



AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Discuss the continuing need to follow pain management guidelines judiciously to mitigate epidemic opioid overdose
- Outline the CDC's recommendations from the 2016 Guideline for Prescribing Opioids for Chronic Pain and lessons learned since their release
- Discuss talking points and approaches to work with prescribers and ensure patient safety when opioids are prescribed
- List patient counseling points regarding the safe use of opioids
- Identify factors that put patients at highest risk of overdose who may need rescue medication

After participating in this activity pharmacy technicians will be able to:

- Describe the principles behind careful pain management
- List common mechanisms used to safeguard opioid use
- Recognize when to refer patients to the pharmacist for issues related to pain management or risk of overdose



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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Rational Opioid Use: Continuous Learning after the CDC Guideline

ABSTRACT: Daily (chronic) pain is common among adults living in the United States. It is often treated with opioids despite the lack of evidence for long-term benefit. Given the opioid overdose epidemic in the US, the Centers for Disease Control and Prevention has created an evidence- and expert-opinion-based guideline for prescribing opioids for chronic pain. The overall guideline has been developed to help identify the risks and benefits of opioid therapy and improve long-term safety. Included are 12 recommendations on determining when to use opioids for chronic pain; optimal prescribing (selection, dosage, duration, follow-up, discontinuation); and assessing risks and addressing harms of opioid therapy. The pharmacy team, both pharmacists and pharmacy technicians, have an important role in counseling patients about safe use of opioids. The team can also work with prescribers to ensure their optimal and safe use in patients with chronic pain. Identification of factors putting patients at high risk for opioid overdose and methods to minimize those risks are provided.

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INTRODUCTION

Approximately 20% of adults (50 million) in the United States suffer from daily (chronic) pain, and another 8% (20 million) have reported severe pain (i.e., pain that frequently limits life or work activities).¹ This pain is often severe enough to cause worsening health, increased use of healthcare resources, and disability. Results of randomized clinical trials of opioids for treatment of pain have shown their effectiveness when used in the short term (12 weeks or fewer).² However, the benefit of long-term use (more than three months) is limited.³ Despite this data, prescribers often use opioids to treat chronic pain, with one in five adults with noncancer-related pain prescribed opioids.⁴ In fact, the rate of prescribing

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Pause and Ponder:

How many prescriptions for opioids do you see in a typical day? Do you know these patients and why they are taking opioid analgesics?

opioids for pain nearly quadrupled from 1999 to 2014.⁵ At the same time, prescription opioid deaths from both illicit opioids and misuse of prescription opioids tripled, resulting in the opioid overdose epidemic.⁶

In the midst of this opioid overdose epidemic, the Centers for Disease Control and Prevention (CDC) created a guideline for prescribing opioids for chronic pain in adult patients with chronic pain treated in an outpatient setting (Table 1).⁷ Other pain-related guidelines are available and should be used for patients with cancer or palliative chronic pain and patients with acute pain treated by specialists like emergency clinicians or surgeons.⁸⁻¹¹ Since this guideline's publication, the opioid prescribing rate, including high dosage opioid prescriptions, is decreasing, yet drug overdose deaths reached an all-time high in the latest report analyzing data through 2016. Thus, understanding appropriate opioid use and prescribing continues to be a hot topic and one in which pharmacy teams should be well versed. This article provides the pharmacy team with a guideline overview, updates related to opioids, and tools they need to apply it to their practice.

CDC Guideline Development

The CDC obtained input from experts, stakeholders, the public, and a federally chartered advisory committee as well as individual perspectives from subject experts, primary care professional society representatives, and state agency representatives. The committee reviewed clinical evidence addressing key questions of effectiveness and comparative effectiveness, harms and adverse events, dosing strategies, risk mitigation strategies, and effect of opioid use for acute pain on long-term use.^{7,12} Overall, insufficient evidence existed supporting long-term opioid use for chronic pain because of the lack of documented long-term benefit and the risk of serious harm.

What is interesting is that at the time of the review, no randomized studies on the use of opioids for chronic pain had evaluated long-term outcomes (i.e., one year or more) related to pain, function, or quality of life. Most placebo-controlled studies were six weeks or shorter in duration. Long-term opioid use, however, was associated with opioid abuse or dependence (i.e., unsuccessful efforts to reduce or control use, resulting in failure to fulfill major role obligations at work, school, or home), risk of fatal and nonfatal overdose, cardiovascular events, endocrinologic harms, and road trauma. The committee also evaluated dosing strategies, but outcome results were inconsistent. One study found that using an extended-release/long-acting (ER/LA)

formulations rather than initiating therapy with an immediate-release (IR) opioid was associated with greater risk of overdose, particularly during the first two weeks of therapy. The committee determined accuracy of risk assessment tools to identify patients at risk of opioid abuse/misuse was inconsistent, and found no studies evaluating risk mitigation strategies. Finally, studies showed that patients undergoing low-risk surgery or those with injury-related low back pain who received opioids were more likely to have long-term opioid use than those treated for other acute pain episodes.

Based on the review and an additional contextual evidence review assessing the benefits and harms of opioid therapy, values and preferences of providers and patients, resource allocation, and effectiveness of nonpharmacologic and nonopioid therapies, the committee made 12 recommendations. These were grouped into three categories:

1. determining when to use opioids (initiate or continue) for chronic pain
2. prescribing opioids (selection, dosage, duration, follow-up, discontinuation)
3. assessing risk and addressing harms of opioids.

When to Use Opioids in Chronic Pain

Opioids should not be considered first-line therapy for routine treatment of chronic pain (unrelated to cancer or end-of-life pain) because of the small-to-moderate short-term benefit, uncertain long-term benefits, and serious risks. Instead, nonpharmacologic therapy for chronic pain, such as weight loss, exercise therapy, cognitive behavioral therapy, and interventional approaches, should be used to reduce pain and improve function in patients with chronic pain. For example, high-quality exercise therapy for hip or knee osteoarthritis has been shown to reduce pain sustainably and improve function for two to six months.^{13,14} This has also been found to be true in patients with low back pain and fibromyalgia.^{13,15} The pharmacy team can encourage patients to work with their primary care team to have an active role in developing their care plan and support patients engaging in exercise.

