Pharmacist perspective on the CDC guideline for prescribing opioids for chronic pain

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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 evidence- and expert-opinion-based guidelines 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 risk and addressing harms of opioid therapy. The pharmacy team, both pharmacists and pharmacy technicians, have an important role in counseling patients about the 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.

Introduction

Approximately 11% of adults in the United States suffer from daily (chronic) pain, and another 10% have reported severe pain.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).2 However, the benefit of long-term use (>3 months) is limited.3 Despite this data, opioids are often used to treat chronic pain, with 1 in 5 adults with noncancer–related pain prescribed opioids. In fact, the rate of prescribing opioids for pain nearly quadrupled from 1999 to 2014.4 At the same time, prescription opioid deaths from both illicit opioids and misuse of prescription opioids have tripled.5

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Thus, the US is in the midst of an opioid overdose epidemic. In an effort to curb this epidemic, the Centers for Disease Control and Prevention (CDC) created guidelines for prescribing opioids for chronic pain. The “CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016” has been developed to improve communication between clinicians and patients about the risks and benefits of opioid therapy for chronic pain, improve safety and effectiveness of pain treatment, and reduce the risks of long-term opioid therapy (Table 1). The guideline is intended for use by primary care clinicians treating adult patients with noncancer or nonpalliative/end-of-life chronic pain in an outpatient setting. Other pain-related guidelines, however, should be used for patients with cancer or palliative chronic pain, patients with acute pain, and by specialists such as emergency clinicians or dentists. This article provides an overview of the guideline and provides the pharmacy team with the tools they need to apply it to their practice.

The ‘CDC Guideline for Prescribing Opioids for Chronic Pain–United States, 2016” is intended for use by primary care clinicians treating adult patients with noncancer or nonpalliative/end-of-life chronic pain in an outpatient setting.”

CDC guideline development
The CDC used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method for guideline development. This method allows the quality of available evidence to be graded and the guideline recommendations to be placed into categories based on the quality of evidence, balance of benefits and harm, values and preferences, and resource allocation. The evidence type is graded from type 1 (highest level of evidence, eg, randomized clinical trials or overwhelming evidence from observational studies) to type 4 (clinical experience and observations or studies with major limitations). The category of recommendations was either A (applies to all patients and patients should receive) or B (requires individual decision making to apply to different patients). CDC initially obtained input from experts, stakeholders, the public, and a federally chartered advisory committee and then obtained individual perspectives from subject experts, primary care professional society representatives, and state agency representatives.

The clinical evidence review consisted of an update to the systematic review sponsored in 2014 by the Agency for Healthcare Research and Quality (AHRQ) on effectiveness of long-term opioid treatment of chronic pain. It addressed the 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. Overall, this updated clinical evidence review showed that insufficient evidence exists supporting long-term opioid use for chronic pain because of the lack of documented long-term benefits and the risk of serious harm. Key findings are summarized here, but full details can be found in the guideline including grading of the evidence.

The updated review confirmed that no randomized studies on the use of opioids for chronic pain have evaluated long-term (ie, ≥1 year) outcomes related to pain, function, or quality of life. Most placebo-controlled studies have been 6 weeks or shorter in duration. Long-term opioid use, however, was associated with opioid abuse or dependence (ie, 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.

Dosing strategies were evaluated in this clinical review, but outcome results were inconsistent. One study found that using an extended-release/long-acting (ER/LA) formulation rather than initiating therapy with an immediate-release (IR) opioid was associated with greater risk of overdose, particularly during the first 2 weeks of therapy. Accuracy of risk assessment tools to identify patients at risk of opioid abuse/misuse was determined to be inconsistent, and no studies evaluating risk mitigation strategies were found. 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 updated AHRQ systemic 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, 12 recommendations were made. These were grouped into 3 categories: 1) determining when to use opioids (initiate or continue) for chronic pain; 2) prescribing opioids (selection, dosage, duration, follow-up, discontinuation); and 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 that is not pain due to active cancer or for palliative/end-of-life care because of the small-to-moderate short-term benefit, uncertain long-term benefits, and serious risks. Instead, nonpharmacologic therapy, 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 sustainably reduce
pain and improve function for 2 to 6 months. This has also been found to be true in patients with low back pain and fibromyalgia. 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. 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 be effective in treating pain associated with fibromyalgia.

