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A Review of Opioid Guidelines to Help Pharmacists Curb the Opioid Epidemic

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Learning Objectives:

1. Pharmacists and technicians will be able to explain the pharmacology of opioids.
2. Pharmacists and technicians will be able to describe the mechanisms by which dependence, tolerance, and overdose occur.
3. Pharmacists and technicians will be able to identify measures in place to curb the opioid epidemic.
4. Pharmacists will be able to recommend guideline-directed maintenance therapy in their practice.
5. Pharmacists will be able to apply opioid conversion factors to attain morphine milliequivalents from a prescription.

Abstract:
The purpose of this paper is to acquaint the reader with knowledge of how opioids should be prescribed, acquire information on the prevalence of the epidemic, and realize a pharmacist's role in impeding the epidemic. Each day, more and more people become addicted to opioids following acute treatment of an ailment. In South Carolina and the United States, deaths from opioid overdose have increased dramatically. The economic burden of these deaths reaches $78.5 billion yearly. Repeated exposure to opioid drugs induces the brain mechanisms of dependence, which leads to daily drug use to avert the unpleasant symptoms of drug withdrawal. The current recommendations state that nonpharmacological and nonopioid therapy should be used before considering opioids, but when opioids are necessary, opioids should be prescribed at the lowest effective dose and for the shortest amount of time. Morphine milliequivalents are used to standardize doses so a comparison can be made. Morphine milliequivalents greater than 50 should be accompanied with an offer of naloxone, an opioid antagonist whose administration reverses the effects of opioid overdose. Measures to help the epidemic include recommendations on tapering opioids to discontinuation, new legislature to increase funds for education and studies, and new nonaddictive therapies.

Keywords: opioids, prevalence, pharmacist, opioid overdose, opioid epidemic, morphine milliequivalents, dependence, recommendations, CDC guidelines, prescribing, drugs, drug withdrawal, naloxone, opioid agonist, opioid antagonist

Introduction

Every day, more than 115 people in the United States die after overdosing on opioids.[1] An estimated 20% of patients presenting to physician offices with noncancer pain symptoms or pain-related diagnoses (including acute and chronic pain) receive an opioid prescription.[2] In South Carolina, opioid overdose deaths increased proportionately with nationwide deaths through 2013. Since then, the rate has increased from 5.2 deaths per 100,000 persons to 13.1 deaths per 100,000 persons in 2016 – equivalent to 247 to 628 deaths.[3] In South Carolina in 2015, almost 4.5 million opioid prescriptions were filled – about 109 opioid prescriptions per 100 persons compared to the national opioid prescribing rate of 70 opioid prescriptions per 100 persons. The Centers for Disease Control and Prevention (CDC) estimates that the total economic burden of prescription opioid misuse alone in the United States is $78.5 billion a year, including costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement.[4] The need for improved procedures on prescribing opioids and managing and treating dependence is obvious.

Opium, the source of morphine, is obtained from the poppy plants, *Papaver somniferum* and *Papaver album*.[5] After incision, the poppy seed pod exudes a white substance that turns into a brown gum; this gum is crude opium. Opium contains many alkaloids, the principal one being morphine, which is present in a concentration of approximately 10 percent. The term "opioid" describes all