When nonpharmacologic therapy alone is not enough to improve pain and function, consider nonopioid pharmacologic therapy, such as nonsteroidal anti-inflammatory agents (NSAIDs), acetaminophen, selected antidepressants, and anticonvulsants.⁷ Acetaminophen and NSAIDs are effective for osteoarthritis and low back pain. Pregabalin and gabapentin have proven efficacy in diabetic neuropathy and postherpetic neuralgia. Other types of neuropathic pain have been effectively treated with pregabalin, gabapentin, carbamazepine, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors. Pregabalin and duloxetine can effectively treat pain associated with fibromyalgia. Nonopioid drugs are generally not associated with substance use disorders or are rarer causes of overdoses compared with opioids. Yet these drugs are not

Table 1. CDC Guideline Recommendations for Prescribing Opioids for Chronic Pain⁷

Recommendation

- Nonpharmacologic therapy and nonopioid pharmacologic therapy preferred for chronic pain
 - Consider opioid therapy only if benefits for both pain and function outweigh risks
 - If opioids are used, combine with nonpharmacologic therapy and nonopioid therapy
-
- Before starting opioids, establish treatment goals, including realistic goals for pain and function
 - Consider how opioid therapy will be discontinued if risks > benefits
 - Continue opioid therapy only if clinically meaningful improvement in pain and function > risks
-
- Before starting and periodically during, discuss
- known risks and realistic benefits of opioid therapy
 - patient and clinician responsibilities for managing therapy
-
- Prescribe IR opioids instead of ER/LA opioids
 - Prescribe lowest effective dosage
 - Use caution when prescribing any dosage
 - Carefully reassess evidence of individual benefits and risks when dosage ≥ 50 MME/day
 - Avoid increasing to ≥ 90 MME/day or carefully justify decision to titrate to ≥ 90 MME/day
-
- When opioids used for acute pain prescribe:
- lowest effective IR opioid dose
 - no greater quantity than needed for expected duration of pain severe enough to require opioids (e.g. ≤ 3 days; > 7 days will rarely be needed).
-
- Evaluate benefits and harms within 1-4 weeks of starting opioid or dose escalation and every 3 months
 - If harms > benefits,
 - Optimize other therapies
 - Work with patients to taper opioids to lower dosages or taper and discontinue opioids
-
- Before starting and periodically during, clinicians should
- evaluate risk factors for opioid-related harms
 - incorporate strategies to mitigate risk, including considering offering naloxone when factors increasing risk for opioid overdose (e.g., history of overdose, substance use disorder, higher opioid dosages [≥ 50 MME/day], or concurrent benzodiazepine use)
-
- Review PDMP data to determine whether patient receiving opioid dosages or dangerous combinations at risk for overdose
 - When starting opioid therapy
 - Periodically during opioid (e.g. every prescription to every 3 months)
-
- Use urine drug testing before starting and consider annual testing assess for prescribed medications and other controlled prescription drugs and illicit drugs
-
- Avoid prescribing opioid pain medication and benzodiazepines concurrently when possible
-
- Offer/arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid-use disorder

ABBREVIATIONS: ER/LA, extended-release/long-acting; IR, immediate-release; MME, morphine milligram equivalents; PDMP, prescription drug monitoring program

without risks, particularly in geriatric patients and those with cardiovascular, renal, gastrointestinal, and/or liver disease. Thus, clinicians should individualize therapy based on benefit versus risk. For more information, see a previously published article by my colleague Kevin Chamberlin and me that provides some guidance on NSAIDs and acetaminophen use.¹⁶ The CDC has both a free training series and a guideline resource that provide more in-depth discussion about use of non-opioids.^{17,18}



For complex pain syndromes, specialty teams should be consulted for diagnosis and management. Pain associated with diseases like diabetes and rheumatoid arthritis may be ameliorated by improving disease control (e.g., glucose control with diabetes to prevent progression of diabetic neuropathy, immune-modulating therapy for rheumatoid arthritis).⁷ In some situations, opioids may indeed be appropriate even if the patient has not failed nonpharmacologic or nonopioid therapy as long as the expected benefits have been weighed against risks. For example, consider a patient with serious illness and poor prognosis who has contraindications to nonopioid pharmacologic therapies and the goal of care is comfort; opioids may be an appropriate option as long as patient and provider have discussed benefits and risks.

If opioids are determined to be appropriate, they should be combined with nonpharmacologic therapy and nonopioids as appropriate and the patient and provider should develop treatment goals. The review of clinical evidence did not find studies evaluating written agreements or plans, yet those who set a plan in advance will be able to clarify expectations of opioid therapy (e.g., how prescribed, how monitored, when doses are discontinued or tapered if goals not met). Treatment goals would ideally include improvements in both pain relief and quality of life and/or function (physical, emotional, psychologic). Validated instruments such as the pain average, interference with enjoyment of life, and interference with general activity (PEG) assessment scale can be used to track outcomes.¹⁹ PEG uses an 11-point visual analog scale to have patients describe their average pain in the past week; how the pain interfered with enjoyment of life in the past week; and how the pain interfered with general activity in the past week. Studies have shown that a clinically meaningful improvement for pain and function is 30%.²⁰ Additionally, clinicians should discuss safety issues. **Table 2** provides important considerations in patient education about opioid therapy.^{7,21}

Safely Prescribing Opioids

IR opioids, rather than ER/LA opioids (e.g., extended-release opioids, methadone, transdermal fentanyl) should be used for initiation of opioid therapy for chronic pain. Overdose risks are higher with ER/LA opioids, and no difference in efficacy or safety was observed between continuously scheduled ER/LA opioids and intermittent use of IR opioids.^{7,22} An ER/LA opioid should be reserved for patients with severe, continuous pain who have received IR opioids daily for at least one week. When selecting an ER/LA opioid for a patient, the guideline recommends avoiding methadone and transdermal fentanyl unless the clinician is familiar with the unique risk profiles of these drugs (i.e., unpredictable pharmacokinetics/dynamics of methadone, dosing/absorption properties of fentanyl). Unlike in patients with cancer pain or opioid use for palliative or end-of-life-related pain, routinely prescribing an IR opioid with an ER/LA opioid for breakthrough pain is not recommended because of the lack



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of evidence supporting safe combined use. Some patients may benefit from the combination, however, and this should be individualized after assessing risks and benefits.