### TABLE 1

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>CATEGORY*</th>
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<tr>
<td>Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if benefits for both pain and function are anticipated to outweigh risks to patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid therapy, as appropriate.</td>
<td>CATEGORY A Evidence type 3</td>
</tr>
<tr>
<td>Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with patients, including realistic goals for pain and function and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. They should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.</td>
<td>CATEGORY A Evidence type 4</td>
</tr>
<tr>
<td>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.</td>
<td>CATEGORY A Evidence type 3</td>
</tr>
<tr>
<td>When starting opioid therapy for chronic pain, clinicians should prescribe IR opioids instead of ER/LA opioids.</td>
<td>CATEGORY A Evidence type 4</td>
</tr>
<tr>
<td>When opioids are started, clinicians should prescribe lowest effective dosage. They should use caution when prescribing opioids at any dosage, carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 MME/day, and avoid increasing to ≥90 MME/day or carefully justify decision to titrate to ≥90 MME/day.</td>
<td>CATEGORY A Evidence type 3</td>
</tr>
<tr>
<td>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 IR opioids and no greater quantity than needed for the expected duration of pain severe enough to require opioids. Often sufficient will be &lt;3 days; ≥7 days will rarely be needed.</td>
<td>CATEGORY A Evidence type 4</td>
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<tr>
<td>Clinicians should evaluate benefits and harms with patients within 1-4 weeks of starting opioid therapy for chronic pain or dose escalation. They should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or taper and discontinue opioids.</td>
<td>CATEGORY A Evidence type 4</td>
</tr>
<tr>
<td>Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. They should incorporate into management plan strategies to mitigate risk, including considering offering naloxone when factors increasing risk for opioid overdose, eg, history of overdose, substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present.</td>
<td>CATEGORY A Evidence type 4</td>
</tr>
<tr>
<td>Clinicians should review patient’s history of controlled substance prescriptions using PDMP data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at risk for overdose. PDMP data should be reviewed when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.</td>
<td>CATEGORY A Evidence type 4</td>
</tr>
<tr>
<td>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 and other controlled prescription drugs and illicit drugs.</td>
<td>CATEGORY B Evidence type 4</td>
</tr>
<tr>
<td>Clinicians should avoid prescribing opioid pain medication and benzodiazipines concurrently whenever possible.</td>
<td>CATEGORY A Evidence type 3</td>
</tr>
<tr>
<td>Clinicians should offer/arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid-use disorder.</td>
<td>CATEGORY A Evidence type 2</td>
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</tbody>
</table>

*Category A, applies to all persons; most patients should receive recommended source of action; Category B, individual decision-making needed; different choices appropriate for different patients; Clinicians help patients arrive at decision consistent with patient values/preferences and specific clinical situation; Level 1, randomized clinical trials or overwhelming evidence from observational trials; Level 2, randomized clinical trials with important limitations or exceptionally strong evidence from observational trials; Level 3, observational studies or randomized clinical trials with notable limitations; Level 4, clinical experience and observations or studies with major limitations.

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

Source: Ref 7
Nonopioid drugs are generally not associated with substance use disorders or are rarer causes of overdoses compared with opioids. Yet these drugs are not 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 Drug Topics article and CDC guideline resources.16,17

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 (eg, 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 received IR opioids daily for at least 1 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 (ie, 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, it is not recommended to routinely prescribe an IR opioid with an ER/LA opioid for breakthrough pain because of the lack of evidence supporting its safe combined use. Some patients may benefit from the combination, however, and this should be individualized after assessing risks and benefits.

The lowest possible opioid dose should be selected for initial therapy. Opioid overdose risk increases in a dose-response manner: doses 50–100 morphine milligram equivalents (MME)/day increase risk 1.9 to 4.5 times and 100 MME/day or more increase risk 2 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 5 half-lives of the drug before making a dose change.22 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 (eg, Washington state requires a pain specialist consult for any prescription >120 MME/day).23

Continual reassessment of effectiveness, adverse effects, and harm risks

A patient arrives at your community pharmacy with a new prescription for immediate-release oxycodone 5 mg every 6 hours as needed for low-back pain. What patient education would you provide this patient at the time of dispensing?

failed nonpharmacologic or nonopioid therapy as long as the expected benefits have been weighed against the risks. For example, in 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 (eg, how prescribed, 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.18 PEG uses an 11-point visual analog scale to have the patient 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%.19