compounds that work at opioid receptors. In contrast, the term "opiate" specifically describes the naturally occurring alkaloids: morphine, codeine, thebaine, and papaverine. Interestingly, "narcotic" was originally used to describe sleep-inducing medications, but, in the United States, its usage has shifted into a legal term. Morphine is a full agonist at the μ (mu) opioid receptor, the major analgesic opioid receptor. Remember that agonists can activate their receptor-effector systems to the maximum extent of which the system is capable. Simple substitution of an allyl group (H_2C=CH-CH_2R) on the nitrogen of the full agonist morphine plus addition of a single hydroxyl (OH) group results in naloxone, a strong mu-receptor *antagonist*. Antagonists refer to any chemical, specifically a drug in this instance, that, when present at the receptor site, blocks access of agonists to the receptor and prevents the usual agonist effect. The functions of mu receptors include supraspinal and spinal analgesia, sedation, inhibition of respiration, slowed gastrointestinal transit, and modulation of hormone and neurotransmitter release. When an opiate travels through the bloodstream to the brain, the chemicals attach to mu opioid receptors on the surface of opiate-sensitive neurons.[6] The linkage of these chemicals with the receptors triggers the same biochemical brain processes that reward people with feelings of pleasure when they engage in activities that promote basic life functions, such as eating and sex. Opioids are prescribed therapeutically to relieve pain, but when opioids activate these reward processes in the absence of significant pain, they can motivate repeated use of the drug simply for pleasure. The mesolimbic reward system is one of the brain circuits activated by opioids. This system generates signals in a part of the brain called the ventral tegmental area (VTA) that result in the release of the chemical dopamine (DA) in another part of the brain, the nucleus accumbens (NAc). The release of DA into the NAc causes feelings of pleasure. Other areas of the brain create a lasting record or memory that associates these good feelings with the circumstances and environment in which they occur. These memories, called conditioned associations, often lead to the cravings for drugs when the abuser re-encounters those persons, places, or things, and they drive abusers to seek out more drugs in spite of many obstacles. Particularly in the early stages of abuse, the opioid's stimulation of the brain's reward system is a primary reason that some people take drugs repeatedly. However, the compulsion to use opioids builds over time to extend beyond a simple drive for pleasure. This increased compulsion is related to tolerance and dependence.

In order to compare opioids, a morphine milliequivalent (MME) conversion factor is available. Finding the daily milliequivalents involves adding the doses of each individual opioid administered in a 24-hour period and subsequently converting to MME by multiplying by the conversion factor.[7] The final step is to add the MME of all medications. Table 1 provides MME conversion factors for commonly prescribed opioids. The CDC advises caution when prescribing opioids at any dosage and prescribing the lowest effective dose. Furthermore, it advises to take an extra precaution when increasing to more than 50 MME per day by offering naloxone. Prescribing officials should avoid or carefully justify increasing dosages to greater than 90 MME daily. A national sample of Veterans Health Administration patients with chronic pain receiving opioids from 2001-2009 showed that patients who died of opioid overdose were prescribed an average of 98 MME/day, while other patients were prescribed an average of 48 MME/day.[8] The major complication associated with higher MME is respiratory depression that can lead to death, even while maintaining prescribed dosing regimens. Opioids induce respiratory depression via activation at specific sites in the central nervous system (CNS) including the pre-Böltzinger complex, a respiratory rhythm generating area in the pons.

High MMEs are being reported due to tolerance to opioids. Acquired tolerance associated with long term opioid use is characterized by an increased capacity to metabolize or eliminate the drug which results in lower drug concentrations at target receptors for a given dose. Additionally, synapses are modified and new synapses are created, along with re-wiring of the brain which may enhance cravings.[5] Gradually, opioid receptors in the brain become less responsive to opioid stimulation and together, these mechanisms promote a need for more drug to reach the same physiological effect. An increased opioid dose is needed to stimulate the VTA brain cells of the mesolimbic reward system to release the same amount of DA.[6] Withdrawal symptoms occur only in patients who have developed tolerance, and opioid withdrawal is one of the most powerful factors driving opioid dependence and addictive behaviors. Opioid dependence changes the locus coeruleus (LC), resulting in some of the most distressing opioid withdrawal symptoms. Neurons in the LC produce norepinephrine (NE) and distribute it to other parts of the brain where it stimulates wakefulness, breathing, blood pressure, and general alertness, among other functions. When opioid molecules link to mu receptors on brain cells in the LC, they suppress the neuron's release of NE, resulting in drowsiness, slowed respiration, low blood pressure – familiar effects of opioid intoxication. With repeated exposure to opioids, however, the LC neurons adjust by increasing their level of activity. Subsequently, when

opioids are present, their suppressive impact is offset by this heightened activity, such that roughly normal amounts of NE are released and the patient feels more or less normal. When opioids are not present to suppress the LC brain cells' enhanced activity, however, the neurons release excessive amounts of NE, triggering jitters, anxiety, muscle cramps, and diarrhea. Subsequently, repeated exposure to opioid drugs induces the brain mechanisms of dependence, which leads to daily drug use to avert the unpleasant symptoms of drug withdrawal. Signs and symptoms of opioid use disorder (OUD) include strong desire for opioids, inability to control or reduce use, continued use despite interference with major obligations or social functioning, use of larger amounts over time, development of tolerance, spending a great deal of time to obtain and use opioids, and withdrawal symptoms that occur after stopping or reducing use. These withdrawal symptoms include negative mood, nausea or vomiting, muscle aches, diarrhea, fever, and insomnia.[9]