Prescribers should select the lowest possible opioid dose for initial therapy. Opioid overdose risk increases in a dose-response manner: doses 50 to 100 morphine milligram equivalents (MME)/day increase risk 1.9 to 4.5 times and 100 MME/day or more increase risk two to 8.9 times compared with less than 20 MME/day.⁷ Based on this data, the CDC guideline recommends that the overdose risk is reduced (although not eliminated) if the dose is kept at less than 50 MME/day. Again, this is only true for patients with noncancer-related chronic pain. It is also important to understand that geriatric patients and those with renal or hepatic insufficiency will likely have decreased clearance of opioids, and thus low doses and small increases are recommended. When changing doses of opioids, the general rule is to wait at least five half-lives of the drug before making a dose change.²³ For patients whose doses escalate above 50 MME/day in an effort to control pain and improve function, clinicians should reassess whether opioid treatment is the best approach. Other methods of pain management may be more beneficial. Some states have requirements for MME thresholds or associated clinical documentation (e.g., Washington state requires a pain specialist consult for any prescription >120 MME/day).²⁴

Continual reassessment of effectiveness, adverse effects, and harm risks is necessary for all patients receiving opioids. Opioid therapy lasting longer than three months is associated with an increased risk of opioid-use disorder, and patients without pain relief at one month are unlikely to have pain relief with opioids at six months.⁷ Furthermore, opioid overdose risk is greatest within the first three to seven days following opioid initiation or dosage increases, especially with methadone and transdermal fentanyl. Thus, it is important for clinicians to evaluate patients continually while receiving opioid therapy. Initial follow-up should occur within the first three days in patients initiating or dose-escalating

Table 2. Patient Education for Opioid Use in Patients with Chronic Pain^{7,20}

- Be explicit and realistic about expected benefits of opioids:
 - Opioids reduce short-term pain
 - Unknown benefit of opioids to improve pain and function with long-term use
 - Complete pain relief is unlikely
- Emphasize improvement in function is primary goal and functional improvement can occur even when pain is present
- Discuss potential serious side effects
 - Fatal respiratory depression
 - Development of life-long opioid-use disorder
- Advise about common side effects and how to mitigate
 - Constipation: increase hydration and fiber intake, and maintain or increase physical activity to prevent constipation. Stool softeners or laxatives should be taken regularly with ER/LA opioids and may be needed with IR opioids.
 - Dry mouth: chronic dry mouth can lead to tooth decay. Advise patients to use regular and gentle dental hygiene and have regular dental visits. Saliva substitutes may be considered.
 - Nausea and/or vomiting: usually transient lasting two to three days after opioid initiation in some but not all patients; as-needed antiemetics may be provided. Chronic nausea may occur in 15% to 30%; switching to another opioid may eliminate nausea.
 - Drowsiness: usually transient after opioid initiation and dose escalation until tolerance is developed. Avoid driving during these periods.
 - Confusion: usually transient after opioid initiation and dose escalation until tolerance is developed, typically after a few days and sometimes a few weeks. If not resolving, talk with provider to rule out other causes.
 - Tolerance is defined as diminished response to a drug with repeated use that may require patient to need higher doses of opioids over time. Monitor patient for development of tolerance and if needed, increase opioid dose.
 - Physical dependence: defined as adaptation to a drug that produces symptoms of withdrawal when drug is stopped. Emphasize to patient that physical dependence is not addiction, but means they should not abruptly stop opioids and work with provider to gradually taper off at time of discontinuation to avoid withdrawal symptoms.
- Discuss that opioids impair ability to safely operate a vehicle, particularly when opioids are initiated, doses increased, or when other CNS system depressants, e.g., benzodiazepines or alcohol, are concurrently used
- Discuss importance of taking dose of opioids as prescribed because of risk of serious side effects with
 - Higher doses or taking more often than that prescribed
 - Use with other medications: benzodiazepines, sedatives, alcohol, illicit drugs
- Discuss risks to household members and others if opioids are intentionally or unintentionally shared, and include discussion of
 - Proper storage in a secure, preferably locked location
 - Options for safe disposal of unused opioids
 - Availability and proper use of naloxone for overdose reversal (consider prescribing/dispensing if state regulations allow)
- Discuss importance of periodic reassessment to ensure goals are met and/or consideration of other alternatives if opioids are not effective or harmful
- Discuss planned use of precautions to reduce risk
 - Prescription drug monitoring program
 - Urine drug testing (if used)

methadone or transdermal fentanyl, and within one week for patients initiating or dose-escalating IR or ER/LA opioids. At follow-up, clinicians should assess benefits in function, pain control, and quality of life. Tools such as the PEG assessment scale can be used. Clinicians should also assess adverse effects such as constipation and drowsiness, and warning signs of overdose (e.g., sedation or slurred speech) or opioid-use disorder (e.g., craving, using larger-than-prescribed quantities). Finally, clinicians should ask patients about their preference about continuing opioids, given their effects on pain/function and adverse effects. If opioids are continued, reassessment should take place. The optimal frequency, however, is unknown.

With dose escalations, the guideline recommends a follow-up reassessment for most opioids within one to four weeks of the dose escalation. However, for methadone, this follow-up reassessment should be done within three days and when total daily opioid dose is 50 MME/day or greater, follow-up reassessment should be done within one to two weeks. When a patient is on a stable dose, reassessment is recommended at least every three months. Ideally, the reassessments take place in person, but that may not always be possible.

Technician Talk

Technicians should become familiar with state and federal laws and regulations regarding opioids because as part of the pharmacy team, they can help identify potential opioid-related issues. Below are some tips for opioid prescriptions:

- Receive any new opioid prescription: 1) calculate cumulative dose of all opioid prescriptions; 2) note if any benzodiazepine prescriptions on profiles; and 3) notify pharmacist who would double check calculations and contact provider if ≥ 90 MME
- Receive a new prescription for a quantity exceeding a 7-day supply: notify the pharmacist to complete a review of appropriateness and he or she can contact the provider if required by law or insurance plan or red flags exist
- Receive a new prescription for an extended-release opioid: 1) note if any previous immediate-release or extended-release opioids exist on the patient's profile; 2) notify pharmacist so he or she may contact provider if no previous opioid use
- Note any signs of abuse/aberrant behavior from patient; 1) stay calm and polite; 2) notify pharmacist in an area of the pharmacy that is out of the patient's sight and earshot
- Note any signs of pending overdose: 1) implement emergency plan—call 911, have pharmacist or any other person trained with CPR and to administer naloxone present; 2) monitor patient closely, keep awake and upright; 3) communicate all information to medical personnel upon arrival; 4) if pharmacist takes over, keep customers away and calm. *Consider becoming certified (if allowed via state laws) to administer naloxone*

If clinically meaningful improvements in pain and function are not achieved or sustained, or the balance of harms outweigh the benefits, patients may need to be tapered off opioids and nonpharmacologic or nonopioid pharmacologic treatment should be used or a pain specialist consulted. Patients should not self-taper off opioids. Previously published guidelines recommend reducing weekly dosage by 10% to 50% of original dosage.²⁵ Rapid dose escalations over two to three weeks can be accomplished if patients have severe adverse drug reactions to opioids. Slower tapers of a 10% dose reduction per week or month may be better tolerated in patients who have been on opioids for years. Essentially, the idea is to taper slowly enough to minimize withdrawal symptoms (e.g., drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia). Individualizing the taper is reasonable based on patient goals, concerns, and ability to follow directions. It may be that the taper needs to be paused and restarted when patients reach low dosages to avoid withdrawal symptoms. When the smallest available dose is reached, the interval can be extended, and opioids can be stopped when taken less frequently than once per day. Before a taper starts, clinicians should discuss the increased risk of overdose with an abrupt return to their starting dose with patients. They should also provide detailed education about the taper schedule, withdrawal symptoms, and whom to contact if any questions/withdrawal symptoms occur. Several resources are available for suggested tapering and discontinuation schedules.^{25–28}

