related behavior. The section of abuse is a small component of the whole tool. The screening tool by Michna et al (77) addressed only 3 items, and is not comprehensive enough to identify abuse. The Opioid Risk Tool (ORT) (78) is a 5-item tool which is also not comprehensive. The items in this tool are not predictors of abuse. PDUQ and PDUQP tools were developed by the same group. PDUQP (70) is a modified, improved version of PDUQ (69) as all the questions are related to abuse, and questions related to psychopathology were eliminated. Among the tools selected, the first 3 tools are subjective (SOAPP, PMQ and PDUQP) and the last 3 are objective tools (DIRE score, ABC checklist and the tool by Atluri and Sudarshan). Although there has been a call for the use of these subjective tools (79-82), abusers tend not be truthful in subjective questionnaires (83-87). The screening tool developed by Wu et al (71), the DIRE Score (72), and the screening tool created by Atluri and Sudarshan (73) may have more value since they incorporate objective measures. These tools can be used singularly or in combination. Generic screening tools for drug and alcohol abuse are not as useful as those specifically designed for prescription opioid abuse. Guidelines developed for opioid use for chronic pain (27,87,88) include recommendations for using screening tools, but with the reservation that risk stratification is currently underutilized (89,90). Classifying patients into high and low risk groups helps tremendously with opioid management and might possibly be one of the cornerstones in abuse prevention. As described below, screening patients into different risk categories determines the frequency of monitoring, aggressiveness of dosage, and frequency of follow-up visits.

Urine Drug Screens

Currently, urine drug screens (UDS) remain one of the most important tools for detecting inappropriate use of opioids. Although Starrels et al (91) concluded in their review that the evidence in support of the effectiveness of UDS for reducing opioid misuse in chronic pain is relatively weak, they have also noted that based on cross-sectional studies and case series, UDS is a valuable tool for detecting the use of unprescribed drugs and for confirming adherence to prescribed medications with a higher degree of accuracy than when identified by patient self-report or the impression of the treating physician. Starrels et al (91) also suggested that UDS might improve the provider-patient relationship and clinic morale. After a review of the literature regarding the role of UDS and opioids, Christo et al (92) concluded that, "UDS is one of the major tools of adherence monitoring in the assessment of the patient's predisposition to, and patterns of, drug misuse/abuse – a vital first step towards establishing and maintaining the safe and effective use of opioid analgesics in the treatment of chronic pain." Katz et al (93) have shown that using UDS along with monitoring aberrant behaviors enhances abuse detection. In Manchikanti et al's study (94), random UDS reduced illicit drug use in the chronic pain population. In a separate study, Manchikanti et al (95) have shown that by using UDS they could identify a combined use of illicit drugs and the misuse of prescription drugs in 24% of patients on hydrocodone and in 33% of patients receiving methadone (96). The Federation of State Medical Boards has formally included UDS in current guidelines for using opioids in the management of chronic noncancer pain (97). Since there is evidence that UDS have not been universally adopted by physicians treating chronic pain (98,99), the use of UDS must be encouraged. Random UDS may have more value in detecting abuse as patients may change their behavior when expected to be tested (27).

Prescription Monitoring Programs

Prescription monitoring programs (PMPs) serve as a means of data collection for opioid prescriptions, providing physicians with information about who wrote the prescriptions and the pharmacies that dispensed them. Physicians have access to this data to check if patients are getting opioid prescriptions from more than one physician at the same time. This information becomes extremely useful especially if the patient signs an opioid contract agreeing to obtain the prescription from only one physician and to fill it in only one pharmacy. Currently, there are 38 states with this program (66). A national program would be invaluable in curbing abuse and doctor shopping (100). The National All Schedule Prescription Electronic Reporting Act (NASPER) was enacted by Congress in 2005 but has not yet been fully implemented (101). Calls for immediate funding and rapid implementation of NASPER have been made. This law requires states to collect prescription information for Schedule II, III, and IV medications. It also requires states to have the capability to share this information with one another. This would potentially decrease cross-border opioid trafficking and would be invaluable in curbing abuse and doctor shopping (15,102,103). Paulozzi et al's study (104) recommends using PMP to curb overuse, noting that the rate of overdose deaths is higher in those who use multiple pharmacies and doctors. This assertion is also expressed by White et al (105). In one study, 21% of overdose deaths resulted from doctor shopping (106). In response to the epidemic of prescription drug abuse, the White House Office of National Drug Control Policy issued a document in which it recommended enhanced use of prescription drug monitoring programs (106). The National Alliance for Model State Drug Laws indicates that these databases foster the legitimate medical use of controlled substances while limiting drug abuse and diversion (102). Access to PMP can help clinicians curb diversion and abuse and to decrease the number of unnecessary prescriptions while still providing analgesia to those who need it (102). Manchikanti et al (107) have recently shown that the Kentucky's PMP, KASPER (Kentucky All Schedule Prescription Electronic Reporting Program) has led to a decrease in doctor shopping from 18% in 2001 to 2.1% in 2011. Baehren et al (108) showed that in an emergency department setting, the use of PMP positively influenced the opioid prescribing pattern. Based on the PMP results, 61% of their study patients were prescribed less opioid medication than originally planned, whereas 39% received more opioid medication than previously planned. Paulozzi et al (109) reported that PMPs were not significantly associated with lower rates of drug overdose or opioid overdose mortality or lower rates of consumption of opioid drugs. An accompanying editorial (110) clarified that the lack of impact of PMPs is due to their underutilization.

A Case for Dose Limitation

The evidence in favor of long-term opioid use for chronic pain is at best problematic. Considering the irrefutable evidence showing widespread abuse and diversion, the rationale for high dose opioids should be reexamined. Patients who do not respond to a low/medium dose of opioids generally would not find their pain alleviated by larger doses. In 2007, the state of Washington issued guidelines that in general, the daily dose should not exceed 120 mg of MED (87). The guidelines by APS and AAPM in 2009 defined high dose as 200 mg MED (27). The Canadian guidelines in 2010 identified 200 mg MED as a watchful dose (88). Until recently, however, there was only limited data verifying the safety of these recommended doses, especially in high risk patients. Five recent studies showed that the rate of overdose was directly proportional to the prescribed opioid dose (57,104,111-113). Bohnert et al's study (111) in a national sample of Veterans Health Administration patients revealed that there was a dose-response relationship between the maximum daily prescribed dose of opioid and the risk of opioid overdose death. The overdose death rate for patients receiving a dose of less than 20 mg MED was 0.11 per 1,000 compared to those getting more than 100 mg MED, for whom the death rate was 1.24/1,000. This difference was even higher in those with a history of substance abuse (0.54 versus 2.97). Since the death rates were higher in patients receiving doses of 50 mg MED versus those getting less than 50 mg MED, the authors concluded that that the risk of opioid overdose increased when the opioid dose was equivalent to 50 mg MED.

Dunn et al (112) reported that in a population from a health maintenance organization in Washington State , there was a 9-fold increase in opioid overdose in patients receiving high dose opioids (more than 100 mg MED) to those getting low dose (less than 20 mg). There was a 3.7-fold increase in overdose events in patients receiving doses between 50-99 mg MED versus those getting less than 20 mg MED. Paulozzi et al (104) found that compared to patients receiving lower opioid doses or no opioid prescriptions, the risk of overdose was greatest at daily opioid doses above 40 mg

MED. Braden et al (113) found that patients (Arkansas Medicaid and HealthCore commercially insured enrollees) receiving MEDs of more than 120 mg/d are more likely to have drug-related encounters than those getting lower doses. There were no differences between these 2 groups regarding emergency department visits. Gomes et al (57) found that patients from Ontario's public drug plan receiving "very high" doses (> 400 mg MED) and "high" doses (200-400 mg MED) had a much higher overdose death than those getting "moderate" doses (< 200 mg MED). In "very high" and "high" dose patients the opioid-related mortality rates were 9.94/1,000 for "very high" and 7.92/1,000 for "high." Comparatively, the opioid-related mortality rate was 1.63/1,000 in those with "moderate" doses. Also, the overall death rate (from any cause) was much higher in patients receiving opioids (20.05/1,000) when compared to those who were not getting any opioids (4.00/1,000).

In the above 5 studies, the doses which are related to an emergency department admission for overdoses or death are 40 mg MED (104), 50 mg MED (111,112), 120 mg MED (113), and 200 mg MED (57). We did not find any study in which a higher dose did not correlate with increased mortality and only one study where there was no correlation between higher opioid dose and emergency department visits. Moreover, Paulozzi et al (15) reported that in 80% of all patients receiving opioids, the dose was less than 100 mg MED and was obtained from one physician. This patient pool constituted 20% of the overall overdose deaths. Even though only 10% of all patients were receiving a dose of greater than 100 mg MED from a single prescriber, the overdose death rate in this population was as high as 40%. Patients receiving more than 100 mg MED from multiple physicians constituted the rest of the 10%. The percentage of overdose deaths was 40% in this segment. In other words, patients receiving more than 100 mg MED (from single or multiple prescribers), contributed to 80% of all the overdose deaths, whereas patients on doses of less than 100 mg MED contributed to only 20% of the overall overdose deaths, implying that 100 mg MED is a dangerous dose. There has been a call for establishing a maximum daily dose in order to guide physicians treating patients with chronic pain (114). Based on the current available evidence presented above, defining 50 mg MED/d as a high dose does not seem unreasonable. The dose limits recommended earlier by Washington State (120 mg MED) (109) and the Canadian guideline (200 mg MED) (110) seem excessive. Defining 200 mg MED by APS and AAPM as a high dose also appears to be harmful. We agree with Katz (114) that having dose limits will provide a guide for practicing physicians, reduce harm by eliminating high doses, assist in the negotiation process between physicians and patients pressing for higher doses and finally, impel high dose prescribers to exercise more caution. We concur with Manchikanti et al (20) that commencing long-acting opioid therapy is often the starting point for high dose opioid therapy, a practice that growing evidence suggests is harmful to patients and increases the black market availability of opioids through diversion. Many argue that chronic pain is undertreated and opioids must be used more liberally. We agree that chronic pain is undertreated, but we completely disagree, based on evidence, that aggressive opioid use is the answer to alleviating undertreated chronic pain. Given our awareness of the inadequacy and adverse effects of using opioids for the treatment of chronic pain, the failure to set dose limits is irresponsible and hazardous both to the individual and to society.

Algorithmic Approach to Prevent Opioid Abuse

Opioids play an important but limited role in treating chronic pain. The challenge for the physician is to make opioids available for those who are truly in need, and to withhold them from those who are either abusing or diverting. Although difficult, this can be achieved in most cases. If all nonopioid measures fail in alleviating pain, and if opioids are being used, the following steps would be very helpful. The 3 cornerstones for responsible prescribing are stratifying patients by using screening tools into high, medium and low risk groups; monitoring patients by using UDS, PMPs and pill counts; and lastly, establishing dose limits (Fig. 1).

Stratification of patients into different risk categories is the first step. This requires the use of existing screening tools designed specifically to screen for opioid misuse (subjective tools like SOAPP (67), PMQ (68), PUDQP (70) or objective tools like ABC checklist (71), DIRE Score (72) and the tool by Atluri and Sudarshan (73) to classify patients as high risk, medium risk and low risk. As mentioned earlier, objective tools may be better than subjective tools. Those who are categorized as "high risk" should be monitored closely by performing UDS every 3 to 6 months and PMP every 2-4 months. Opioids should be either avoided or prescribed in low doses. Doses of more than 50 mg MED should be very rarely used and only under specialized settings in conjunction, when available, with addiction specialists. Pa-