Recommendations

Current recommendations by the CDC on determining when to initiate or continue opioids for chronic pain stress utilizing nonpharmacologic and nonopioid therapy for chronic pain.[10] There are many nonpharmacologic therapies available such as weight loss, psychological therapies such as CBT, and certain interventional procedures that can ameliorate chronic pain. There is high-quality evidence that exercise therapy for hip[11] or knee[12] osteoarthritis reduces pain and improves function immediately after treatment and that the improvements are sustained for at least 2-6 months. Exercise therapy also can help reduce pain and improve function in low back pain and can improve global well-being and physical function in fibromyalgia.[13,14] Multimodal therapies and multidisciplinary biopsychosocial rehabilitation-combining approaches (e.g., psychological therapies with exercise) can reduce long-term pain and disability compared with usual care and compared with physical treatments (e.g., exercise) alone.[10]

Several nonopioid pharmacologic therapies (including acetaminophen, NSAIDs, and selected antidepressants and anticonvulsants) are effective for chronic pain. In particular, acetaminophen and NSAIDs can be useful for arthritis and low back pain. Anticonvulsants such as pregabalin and gabapentin can improve pain in diabetic neuropathy and post-herpetic neuralgia. In patients with or without depression, tricyclic antidepressants and selective norepinephrine reuptake inhibitors (SNRI) provide effective analgesia for neuropathic pain conditions, including diabetic neuropathy and post-herpetic neuralgia, often at lower dosages and with a shorter time to onset of effect than for treatments of depression. The SNRI duloxetine is FDA-approved for the treatment of diabetic neuropathy and fibromyalgia. Nonopioid therapies are not generally associated with substance use disorder, and the number of fatal overdoses associated with nonopioid medications are a fraction of those associated with opioid medications. For example, acetaminophen, NSAIDs, and opioid pain medication were involved in 881, 228, and 16,651 pharmaceutical overdose deaths in the United States in 2010.[15] Of course, nonopioid pharmacologic therapies do not come without their own risks, particularly in older patients, pregnant patients, and patients with certain comorbidities such as cardiovascular, renal, gastrointestinal and liver disease.[10] Clinicians should review FDA-approved labeling including boxed warnings before initiating treatment with any pharmacologic therapy. While benefits for pain relief, function, and quality of life with long-term opioid use for chronic pain are uncertain, risks associated with long-term opioid use are clear and significant.

If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety. Clinically meaningful improvement has been defined as a 30% improvement in scores for both pain and function.[16] Monitoring progress toward patient-centered functional goals (e.g., walking the dog or walking around the block, returning to part-time work, attending family sports or recreational activities) can also contribute to the assessment of functional improvement.[10] Because depression, anxiety, and other psychological comorbidities often coexist and interfere with resolution of pain, clinicians should use validated instruments to assess for these conditions and ensure that treatments for these conditions are optimized. If patients receiving opioid therapy for chronic pain do not experience meaningful improvements in both pain and function compared with prior to initiation of opioid therapy, clinicians should consider working with patients to taper and discontinue opioids and should use nonpharmacologic and nonopioid pharmacologic approaches to pain management.

Before starting and periodically during opioid therapy, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy. Many patients lack information about opioids, and concerns have been identified that some clinicians miss opportunities to

effectively communicate about safety. Given the substantial evidence gaps on opioids, uncertain benefits of long-term use, and potential for serious harms, patient education and discussion before starting opioid therapy are critical so that patient preferences and values can be understood and used to inform clinical decisions. Experts agree that essential elements to communicate to patients before starting and periodically during opioid therapy include realistic expected benefits, common and serious harms, and expectations for clinician and patient responsibilities to mitigate risks of opioid therapy. Clinicians should involve patients in decisions about whether to start or continue opioid therapy. Given potentially serious risks of long-term opioid therapy, clinicians should ensure that patients are aware of potential benefits of, harms of, and alternatives to opioids before starting or continuing opioid therapies. Clinicians are encouraged to have open and honest discussions with patients to inform mutual decisions about whether to start or continue opioid therapy. Figure 2 is an example of a stepwise approach for initiating opioid therapy that can be utilized by prescribers and pharmacists.[10,17]