Despite the updated AHRQ review not revealing studies evaluating effectiveness of patient education and risk-mitigation strategies, the contextual evidence review found that many patients lack information about opioids and identified concerns that clinicians have missed opportunities to discuss safety issues. Table 2 provides important considerations in patient education about opioid therapy.7,20

Safely prescribing opioids

IR opioids, rather than ER/LA opioids (eg, extended-release opioids, methadone, transdermal fentanyl) should be used for initiation of opioid therapy for chronic pain. The risks of overdose 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.7,21 An ER/LA opioid should be reserved for patients with severe, continuous pain who have received IR opioids daily for at least 1 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 (ie, 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, it is not recommended to routinely prescribe an IR opioid with an ER/LA opioid for breakthrough pain because of the lack of evidence supporting its safe combined use. Some patients may benefit from the combination, however, and this should be individualized after assessing risks and benefits.
is necessary for all patients receiving opioids. Opioid therapy lasting longer than 3 months is associated with an increased risk of opioid-use disorder, and patients without pain relief at 1 month are unlikely to have pain relief with opioids at 6 months.7 Furthermore, opioid overdose risk is greatest within the first 3 to 7 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 3 days in patients initiating or dose escalating methadone or transdermal fentanyl, and within 1 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. Adverse effects such as constipation and drowsiness, and warning signs of overdose (eg, sedation or slurred speech) or opioid-use disorder (eg, craving, using larger-than-prescribed quantities) should also be assessed. Finally, patients should be asked about their preference to continue 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 1 to 4 weeks of the dose escalation. However, for methadone, this follow-up reassessment should be done within 3 days and when total daily opioid dose is 50 MME/day or greater, follow-up reassessment should be done within 1 to 2 weeks. When a patient is on a stable dose, reassessment is recommended at least every 3 months. Ideally, the reassessments take place in person, but that may not always be possible.

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 of opioids. The AHRQ clinical evidence review did not find any high-quality studies comparing effectiveness of different opioid-tapering protocols.24 Previously published guidelines recommend reducing weekly dosage by 10% to 50% of original dosage.24 Rapid dose escalations over 2 to 3 weeks can be accomplished with severe adverse drug reactions, and slower tapers of a 10% dose reduction per week or month may be better tolerated in patients

Continued on page 30.  

### TABLE 2

**Patient Education for Opioid Use in Patients with Chronic Pain**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td><strong>Be explicit and realistic about expected benefits of opioids</strong></td>
<td>• Opioids reduce short-term pain&lt;br&gt;• Unknown benefit of opioids to improve pain and function with long-term use&lt;br&gt;• Complete pain relief is unlikely</td>
</tr>
<tr>
<td><strong>Discuss potential serious side effects</strong></td>
<td>• Fatal respiratory depression&lt;br&gt;• Development of life-long opioid-use disorder</td>
</tr>
<tr>
<td><strong>Advise about common side effects and how to mitigate</strong></td>
<td>• <strong>CONSTIPATION:</strong> 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.&lt;br&gt;• <strong>DRY MOUTH:</strong> 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.&lt;br&gt;• <strong>NAUSEA AND/OR VOMITING:</strong> Usually transient lasting 2–3 days after opioid initiation in some but not all patients; as-needed antiemetics may be provided. Chronic nausea may occur in 15%–30%; switching to another opioid may eliminate nausea.&lt;br&gt;• <strong>DROWSINESS:</strong> Usually transient after opioid initiation and dose escalation until tolerance is developed. Avoid driving during these periods.&lt;br&gt;• <strong>CONFUSION:</strong> 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.&lt;br&gt;• <strong>TOLERANCE:</strong> Defined as diminished response to a drug with repeated use that may require patient to need higher doses of opioids over time.&lt;br&gt;• <strong>PHYSICAL DEPENDENCE:</strong> 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.</td>
</tr>
<tr>
<td><strong>Discuss that opioids impair ability to safely operate a vehicle, particularly when opioids are initiated, doses increased, or when other CNS system depressants, eg, benzodiazepines or alcohol, are concurrently used</strong></td>
<td>• Higher doses or taking more often than that prescribed&lt;br&gt;• Use with other medications: benzodiazepines, sedatives, alcohol, illicit drugs</td>
</tr>
<tr>
<td><strong>Discuss risks to household members and others if opioids are intentionally or unintentionally shared, and include discussion of</strong></td>
<td>• Proper storage in a secure, preferably locked location&lt;br&gt;• Options for safe disposal of unused opioids&lt;br&gt;• Availability and proper use of naloxone for overdose reversal (consider prescribing/dispersing if state regulations allow)</td>
</tr>
<tr>
<td><strong>Discuss importance of periodic reassessment to ensure goals are met and/or consideration of other alternatives if opioids are not effective or harmful</strong></td>
<td>• Prescription drug monitoring program&lt;br&gt;• Urine drug testing (if used)</td>
</tr>
<tr>
<td><strong>Discuss planned use of precautions to reduce risk</strong></td>
<td>• During patient education session, consider if cognitive limitations interfere with management. If so, contact prescriber to discuss if caregiver can responsibly co-manage therapy. Abbreviations: CNS, central nervous system; ER/LA, extended-release/long-acting; IR, immediate-release. Source: Refs 7,20</td>
</tr>
</tbody>
</table>
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 doses 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 with patients the increased risk of overdose with an abrupt return to their starting dose. 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 discontinue 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 3 days or less of opioid therapy is sufficient and more than 7 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.