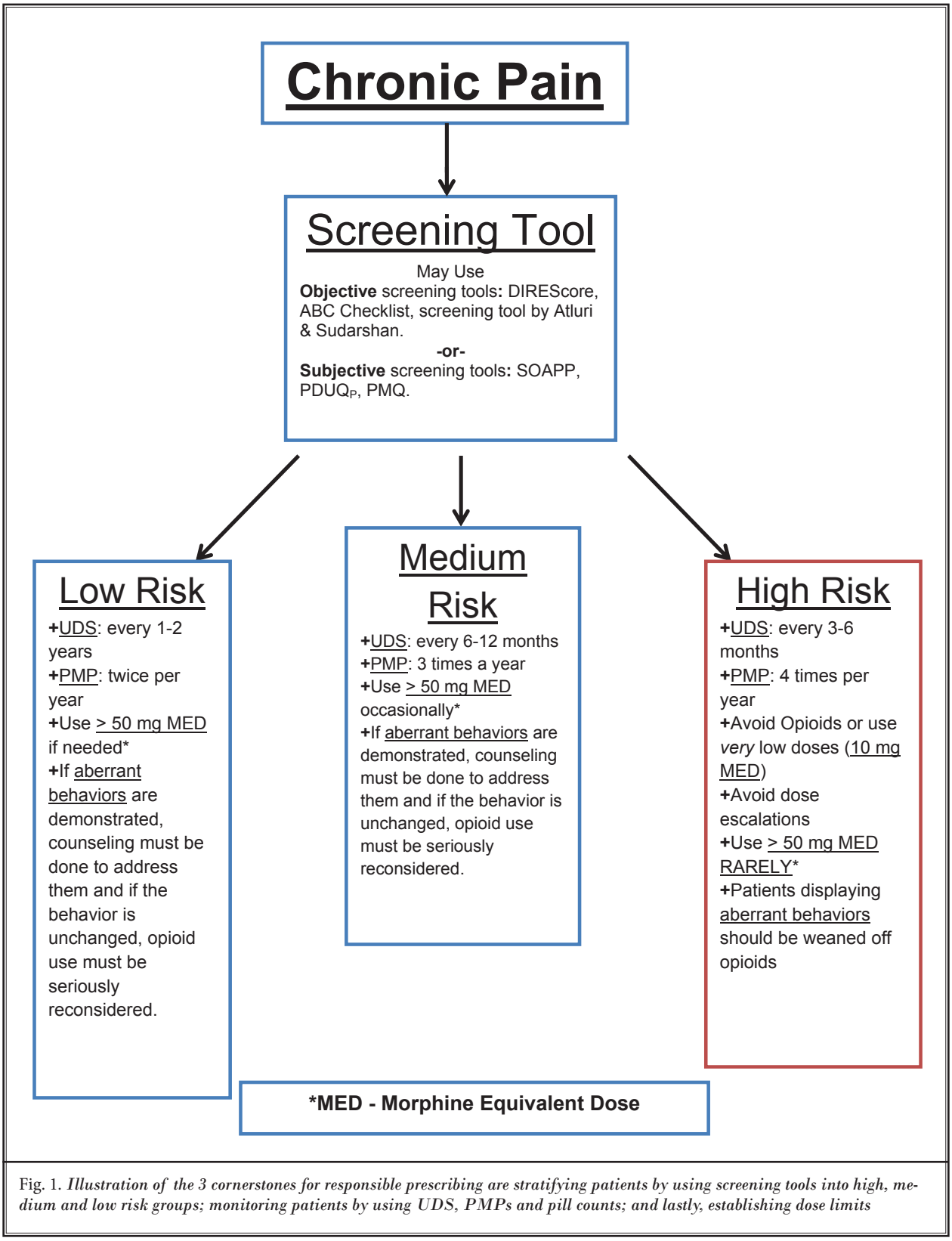

Fig. 1. *Illustration of the 3 cornerstones for responsible prescribing are stratifying patients by using screening tools into high, medium and low risk groups; monitoring patients by using UDS, PMPs and pill counts; and lastly, establishing dose limits*

tients displaying aberrant behaviors (asking for early refills, frequent visits to an emergency department for opioids, doctor shopping, taking opioids from others, etc.) should be weaned off opioids. Patients falling into the "low risk" category should be subjected to UDS every 1-2 years and PMP every 6 months to 1 year. Dose escalations can be done more liberally if required, keeping in mind that doses more than 50 mg MED/d should be an exception rather than the rule. If aberrant behaviors are present, counseling must commence. If counseling does not alter the behavior, opioid use must be seriously reconsidered. Those who are deemed as "medium risk" should be monitored with UDS every 6-12 months and PMP every 3-6 months. Opioid doses and their escalations should be guarded. Doses more than 50 mg MED/d can be used occasionally in carefully selected patients. If aberrant behaviors are present, counseling must commence, with a reconsideration of opioid use if the behavior does not change. These measures, along with an opioid agreement requiring patients to use a single prescriber and a single pharmacy, discouraging self dose escalations, giving limited refills, establishing regular office follow-ups, explaining the risks and benefits of opioids along with insisting on compliance with the opioid agreement should be useful in curbing inappropriate use of opioids.

Conclusion

To tackle the epidemic of prescription opioid abuse, the following is suggested by Paulozzi et al (15).

1. Improving legislation and enforcement of existing laws regarding doctor shopping, diversion, and unscrupulous physicians.
2. Improving medical practice in prescribing opioids through proper education. In our opinion, and in order to encourage proper prescribing, this education should be based on evidence and not influenced by pharmaceutical companies. Currently, most of the education in this field is sponsored by pharmaceutical companies. Not surprisingly, there has been an escalation of abuse despite "voluntary" education (14). There is some evidence that the risk reduction strategies are not employed by primary care physicians, even in high risk patients (115). Mandatory education for those prescribing opioids for chronic pain may be helpful.
3. Pain organizations and societies should establish guidelines based on sound science without conflict of interest. Opioid management should be based on evidence and not on consensus of experts, no matter how learned they may be (116).

Opioids have an important but limited role in chronic pain. Their use should not be curtailed. The aim of this article is to encourage opioid use for patients who need it and at the same time deny it to those who abuse it. Unless the medical community takes an active role in curbing abuse, opioid use will be subject to excessive regulation by the government, making it difficult for us to prescribe. Responsible opioid prescribing, entails employing screening tools, monitoring patients, and establishing dose limits, and is required to prevent harm and preserve access to those who need it. Lest, we should forget, "first do no harm."

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OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Original Research Article

Benzodiazepine Use among Chronic Pain Patients Prescribed Opioids: Associations with Pain, Physical and Mental Health, and Health Service Utilization

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Abstract

Objective. Benzodiazepines (BZDs) are commonly used by chronic pain patients, despite limited evidence of any long-term benefits and concerns regarding adverse events and drug interactions, particularly in older patients. This article aims to: describe patterns of BZDs use; the demographic, physical, and mental health correlates of BZD use; and examine if negative health outcomes are associated with BZD use after controlling for confounders.

Subjects. A national sample of 1,220 chronic noncancer pain (CNCP) patients prescribed long-term opioids.

Methods. We report on baseline data from a prospective cohort study comparing four groups based on their current BZD use patterns. General demographics, pain, mental and physical comorbidity, and health service utilization were examined.

Results. One-third (N = 398, 33%) of participants reported BZD use in the past month, and 17% (N = 212) reported daily BZD use. BZD use was associated with: 1) greater pain severity, pain interference with life, and lower feelings of self-efficacy with respect to their pain; 2) being prescribed "higher-risk" (>200 mg oral morphine equivalent) doses of opioids; 3) using antidepressant and/or antipsychotic medications; 4) substance use (including more illicit and injection drug use, alcohol use disorder, and daily nicotine use); and 5) greater mental

health comorbidity. After controlling for differences in demographic characteristics, physical and mental health, substance use, and opioid dose, BZD use was independently associated with greater past-month use of emergency health care such as ambulance or accident and emergency services.

Conclusions. CNCP patients using BZDs daily represent a high-risk group with multiple comorbid mental health conditions and higher rates of emergency health care use. The high prevalence of BZD use is inconsistent with guidelines for the management of CNCP or chronic mental health conditions.

Key Words. Chronic Noncancer Pain; Opioid; Benzodiazepines; Mental Health

Introduction

The prescription of opioids for people with chronic noncancer pain (CNCP) has increased dramatically in the United States, Canada, and Australia [1–6]. Benzodiazepine (BZD) use, although common, is reported at much lower rates in the general population than in chronic pain populations. A national household survey in the US study found 4% of respondents reported tranquilizer use and 6% reported using sleeping pills or other sedative use [7]. General population studies in the UK estimate that 3% of the population use BZDs [8]. Although there has been some reduction in BZD use [9,10], BZDs continue to be prescribed despite there being few indications for their use.

Significant proportions (18–38%) of CNCP patients are concurrently prescribed opioids and BZDs [11–13]. Although there are a range of reasons why BZDs may be prescribed to patients with CNCP, there are few indications for chronic BZD use specifically in the treatment of CNCP. One review, conducted two decades ago, identified a potential role for BZD in acute pain, but there is little evidence from controlled studies to support their general use in chronic pain [14]. The exceptions were just three specific conditions where some evidence of their efficacy in treating pain was found: chronic tension headache, temporomandibular disorders, and tic douloureux [14]. Nondrug treatments and other medications such as antidepressants are considered first-line treatments for chronic anxiety or insomnia, with BZDs reserved for second-line use when patients are unable to tolerate first-line medications, or after nondrug treatments have failed [14]. Guidelines state that BZD are "not recommended" for use in noncancer persistent pain [15], whereas expert opinion is divided [16]. Although BZD are effective when used acutely for generalized anxiety or panic disorders, they are not listed in clinical guidelines as first-line treatments for these conditions. These guidelines indicate short-term use, or only where antidepressants are not tolerated [17,18].

Concurrent use of BZDs and opioids carries potential risks, particularly in older adults who are more vulnerable to adverse events and drug interactions [19]. Combined BZD and opioid use may increase sedation, cognitive and psychomotor impairment, falls, respiratory depression, and risk of overdose [20,21]. Chronic BZD and chronic opioid use are associated with additive effects in sleep-disordered breathing [22,23] and have the additional well-known clinical complications of physiological neuroadaptation with long-term use, and the potential for development of substance use disorders among some patients.

Few studies have investigated the possible effects of BZD use on long-term outcomes for chronic pain patients. One study of chronic pain patients enrolled in a tertiary pain clinic found that BZD use was correlated with deteriorating physical functioning and depression, after controlling for opioid use [24]. A longitudinal study of older adults found that new-onset chronic BZD use was predicted by increasing age, female gender, symptoms of depression, pain, and poor physical health [25].

Given the potentially serious adverse consequences of BZD use in chronic pain patients, we examined the prevalence and correlates of past, occasional, and daily BZD use in a sample of CNCP patients who are prescribed long-term opioid analgesics. Three a priori aims were defined for these analyses:

1. to describe patterns of BZD use amongst a sample of CNCP patients prescribed opioids;
2. to examine demographic, physical, and mental health and substance correlates of BZD use; and
3. to examine if negative health outcomes, including emergency health care utilization, were independently associated with BZD use, after controlling for other patient characteristics.

Methods

Study Design and Setting

The sample comprised 1,220 participants from the baseline data collected on a prospective cohort study of persons who have been prescribed opioids for CNCP (the POINT Study [Pain and Opioids IN Treatment]). The parent study will collect prospective longitudinal data from this cohort at four time points over a 2-year follow-up. A detailed description of the methodology is available elsewhere [26].

Eligibility Criteria

POINT participants had to be: 18 years or older; competent in English; mentally and physically able to complete telephone and self-complete interviews; without serious cognitive impairments; living with CNCP (by definition, of at least 3 months' duration); prescribed a Schedule 8 opioid (an Australian classification of drugs of dependence that are subject to additional regulatory controls regarding

their manufacture, supply, distribution, possession, and use [27]); and having taken such opioids for CNCP for more than 6 weeks. Schedule 8 opioids include morphine, oxycodone, fentanyl, buprenorphine, methadone, hydromorphone, and codeine phosphate tablets as a single ingredient. Schedule 8 does not include tramadol or codeine in combination with paracetamol.

Patients currently prescribed pharmaceutical opioids for opioid substitution therapy for heroin dependence and those taking opioids for cancer pain were ineligible for this study.

Recruitment

A database of pharmacies and chemists across Australia and their contact details was purchased in May 2012 [28]. The list included 7,136 pharmacies. After removing duplicates, those that had closed down, or were not suitable for the study (i.e., located in a hospital or were a compounding pharmacy), we had a final list of 5,994 pharmacies.

Pharmacies were invited to participate in the study and to refer eligible participants using a purpose-designed fax referral form. Pharmacists were asked to approach any customers who were prescribed a Schedule 8 opioid for CNCP for a period of greater than 6 weeks.

POINT staff determined the eligibility of interested customers who were referred to the study, or who contacted the POINT team. Eligible participants went through a voluntary informed consent process. After being given details of the study, those who were willing to participate were booked in for their initial interview, which was conducted over the phone and took approximately 1–1.5 hours, and were sent a self-complete survey in the mail at the same time.

The study was approved by the Human Research Ethics Committee of the University of New South Wales (HREC reference: # HC12149).

Interview Procedure

Baseline phone interviews were conducted by trained interviewers who had previously received suicide assistance training. They had a minimum 3-year health or psychology degree and were provided with glossaries of chronic pain medications and conditions. Participants were reimbursed $A40 for the baseline interview.

Measures

Key measures included: demographic characteristics, current pain (as measured by the Brief Pain Inventory [BPI] [29]), opioid and BZD use and/or dependence (using International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10] dependence criteria assessed via the Composite International Diagnostic Interview [CIDI] [30]) pain self-efficacy (using the Pain Self-Efficacy Questionnaire [PSEQ] [31,32]), health service utilization, alcohol and illicit drug use, and depression and generalized anxiety disorder (GAD; as measured by the Patient Health Questionnaire-9 [PHQ-9] and GAD generalized anxiety disorder-7 modules of the Patient Health Questionnaire [33]). Previously validated cut-offs were used for screening tools as follows: symptoms indicating major depressive disorder were defined at a score of ≥10 on the PHQ-9 [34], symptoms of moderate to severe anxiety were defined as a score of ≥10 on the GAD-7 [35]. A score of ≥3 on the Primary Care Post Traumatic Stress Disorder screen (PC-PTSD) was used to indicate presence of PTSD [36].

Weekly income was classified as greater or less than $A400/week, with less than $AUD400/week comparable with unemployment or disability benefits.

In addition to reporting the number of days on which each medication was used in the past month, participants were also asked to return a medication diary that reported all medication taken over a 7-day period. Of the 1,220 participants, 853 had medication diaries available for analysis. Where BZD doses were reported, these data only represent the subset of patients that returned the medication diary. Oral morphine equivalent daily doses were calculated using available references [15,37–39]. A "high risk" opioid dose variable was created, which was defined as more than 200 mg/day oral morphine equivalents [40,41].

Data Analysis

We defined four distinct BZD use groups: patients who had used BZDs every day for the past month (referred to as "Current Daily" users throughout) (N = 212), those who had used BZDs less than daily in the past month (referred to as "Current Less Than Daily") (N = 186), those who had used BZDs previously but not in the past month (referred to as "Past BZD Use") (N = 372), and those who had never used BZDs (referred to as "Never BZD Use") (N = 450).