When an ER/LA opioid is prescribed, using one with predictable pharmacokinetics and pharmacodynamics is preferred to minimize unintentional overdose risk. Furthermore, when selecting dosage, duration, follow-up, and discontinuation, clinicians should prescribe immediate-release opioids instead of extended-release or long-acting (ER/LA) opioids when initiating opioid therapy for chronic pain. ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of oxycodone, oxymorphone, hydrocodone, hydromorphone, and morphine. The clinical evidence reviews from the CDC guideline found a fair-quality study showing a higher risk for overdose among patients initiating treatment with ER/LA opioids than among those initiating treatment with immediate-release opioids.[18] The FDA has noted some ER/LA opioids are only appropriate for opioid-tolerant patients, defined as patients who have received certain dosages of opioids (e.g., 60mg daily of morphine, 30mg daily of oral oxycodone, or equianalgesic dosages of other opioids) for at least 1 week.[19] Time-scheduled opioid use can be associated with greater total average daily opioid dosage compared with intermittent, as-needed opioid use.[10] In addition, experts indicated that there was not enough evidence to determine the safety of using immediate-release opioids for breakthrough pain when ER/LA opioids are used for chronic pain outside of active cancer pain, palliative care, or end-of-life care, and that this practice might be associated with dose escalation. Abuse-deterrent technologies have been employed to prevent manipulation intended to defeat extended-release properties of ER/LA opioids and to prevent opioid use by unintended routes of administration, such as injection of oral opioids. As indicated in FDA guidance for industry on evaluation and labeling of abuse-deterrent opioids[20], although abuse-deterrent technologies are expected to make manipulation of opioids more difficult or less rewarding, they do not prevent opioid abuse through oral intake, the most common route of opioid abuse, and can still be abused by nonoral routes.[10] Thus, the "abuse-deterrent" label does not indicate that there is no risk for abuse. There are currently no guideline-based recommendations related to use of abuse-deterrent formulations.

Clinicians should take note of some important characteristics of ER/LA opioids. Methadone is associated with cardiac arrhythmias along with QT prolongation on the electrocardiogram, and it has complicated pharmacokinetics and pharmacodynamics, including a long and variable half-life and peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect. The pharmacodynamics of methadone are subject to more inter-individual variability than other opioids. Experts note that risks for opioid overdose are greatest during the first 3-7 days after opioid initiation or increase in dosage, particularly when methadone or transdermal fentanyl are prescribed; that follow-up within 3 days is appropriate when initiating or increasing the dosage of methadone; and that follow-up within 1 week might be appropriate when initiating or increasing the dosage of other ER/LA opioids. With regard to transdermal fentanyl, experts note that its absorption and pharmacodynamics of transdermal fentanyl are complex, with gradually increasing serum concentration during the first part of the 72-hour dosing interval, as well as variable absorption based on factors such as external heat. The complexities of both drugs might increase the risk for fatal overdose when methadone or transdermal fentanyl is prescribed to a patient who has not used it previously or by clinicians who are not familiar with its effects. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week. Furthermore, methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients, should consider prescribing methadone for pain. A clinical practice guideline that contains further guidance regarding methadone prescribing for pain has been published previously by the American Pain Society.[21] Finally, because dosing effects of transdermal fentanyl are often misunderstood by both clinicians and patients, only

clinicians who are familiar with the dosing and absorption properties of transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.[10]