Assessing risk and addressing harms of opioid use

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) recommends 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. Assessing risk factors should be done periodically and may differ depending on the risk. For example, factors such as alcohol use can vary over time and require more frequent follow-up. Simple questions can be used 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 when compared with standardized diagnostic interviews. Other methods for assessing risk and addressing harms of opioid use include reviewing the prescription drug monitoring program (PDMP), urine drug testing, avoiding prescribing and use of opioids and benzodiazepines concurrently, offering naloxone for opioid reversal, and referral or treatment for opioid-use 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. Operational PDMPs are currently available in 49 states, the District of Columbia, and Guam.29 Missouri is the only state that does not have a currently operational PDMP. 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 as well as requirement policies, however, vary from state to state. For example, in Connecticut, authorized agents of the prescriber, including pharmacists who may work with the provider, are allowed to review the PDMP data on behalf of the provider.30 This may assist with provider workload and allow timely assessment of risk.

Because 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, the PDMP should be reviewed before each prescription is written. In states where the PDMPs are not fully functional with timely data transmission, however, this may not be possible. Thus, the guidelines recommend reviewing the PDMP at least every 3 months, unless factors that increase the opioid-related harms are not present 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 con-

“...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.”
trolled 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 as well as 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. Information gained from reviewing the PDMP should be discussed 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 have a discussion with the patient about safety concerns and possibility of taper to a safer dose. If dangerous combinations are identified, the clinician should initiate a discussion with other providers involved in prescribing the medications and then with the patient if the combination is deemed necessary, such 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 (eg, 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 opioids (eg, fentanyl or methadone) are not detected and semisynthetic opioids (eg, oxycodone) may not be either. Use of confirmatory tests, tests which 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. Guidance on interpreting results can be found in previously published guidelines and a *Drug Topics* article.23,31

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 and ask the patient about how they are using prescribed drugs, and if and how they are using any other drugs (nonprescribed or even illicit drugs). It is also recommended to ask the patient “should I expect an unexpected result on the urine drug test,” as this can allow the patient 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; more frequent monitoring and evaluation; offering naloxone; and/or referral 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.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 will allow the clinician 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 coordination of care. 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 1 to 2 weeks depending on patient symptoms.32 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.33 Typi-
**TABLE 3**

High-Risk Groups and Opioid Use

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<th>HIGH-RISK GROUP</th>
<th>COMMENTS/RECOMMENDATIONS</th>
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| SLEEP-DISORDERED BREATHING (eg, SLEEP APNEA) | • 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 | • Risk to mother and fetus (eg, 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 | • Use caution and increase monitoring to minimize risks because opioid accumulation may occur |
| AGE ≥65 YEARS | • 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 | • Assess all patients for psychologic distress using validated instruments for anxiety PTSD, and/or depression (eg, 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 | • 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 | • 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. **Source:** Ref 7

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In these cases, this will be medication-assisted therapy with buprenorphine or methadone maintenance therapy along with cognitive behavioral therapy. Oral or long-acting naloxone 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. To find opioid treatment programs, behavioral health treatment services, and buprenorphine physician and treatment programs, see https://www.samhsa.gov/find-help.