Multinomial regression was used to compare the four use groups. Medians and nonparametric statistics were used to compare groups where the distribution was non-normal. Analysis of covariance was used to examine whether pain self-efficacy differed between the BZD use groups, after controlling for pain severity as the covariate. Multivariate logistic regression models were used to determine whether patterns of BZD use were independently associated with ambulance and accident and emergency attendance, after controlling for differences between the BZD use groups identified through univariate analyses.

Results

BZD Use Patterns

Four hundred fifty participants (36.9%) reported never having used a BZD ("Never BZD Use"). Three hundred seventy-two (30.5%) reported past BZD use only ("Past BZD Use"), 186 (15.2%) reported current less than daily use ("Current Less Than Daily"), and 212 reported current

daily use ("Current Daily") in the past month (17.3%; Table 1). Of those currently using BZDs (N = 398), 53% were using them daily.

Those reporting current less than daily BZD use had used BZDs on a mean of 8.2 days in the previous 28 days (standard deviation [SD] 6.8, range 1–25 days). Multinomial logistic regression did not detect a significant difference in age of first BZD use between the groups: the mean age of first use for the Past BZD Use group was 38.8 years (SD 14.7 years), 39.7 years (SD 15.1 years) for the current less than daily group, and 40.4 years (SD 16.8 years) for the current daily group.

Sixty-two people (5.1% of the sample) endorsed the CIDI BZD screening question (i.e., "was ever used so regularly that they could not stop using the sedative or tranquilizer prescribed" to them) and were further assessed using the CIDI for a BZD use disorder (using ICD-10 criteria). Those using BZDs daily in the past month were more likely to meet criteria for a BZD use disorder (8.5%, N = 18, odds ratio [OR]: 3.36, 95% confidence interval [CI]: 0.152–7.42) than past BZD users (2.7%, N = 10).

Demographic Differences by BZD Use Group

Participants who reported any BZD use were younger than those in the Never BZD Use (reference) group (Table 1). Current daily BZD users reported lower levels of current employment/study compared with the Never BZD use reference group.

Types of BZDs Used

Diazepam was the most common BZD reported by the subset of participants that used a BZD in the past month and returned a medication diary (N = 254). Its use was reported by 48% (N = 122, mean daily dose 9.1 mg, SD 8.8 mg), followed by temazepam (22%, N = 56, mean daily dose 10.3 mg, SD 7.0 mg), oxazepam (12%, N = 30, mean daily dose 28.4 mg, SD 14.4 mg), nitrazepam (10%, N = 25, mean daily dose 6.9 mg, SD 7.6 mg), alprazolam(5%, N = 12, mean daily dose 2.0 mg, SD 1.8 mg), and clonazepam (5%, N = 12, mean daily dose 2.4 mg, SD 2.75 mg). A small number of participants also reported use of BZD-like drugs zopiclone (N = 8) and zolpidem (N = 11). Twenty-nine (11%) reported using two BZDs in the same week, and two participants (1%) reported using three BZDs in the same week.

Aberrant BZD Use

Participants were asked if they had ever used BZDs in a range of unsanctioned ways. Of those who had ever used BZDs (N = 770), 5.5% (N = 42) reported ever using someone else's BZDs, and 4.5% (N = 35) reported using their own prescribed BZDs in a way that was not as prescribed, (i.e., injected, or used for recreational purposes). Having ever used someone else's BZDs was reported by more of those currently using BZDs less than daily (8.1%, OR: 2.26, 95% CI: 1.07–4.78), compared

Table 1 Sample characteristics and benzodiazepine (BZD) use patterns in patients with chronic noncancer pain patients-prescribed opioids

BZD Use Group	Never BZD Use (N = 450)	Past BZD Use (N = 372)	OR (95% CI)	Current Less Than Daily BZD Use (N = 186)	OR (95% CI)	Current Daily BZD Use (N = 212)	OR (95% CI)
Age (mean, SD)	60.5 (13.6)	56.6 (13.1)***	0.98 (0.97–0.99)	53.8 (12.6)***	0.96 (0.95–0.98)	54.5 (12.9)***	0.97 (0.95–0.98)
% Male	51.3	39.5**	0.69 (0.52–0.91)	49.5%	1.03 (0.73–1.45)	39.2*	0.68 (0.49–0.95)
Born in Australia (%)	81.1	80.9	0.99 (0.70–1.40)	80.6	0.97 (0.63–1.50)	78.8	0.86 (0.58–1.30)
Employed/student (%)	19.6	16.9	0.84 (0.59–1.20)	19.9	1.02 (0.67–1.57)	10.4**	0.48 (0.29–0.79)
Weekly income < $400† (%)	62.4	58.9	0.86 (.65–1.14)	53.8*	0.70 (0.50–0.99)	68.4	1.30 (0.92–1.84)
Average age at first opioid prescription (mean, SD)	46.4 (17.1)	38.1 (15.9)***	0.97 (0.96–0.98)	36.2 (14.8)***	0.96 (0.95–0.97)	38.0 (16.3)***	0.97 (0.96–0.98)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
†The cut-off of <$400 is comparable with the income from unemployment or disability benefits.

with past BZD users (Reference category, 3.8%). The difference was not significant between past and daily BZD users (6.3%, OR: 1.72, 95% CI: 0.79–3.74). Those using BZDs daily were more likely to report recreational or intravenous use (7.8%, OR: 2.15, 95% CI: 1.03 – 4.51) compared with past BZD users (3.8%) and less than daily BZD users (2.7%, OR: 0.71, 95% CI: 0.25–2.00).

Pain

There was no difference in the duration of pain experience, or of duration of opioid prescription between the groups, although BZD users had received their first opioid prescription at a younger age than those who did not report using BZDs. The types of pain conditions reported within the past 12 months were broadly comparable across the three categories of BZD use groups, except that the current daily BZD use group reported the highest mean number of pain conditions. The current daily BZD use group reported the highest Pain Severity and Pain Interference scores on the BPI.

Any BZD use (past or current) was associated with poorer pain self-efficacy (i.e., less confidence in their ability to do a range of activities including household chores, socializing, work, and to cope with their pain) as measured with the Pain Self-Efficacy Questionnaire, where lower scores reflect poorer self-reported efficacy in managing pain. The current daily use group had the lowest pain self-efficacy scores (see Table 2). BZD use was independently associated with significantly lower mean pain self-efficacy scores after controlling for pain severity ($F(2, 1127) = 14.86$, $P < 0.001$). Adjusted means for the pain self-efficacy score were 31.8 (SD 12.3) for the Never BZD Use group, 29.4 (SD 18.8) for the Past BZD Use group, 27.5 (SD 8.5) for the Current Less Than Daily group, and 25.6 (SD 12.9) for the Current Daily Use group. The lower level of self-efficacy in the daily use group compared with the Never BZD Use group was of moderate magnitude (Hedges' $g = 0.49$). Differences between other groups were either small (poorer self-efficacy in the Less Than Daily group compared with Never Use, $g = 0.37$) or not meaningful (all others $g < 0.22$).

Other Medication Use

A higher proportion of BZDs users had been also prescribed antidepressant and/or antipsychotic medication (Table 2). Two-thirds (68.4%) of the current daily use group had used antidepressants and 11.2% had used an antipsychotic medication in the past month, compared with 44.9% and 3.1% in the Never BZD Use group.

Participants who had used BZDs were also prescribed more opioids and reported a greater median opioid dose. We examined the proportion of each group prescribed a "high risk" opioid dose (>200 mg/day oral morphine equivalents). The two current BZD use groups (Daily and Less Than Daily) had higher proportions of "high risk" opioid doses in past month (21.4% in the Current Less Than Daily and 27.9% in Current Daily BZD use) compared with 8.9% in Never BZD Use group).

Substance Use and Mental Health

BZD users were more likely to report lifetime illicit drug use, injection drug use, and an alcohol use disorder (using ICD-10 definitions) than those who had never used BZDs (Table 3). Current daily nicotine use was more likely among current BZD users (whether using daily or less than daily) compared with those who had never used BZDs.

Most BZD users reported a lifetime diagnosis or development of a mental health condition, and a more mental health conditions than nonusers (Table 3). BZD users reported more symptoms of moderate to severe depression, anxiety, and were more likely to meet criteria for PTSD and past month panic attacks. The daily BZD use group had the highest proportion reporting symptoms that met criteria for each of these conditions (Table 3).

BZD Use and Emergency Health Service Utilization

At a univariate level, the daily BZD use group reported more visits to the general practitioner in the past month and were more likely to use emergency health care compared with those who had never used BZDs. Those who reported daily BZD use were more likely to have used an ambulance in the past month (OR: 2.7, 95% CI: 1.12–6.41) and more likely to have attended a hospital emergency department (OR: 2.01, 95% CI: 1.06–3.81) than those who had not used BZDs, after controlling for differences in age, gender, income, number of pain and other chronic conditions, moderate to severe anxiety and depression symptoms and history of illicit drug use and drug injection, and receiving a "high risk dose" of opioids. The three BZD use groups were more likely to report a lifetime drug overdose compared with the group that had never used BZDs.

Discussion

In this national sample of CNCP patients-prescribed opioids, approximately one-third (33%) had used a BZD in the previous month and half of those (53%) reported daily BZD use. Although a high proportion of these CNCP patients reported using BZDs regularly, most participants reported using only one type of BZD. This was most often diazepam, temazepam, oxazepam, or nitrazepam, which jointly accounted for approximately 90% of all recent BZD use. These are the most commonly utilized BZDs in routine prescribing data for the general Australian population [9].

The mean self-reported BZD doses used were within therapeutic norms, and few participants reported aberrant BZD use. Nearly one in 10 (9%) of current daily BZD users met diagnostic criteria for a lifetime BZD use disorder, compared with below 3% in all other groups. In short, although many patients had recently used BZDs, there

Table 2 Pain, opioid medications, and health service utilization by benzodiazepine (BZD) use group

	Never BZD Use (N = 450)	Past BZD Use (N = 372)	OR (95% CI)	Current Less Than Daily BZD Use (N = 186)	OR (95% CI)	Current Daily BZD Use (N = 212)	OR (95% CI)
Pain							
Pain severity (BPI) mean (SD)	4.9 (1.8)	5.1 (1.8)	1.08 (1.00–1.17)	5.0 (1.7)	1.05 (.96–1.16)	5.5 (1.7)***	1.24 (1.13–1.37)
Pain interference (BPI) mean (SD)	5.2 (2.2)	5.9 (2.2)***	1.14 (1.07–1.22)	5.9 (2.1)**	1.13 (1.05–1.23)	6.4 (2.2)***	1.30 (1.19–1.41)
Pain coping and self-efficacy mean (SD)	32.3 (13.5)	29.2 (12.6)**	0.98 (0.97–0.99)	27.62 (13.08)***	0.97 (0.96–0.99)	24.4 (13.4)***	0.96 (0.94–0.97)
Duration of pain (years) median§	10.0 (IQR 15.0)	10.0 (IQR 15.0)		12.0 (18.3)*		12.0 (16.0)*	
Duration of pain before starting opioids (years) median†	0.7 (IQR 6.0)	1.0 (IQR 5.0)		0.5 (IQR 5.2)		0.3 (IQR 4.0)	
Duration of continuous opioid use (years) median‡	4.0 (IQR 8.2)	5.0 (IQR 8.5)		5.0 (IQR 10.1)		5.0 (IQR 8.0)	
Past 12 months pain conditions (%)							
Arthritis (inc. rheumatoid arthritis)	65	61	0.84 (0.63–1.12)	53**	0.59 (0.42–0.84)	58*	0.73 (0.53–1.03)
Chronic back or neck pain	69	78**	1.56 (1.14–2.13)	79*	1.69 (1.12–2.53)	84***	2.42 (1.59–3.70)
Frequent or severe headache	23	31**	1.53 (1.12–2.08)	35**	1.81 (1.25–2.63)	36***	1.92 (1.35–2.74)
Visceral pain	16	25**	1.75 (1.24–2.47)	24*	1.63 (1.07–2.48)	28***	2.07 (1.40–3.06)
Fibromyalgia	2	5*	2.15 (1.01–4.57)	7**	3.00 (1.32–6.82)	6*	2.61 (1.15–5.92)
No. of pain conditions past 12 months, mean (SD)	2.1 (1.09)	2.30 (1.11)**	1.21 (1.07–1.34)	2.30 (1.13)*	1.22 (1.05–1.42)	2.49 (1.30)***	1.39 (1.20–1.60)
No. other physical conditions past 12 months, mean (SD)	0.84 (1.06)	0.83 (1.07)	0.99 (0.87–1.13)	0.76 (0.95)	0.93 (0.79–1.10)	0.84 (1.12)	1.00 (0.86–1.17)
Medication and health service utilization							
No. of opioids currently prescribed, mean (SD, range)	1.7 (0.7, 1–4)	1.8 (0.8, 1–5)*	1.23 (1.03–1.47)	1.8 (0.7, 1–4)*	1.32 (1.06–1.64)	1.9 (0.8, 1–5)**	1.41 (1.15–1.74)
Median daily dose oral morphine equivalent mg (IQR)¶ (N = 826)††	60.0 (90.0 mg)	75.0 mg (100.0 mg)		83.6 mg (133.3 mg)		102.5 mg (163.2 mg)	
Taking more than 200 mg oral morphine equivalents daily (N = 826)	29 (8.9%)	31 (12.2%)	1.42 (0.83–2.43)	25 (21.4%)**	2.78 (1.55–4.99)	35 (27.1%)***	3.81 (2.21–6.57)
Taken antidepressants past month	202 (44.9%)	207 (55.6%)**	1.54 (1.17–2.03)	96 (51.6%)	1.31 (0.93–1.84)	145 (68.4%)***	2.66 (1.88–3.75)
Taken antipsychotics past month	14 (3.1%)	18 (4.8%)	1.58 (0.78–3.23)	21 (11.3%)***	3.96 (1.97–7.98)	25 (11.8%)***	4.16 (2.12–8.19)
Used ambulance in past month	19 (4.2%)	24 (6.5%)	1.56 (0.84–2.90)	15 (8.1%)	1.99 (0.99–4.01)	23 (11%)**	2.76 (1.47–5.19)
Attended emergency past month	41 (9%)	49 (13%)	1.51 (0.98–2.35)	23 (12%)	1.41 (0.82–2.42)	41 (19.5%)***	2.39 (1.50–3.82)
Number of general practitioner visits in past month	1.9 (1.6)	2.1 (1.8)	1.10 (1.00–1.20)	2.2 (1.4)*	1.14 (1.02–1.26)	2.2 (1.4)*	1.13 (1.02–1.25)
Ever used nonmedication-based pain treatment‡‡	390 (86.7%)	343 (92.2%)*	1.82 (1.14–2.90)	171 (91.9%)	1.75 (0.97–3.18)	198 (93.4%)*	2.18 (1.19–3.99)
Ever accidently overdosed on a drug	46 (10.2%)	80 (21.5%)***	2.41 (1.63–3.56)	36 (19.4%)**	2.11 (1.31–3.39)	55 (25.9%)***	3.08 (2.00–4.74)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