Opioid use for acute pain—pain with abrupt onset and caused by injury or surgery—has been associated with long-term opioid use.⁷ Although acute pain can often be managed without opioids, in some cases opioids can be beneficial, such as following surgery or trauma. When opioids are used, the CDC guideline recommends providing a duration that is appropriate for the expected duration of the pain. For example, for most surgical pain, often three days or less of opioid therapy is sufficient and more than seven days is rarely needed. Rather than prescribing opioids for the “just in case” situation, clinicians should

be prepared to re-evaluate patients who have persistent pain to determine appropriate management. Only IR opioids should be used. This practice not only eliminates the potential for physical dependence but also minimizes the number of leftover pills available for unintentional or intentional diversion. Of note, the US Food and Drug Administration is in the process of developing federal guidelines for management of acute pain, which should help guide providers on best practices.²⁹

Opioid Use: Assessing Risk and Addressing Harms

Despite the clinical evidence review providing insufficient evidence as to how best to determine harms of opioids based on specific patient comorbidities or demographics, the panel (based on contextual evidence and expert opinion) recommend that certain risk factors are likely to increase susceptibility to opioid-related harms.⁷ **Table 3** lists the high-risk groups for opioid use in chronic pain management.⁷ It also provides recommendations for these groups when considering opioid therapy. Clinicians should assess risk factors periodically and note risk factors may differ depending on the risk. For example, factors such as alcohol use can vary over time and require more frequent follow-up. Clinicians can ask simple questions to assess drug and substance abuse. 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?” has been shown to be 100% sensitive and 74% specific for detecting a drug use disorder compared with standardized diagnostic interviews. Other methods for assessing risk and addressing harms of opioid use include

- reviewing the prescription drug monitoring program (PDMP)
- ordering urine drug testing
- avoiding prescribing and use of opioids and benzodiazepines concurrently
- offering naloxone for opioid reversal, and
- referring or treating opioid-use disorder.

Table 3. High-Risk Groups and Opioid Use⁷

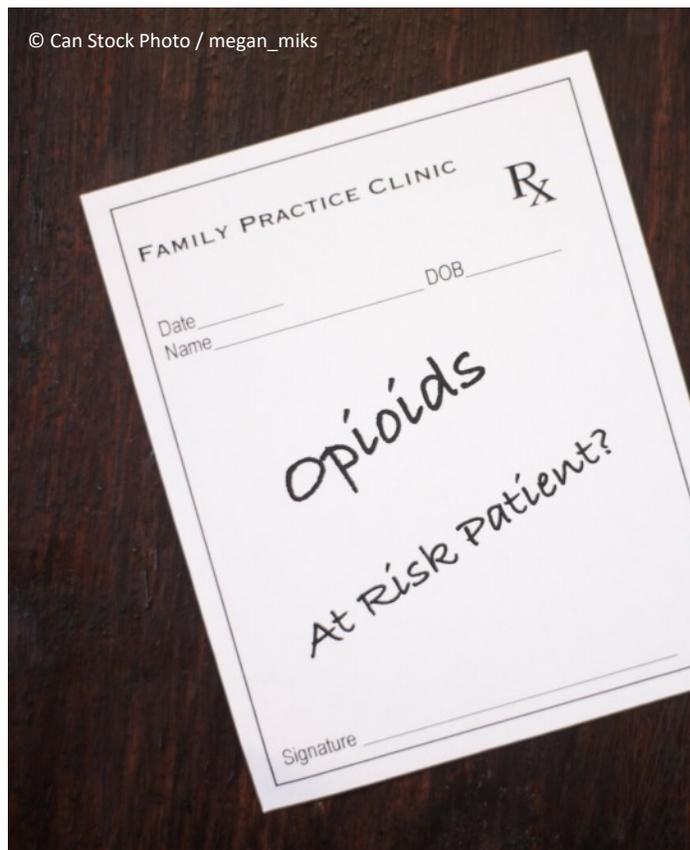
High-risk group	Comments/recommendations
Sleep-disordered breathing (e.g., sleep apnea)	<ul style="list-style-type: none"> • Risk factors: CHF, obesity • Carefully monitor during opioid therapy • Cautious opioid dose titration • Avoid prescribing if moderate–severe disorders
Pregnancy, breast-feeding, reproductive-age women	<ul style="list-style-type: none"> • Risk to mother and fetus (e.g., stillbirth, poor fetal growth, opioid withdrawal syndrome) • Patients and providers together carefully weigh risks and benefits • For reproductive-age women, discuss family planning and risks during pregnancy • Consult experts if tapering during pregnancy to prevent patient/fetus withdrawal • Use buprenorphine or methadone for pregnant women with opioid-abuse disorders • Use a facility prepared to monitor, evaluate, and treat opioid neonatal withdrawal for delivery for neonates in pregnant women receiving opioids, methadone, or buprenorphine • Avoid codeine in breast-feeding women (may cause neonatal toxicity/death). If needed, use lowest possible dose and ≤4-day supply
Renal or hepatic insufficiency	<ul style="list-style-type: none"> • Use caution, increase monitoring to minimize risks because opioid accumulation may occur
Age ≥65 years	<ul style="list-style-type: none"> • Risks: inadequate pain management, reduced renal function, propensity to accumulate opioids, cognitive impairment, likelihood of drugs that interact because of comorbid conditions • Use caution and increase monitoring • Educate patients to avoid obtaining opioids from multiple providers and saving unused quantities • Initiate exercise and bowel regimens to prevent constipation, risk assessment for falls, and cognitive impairment monitoring
Mental health conditions	<ul style="list-style-type: none"> • Assess all patients for psychologic distress using validated instruments for anxiety, PTSD, and/or depression (e.g., GAD-7, PHQ-9, PHQ-4) • Use caution and additional monitoring • Do not initiate in patients during acute psychiatric instability or with uncontrolled suicide risk • Consider behavioral health specialist consultation before initiating opioids in patients with history of suicide attempt or psychiatric disorder • Avoid benzodiazepines for patients with anxiety or other mental health conditions • Optimize treatment for depression and other mental health conditions, which can improve pain
Substance use disorder	<ul style="list-style-type: none"> • Ask about alcohol and illicit drug use • Review PDMP data • Consider urine drug testing as appropriate • Provide counseling about increased risk of overdose when opioids are combined with alcohol or other drugs • Ensure patients receive appropriate treatment for substance abuse disorder when needed • Discuss risks, consider if benefits outweigh risks in patients with history of substance use disorder before opioids are prescribed. If prescribed, incorporate strategies to mitigate risks, consult with substance use disorder and pain specialists, and offer naloxone • Communicate with substance use disorder treatment providers if opioids are prescribed
Previous nonfatal overdose	<ul style="list-style-type: none"> • Work with patient to reduce opioid dosage and discontinue opioids when possible • Discuss increased risk and whether benefits > risks if continued opioid use is needed, incorporate strategies to mitigate risks, and offer naloxone

ABBREVIATIONS: CHF, congestive heart failure; GAD, generalized anxiety disorder; PHQ, patient health questionnaire; PTSD, post-traumatic stress disorder.