When opioids are started, clinicians should prescribe the lowest effective dosage. As stated before, clinicians should use caution when prescribing opioids at any dosage, should reassess evidence of individual benefits and risks when increasing dosage to 50 MME/day or greater, and should avoid increasing doses greater than 90 MME/day. Opioid overdose risk increases in a dose-response manner and with doses of 50 to less than 100 MME/day have been found to increase risks for opioid overdose by factors of 1.9 to 4.6 compared with dosages of 1 to less than 20 MME/day. Dosages ≥ 100 MME/day are associated with 2.0-8.9 times the risk of overdose at 1 to less than 20 MME/ day. Lower dosages of opioids reduce the risk for overdose, but a single dosage threshold for safe opioid use has not been identified. With this in mind, it is imperative that clinicians not create a scenario where susceptible patient populations go under-treated. In general, increasing dosages to ≥ 50 MME/day increases overdose risk without necessarily adding benefits for pain control or function. Clinicians should use additional caution when initiating opioids for patients aged ≥ 65 years and for patients with renal or hepatic insufficiency because decreased clearance of drugs in these patients can result in accumulation of drug concentrations to toxic levels. Clinicians should use caution when increasing opioid dosages and increase dosage by the smallest practical amount, because overdose risk is directly proportional to opioid dosage. Although there is limited evidence to recommend specific intervals for dosage titration, a guideline published prior to the current CDC guideline recommended waiting at least 5 half-lives before increasing dosage of most opioids and waiting at least a week before increasing dosage of methadone to make sure that full effects of the previous dosage are evident.[22]

Long-term opioid use often begins with treatment of acute pain.[10] When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed. Clinical evidence reviews found that opioid use for acute pain (i.e., pain with abrupt onset and caused by an injury or other process that is not ongoing) is associated with long-term opioid use, and that a greater amount of early opioid exposure is associated with greater risk for long-term use. Several guidelines on opioid prescribing for acute pain from emergency departments[22-25] and other settings[26,27] have recommended prescribing ≤ 3 days of opioids in most cases, whereas others have recommended ≤ 7 days[28] or less than 14 days.[29] Because physical dependence on opioids is an expected physiologic response in patients exposed to opioids for more than a few days, limiting the days' supply prescribed should also minimize the need to taper opioids for the purpose of preventing distressing or unpleasant withdrawal symptoms.[10] More than a few days of exposure to opioids significantly increases hazards, each day of unnecessary opioid use increases likelihood of physical dependence without adding benefit, and prescriptions with fewer days' supply will minimize the number of pills available for unintentional or intentional diversion. Furthermore, prescribing at the lowest effective dose for no longer than the expected duration required minimizes unintentional initiation of long-term opioid use. The lowest effective dose can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency. As mentioned previously, acute pain can often be managed without opioids. It is important to evaluate the patient for reversible causes of pain, for underlying etiologies with potentially serious sequelae, and to determine appropriate treatment. Clinicians should re-evaluate the subset of patients who experience severe acute pain that continues longer than the expected duration to confirm or revise the initial diagnosis and to adjust management accordingly. Given longer half-lives and longer duration of effects (e.g., respiratory depression) with ER/LA opioids such as methadone, fentanyl patches, or extended release formulations of opioids, clinicians should not prescribe ER/LA opioids for the treatment of acute pain.

Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently if clinically indicated. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or discontinue. It was found that continuing opioid therapy for 3 months substantially increased risk for OUD; therefore, follow-up earlier than 3 months might be necessary to provide the greatest opportunity to prevent the development of OUD. In addition, risk for overdose associated with ER/LA opioids might be particularly high during the first 2 weeks of treatment. Furthermore, it was found that patients who do not have pain relief with opioids at 1 month are unlikely to experience pain relief with opioids at 6 months. Although evidence is insufficient to determine precisely what point within the first 3 months of opioid therapy the risks for

OUD increase, reassessment of pain and function within 1 month of initiating opioids provides an opportunity to minimize risks of long-term opioid use by discontinuing opioids among patients not receiving a clear benefit from these medications. Clinicians should evaluate patients to assess benefits and harms of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation. Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased or when total opioid dosage is ≥ 50 MME/day. Shorter follow-up intervals (within 3-7 days) should be strongly considered when starting or increasing the dosage of methadone. At follow up, clinicians should assess benefits in function, pain control, and quality of life using tools such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale[30] and/or asking patients about progress toward functional goals that have meaning for them.[10] Clinicians should also assess for common adverse effects such as constipation and drowsiness, as well as asking about and assessing for effects that might be early warning signs for more serious problems such as overdose (e.g., sedation or slurred speech) or OUD. In practice settings where virtual visits are part of standard care (e.g., in remote areas where distance or other issues make follow-up visits challenging), follow-up assessments that allow the clinician to communicate with and observe the patient through video and audio could be conducted, with in-person visits occurring at least once per year. Patients who are exposed to greater risk of OUD such as those with depression or other mental health conditions, history of substance use disorder, a history of overdose, taking ≥ 50 MME/day, or taking other CNS depressants with opioids should be re-evaluated more frequently than every 3 months.