†Independent samples medians test $P = 0.537$; ‡Independent samples medians test $P = 0.084$; §Independent samples medians test $P = 0.045$; ¶Independent samples median test $P = 0.97$; ††Independent samples medians test $P = 0.002$; ‡‡Included physiotherapy, chiropractor, acupuncture, psychologist/psychiatrist/counselor (specifically related to pain), support or pain management groups.

Table 3 Substance use and mental health by benzodiazepine (BZD) use group

BZD Use Group	Never BZD Use (N = 450)	Past BZD Use (N = 372)	OR (95% CI)	Current Less Than Daily BZD Use (N = 186)	OR (95% CI)	Current Daily BZD Use (N = 212)	OR (95% CI)
Substance use history (%)							
Ever diagnosed/suffered substance abuse/dependence	6.0	12.1**	2.16 (1.31–3.55)	17.7***	3.38 (1.97–5.81)	19.8***	3.87 (2.31–6.48)
Ever used an illicit drug	31.8	45.2***	1.77 (1.33–2.35)	60.2***	3.25 (2.28–4.63)	50.9***	2.07 (1.48–2.89)
Ever injected a drug	1.1	3.2*	2.97 (1.04–8.50)	5.9**	5.59 (1.95–16.33)	7.1***	6.77 (2.43–18.91)
Met criteria for alcohol use disorder (ICD-10)	24.7	32.5*	1.47 (1.09–2.00)	36.6**	1.76 (1.22–2.54)	35.4**	1.67 (1.12–2.38)
Daily nicotine use (past month)	24.9	28.2	1.19 (.87–1.62)	38.7**	1.91 (1.32–2.74)	41.0***	2.10 (1.48–2.97)
Mental health (%)							
Lifetime reporting of any mental health condition	60.0	81.7***	2.98 (2.16–4.12)	83.3***	3.33 (2.12–5.12)	83.5***	3.37 (2.24–5.07)
Number of lifetime mental health conditions, mean (SD)	0.93 (1.0)	1.6 (1.3)***	1.72 (1.51–1.96)	1.8 (1.3)***	1.91 (1.65–2.22)	2.1 (1.6)***	2.20 (1.91–2.54)
Moderate to severe depression symptoms (N = 1,164)	14.5	23.3**	1.79 (1.24–2.57)	26.7***	2.25 (1.47–3.43)	39.6***	3.86 (2.61–5.71)
Moderate to severe generalized anxiety disorder (N = 1,164)	15.9	21.5*	1.46 (1.01–2.09)	28.0**	2.07 (1.36–3.13)	37.7***	3.22 (2.19–4.73)
PTSD	8.2	15.3**	2.02 (1.30–3.13)	19.4***	2.68 (1.63–4.40)	22.6***	3.27 (2.05–5.20)
Panic attack past 4 weeks	35 (7.6%)	65 (17.5%)***	2.59 (1.67–4.02)	56 (30.1%)***	5.27 (3.30–8.43)	67 (31.6%)***	5.65 (3.59–8.90)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

was little evidence of patients using them other than as prescribed and few endorsed criteria for substance use disorder or reported nonmedical use.

Nonetheless, the high rates of BZD use in this population are at odds with clinical guidelines that do not recommend the long-term prescription of BZDs for the vast majority of chronic pain or mental health conditions. Few patients suffered from the short list of chronic pain conditions for which BZDs may have some therapeutic role [14]. Although being unable to tolerate antidepressants is identified as a possible indication for using BZDs [17], the large number of patients concurrently prescribed antidepressants and BZDs suggests that this is not the reason for BZD use.

BZD use in this sample was broadly associated with three factors: 1) *pain* (including number and type of pain conditions, greater self-reported recent pain severity and pain interference, and poorer pain self-efficacy), 2) *mental disorders* (including current depression and generalized anxiety disorder); and 3) *substance use* (including alcohol use disorders, tobacco use, injecting drug use, and illicit drug use).

One way of understanding the high prevalence of BZD use in this sample is to consider how CNCP patients who use BZD might differ from other patients in their approach to treatment. Daily BZD users reported the highest levels of current antidepressant and antipsychotic medications, were more likely to be taking high opioid doses (>200 mg oral morphine equivalent mg daily), and reported the lowest self-efficacy in managing their pain. BZD users also reported higher rates of alcohol and other illicit drug use. In summary, BZD users also used more prescribed and recreational drugs that may suggest a pattern of "chemical coping" [42] or may reflect the high levels of substance use and comorbid mental disorders in this group.

It is unclear whether the greater use of medication and other substances among BZD users is in response to, or contributes to more severe pain and psychological distress. Alternatively, it may be that current approaches to pain treatment using opioid medications and antidepressants fail to satisfactorily address these patients' pain and distress, and so that higher opioid doses and a wider variety of medications are used in an attempt to achieve better pain relief. This raises the value of comprehensive approaches to pain management that broadly address the range of biopsychosocial aspects of chronic pain and reduce reliance upon psychoactive medication for symptom control as the predominant intervention [43,44]. Indeed, the triple comorbidities of chronic pain, mental health, and substance use disorders highlight the many needs of this patient population. The complexity of the population not only demands a multifaceted rather than only a medication-based approach to pain, but also suggests the need for additional strategies that may address patients' mental health or substance use problems.

Those using BZDs generally reported poorer health outcomes, greater utilization of health services, and in particular greater use of emergency services such as ambulance, emergency department presentations, and a higher likelihood of having a history of accidental overdose than those who did not use BZDs. A history of overdose was reported in approximately a quarter of daily BZD users (compared with 10% of non-BZD users). The high rates of polypharmacy are of particular concern, especially in older patients who are more vulnerable to drug interactions and related adverse events.

The high prevalence of BZD use in CNCP is an issue that requires more clinical and research attention in light of the limited number of accepted indications for long-term BZD prescribing for either pain or mental health conditions and the poorer health outcomes in these patients. Although it is not possible from this cross-sectional study design to identify whether BZD use is safe, effective, or appropriate in CNCP patients, the high prevalence of BZD use is clearly inconsistent with therapeutic guidelines recommendations on the management of CNCP or chronic mental health conditions. This raises questions about the adequacy of the assessment and clinical decision making in these patients. There have been many approaches to identifying high risk CNCP patients in whom opioid medication should be used cautiously [41], where a personal or family history of substance abuse is a constant theme. We are unaware of similar approaches to identifying risk factors for BZD use in CNCP patients.

There are some study limitations that need to be considered. Although a clear strength of the study was that all Australian community pharmacies were approached and many assisted with recruitment, we have limited data on those pharmacists and patients who did not participate. Furthermore, we rely on self-report data which, while being generally reliable when there are no disincentives for being honest [45], may be subject to biases. All participants were informed that their responses would be de-identified and confidential, which traditionally results in more valid reports of substance use [46]. Furthermore, we do not know the indications for each of the medications used by participants. Future work that can explore reasons for BZD initiation and continued use in these patients would be a valuable addition to the literature. Finally, as this is a cross-sectional analysis, we are not able to assess causality. We do not know what the outcomes for these patients would have been had they not been prescribed BZDs. The longer term findings for this study will provide important data on outcomes for those that use BZDs over time.

This study identified a high prevalence of BZD use in CNCP patients, with approximately one-third of patients reporting use within the past month. CNCP patients with daily BZD use represent a highly distressed group of patients: they reported greater pain severity and more interference with daily life, multiple mental health problems, and a higher rate of substance use disorders. They are at risk of adverse events from polypharmacy and

report higher rates of emergency health care use and opioid-related overdose. Careful consideration needs to be given to the role of BZDs in the treatment of CNCP, and there is a need for ongoing monitoring of BZD use. In light of the current concerns with opioid-related harms, those using opioids and BZDs appear to represent a particularly high-risk group.

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Risks, Management, and Monitoring of Combination Opioid, Benzodiazepines, and/or Alcohol Use

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Abstract

The concurrent use of opioids, benzodiazepines (BZDs), and/or alcohol poses a formidable challenge for clinicians who manage chronic pain. While the escalating use of opioid analgesics for the treatment of chronic pain and the concomitant rise in opioid-related abuse and misuse are widely recognized trends, the contribution of combination use of BZDs, alcohol, and/or other sedative agents to opioid-related morbidity and mortality is underappreciated, even when these agents are used appropriately. Patients with chronic pain who use opioid analgesics along with BZDs and/or alcohol are at higher risk for fatal/nonfatal overdose and have more aberrant behaviors. Few practice guidelines for BZD treatment are readily available, especially when they are combined clinically with opioid analgesics and other central nervous system–depressant agents. However, coadministration of these agents produces a defined increase in rates of adverse events, overdose, and death, warranting close monitoring and consideration when treating patients with pain. To improve patient outcomes, ongoing screening for aberrant behavior, monitoring of treatment compliance, documentation of medical necessity, and the adjustment of treatment to clinical changes are essential. In this article, we review the prevalence and pharmacologic consequences of BZDs and/or alcohol use among patients with pain on chronic opioid therapy, as well as the importance of urine drug testing, an indispensable tool for therapeutic drug monitoring, which helps to ensure the continued safety of patients. Regardless of risk or known aberrant drug-related behaviors, patients on chronic opioid therapy should periodically undergo urine drug testing to confirm adherence to the treatment plan.

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Keywords

urine drug testing; opioid; benzodiazepine; alcohol; respiratory depression; chronic pain

Prevalence and Risk Factors

Co-Abuse of Opioids, Benzodiazepines, and/or Alcohol: Consequences for General Health and Overdose Lethality

The escalating use of opioid analgesics to treat chronic pain and the concomitant rise in opioid-related abuse and misuse are widely recognized trends. In 2011, the US Institute of Medicine declared pain a public health challenge and identified a number of barriers to adequate pain care. These include regulatory, legal, educational, and cultural barriers that inhibit the medically appropriate use of opioid analgesics.[1] Also, in 2011, the US Food and Drug Administration introduced mandatory safety measures for opioid prescribing, such as Risk Evaluation and Mitigation Strategies.[2] Various organizations, including the American Pain Society, the American Academy of Pain Medicine, and the American Society of Interventional Pain Physicians, among others, have since developed clinical guidelines for responsible opioid prescribing.[3–7]

Perhaps somewhat underappreciated is the contribution of concurrent use of alcohol and other sedative agents to the mounting incidence of opioid-related morbidity and mortality, even when used appropriately. The literature suggests that benzodiazepine (BZD) users are more likely to receive prescription opioids than non-BZD users.[8,9] Although the World Health Organization described the rational use of BZDs in 1996,[10] few practice guidelines for BZD treatment are readily available, especially when BZDs are used clinically along with opioid analgesics and other central nervous system (CNS)–depressant agents.