Reviewing the PDMP. PDMP are statewide electronic databases that collect, monitor, and analyze controlled substance prescribing and dispensing data submitted by pharmacies and dispensing providers. All states except Missouri have statewide PDMPs.³⁰ However, some counties within Missouri have PDMPs and legislators have introduced a bill for a statewide program. All PDMPs collect information about schedule II to IV controlled substances, and 35 states also collect information about schedule V controlled substances. Some states require providers to review the PDMP before prescribing opioids. The timeliness of transmitted data and requirement policies, however, vary from state to state. For example, in Connecticut, the prescriber's authorized agents, including pharmacists who may work with the provider, are allowed to review the PDMP data on the provider's behalf.³¹ This may assist with provider workload and allow timely risk assessment.

Opioid overdoses often occur in patients receiving opioids from multiple providers and/or with high total daily dosages of opioids; it is prudent to review this information during the risk assessment before initiating and during opioid therapy. Ideally, prescribers should review the PDMP before each prescription is written. In states where the PDMPs are not fully functional with timely data transmission, however, this may be impossible. Thus, the guideline recommends reviewing the PDMP at least every three months, unless factors that increase the opioid-related harms are absent and it is not required by state law. The review should include data for opioids and other controlled substances. This will allow the clinician to evaluate the total opioid dosage and dangerous combinations (e.g., benzodiazepines and opioids) that may increase risk of opioid overdose. PDMPs require community pharmacists to submit electronic data related to dispensing of controlled substances within a timely manner as determined by state law. Community pharmacists, however, can also review the PDMP prior to dispensing a controlled substance prescription and alert the provider if risks are identified before dispensing the prescription. They can also discuss safety concerns with the patient.

If high opioid dosages, multiple controlled substance prescriptions, or dangerous combinations are found, the pharmacist should attempt to improve the patient's safety. Pharmacists should discuss the information gained from PDMP review with the patient. Occasionally, information may be incorrect, particularly if the wrong name or birthdate was entered or another person has used the patient's identity to fill a prescription. When high total MME/day dosages are calculated, the clinician should discuss safety concerns and possibility of taper to a safer dose with the patient. If dangerous combinations are identified, the clinician should initiate a discussion with other providers involved in prescribing the medications. If the combination is deemed necessary, the clinician should talk with the patient so that the patient understands the risks. In the case of a possible substance use disorder, discussing concerns and referring the patient to a program is important. Finally, if suspicion exists



that the patient is sharing or selling the opioids, clinicians should consider urine drug testing to determine whether opioid cessation can occur without inducing withdrawal.

Urine drug testing. Clinicians can employ urine drug testing to provide information about drug use that the patient has not reported and opioid nonadherence.⁷ Urine drug testing, however, does not provide accurate information on dose or quantity of opioids used, is subject to misinterpretation, can sometimes be used to harm patients (e.g., stigmatization), increases costs to patients, and requires clinicians have the appropriate training and time to effectively interpret, confirm, and communicate results. The guideline experts did recommend urine drug testing before initiating opioids and periodically during therapy (at least annually) certainly for individual patients at high risk. More frequent urine drug testing may be appropriate for patients with substance use disorders.

Typically, urine drug testing can be completed using a relatively inexpensive immunoassay panel that tests for commonly prescribed opioids and illicit drugs. Each institution's immunoassay may be different. Thus, it is critical that clinicians understand how to interpret the results. For example, a positive "opioid" immunoassay typically detects morphine. This may not only reflect a patient's use of morphine but also codeine and heroin, because these drugs are metabolized into morphine. Furthermore, synthetic and opioids (e.g., fentanyl or methadone) are not detected, and semisynthetic opioids (e.g., oxycodone) may not be either. Immunoassays can also cross-react with other

medications and give false positive results.³² False negative results are also possible. Use of confirmatory tests, tests that confirm a positive or negative urine drug test typically using gas chromatography/mass spectrometry, should only be completed when there is a need to detect specific opioids not available on standard assays or the presence of unexpected results. A recent review by American Academy of Family Physicians provides guidance on interpreting results.³²

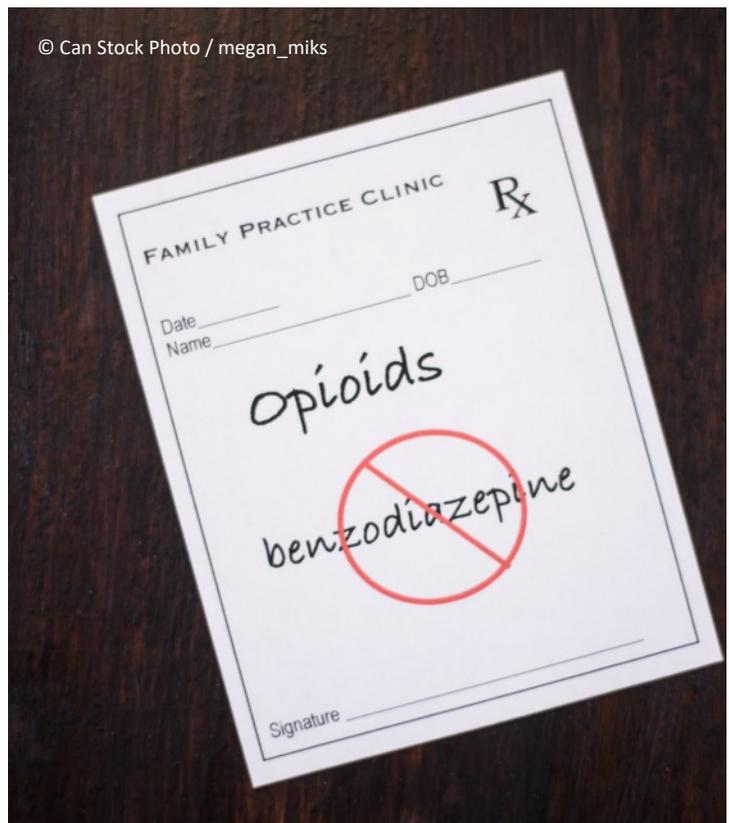
Clinicians should also have a plan in place for how to handle the results of urine drug tests before ordering the tests. For example, before the urine drug test is done, clinicians should explain the testing is done to improve patient safety. They should ask patients about how they are using prescribed drugs, and if and how they are using any other drugs (nonprescribed or even illicit drugs). This guideline also recommends asking, “Should I expect an unexpected result on the urine drug test?” This can allow patients to provide important information about any changes in their use of opioid drugs that may affect the urine drug test results. If unexpected results occur, initiating a similar post-testing discussion can be useful to reveal important information about why a particular result was reported before the clinician determines whether confirmatory testing is needed, which is expensive and may be unnecessary. Unexpected results also offer the clinician the opportunity to improve patient safety by tapering/discontinuing opioids; providing more frequent monitoring and evaluation; offering naloxone; and/or referring for substance use disorder.