Recommendations on approaching withdrawal and discontinuing opioids are vague but offer ways to get patients off of their current high dosages. Established patients already taking high dosages of opioids, as well as patients transferring from other clinicians, might consider the possibility of opioid dosage reduction to be anxiety-provoking, and tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence. However, these patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk. Clinicians should explain in a non-judgmental manner to patients already taking high opioid dosages (≥ 90 MME/day) that there is now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages. Clinicians should empathetically review benefits and risks of continued high-dosage opioid therapy and should offer to work with the patient to taper opioids to safer dosages. For patients who agree to taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan. Patients tapering opioids after taking them for years might require very slow opioid tapers as well as pauses in the taper to allow gradual accommodation to lower opioid dosages. Clinicians and patients should remain alert to signs of anxiety, depression, and OUD that might be unmasked by an opioid taper and arrange for management of these comorbidities. For patients agreeing to taper to lower opioid dosages, clinicians should establish goals with the patient for continued opioid therapy, maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate, and consider consulting a pain specialist as needed to assist with pain management. A weekly dosage taper of 10-50% of the original dosage has been recommended by clinical guidelines[31], and a rapid taper over 2-3 weeks has been recommended in the setting of a severe adverse event such as an overdose.[29] Of note, tapers slower than 10% per week (e.g., 10% per month) also might be appropriate and better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations. Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor and clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the expectant mother and to the fetus if the patient goes into withdrawal. Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome. For pregnant women with OUD, medication-assisted therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered.[32]

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used. A decrease of 10% of the original dose per week is a reasonable starting point; experts agree that taper plans may be individualized based on patient goals and concerns. Experts also note that at times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages. Tapers may be considered successful as long as the patient is not experiencing withdrawal symptoms during the taper. Once the smallest available dose is reached, the interval between doses can be extended. Opioids may be stopped

when taken less frequently than once a day. More rapid tapers, such as over 2-3 weeks, might be needed for patient safety under certain circumstances (e.g., for patients who have experienced accidental overdose on their current dosage). Ultrarapid detoxification under anesthesia is associated with substantial risks, including death, and should not be used.[33] Clinicians should discuss with tapering patients the increased risk for overdose on abrupt return to a previously prescribed higher dose. Primary care clinicians should collaborate with mental health providers and with other specialists as needed to optimize nonopioid pain management as well as provide psychosocial support for anxiety related to the taper. If a patient exhibits signs of OUD, clinicians should offer or arrange for treatment of OUD and consider offering naloxone for overdose prevention. Because of greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and because tapering opioids can be associated with anxiety, when patients require tapering for both agents, to reduce risk for fatal respiratory depression, it might be safer and more practical to taper opioids first.

Besides a taper, other options also exist that can aid in helping with addiction. Buprenorphine is an opioid medication indicated for the treatment of opioid addiction and can be prescribed by any physician with a special "X" number issued by the DEA.[34] However, there exists other restrictions for those who want to prescribe it for opioid addiction treatment. Doctors must take an 8-hour class on addiction treatment, or already possess such credentials, and then apply for a special DEA number. Once this number is obtained, each physician is limited to treating only 30 patients at a time. Buprenorphine is an opioid partial agonist. This means that, like opioids, it produces effects such as euphoria and respiratory depression; however, these effects are weaker than those of full agonists such as heroin, morphine, and methadone. The opioid effects of buprenorphine increase with each dose until they level off. This plateau remains even with further dose increases. This "ceiling effect" lowers the risk of misuse, dependence, and side effects. An additional method in lieu of a taper is methadone. Methadone is a cheaper alternative to buprenorphine that works by lessening the painful symptoms of opiate withdrawal and blocks the euphoric effects of opiate drugs such as heroin, morphine, and codeine, as well as semi-synthetic opioids like oxycodone and hydrocodone. In addition to the above treatments, the FDA has approved a wearable device for the treatment of opioid withdrawal symptoms, including agitation, anxiety, depression, and opiate cravings.[35] The new device, Primary Relief®, works by providing Percutaneous electrical nerve stimulations (PENS) to administer auricular neurostimulation treatment over several days. The device allows continuous neurostimulation over a period of several days while offering the patient a high degree of comfort and mobility and a nonaddictive treatment.