Recent guidelines for opioid prescribing merely recommend considering concomitant BZD use when evaluating contraindications to opioid use in patients with chronic noncancer pain.[5] Canadian guidelines refer to BZD tapering when used in chronic noncancer pain populations who are elderly and may exhibit greater sensitivity to the respiratory effects of opioids.[11] Yet, the use of BZDs in combination with other substances can have severe, and even fatal, consequences.[12] Furthermore, the rates of BZD abuse are increasing. Substance abuse treatment admissions for BZD abuse nearly tripled from 22 400 in 1998 to 60 200 in 2008, with the concurrent abuse of opiates accounting for the majority of admissions, followed by alcohol (Figure 1).[12] In fact, treatment admissions due to co-abuse of BZDs and narcotic pain relievers increased by 569.7% from 2000 to 2010, while those related to all other substance abuse decreased by 9.6% in the same time period.[13]

Emergency department (ED) visits resulting from the misuse or abuse of prescription drugs in general increased by 76% between 2005 to 2010 (Figure 2).[14,15] Even when medications were taken as prescribed, adverse reactions (ie, side effects, drug–drug interactions, and drug–alcohol interactions) caused an 86% increase in ED visits during the same time period.[14] Specifically, accidental opioid-related fatalities increased by 4-fold from 1999 to 2009.[16] An analysis by investigators at the Centers for Disease Control and Prevention in Atlanta, GA, showed that 75.2% of deaths from pharmaceutical agents involved opioids,

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followed by BZDs (29.4%), antidepressants (17.6%), and antiepileptic and antiparkinsonism agents (7.8%), either alone or combined with other drugs. Of these overdose deaths, 74.3% (16 451) were unintentional, 17.1% (3780) were suicides, and 8.4% (1868) were of undetermined intent.[17]

The Utah Medical Examiner's office also investigated the rise in unexpected deaths from prescription drug overdose between October 2008 and 2009, and found similar results.[18] Among the 278 opioid-related overdose deaths, 86% did not involve any illicit drugs and 83% of decedents experienced chronic pain.[16] Oxycodone was the drug most frequently mentioned as a contributing cause of death, followed by methadone and hydrocodone. Calcaterra et al[16] found that prescription opioid–related deaths commonly involve additional substances, including alcohol, sedatives, and/or illicit drugs (as identified from death certificates). The most common cause of polysubstance overdose fatality was the combined use of opioids and BZDs.[16] Several studies[19–24] suggest that BZDs may play a role in as much as 80% of unintentional overdose deaths involving opioids, primarily due to respiratory depression.[8,25]

Respiration is controlled at medullary respiratory centers with input from peripheral chemoreceptors. Glutamate and gamma-aminobutyric acid (GABA) are the major excitatory and inhibitory neurotransmitters, respectively, mediating the control of respiration. Opioids produce inhibition both in the medulla and at peripheral chemoreceptors, while BZDs and alcohol facilitate inhibitory effects of GABA at the $GABA_A$ receptor. Alcohol also decreases the excitatory effect of glutamate at *N*-methyl-D-aspartate receptors. Therefore, while the respiratory-depressant effects of alcohol and BZDs are mild, the concurrent use of these drugs with opioids has the potential to increase and/or prolong the respiratory-depressant effects of opioids. In addition, tolerance to respiratory depression is incomplete, and may be slower than tolerance to euphoria and other effects. One often underappreciated consequence of this phenomenon may be a relatively high risk of overdose among experienced opioid users.[25]

Risk factors for respiratory depression due to opioids may include age > 55 years, preexisting chronic obstructive pulmonary disease, known or suspected sleep-disordered breathing problems, anatomic oral or airway abnormalities, and comorbidities (eg, advanced systemic disease, renal or hepatic impairment).[26]

Pharmacologic Consequences of Combination Opioid and BZD Use

Benzodiazepines are reported to enhance the positive subjective effects of opioids (ie, euphoria) but it is unclear whether the reinforcing effects are additive or supra-additive (ie, synergistic). The reasons for combination use and misuse vary, but it appears likely that the motivation for clinicians may be different from that of patients. Clinicians may combine BZDs with opioids to take advantage of the anxiolytic and skeletal muscle–relaxant properties of BZDs. Patients may experience a pharmacodynamic interaction between the opioid and BZD that enhances the CNS effects and potential feelings of euphoria, especially if the drugs are misused or not taken as directed. Among patients on long-term opioid treatment, ≥ 25% said that they initiated BZD use out of curiosity, or to relax, relieve tension/anxiety, feel good, or get high.[27] Subjective ratings of *high, euphoria, good, like*,

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and *strong* increase with combination use of BZDs and opioids.[28–30] In a study of opioid-dependent patients with histories of BZD abuse, Preston et al[31] found that diazepam coadministered with methadone increased the positive subjective effects of opioids and induced greater constriction of the pupil than either drug alone. (Pupil constriction is an opioid effect; the level of decrease in pupil diameter is proportional to the sedative-hypnotic effect of the drug.[32]) Multiple BZDs, including diazepam, have significant abuse liability, producing increased positive subjective ratings and functional impairment when used along with opioids (Figure 3).[28–30]

Respiratory depression is the primary mechanism contributing to fatal opioid overdose, which, as discussed, may be exacerbated by concomitant BZD use.[25] Among patients undergoing various medical and surgical procedures, > 80 deaths have occurred after using midazolam, often combined with opioids.[33] Bailey et al[33] reported that coadministration of midazolam and fentanyl increased the incidence of hypoxemia and apnea among healthy study volunteers. In another study by Faroqui et al,[34] of the 64 patients who underwent anesthesia and received both buprenorphine and diazepam, 11 experienced sudden respiratory depression requiring manual ventilation.

It is now well established that the cytochrome P450 (CYP) enzyme system plays an important role in the metabolism of a large number of medications in many therapeutic classes, including opioids.[35–37] Although some BZDs, such as oxazepam, lorazepam, and temazepam, are directly conjugated via glucuronyl transferase, others, such as alprazolam and diazepam, are first metabolized by the CYP isozyme 3A4 and/or 3A5.[36] Thus, when certain BZDs are coadministered with inhibitors of the CYP system, one would expect a decrease in BZD clearance associated with potentially increased somnolence and respiratory depression, especially when combined with opioids.[35,36]

Pharmacologic Consequences of Combination Opioid and Alcohol Use

One of the major concerns when combining alcohol with opioid analgesics is the pharmacokinetic consequence of "dose dumping." Dose dumping is defined as the unintended, rapid release (over a short period of time) of the entire amount or a significant fraction of the drug contained in a modified-release dosage form. Alcohol is linked to dose-dumping effects across specific long-acting opioid (LAO) formulations, and significantly increases their dangers, as well as their abuse liability. In the most pronounced case, co-ingestion of the previously available analgesic Palladone™ (Purdue Pharma; hydromorphone hydrochloride extended-release capsules) with alcohol produced significantly higher plasma levels of hydromorphone (up to 16-fold greater), especially in the fasted state. This finding prompted its discontinuation and withdrawal from the market.[38] In vitro studies of another LAO, Avinza® (Pfizer Inc; morphine sulfate extended-release capsules), displayed accelerated release of morphine that was alcohol concentration dependent (Figure 4).[39] Box warnings for Avinza®, as well as other extended-release/long-acting opioids,[40] advise patients not to drink alcoholic beverages or use prescription or nonprescription medications containing alcohol during therapy, as it may result in the rapid release and absorption of a potentially fatal dose of opioid.

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The mechanisms by which alcohol alters the pharmacokinetic properties of LAOs are poorly understood. Several studies have shown that concurrent use of alcohol increases the maximum plasma concentration (C_{max}) of certain opioids and decreases the time to C_{max} (t_{max}), despite no evidence of dose dumping.[41–43] The clinical significance of the additive effects in C_{max} and t_{max} from combination alcohol and opioid use has not been characterized directly. However, coadministration of ethanol and opioids may increase the related dangers as well as enhance positive subjective effects that contribute to abuse liability while adversely affecting physical function and cognition. These responses stress the importance of instructing patients not to consume alcoholic beverages or use prescription or nonprescription products containing alcohol while on LAO therapies.

Fatal poisonings involving prescription opioids are frequently associated with alcohol use and are likely due to combined CNS- and respiratory-depressant effects.[5,44,45] In a study by Ali et al,[46] opioids significantly decreased the ventilatory response to hypercapnia when administered along with ethanol. No pharmacokinetic interaction was observed for either drug. Increases in positive subjective effects (eg, "drug liking," "take again," "pleasant body sensations") have been reported by healthy volunteers administered a combination of oxycodone (10 mg) and ethanol (0.3 or 0.6 g/kg) compared with when they received either substance alone (Figure 5).[47] Psychomotor and cognitive performances were not affected by any of the active drug scenarios.

Combination Use of Opioids, BZDs, and/or Alcohol Among Patients With Chronic Pain

Concurrent use of opioids, BZDs, and/or alcohol poses a formidable challenge for clinicians who manage patients with chronic pain. In recent reviews of outpatient pharmacy and clinical databases, patients with chronic pain who concurrently used opioid analgesics and BZDs had more pain-related and behavioral management problems, and were at higher risk for fatal/nonfatal overdose.[48,49] Among patients with noncancer pain, in particular, concomitant use of BZD was associated with more total months of prescribed opioid, higher mean daily doses, and a greater risk of a psychogenic chronic pain diagnosis and alcohol abuse/dependence.[48] Similarly, Bachs et al[50] found that users who were dispensed the highest doses of codeine (according to prescription records) were significantly more likely to use high doses of BZDs as well. In fact, BZD use was a stronger predictor of future prescription opioid use than musculoskeletal or chronic pain.[9] Furthermore, patients with chronic pain who were diagnosed with alcohol abuse/dependence independently exhibited a trend toward longer oxycodone/acetaminophen use (Figure 6), suggesting additional treatment challenges among that comorbid population as well.[48]

Despite adverse consequences, many patients continue to use an opioid concurrently with a BZD and/or alcohol. Approximately 40% of patients with pain who are on chronic opioid therapy are also prescribed BZDs.[49,51–53] In one study of patients with chronic pain, 5.8% reported using alcohol ≥ 10 times in the past 30 days, and 2.4% were intoxicated > 6 times.[54] Saunders et al[52] recently reported concurrent use of opioids and alcohol or sedatives in 12% and 32% of patients with chronic noncancer pain, respectively (Figure 7). Approximately 3% of patients used all 3. As with any drug use/misuse, patients commonly underreport their consumption. Objective screening measures that assess recent alcohol use

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have been inadequate in the clinical setting. With advances in toxicology and the recognition of screening biomarkers, such as ethyl glucuronide (EtG) and ethyl sulfate (EtS), a more accurate reflection of the true incidence of alcohol use along with pharmaceutically controlled substances is now possible.

Opioid-Related Morbidity and Mortality: Associations With Abuse, Misuse, and Addiction

The risks for opioid-related morbidity and mortality are not limited to patients with pain who have aberrant drug-related behavior or comorbid substance use disorders (SUDs). Even when patients are adherent to treatment and medications are taken as prescribed, adverse reactions, including drug–drug and drug–alcohol interactions, can occur. In 2010 alone, there were > 2 million drug-related ED visits due to adverse reactions from medications taken as prescribed.[14] Patients undergoing chronic opioid therapy may underestimate the dangers of alcohol use and the quantities that they ingest. A recent study by the UK Department of Health found that moderate drinkers in England underestimate the amount of alcohol they drink by as much as 40%.[55] Whether patients will combine these 3 agents has little to do with preexisting SUDs. Figure 8 illustrates how rates of concurrent alcohol and/or sedative use are surprisingly similar among patients with pain who are on chronic opioid therapy with or without an SUD.[52]

Given the comorbidity of chronic pain and psychiatric disorders, patients may be prescribed both opioid therapy and BZD treatment by different physicians. Patients receiving chronic opioid therapy may self-medicate with their BZDs because of inadequate control of chronic pain and/or the symptoms of impaired mood and anxiety. Although the majority of patients report initiating BZD use after the onset of pain, these agents provide little analgesic benefit for patients with most chronic pain conditions.[51] Simply screening patients for risk of aberrant drug-related behavior or SUDs may not be sufficient for identifying all patients who are at risk for combination use. Because distinguishing motives among patients abusing their medications may be difficult, clinicians must use risk-stratification tools as part of every patient's assessment. Management should be tailored based on whether patients are using their medications safely and appropriately or to address reasons for misuse.

Clinical Management

Assessing Risk for Co-Abuse and Opioid-Related Morbidity and Mortality

There is an urgent need to develop validated assessment tools to evaluate the initial and ongoing risk of concomitant opioid, BZD, and/or alcohol use.[8,52,56] Clinicians should conduct multidimensional assessments of patient medical and psychiatric comorbidities, as well as consider patients' current medications and their respective effects on the risk of respiratory depression and other related morbidities. Psychiatrists, as well as primary care and pain management clinicians, should join forces to develop strategies for safe and effective opioid and BZD use, while employing methods to limit alcohol consumption.

Table 1 lists predictors of concurrent alcohol and sedative use identified in patients with pain who are on long-term opioid treatment.[52] Compared with opioid abusers, concurrent users of BZDs and opioids take higher doses of the drugs for longer periods of time, are

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more likely to abuse additional substances (eg, alcohol), and are more likely to have a psychiatric comorbidity.[57–60]

Screening instruments, such as the Cut Down, Annoyed, Guilty, Eye-Opener (CAGE)[61] or the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C)[62] (Figure 9), among others, may help to structure assessment of risks related to alcohol. Although the utility of these tools is limited because they rely on patient self-report, the sensitivity and specificity of the tests in detecting problematic alcohol use are generally ≥ 80%.[56] Even a single-item test asking "How many times in the past year have you had 5 [4 for women] or more drinks in a day?" is 82% sensitive and 79% specific for identifying unhealthy alcohol use.[63] Screening instruments to assess risks related to BZD use are not readily available. In the next section, we discuss more objective screening and monitoring tools for alcohol, opioid, and BZD use.

Monitoring Treatment Adherence

Treatment adherence monitoring has been shown to increase compliance rates and reduce rates of drug abuse among patients with chronic pain.[64] Risk stratification, behavioral assessment, prescription monitoring programs (PMPs), and baseline and unscheduled drug testing are currently the best available tools for tracking treatment adherence.[65] Most guidelines also recommend an opioid treatment agreement, which may facilitate patient–provider communication, improve adherence rates, and reduce opioid misuse.[66] Educating patients about the consequences and dangers of combined alcohol and BZD use as part of the opioid treatment agreement may be particularly useful for encouraging patients to remain abstinent from these substances.