**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. Currently, 8 FDA-approved formulations are available and only 1 (naloxone hydrochloride injection via Carpuject™) is not recommended for lay-person or take-home use because of its complicated assembly. Naloxone can be administered for opioid overdose intranasally, intramuscularly, and subcutaneously. Administration by lay persons has been shown to save lives. Although naloxone is a prescription product in the US and the District of Columbia, accessibility varies from state to state. In many states, providing naloxone to lay per-
sons who might witness an overdose in their family or friends or to service providers (eg, emergency medical personnel, policeman, behavioral health specialists) has been one mechanism.36 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.37

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; and 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.38 If naloxone is prescribed, appropriate education about using naloxone and subsequent steps (eg, calling 911) is essential. This education ideally is provided by prescribers and pharmacists (when the pharmacist is not the prescriber of naloxone) to reinforce patient understanding. Resources for prescribing naloxone can be found at: http://prescriptoprevent.org.

Role of pharmacy team

Because pharmacists and pharmacy technicians are on the front lines of dispensing opioid pain medication and providing medication-related services, they are in an optimal position 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 that the patient may be struggling with opioid use disorder or diverting medications, is feasible. Red flags include forged prescriptions (ie, lack of common abbreviations; atypical quantities, directions, or dosages; overly legible handwriting); prescriptions originating from outside of the immediate geographic area; altered prescriptions (eg, multiple ink colors, differing handwriting styles); cash payments; inconsistent or early prescription fills; and multiple prescribers.7,39 Other concerning and potentially drug-seeking behaviors include unusual or overly assertive behavior; unkempt or overdressed appearance; unusual knowledge of controlled substances; substances of no regular healthcare provider or health insurance; calling or coming in after regular hours; claims to be traveling or visiting relatives; claims of lost or stolen; or signs of drug abuse, such as skin tracks or scars on neck, arms, feet, or ankles.39 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, concerning concurrent therapies, 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.7 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 CDC guidelines 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 guidelines. 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. If conversations with the patient identify that 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; and tips for pharmacists. Additionally, there are trainings available, posters, and patient resources. These all can be found at: https://www.cdc.gov/drugoverdose/prescribing/resources.html.

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When opioids are dispensed, consideration of educating, offering, and/or dispensing naloxone (based on available state laws) can be prudent to prevent opioid overdose. Pharmacists can help their patients understand the proper use, side effects, and management of opioids. The 2016 Guideline for Prescribing Opioids for Adult Pain provides 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 safely use opioids for the treatment of chronic 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. CDC guidelines 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 safely use opioids for the treatment of chronic pain.

References are available online at www.drugtopics.com/cpe.

TEST QUESTIONS

FOR PHARMACISTS

1. Results of randomized clinical trials evaluating opioids for adult pain have shown they are:
   a. Effective for pain lasting 12 weeks or less.
   b. Effective for pain lasting more than 12 weeks.
   c. Effective for pain lasting more than 12 weeks but less than 1 year.
   d. Effective for pain lasting more than 1 year.

2. Opioids are prescribed for noncancer-related pain:
   a. 1 in 3 adults.
   b. 1 in 4 adults.
   c. 1 in 5 adults.
   d. 1 in 6 adults.

3. Since 1999, opioid deaths from illicit opioids and misuse of prescription opioids have:
   a. Decreased by one-half.
   b. Doubled.
   c. Decreased by one-third.
   d. Tripled.

4. Which of the following statements is most accurate regarding the 2016 Guideline for Prescribing Opioids for Chronic Pain?
   b. Extended-release/long-acting opioids should always be prescribed with immediate-release opioids in treatment of adult noncancer-related chronic pain.
   c. Treatment of acute pain should be treated with at least a 7-day supply of opioids to maximize pain relief.
   d. Opioid dosages >50 MME/day require justification.