Naloxone is an important therapy for patients with opioid dependence that works as an opioid receptor antagonist. It is administered when a patient is showing signs of opioid overdose. The medication can be administered via intranasal spray, intramuscular, subcutaneous, or intravenous injection. It is also available in combination with buprenorphine (Suboxone®) to decrease the likelihood of diversion and misuse of the combination drug product. Naloxone has become increasingly easier to attain for patients on opioids who are at an increased risk for overdose. Figure 1 contains a list of FDA approved opioids used in the management of severe pain.

To assess risk and address harms of opioid use, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Per South Carolina law, clinicians are required to review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from each prescription to every 3 months. South Carolina has a PDMP called South Carolina Reporting & Identification Prescription Tracking (SCRIPTS). This system checks for controlled substance schedules II, III, and IV such as OxyContin®, Percocet®, Vicodin®, Klonopin®, Xanax®, and Valium®. The report shows information for controlled substance prescriptions that a patient has filled for the specific time period, as well as the prescriber who prescribed them and the dispensing pharmacy. SCRIPTS is recommended for new patient encounters, monitoring compliance, avoiding therapeutic duplication or drug interactions, and coordination of care.

Drug testing should be used before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs. Concurrent use of opioid pain medications with other opioid pain medications or heroin can increase patients' risk for overdose. Urine drug tests can provide information about drug use that is

not reported by the patient. In addition, urine drug tests can assist clinicians in identifying when patients are not taking opioids prescribed for them, which might in some cases indicate diversion or other clinically important issues such as difficulties with adverse effects. Clinicians should use unexpected results for improving patient safety, tapering or discontinuation of opioids, more frequent re-evaluation, offering naloxone, or referral for treatment for substance use disorder, as appropriate. If tests for prescribed opioids are repeatedly negative, confirming that the patient is not taking the prescribed opioid, clinicians can discontinue the prescription without a taper. Importantly, clinicians should not dismiss patients from care based on a urine drug test result, because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.

The above-mentioned resources can also uncover use of benzodiazepines and opioids concomitantly. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. Benzodiazepines and opioids both cause CNS depression and can decrease respiratory drive. Thus, concurrent use is likely to put patients at greater risk for potentially fatal overdose. A case-cohort study found concurrent benzodiazepine prescriptions with opioid prescriptions to be associated with a near quadrupling of risk for overdose related death compared with opioid prescriptions alone.[36] Clinicians should consider involving pharmacists and pain specialists as part of the management team when opioids are co-prescribed with other CNS depressants.[10]

Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with OUD. Opioid agonist or partial agonist treatment with methadone maintenance therapy or buprenorphine has been shown to be more effective in preventing relapse among patients with OUD.[37-39]Recent studies among patients with prescription opioid dependence have found maintenance therapy with buprenorphine and buprenorphine-naloxone effective in preventing relapse.[40,41] Physicians not already certified to provide buprenorphine in an office-based setting can undergo training to receive a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) that allows them to prescribe buprenorphine to treat patients with OUD.[10] Physicians prescribing opioids in communities without sufficient treatment capacity for OUD should strongly consider obtaining this waiver. Information about qualifications and the process to obtain a waiver are available from SAMHSA.[42] Clinicians unable to provide treatment themselves should arrange for patients with OUD to receive care from a substance use disorder treatment specialist, such as an office-based buprenorphine treatment provider, or from an opioid treatment program certified by SAMHSA to provide supervised medication-assisted treatment for patients with OUD.[10] Clinicians should not dismiss patients from their practice because of a substance use disorder, but should assist patients in finding qualified treatment providers and arranging for patients to follow up with these providers as well as arranging for ongoing coordination of care. All of the above recommendations (excluding those about drug testing) are category A for patients outside of active cancer treatment, palliative care, and end-of-life care. Recommendations in which drug testing is referenced, which is category B and requires individual decision making.