Prescription monitoring programs provide data on patterns of prescription use and reduce rates of prescription drug abuse and "doctor shopping."[5,67–69] Most states have PMPs in place and monitor controlled substances that are classified as schedule II–V, which include opioids and BZDs.[70] Clinicians are advised to use PMPs when monitoring patients for compliance.[5] While there is good evidence that PMPs provide data on patterns of prescription drug use, the programs do not report drugs obtained illegally (ie, from friends or other outside sources), nor do most yet allow for monitoring across states. As these programs have only recently become available in many states, there is limited evidence to date to indicate that PMPs reduce rates of ED visits and drug overdose.[6]

Urine drug testing (UDT) has been advocated by many state, policy, and society guidelines.[3–7] It is impossible to determine beforehand with any certainty who will become a problematic user of prescription medications. Patient demographics (excluding age) and prescribed opioid dose were found to be poor predictors of aberrant behavior.[71] Urine drug testing provides a more objective way to monitor treatment adherence and detect polysubstance use (Figure 10).[71] The percentage of patients with pain who are treated with opioids and have aberrant UDT results is surprisingly high—in some studies > 50%—reinforcing the need to test and the drawback of relying on self-report alone.[65]

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Best Practices in Opioid, BZD, and Alcohol Testing

Urine drug testing and PMPs can inhibit prescription drug abuse or doctor shopping by identifying patients who are nonadherent or abusing prescription and/or illicit drugs.[6] When initiating and maintaining chronic opioid therapy, drug testing can be used to establish a baseline measure of risk or to monitor adherence.[5]

Regardless of risk or known aberrant drug-related behaviors, patients on chronic opioid therapy should periodically undergo UDT to confirm adherence to the treatment plan.[3] Implementing a universal and consistent UDT policy for all patients can help to "de-stigmatize" drug testing and maintain patient–provider relationships.[5] At the same time, comprehensive risk assessment must be individualized for each patient according to medical necessity, as risk is a dynamic phenomenon.[66] Practice guidelines[4,5,72] recommend stratifying patients into 1 of 3 risk categories—low, moderate, or high risk—for aberrant drug-related behavior. Therapeutic drug monitoring is reasonable and medically necessary for patients with chronic pain in whom there is a probability of nonadherence to the prescribed drug regimen, that is, a suspected history of substance abuse or dependence. Drug screening is also indicated for patients with unexplained delirium or coma, suspected drug overdose, or suspected drug misuse.[73]

Drugs or drug classes for which screening is to be performed must be indicated in a written order and should reflect only those likely to be present based on the patient's medical history or current clinical presentation.[73] In some instances, qualitative screening by point-of-care (POC) test methods may not be sufficient to identify all drugs indicated. Laboratory gas or liquid chromatography (GC or LC) followed by mass spectrometry (MS) testing is necessary for detecting drugs or drug classes that cannot be screened with POC devices. Point-of-care testing does not screen for or often does not detect alcohol, certain BZDs (eg, alprazolam, clonazepam, lorazepam), recently ingested medications, and low levels of illicit drugs (eg, marijuana, cocaine). Moreover, urine or saliva samples tested with POC methods should be sent to outside laboratories for confirmation when the result of the drug test is different from that suggested by the patient's medical history, clinical presentation, or own statement.[73]

Opioid Testing—When screening for treatment compliance, clinicians should follow published guidelines on responsible opioid prescribing and drug testing practices.[3–7] There is limited guidance on how to tailor monitoring in patients who are at risk for opioid-related morbidity and mortality. An expert opinion statement presented at the 2012 American Academy of Pain Medicine meeting suggested that all patients prescribed opioid therapy for > 3 months should be subjected to random UDT every 3 to 6 months, depending on their risk for abuse.[74]

Knowledge of opioid metabolism (Table 2)[75] and the detection window (Table 3)[76,77] is also important in selecting test methods and interpreting results. For example, depending on when the drug was last taken, the route of administration, and interpatient variability, a urine specimen can contain the parent drug (eg, oxycodone), an active metabolite (eg, oxymorphone), and/or an end metabolite (eg, noroxycodone) (Table 2). Furthermore, detection limits of POC test devices may be too high, particularly for opioid testing, and therefore may return false-negative results.[68]

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Different cutoff concentrations, cross-reacting substances, and metabolism of opioids should be considered when ordering drug tests and interpreting results. Patients are not usually discharged from treatment based on a single POC or laboratory test result. The detection of morphine in urine and oral fluid can be explained by ≥ 4 different scenarios. Morphine can be present because of 1) morphine use, 2) codeine use, as a metabolite of codeine, 3) heroin (diacetylmorphine) use, as a metabolite of 6-monoacetylmorphine, and 4) ingestion of poppy seeds containing morphine (Table 2). A fifth postulated scenario is that a very small percentage of morphine may be present as a process impurity from the manufacture of other semisynthetic opiates. Communication with the laboratory's staff toxicologist can be essential to the interpretation and understanding of drug monitoring results.

BZD Testing—Approximately 40% of patients with pain who are undergoing opioid therapy also take BZDs.[49,51–53] Recognizing the risks for adverse events when these agents are used in combination, patients on chronic opioid therapy should be screened for BZD use before and throughout the course of treatment. Clinicians should be especially attentive to patient populations who are more likely to concurrently use sedatives (Table 1). Testing is complicated by the many classes of BZDs available and their varying pharmacokinetic parameters. Benzodiazepines are divided into groups based on their metabolism and half-life (Figure 11, Table 3).[76] Clinicians should be familiar with the metabolism of the BZD in question and the sensitivity and specificity of the test for each class of BZDs for which they wish to screen. No individual immunoassay kit can recognize all BZDs at clinically relevant concentrations.[78] Point-of-care immunoassays are designed to detect a specific metabolite and may produce false-negative results if a non–cross-reacting BZD is present. Point-of-care tests for BZDs are usually optimized to detect oxazepam and often yield false-negative results for BZDs of other classes, particularly lorazepam and clonazepam (Figure 11). This stresses the need to send the sample to a laboratory for more advanced qualitative or quantitative screening.

Alcohol Testing—The National Institute of Alcohol Abuse and Alcoholism and the US Preventive Services Task Force recommend that adults be screened with a validated self-report tool for alcohol use annually in primary care settings.[56] Because alcohol can increase the risk of adverse reactions, patients should be assessed for alcohol use before initiating treatment and monitored on an ongoing basis.

Use of breathalyzer tests is an affordable option for objectively assessing recent alcohol use. Another method of assessing alcohol use is via UDT. Alcohol in urine can be detected by assaying ethanol as well as alcohol metabolites, specifically EtG and EtS (Figure 12).[76,79] An advantage of EtG/EtS testing over traditional ethanol testing is its extended window of detection (Table 3), which better allows identification of recent alcohol use and relapse. Even after complete elimination of alcohol from the body, EtG and EtS are still detectable for up to 4 days.[77] Wurst et al[80] compared self-report, breath and urinary ethanol testing, and urinary EtG testing among 35 inpatients over a 12-month period. Of 146 urine samples examined, 14 were positive for EtG, but only 1 was positive for urinary and breath ethanol. In all positive EtG urine sample results, patients had admitted consumption of alcohol 12 to 60 hours before testing.

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False-positive results for EtS may arise from direct ingestion of nonalcoholic beverages, whereas false-positive or false-negative results for EtG may occur because of in vitro production or degradation from bacterial contamination of the urine sample.[81–83] Therefore, to minimize false-positive or false-negative results, simultaneous testing of EtS and EtG is advised because samples positive for both EtS and EtG definitely represent alcohol consumption.[84] As with all drug testing procedures, querying patients for substance use before testing may determine necessity for the test and help with interpreting results.

Interpreting Test Results—Drug test results should be interpreted with the patient history and risk factors taken into consideration. To best understand and minimize false-positive findings, a thorough history of any potentially cross-reacting substance use should be documented.[5,85] Tables for cross-reacting substances are readily available in the literature. In addition, patients should be encouraged to avoid using substances that may interfere with drug testing. False-negative results may occur because of high cutoff concentrations or (rapid) metabolism of the parent drug.[68,85,86] Interpatient variability in metabolism, as well as protein binding, nutritional status, absorption, duration of drug use, dosage, genetic differences, drug interactions, age, body composition, and many other parameters can affect UDT results.[86] When questions arise and before taking any action, confirmatory testing must be performed.[68,85] As discussed, laboratory GC/MS or LC/MS methods remain the gold standard for drug testing.[85,86] Toxicologists at most laboratories are available to help explain unexpected results.

Adjusting Treatment Based on Test Results

Treating individuals who are abusing BZDs, opioids, and/or alcohol presents a special challenge owing to additive risk and physical dependence. When concomitant use of BZDs and/or alcohol with opioid treatment is detected, a discussion with the patient to reinforce abstinence should be pursued. Brief interventions have been shown to improve treatment outcomes in patients with aberrant alcohol or drug use behaviors.[87,88] Increasing frequency of office visits combined with contingency prescribing is a useful strategy for helping patients cease misuse. An example of contingency prescribing may include requiring the patient to produce clean test results or a negative UDT result for the substance in question before receiving a new prescription.[5] Frequent clinic visits can increase the impact of brief interventions in reducing risky alcohol or drug use.[87,88] Communication with the patient's other health care providers may be required if the patient is obtaining prescriptions from multiple sources.

Therapy for opioid-using patients on BZDs should be restructured to incorporate the use of non-CNS depressants, including lower-toxicity antidepressants, atypical antipsychotics, or buspirone instead of BZDs.[24,89] Cognitive behavioral therapy is the mainstay in psychotherapeutic treatment if the patient has an underlying anxiety disorder.[90] Nonpharmacotherapeutic approaches to consider are imagery, distraction, relaxation, meditation, and desensitization for initial or adjunctive management of psychiatric disorders.[89,91] Should the clinical benefits of combination opioid and BZD use outweigh the risks, we recommend that both agents be used at the lowest possible effective doses. Patients

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and their caregivers should be educated with written documentations (informed consent) outlining the precautions and risks associated with combination use.

When prescribing controlled substances and employing therapeutic drug monitoring, meticulous documentation in the medical record is recommended. Clinicians should document test results, interventions, and any other changes in the patient's clinical presentation. Because few evidence-based studies are available, clinicians should adopt an N-of-1 trial when evaluating and mitigating risk and individualizing assessment of treatment adherence, patient function, and results from routine therapeutic drug monitoring and PMP data.

Screening, Brief Intervention, Referral to Treatment

The American Society of Addiction Medicine consensus panel recommends assessing patients for an array of biopsychosocial needs beyond controlled substance use and addiction.[92] Patients should be treated and/or referred to programs that will help them meet their medical and psychiatric needs, as well as provide social assistance. The Screening, Brief Intervention, and Referral to Treatment (SBIRT) model (Figure 13) is designed to routinely assess and treat patients at risk for aberrant substance use.[93] Recently the SBIRT model was highlighted in a clinical practice feature on management of alcohol use.[56]

A comprehensive SBIRT model should be brief, include universal screening, target ≥ 1 specific behavior related to risky alcohol and/or drug use, and be comprehensive.[93] Screening should be accomplished within 10 minutes and can be repeated at various intervals as needed to determine changes in a patient's progress over time. The goals of brief intervention are to educate patients and increase their motivation to reduce risky behavior.[93] In patients with moderate to high risk of problematic behavior, brief treatment of 5 to 12 sessions lasting up to 60 minutes is indicated. If the patient meets diagnostic criteria for substance dependence or other mental illness as categorized by the *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition* or does not cease problematic behaviors, he or she should be referred to specialty treatment.[93] While the SBIRT model has not been extensively studied in patients with chronic pain who are undergoing opioid therapy, screening and brief interventions may prove effective in educating and encouraging patients to remain abstinent from alcohol and BZD use, or at least motivate them to change.

Summary

The use of opioids, BZDs, and/or alcohol occurs at high rates among patients with chronic pain despite the negative consequences on morbidity and mortality. There is a defined increase in rates of adverse events, overdose, and death when these agents are used in combination. Understanding comorbid psychiatric diagnoses and recognizing the prevalence of alcohol and/or BZD use among patients on long-term opioid therapy pose significant challenges to clinicians who manage patients with chronic pain. Clinicians, especially those in primary care and pain management, should consider routine toxicology testing. It is imperative for health care professionals to have objective evidence about the recent substance use of a patient. Urine drug testing and PMPs are 2 indispensible tools that can identify patients who are nonadherent to treatment, have filled multiple prescriptions at

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multiple pharmacies, and/or are abusing prescription drugs and/or illicit drugs. Whether UDTs and PMPs will affect overdose death rates remains to be seen. Ongoing screening for aberrant behavior, monitoring treatment compliance, documentation of medical necessity, and adjusting treatment to clinical changes are essential for improved patient outcomes. Many offices have adopted POC immunoassay testing for prescribed and illicit agents. Although POC tests offer rapid results, clinicians need to understand the limitations (ie, regarding sensitivity/specificity) of these tests and the clinical utility of laboratory confirmations with GC/MS or LC/MS. Recent advances in testing for alcohol use with biomarkers, such as EtG and EtS, have extended the detection window, allowing for improved/extended monitoring of alcohol use. Clinicians should routinely counsel patients about the dangers of combining opioids with BZDs and/or alcohol and discuss compliance testing as part of a safety monitoring program.