Avoiding benzodiazepines and opioids. Because both benzodiazepines and opioids cause central nervous system (CNS) depression and a decrease in respiratory drive, the likelihood of a fatal overdose is increased with concurrent use.⁷ Thus, in general, benzodiazepines should not be prescribed in patients using opioids for chronic, noncancer-related pain. Some situations may be appropriate for concurrent use, such as severe acute pain in patients taking stable low-dose benzodiazepine therapy. Other CNS depressants, such as muscle relaxants and hypnotics, may also be risky. Clinicians should evaluate benefit versus risk for individual patients.

Checking the PDMP before initiating opioids allows clinicians to identify concurrent CNS depressants and involve pharmacists and/or pain specialists to assist with determining risk/benefit and developing a plan for discontinuing the CNS depressants. Coordinating care with mental health professionals is also critical, as they may be able to assist with prioritizing patient goals and care coordination. Benzodiazepines require a gradual taper in patients who have been on long-term therapy to avoid rebound anxiety, hallucinations, seizures, and delirium. Several tapers have been published, but a common regimen includes a 25% dose reduction every one to two weeks depending on patient symptoms.³³ Cognitive behavioral therapy can greatly improve the success rate of benzodiazepine tapering.

Opioid-use disorder treatment. If patient behaviors, information gained from PDMP review, or results from urine drug testing suggest a possible opioid-use disorder, clinicians should discuss these concerns with the patient. This allows the patient an opportunity to disclose related concerns or problems. Patients who meet the criteria for opioid-use disorder according to the *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)* should receive evidence-based treatment.³⁴ Typically, this will be medication-assisted therapy with buprenorphine or methadone maintenance therapy with cognitive behavioral therapy. Oral or long-acting naltrexone may be an option in nonpregnant women. Patient costs may be a barrier for buprenorphine therapy, given that insurance plans often do not cover buprenorphine for opioid-use disorder. In these patients, offering naloxone for an opioid overdose is also recommended. Some patients may have problematic opioid use but do not qualify according to DSM-V criteria for opioid-use disorder. In these patients, tapering and discontinuing opioid therapy is recommended.

Many communities do not offer medication-assisted therapy or maintenance programs, or are over capacity. The guidelines recommend in these cases that providers consider obtaining a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) that would allow them to prescribe buprenorphine in patients with opioid-use disorder or prescribe naloxone, which does not require a waiver.³⁵ To find opioid treatment programs, behavioral health treatment services, and buprenorphine physician and treatment programs, see <https://www.samhsa.gov/find-help>.³⁵



Naloxone. The opioid antagonist naloxone can be used to reverse respiratory depression. It is an antagonist at the mu, kappa, and delta receptors and works by displacing opioid agonists at the opioid receptors. Because it has no agonist activity, patients who have not received opioids and receive naloxone have no effects. Naloxone can be administered for opioid overdose intranasally, intramuscularly, and subcutaneously.³⁶ Administration by lay persons has been shown to save lives.³⁷ Although naloxone is a prescription product in the US, accessibility varies from state to state. In many states, providing naloxone to lay persons who might witness an overdose in their family or friends or to service providers (e.g., emergency medical personnel, policeman, behavioral health specialists) has been one mechanism.³⁷ Other states have allowed pharmacists to prescribe naloxone, either independently or through collaborative practice agreements, to patients or caregivers of patients receiving opioids. For example, in Connecticut, trained pharmacists are allowed to prescribe naloxone to any individual to treat or prevent an overdose as long as appropriate documentation is made.³⁸

The guideline recommends that naloxone be offered to all patients at increased risk for opioid overdose, including

- patients taking benzodiazepines with opioids
- patients at risk for returning to a high dose to which they are no longer tolerant, such as patients recently released from a correctional institution
- patients taking 50 MME/day or more.⁷

Other experts suggest that offering naloxone to all patients receiving opioids is wise, because the risk of an accidental opioid overdose by the patient or someone else with access to opioids within a home or workplace can occur. If naloxone is prescribed, appropriate education about using naloxone and subsequent steps (e.g., calling 911) is essential. This education ideally is provided by prescribers and pharmacies (when the pharmacist is not the prescriber of naloxone) to reinforce patient understanding.

Resources for prescribing naloxone can be found at <http://prescibertoprevent.org>.

WHAT WE'VE LEARNED SINCE CDC GUIDELINE DEVELOPMENT

The opioid epidemic continues despite this guideline. The rise in heroin and illicit fentanyl deaths has rapidly escalated and the death rate from prescription opioids has remained steady since 2009.³⁹ In an effort to curb access to opioids during this "opioid crisis," the Drug Enforcement Agency ordered a decrease in opioid manufacturing by 25% in 2017 and an additional 20% decrease in 2018.^{40,41} Furthermore, many healthcare organizations, insurance plans and healthcare professionals have adopted the CDC guidelines into their practice. In fact, North Carolina adopted the guidelines into state regulations in 2017.⁴² Some providers have rigidly applied the guidelines to patient care, such as the opioid taper/cessation recommendation. In some cases, reports of providers abruptly ceasing prescribing of opioids for patients without appropriate weaning has been reported.⁴³ Because of this, criticism has arisen following these changes in available

PAUSE AND PONDER:

What are the laws pertaining to naloxone in your state? How often have you dispensed naloxone? Are there others among your patients who would also benefit from having naloxone available?



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opioids and adoption of the guideline for all chronic pain patients. Forcing patients off or weaning down on opioid therapy without the support needed to manage chronic pain may in turn lead patients to use illicit opioids. Furthermore, a survey of primary care physician practices on management of chronic pain has highlighted the continued need for education. The pharmacy team is in a key position to do that.⁴⁴

The Centers for Medicare and Medicaid Services issued new policies in 2019 with two goals: (1) to improve safety alerts with opioids prescription dispensing at pharmacies and (2) to increase drug management programs for patients at risk for misuse or abuse of opioids or other frequently abused drugs.⁴⁵ These policies are for Medicare Part D opioid users who are opioid naïve, chronic opioid users, users with potentially problematic concurrent medication use, and high-risk opioid abusers.