5. Neuropathic pain is optimally treated with which of the following medications?
   a. Acetaminophen
   b. Ibuprofen
   c. Morphine
   d. Pregabalin

6. What is the optimal timeframe for initiating extended-release/long-acting opioids for a patient who is having continuous pain with appropriate use of immediate-release opioids for chronic noncancer pain?
   a. 3 days
   b. 7 days
   c. 10 days
   d. 14 days

7. An adult patient with chronic mid-upper back pain due to stenosis unable to undergo corrective surgery because of comorbidities has been taking morphine 15 mg every 6 hours for 6 weeks. She takes 3 tablets daily with some but not complete pain relief. Her primary care physician asks for your recommendation on an appropriate extended-release/long-acting opioid to prescribe because he feels inexperienced with opioid medications. Which of the following would be most appropriate therapy to initiate?
   a. Morphine extended-release/long-acting 20 mg every 12 hours
   b. Transdermal fentanyl 25 μg patch applied every 72 hours
   c. Methadone 15 mg every 12 hours
   d. Oxycodone extended-release/long-acting 20 mg every 12 hours

8. Which of the following statements about patients who require more than 50 MME/day is true?
   a. Avoid increasing beyond this dose
   b. Reassess whether opioid treatment is the best approach
   c. Justify a decision to titrate beyond this dose
   d. Risk of opioid overdose is increased up to 8.9 times.

9. The recommendations provided in the 2016 Guideline for Prescribing Opioids for Chronic Pain are primarily:
   a. Level 1 – randomized clinical trials or overwhelming evidence from observational trials
   b. Level 2 – randomized clinical trials with important limitations or exceptionally strong evidence from observational trials
   c. Level 3 – observational studies or randomized clinical trials with notable limitations
   d. Level 4 – clinical experience and observations or studies with major limitations

10. Which of the following statements is true about the expected benefits of opioids?
    a. Complete pain relief is primary goal.
    b. Improved function is primary goal.
    c. Long-term opioid use improves pain and function.
    d. Functional improvement only occurs with complete pain relief.

11. Which of the following adverse effects and mitigation recommendation is accurate?
    a. A stool softener/stimulant should be used to prevent constipation in all patients.
    b. If confusion occurs, the patient should immediately contact the prescriber.
    c. If drowsiness occurs, tolerance will typically develop and it will cease.
    d. Dry mouth is transient and will resolve in 2–3 days.

12. Risks to household members and other individuals if opioids are intentionally or unintentionally shared can be minimized by all of the following except:
    a. Storage in a locked location
    b. Safe disposal at the community’s drug-take-back program
    c. Use of naloxone for overdose reversal
    d. Regular urine drug testing of patient

13. A patient newly starting on opioids for chronic pain asks you about driving. Which of the following statements is most accurate about opioid impairment of safely operating a vehicle?
    a. Impairment occurs most commonly when opioids are initiated, doses are increased, or with other central nervous system depressants.
    b. Impairment typically only occurs with opioid initiation.
    c. Impairment only occurs with dose changes (ie, increases or decreases).
    d. Impairment only occurs with concurrent alcohol use.

14. All of the following are considered at high risk for opioid-related harms, such as overdose, except:
    a. A 73-year-old woman with congestive heart...
A 32-year-old woman who had been taking opioids for fibromyalgia has just become pregnant. Which of the following is the best recommendation for opioid therapy?

- Refer patient to specialist to slowly taper the woman off opioids
- Continue opioid therapy but increase monitoring of the patient and fetus
- Use injectable naloxone along with a rapid taper of opioids
- Continue opioid therapy because the fetus is in first trimester and risks are minimal

Assessing risk factors for opioid-related harms should be done

- At initiation of opioids
- Periodically during opioid therapy
- Both at initiation and during opioid therapy
- Only in patient with known comorbid conditions

The 2016 Guideline for Prescribing Opioids for Chronic Pain recommends offering naloxone to which of the following groups of patients?

- All patients receiving opioids
- Patients taking benzodiazepines and opioids
- Patients taking >40 MME/day
- Patients >65 years of age

Which of the following statements best describes the role of the pharmacist in managing patients receiving opioids for chronic pain?

- Pharmacist can evaluate and identify risks for opioid-use disorder and overdose by assessing prescriptions and patients for red flags.
- Pharmacist can identify patients who may not be optimally treated for their chronic pain.
- Pharmacist can provide drug information and recommendations for treatment of chronic pain to providers.
- All of the above

Which of the following situations does not accurately describe an appropriate referral to the pharmacist before the patient-counseling portion of the visit?

- A patient who has questions about managing constipation; show the patient the available laxatives in the over-the-counter aisle, no pharmacist referral is needed
- A patient with skin tracks on arm; refer to pharmacist about concerns away from the patient
- A common red flag that a patient may be struggling with an opioid-use disorder or diverting medications includes which of the following?
  - Atypical quantity and directions on a prescription
  - Use of confirmatory drug tests should be used with when immunoassay is positive.