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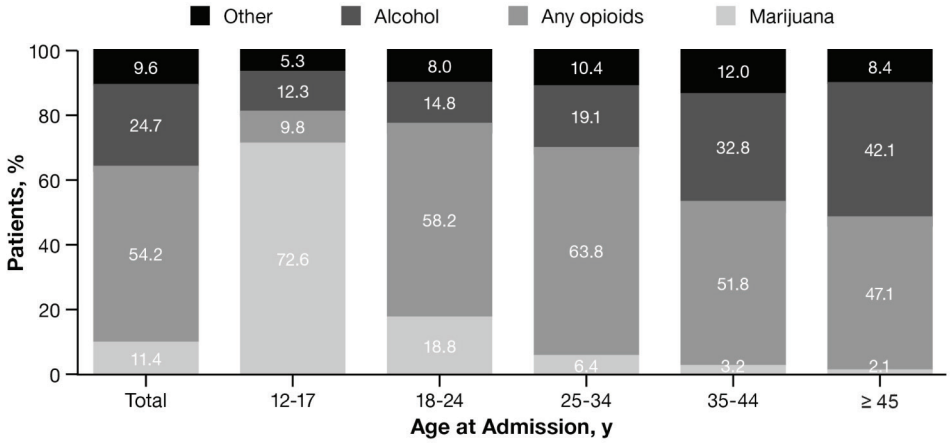

Figure 1.

Primary substance of abuse among treatment admissions reporting secondary benzodiazepine abuse: 2008.[12]

Benzodiazepines were reported as a drug of abuse by approximately 60 200 treatment admissions. The majority of patients indicated that they initiated benzodiazepine use after the abuse of another substance. The primary substance of abuse was opioids in the group aged 18 to 44 years, opioids as well as alcohol in the group aged ≥ 45 years, and marijuana in the group aged 12 to 17 years. Percentages may sum to < 100% because a small number of admissions did not report a primary substance of abuse.

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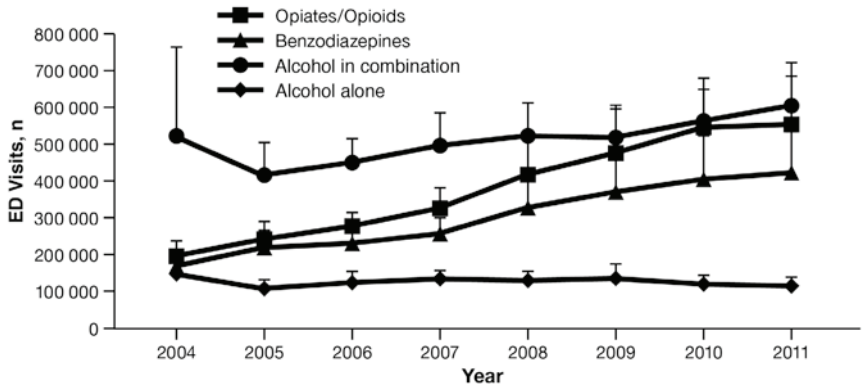

Figure 2.

Number of ED visits involving misused or abused drugs according to major substance of abuse: 2004–2011.[15]

The Drug Abuse Warning Network collects demographic and visit-level information on ED visits resulting from substance misuse or abuse, adverse reactions to drugs taken as prescribed, accidental ingestion of drugs, drug-related suicide attempt, and other drug-related medical emergencies. Only those data for visits involving misused or abused drugs are shown. Curves represent data obtained for the major substance of abuse; however, multiple drugs may be involved in each visit. Data from illicit drugs have been omitted. Alcohol combined with other drugs is recorded for all ages and alcohol only for patients aged ≤ 20 years.

Abbreviation: ED, emergency department.

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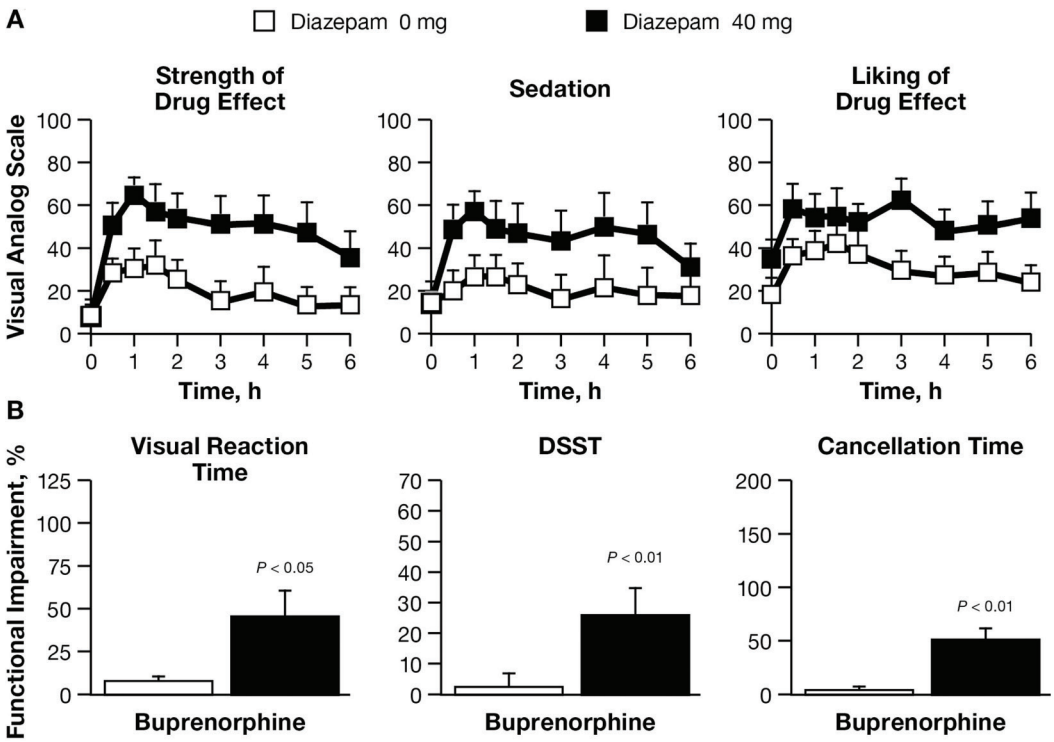

Figure 3.

Diazepam coadministered with buprenorphine increases subjective drug effects and impairs cognitive performance.

Diazepam (0 or 40 mg) was administered to patients maintained on buprenorphine therapy (n = 7) being treated with 100% of their normal buprenorphine dose (mean 11.1 ± 2.8 mg). **A**) Subjective drug effects were determined using visual analog scales of "strength of drug effect," "sedation," and "liking of drug effect" at 0, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours after dosing. **B**) Functional impairment was determined by increases in visual reaction time, a measure of sensory-motor performance, and cancellation time, a measure of focused attention, as well as a decrease in coding skills using the DSST. Data are expressed as mean plus standard error of the mean. *P* values denote significant paired differences versus the diazepam 0 mg condition.

Reprinted from *Drug and Alcohol Dependence*, Volume 91, Edition 2–3, Lintzeris N, Mitchell TB, Bond AJ, Nestor L, Strang J. Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. Pages 187–194, Copyright 2007, with permission from Elsevier.[30]

Abbreviation: DSST, Digit Symbol Substitution Test.

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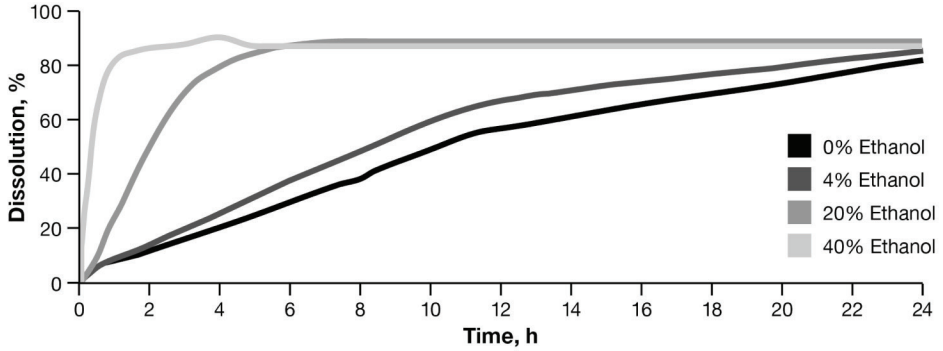

Figure 4.

In vitro dissolution of Avinza® (Pfizer Inc; morphine sulfate extended-release capsules) increases in an alcohol concentration–dependent manner.[39]

Avinza® (30 mg) was dissolved in 900 mL of buffer solutions containing ethanol (0%, 4%, 20%, and 40%). The dissolution without ethanol shows a controlled rate of release over a 24-hour period, which is similar to that of 4% ethanol. Dissolution of Avinza® in 20% and 40% ethanol is accelerated, with 80% of drug released in < 1 hour.

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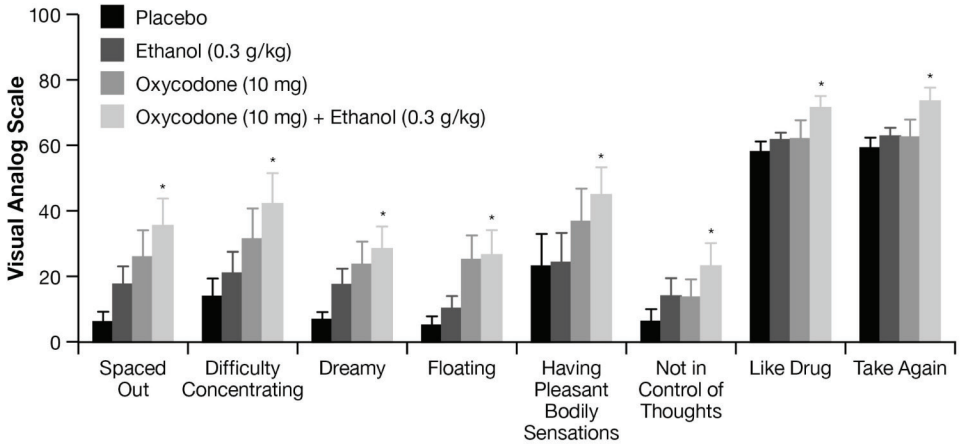

Figure 5.

Oxycodone combined with ethanol increases several abuse liability–related subjective effects.[47]

During separate sessions, 14 healthy volunteers received placebo capsule with placebo beverage, placebo capsule with ethanol 0.3 g/kg beverage, oxycodone 10 mg with placebo beverage, and oxycodone 10 mg with ethanol 0.3 g/kg beverage. The ethanol 0.3 g/kg dose is roughly equivalent to 1.5 standard-sized drinks. Oxycodone (or placebo) was administered 45 minutes before the ethanol (or placebo) drinking period so that both would peak at approximately the same time. Participants were asked to complete assessment forms 24 hours following each session. Data are expressed as mean plus standard error of the mean. *P* values represent significant differences from placebo. $*P < 0.05$.

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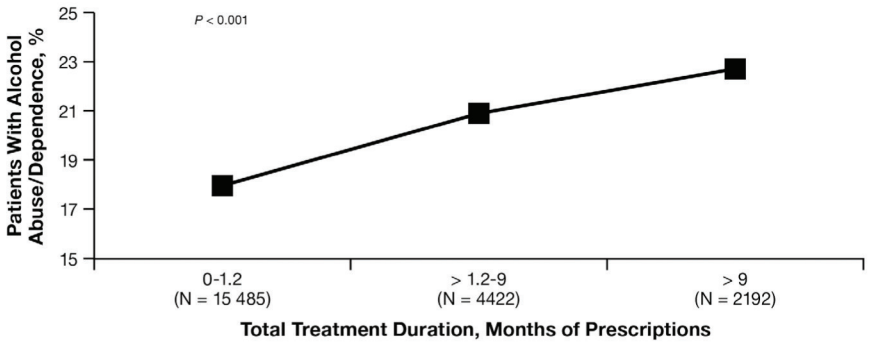

Figure 6.

Alcohol abuse/dependence correlates with long-term opioid analgesic use.[48] Outpatient pharmacy and clinical databases from the New England Veterans Integrated Service Network between January 1, 1998 and June 30, 2001 were analyzed for duration, dose, and dose changes of oxycodone/acetaminophen prescriptions. Diagnosis of alcohol abuse/dependence was defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* and determined from the medical records.

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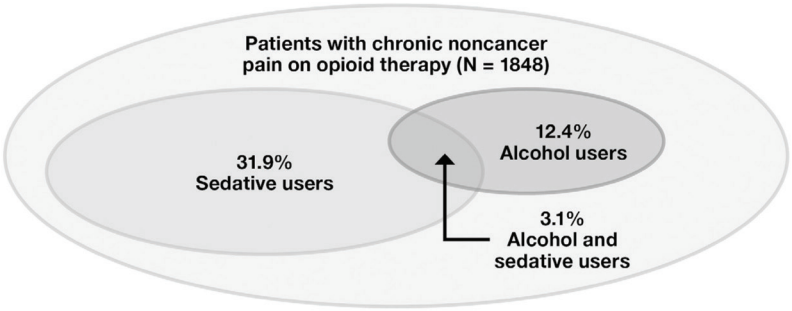

Figure 7.

Concurrent use of alcohol and/or sedatives among patients with chronic noncancer pain on long-term opioid therapy.[52]

Telephone surveys and electronic health care data of 1848 patients prescribed long-term opioid therapy for chronic noncancer pain were assessed. Concurrent alcohol use was based on self-report of ≥ 2 drinks within 2 hours before or after taking opiates within the past 2 weeks. Concurrent sedative use was defined as receiving sedatives for ≥ 45 days of the 90 days preceding interview according to pharmacy data.