Exclusions to these policies include: 1) residents of long-term care facilities; 2) patients under hospice care; 3) patients being treated for active cancer-related pain; and 4) patients receiving palliative or end-of-life care.

Medicare Part D plans will implement five safety alerts (i.e., pharmacy claim edits) which will require pharmacist review at the time of dispensing the opioid in an effort to promote safe utilization.⁴⁶

- The “seven-day supply limit for opioid-naïve patients” is a hard edit, meaning that dispensing more than a 7-day supply will not be allowed unless a coverage determination is submitted and approved. This limit is for those patients who have not filled an opioid prescription within the past 60 days. If a patient needs more than a seven days’ supply, either the patient or prescriber can request a coverage determination (including an expedited review).
- The care coordination edit will occur when the patient presents a prescription at the pharmacy and their cumulative MME across all opioid prescriptions ≥ 90 MME. At this point, pharmacists should consult with the prescriber. They may be able to provide the prescriber with information such as names of other opioid prescribers or the increasing MME level. Once the prescriber attests to the plan that that days’ supply is intended and medically necessary, then the alert can be overridden. Once this consultation has occurred during a plan year, the provider doesn’t have to be contacted on every prescription. Therefore, pharmacist’s documentation of this care coordination will be crucial.
- Other soft edits include an alert if concurrent opioid and benzodiazepine use or duplicative long-acting opioid therapies are noted. Pharmacists will be required to perform a safety review to determine if opioid use is safe and clinically appropriate. The pharmacist will not be required to contact the provider, but may if that facilitates the pharmacist’s assessment.
- Some but not all plans will implement another hard edit when the patient’s cumulative opioid daily dose is 200 MME or more when patients have multiple opioid prescribers and/or dispensing pharmacies. If this alert occurs, dispensing will not be allowed until an override is entered and authorized by the plan. Once the prescriber attests that the identified cumulative MME is intended and medically necessary, the medication can be dispensed. The provider can request a coverage determination in advance of prescribing an opioid to avoid this alert as well.

Pause and Ponder:

Under what circumstances does your state limit quantities of opioids? How often must you explain this to patients? What technique works best?

Sidebar: Signs and Symptoms of Abuse or Addiction

General signs/symptoms

- Being nervous or cranky
- Being tired and sad
- Being overly energetic, talking fast and saying things that don’t make sense
- Disconnecting from friends and loved ones
- Eating more or less than usual
- Getting into trouble with the law
- Having withdrawal symptoms when not using alcohol or other drugs (e.g., anxiety, shakiness, sweating, nausea and/or vomiting, depression, irritability, loss of appetite, fatigue, headaches)
- Hiding activities, injuries, or the extent of opioid use
- Losing control and judgment, especially when it comes to substances (e.g., drinking/using more than meant to, longer than meant to)
- Losing interest in activities
- Mixing with different groups of people or changing friends
- Neglecting responsibilities at home, at work, or in relationships (e.g., missing appointments, attending work or school on an erratic schedule, experiencing financial hardship)
- Not taking care of health or hygiene (e.g., bathing, changing clothes or brushing their teeth)
- Quickly changing moods
- Sleeping at odd hours
- Spending time alone and avoiding time with family and friends
- Taking risks
- Tolerating more and more of the substance to get the same effect

Prescription-related signs/symptoms

- Aggressive complaining
- Alternation of prescriptions or route of delivery
- Complaining about other patients
- Doctor shopping or accessing opioids from other sources
- Drug-seeking behavior with focus on certain types of opioids and benzodiazepines
- Emphatic views on opioid medication and illicit drugs as well as legalization of drugs
- Loss of prescriptions
- Multiple unauthorized dose escalations
- Requests for early refills
- Staff harassment
- Questioning rights and responsibilities

Some key points to remember about the CDC guideline is that the limits on dosages and are not firm limits, rather they are to guide clinicians.⁴³ Dosages should be individualized and in some cases exceeding the 90 MME/day may be warranted. Similarly, opioid taper or cessation should never be done abruptly as this increases the risk for abuse of non-prescribed opioids. Evidence exists that a consensual opioid dose reduction taper with the support of a multidisciplinary team can be effective.⁴⁷ The essence of this is that the CDC guideline is just that—to guide the clinician—but individualization is needed to manage patients' pain effectively and reduce their risk of misuse and abuse. A team approach is most effective. Thus, the pharmacist and pharmacy technician can play an important role in managing patients receiving opioids.

THE PHARMACY TEAM'S ROLE

Because pharmacists and pharmacy technicians are on the front lines of dispensing opioid pain medication and providing medication-related services, they are in optimal positions to engage patients and prescribers in prevention and treatment efforts for opioid-use disorder and overdose.⁷ In the community pharmacy setting, the pharmacy team often has limited time and patient information, yet they can play a critical role in evaluating and identifying risks.

Assessing patients with opioid prescriptions for “red flags,” such as a patient who may be struggling with opioid-use disorder or diverting medications, is feasible. Red flags include forged prescriptions (i.e., lack of common abbreviations; atypical quantities, directions, or dosages; overly legible handwriting); prescriptions originating from outside of the immediate geographic area; altered prescriptions (e.g., multiple ink colors, differing handwriting styles); cash payments; inconsistent or early prescription fills; and multiple prescribers.^{7,48} Other concerning and potentially drug-seeking behaviors include unusual or overly assertive behavior; unkempt or overdressed appearance; unusual knowledge of controlled substances; claims of no regular healthcare provider or health insurance; calling or coming in after regular hours; claims to be traveling or visiting relatives; claims prescription is lost or stolen; or signs of drug abuse, such as skin tracks or scars on neck, arms, feet, or ankles.⁴⁸ Pharmacy technicians should alert their pharmacist if they identify any of these red flags while intaking prescriptions and/or communicating with patients. Additionally, validation of the prescriber DEA registration number and patient identification information can further verify the prescription is not altered. Reviewing the PDMP (if available) and any patient prescription records will allow the pharmacy team to identify multiple prescribers, concurrent therapies of concern, and timing of prescription fills.

Contacting the prescriber with questions or concerns is vital to ensuring patient safety.⁷ Keep in mind that with forged prescriptions, a patient may use his or her own phone number. Therefore, it is best to look up the prescriber's phone number

instead. It is important to have this conversation in an area where the patient cannot hear, as this is humiliating to those who are truly in need of pain relief and may agitate those who are being fraudulent, placing the whole pharmacy team at risk of violence. When discussing questions or concerns with providers, it is essential to do so in a collaborative manner. If the question is not related to a potentially forged prescription but rather optimal application of the CDC guideline for opioid use in chronic pain, then indicating that there are concerns about patient safety may allow a candid and collaborative conversation. Having a recommendation or drug information supporting that recommendation is helpful to facilitate prescriber understanding and addressing any concerns.