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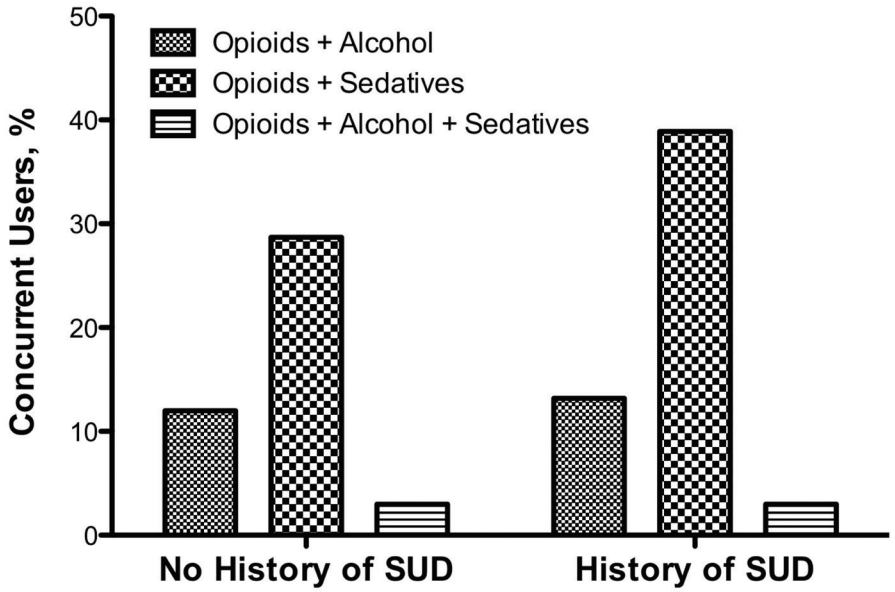

Figure 8.

Rates of concurrent alcohol and/or sedative use among patients with pain on chronic opioid therapy with and without an SUD.[52]

Telephone surveys and electronic health care data of 1848 patients prescribed long-term opioid therapy for chronic noncancer pain were assessed. Concurrent alcohol use was based on self-report of ≥ 2 drinks within 2 hours before or after taking opiates within the past 2 weeks. Concurrent sedative use was defined as receiving sedatives for ≥ 45 days of the 90 days preceding interview according to pharmacy data. Substance use disorders were classified by either a diagnosis of drug or alcohol abuse or dependence according to electronic data in the 3 years before the survey, patient self-report, or a score of ≥ 7 on the Alcohol Use Disorders Identification Test–Consumption.

Abbreviation: SUD, substance abuse disorder.

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	0	1	2	3	4	Points
How often did you have a drink containing alcohol in the past year?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	≥ 4 times a week	☐
How many drinks did you have on a typical day when you were drinking in the past year?	0 to 2	3 or 4	5 or 6	7 to 9	≥ 10	☐
How often did you have ≥ 6 drinks (≥ 4 for women) on 1 occasion in the past year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	☐
					Total points =	☐

Figure 9.

Alcohol Use Disorders Identification Test–Consumption questions.[62]

A score of ≥ 4 for men or ≥ 3 for women is considered positive and optimal for identifying hazardous drinking or active alcohol use disorders.

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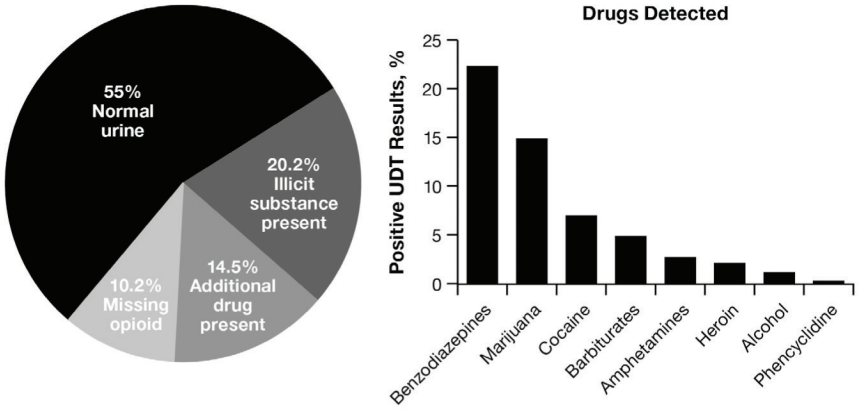

Figure 10.

UDT results among patients with chronic pain (N = 470).[71]

Urine drug testing was performed using gas chromatography/mass spectrometry technology. Abnormal UDT results were defined as the absence of a prescribed opioid, the presence of an additional nonprescribed controlled substance, the detection of an illicit substance, or an adulterated urine sample.

Abbreviation: UDT, urine drug testing.

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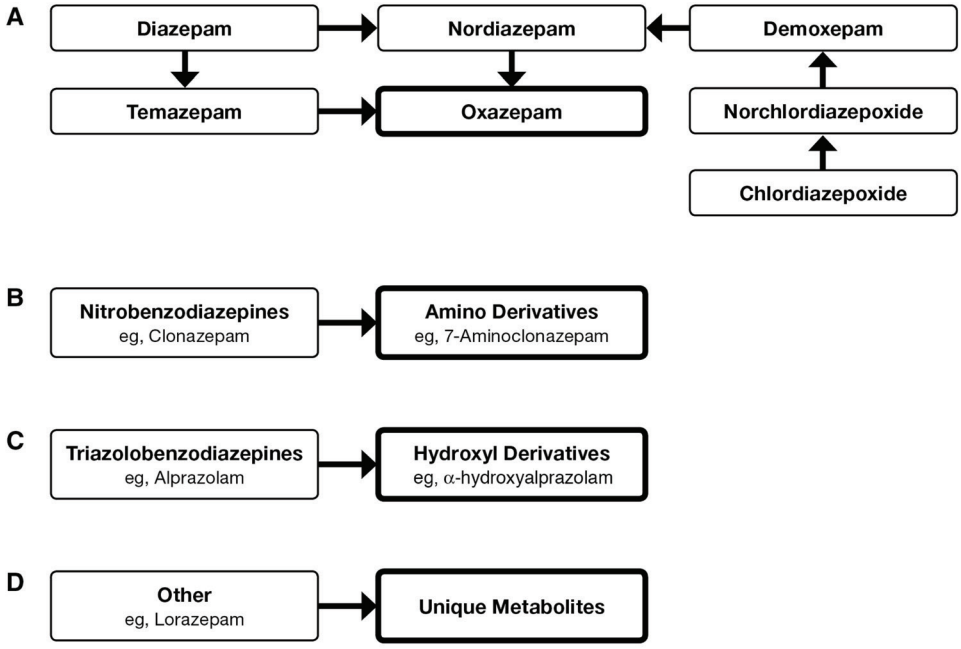

Figure 11.

Benzodiazepine classes according to metabolism.

A) The majority of BZDs are metabolized to oxazepam. **B**) Nitrobenzodiazepines and **C**) triazolobenzodiazepines are metabolized to their corresponding amino or hydroxyl compounds without being converted to oxazepam. **D**) Other BZDs have unique metabolic pathways.

Abbreviation: BZD, benzodiazepines.

Source: Data on file. Alere Toxicology, Waltham, MA.

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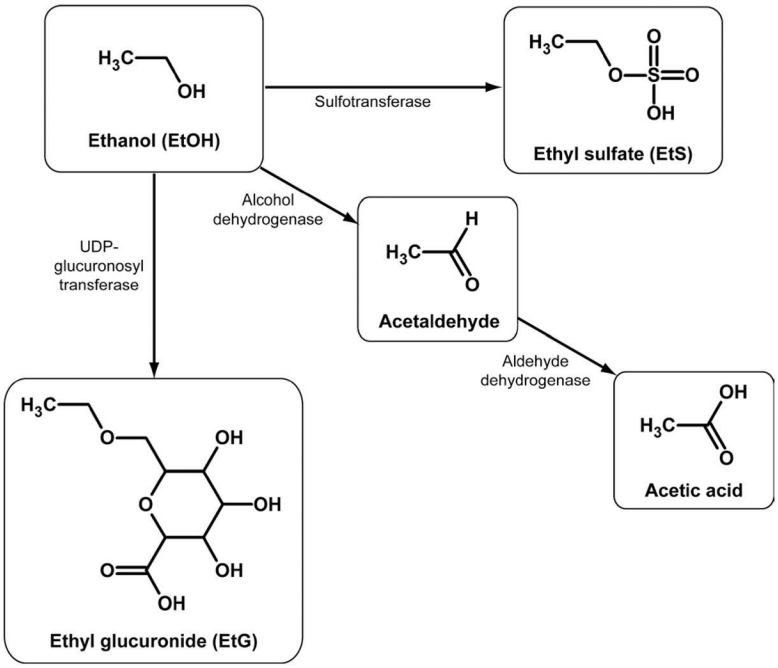

Figure 12.
Alcohol metabolism.[79]

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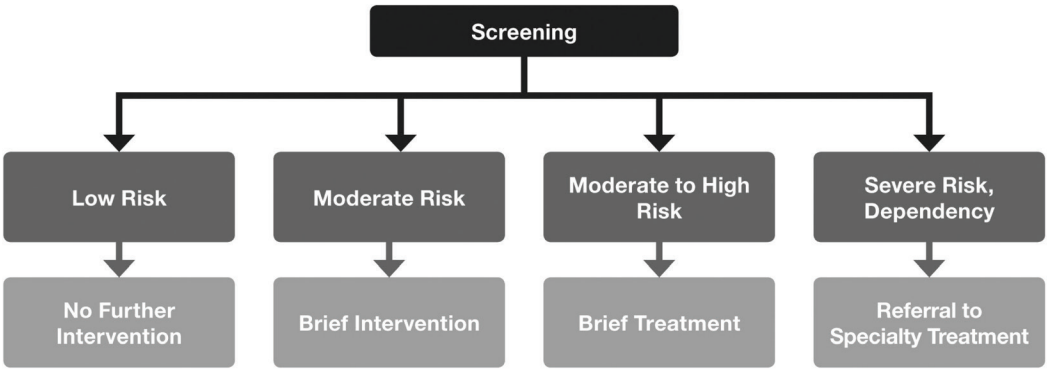

Figure 13.
Flow chart for the Screening, Brief Intervention, and Referral to Treatment process.[93]

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Table 1

Predictors of Concurrent Alcohol and/or Sedative Use in Patients on Long-term Opioid Therapy for Pain[27,52]

Predictors of Concurrent Alcohol Use	Predictors of Concurrent Sedative Use
• Male ($P = 0.0001$)	• Female ($P = 0.0001$)
• Taking opioids at doses < 120 mg morphine equivalents ($P = 0.006$)	• Younger age ($P = 0.0006$)
• Lower average pain intensity ratings ($P = 0.045$)	• Depression ($P < 0.0001$)
• Alcohol use disorder[a] ($P = 0.0003$)	• Anxiety or sleeping problem ($P \leq 0.011$)
• Risky drinking behavior[a] ($P < 0.0001$)	• Using opioid for > 1 pain condition ($P = 0.0005$)
	• Taking opioids at high doses[b] ($P < 0.0001$)
	• Any substance use disorder identification ($P = 0.002$)

[a] Alcohol use disorder and risky drinking behavior were defined by the Alcohol Use Disorders Identification Test–Consumption.

[b] High opioid doses were defined as daily doses ≥ 120 mg.

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Table 2

Metabolites of Opioids[75]

Opioid	Metabolites
Buprenorphine	Norbuprenorphine
	Norbuprenorphine-3-glucuronide
	Buprenorphine-3-glucuronide
Codeine	Hydrocodone (minor)
	Norcodeine
	Morphine
Fentanyl	Norfentanyl
Heroin	Morphine
	Codeine (contaminant)
	6-Monoacetylmorphine
Hydrocodone	Hydromorphone
	Dihydrocodeine
	Normorphine
	Norhydrocodone
	Hydrocodol
	Hydromorphol
Hydromorphone	Dihydromorphine
	Hydromorphone-3-glucuronide
Methadone	2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
	2-Ethyl-5-methyl-3,3-diphenylpyrrolidine
Morphine	Hydromorphone (minor)
	Morphine-3-glucuronide
	Morphine-6-glucuronide
	Normorphine
Oxycodone	Oxymorphone
	Noroxycodone
	Oxycodols and their respective oxide
Oxymorphone	Oxymorphone-3-glucuronide
	Oxymorphol
Tapentadol	Tapentadol-*O*-glucuronide
	Desmethyl tapentadol
	Hydroxy tapentadol
Tramadol	*O*-Desmethyltramadol
	Nortramadol

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Table 3

Windows of Detection for Alcohol, Benzodiazepines, and Opioids in Urine[76,77]

Substance	Estimated Window of Detection
Alcohol	≤ 24 h
Ethyl glucuronide	3–4 d
Ethyl sulfate	3–4 d
Benzodiazepines	
Short acting (eg, triazolam)	≤ 24 h
Intermediate acting (eg, alprazolam, clonazepam, lorazepam, temazepam)	1–12.5 d
Long acting (eg, diazepam)	5–24 d
Chronic abuse	≤ 30 d after last dose
Opioids	
Buprenorphine	Up to 4 d
Codeine	1–2 d
Heroin (metabolite 6-monoacetylmorphine)	1–3 d
Hydrocodone, hydromorphone	1–2 d
Methadone	3–11 d
Morphine	1–2 d
Oxycodone, oxymorphone	1–4 d