Community pharmacists also have a role in assisting with the management of pain and application of these guidelines by educating patients on opioid risks and methods for managing risks. They can work together with providers to review and monitor pain management therapy, assist in implementing treatment plans, and provide drug information and recommendations to the healthcare team based on their pharmaceutical knowledge and the guideline. Because the community pharmacy team may see the patient more frequently than the healthcare provider, they can have a role in identifying patients who may not be optimally treated for their chronic pain. Conversations with patients may reveal they are not receiving optimal relief or are not concurrently using nonpharmacologic therapy. This may provide an opportunity to intervene and discuss potential therapy alternatives or optimization with the patient and providers. The CDC has several resources available to aid in applying guidelines to clinical care, including

- a checklist for prescribing opioids for chronic pain
- an opioid prescribing guideline mobile app
- a pocket guide to tapering opioids
- information on calculating dosages, assessing benefits and harms, PDMPs, and nonopioid treatments
- tips for pharmacists.

Additionally, there are trainings, posters, and patient resources available. These can be found at:

<https://www.cdc.gov/drugoverdose/prescribing/resources.html>.

When opioids are dispensed, educating, offering, and/or dispensing naloxone (based on available state laws) can be prudent to prevent opioid abuse, particularly in those patients at high risk for overdose or potential diversion within their home. Additionally, the pharmacist should discuss proper use, side effects and management, expectation about medication fills and requirements for refills, dangers of stockpiling unused medication, and safe storage and disposal to prevent diversion or misuse.

Case Study – The Pharmacy Team Working Together

A patient arrives at your community pharmacy with a new prescription for immediate-release oxycodone 5 mg every six hours as needed for low-back pain, #50 tablets. The technician notes that this is more than a 7-day supply, which is not recommended by CDC guidelines and prohibited by many state law, except in certain circumstances. How can the team work together to resolve a potential problem?

Although state regulations surrounding the technician's role in dispensing medications differ, pharmacist-technician teamwork is critical to safe dispensing practices. Many technicians have the first contact with a patient while intaking the prescription and/or communicating with the patient when he or she arrives to pick up the medication. As the technician communicates with the patient, he or she should observe the patient's behavior for possible red flags. If a potential red flag is noted, the technician should remain calm and handle the intake per usual practices.



The technician should then communicate the information to the pharmacist so that he or she can be aware of a potential problem. It is best to have a conversation like this in an area of the pharmacy where the patient (and other patients) cannot hear or observe the conversation. If a patient education area is available in the pharmacy, the technician should refer the patient to this area of pharmacy while he or she awaits the prescription processing. Providing patients with as much information as possible to minimize risks is essential to opioid safety.

Next, the pharmacist (or technician if permitted by state regulation) should review the prescription drug monitoring program to identify if any other opioid or controlled substances have been filled and identify other potential red flags (identify multiple prescribers, concerning concurrent therapies, and timing of prescription fills). The pharmacist should also review the patient's pharmacy dispensing profile for appropriate review of medication therapy to identify any other problems.

The team noted upon these reviews that this is the first opioid prescription the patient has received. What are the next steps for the pharmacy team?

Next, the pharmacist would need to contact the prescriber regarding the more than 7 days' supply written on the prescription to confirm. In the discussion with the provider, it would be helpful to provide the rationale of the call (e.g., state regulation or insurance policy exists prohibiting more than a 7-day supply or pharmacist concerned based on current the CDC guideline). Documentation of this conversation within the pharmacy records is critical to allow for communication with other pharmacy team members for any future related prescription reviews and that the appropriate steps were followed. If permitted by state laws, pharmacy technicians can help with documentation process.

In this case, the provider explains the patient has failed many other treatments for low back pain and is ineligible for a surgical procedure. The pharmacy will dispense a 7-day supply and it is expected that the patient will receive opioids for some time if deemed effective.

Once the prescription is filled, the pharmacist should also educate the patient about the medication, being certain to discuss the risks of opioid use, common side effects and how to prevent them, and discuss benefits of also having naloxone on hand (if permitted by state law) – see [Table 2](#) for complete education recommendations.

Together the pharmacy team can help to identify potential problems and mitigate them.

One emerging issue is the abuse potential of gabapentin and pregabalin.⁴⁹ These analogs of gamma-aminobutyric acid have been widely used for pain treatment (both for on-label and off-label uses), and they have become opportunistic drugs of abuse. Gabapentin is not currently a federally scheduled drug, although some states have scheduled it. Pregabalin, however, is a scheduled drug. Furthermore, they are typically low-cost drugs and are more widely available than opioids for treating pain. Patients have reported euphoric effects, and abrupt cessation often results in withdrawal symptoms. Although these drugs offer an alternative to opioids and have proven efficacy in some types of neurologic pain, it is important for pharmacists and pharmacy technicians to be aware of the abuse potential and keep abreast

of data surrounding the most effective use of these drugs in treating pain.

CONCLUSION

With the opioid overdose epidemic occurring in the US, an approach to protecting the public's health and preventing opioid overdose is needed. The CDC guideline for prescribing opioids for chronic pain provide recommendations on determining when to use opioids; optimal prescribing of opioids; and appropriate assessment of risk and harms of opioids. Pharmacists and pharmacy technicians are poised to assist the healthcare team and patients to use opioids for treatment of chronic pain safely .

Figure 1. Advancing Pharmacists and Pharmacy Technicians Role in Safe Opioid Use

Best

- 1 **BE COMMUNITY CHAMPIONS** and follow impending changes to state and federal law that involve opioid prescribing and treatment for addiction
- 2 **Collaborate** with local physicians to enhance information transfer and improve patient safety if patients need pain relief
- 3 **Track illegal drug use trends in your community and in the nation** and volunteer to provide education at schools and public events

Better

- 1 When patients present prescriptions for opioids, **track their therapies carefully**, and **engage them in conversation**
- 2 Find, print, and post a copy of the **CDC guideline for prescribing opioids for chronic pain—United States, 2016**
- 3 **Educate patients thoroughly** about analgesics and the need to use them carefully and store them securely; consider using **Table 2** as a checklist when you counsel!

Good

- 1 **Be familiar with federal and state laws** concerning opioids
- 2 **Educate patients** about the basic precautions when taking opioids
- 3 **Always use your state's prescription monitoring program** and have a plan concerning **how to handle illicit prescriptions**

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