Conclusion

Given the significance of opioid-related negative consequences, several initiatives have been or are being considered to ameliorate these issues. In April 2009, the Washington Post reported that the number of opioid prescriptions filled at retail pharmacies dropped 10 percent in 2017. The information was cited from a report from IQVIA Institute for Human Data Science. This was "the steepest drop in the amount of painkillers dispensed to patients in 25 years." Prescribers who are conscientiously changing their mindset about how many opioid prescriptions they are writing are likely the cause of this shift. The National Institute of Health (NIH) is increasing funding to help with this global problem with the launch of the Helping to End Addiction Long-term (HEAL) Initiative, an aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis.[1] Specifically in South Carolina, the NIH is funding projects at the Medical University of South Carolina and the Ralph H. Johnson VA Medical Center that focus on discontinuing chronic opioid therapy for pain using a buprenorphine taper and mindfulness-based recovery in veterans with substance use disorders, among other projects. Moreover, the Department of Health & Human Services has initiated a 5-point strategy to improve access to therapy, increase Public Health Surveillance and Research, and decrease patient dependence through education.[43] With deliberate attention, health care providers can decrease the amount of deaths brought about by opioids. Continual education about the matter can further reduce mortality while improving the socioeconomic burden that this epidemic entails.

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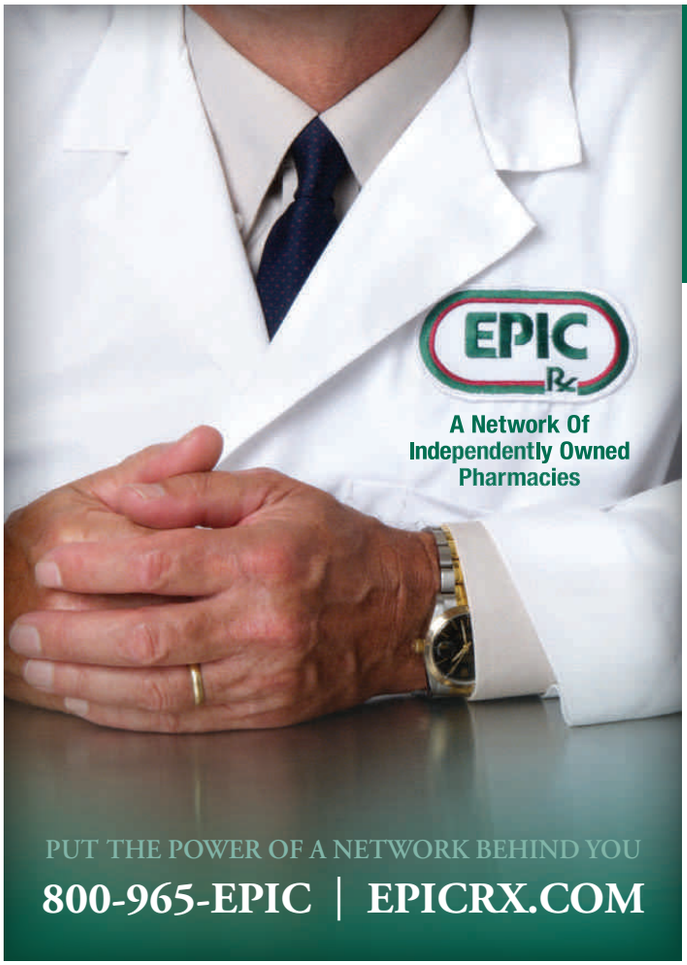

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Figures and Tables

Table 1

Calculating Morphine Milligram Equivalents (MME)[8]	
Opioid (doses in mg/day except where noted)	**Conversion Factor**
Codeine	0.15
Fentanyl Transdermal (mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Figure 1.

Opioids Available for Prescription Use[5]			
Drug	Mechanism	Half-life (hr)	Duration (hr)
Codeine	Agonist	prodrug	4-6
Morphine	Agonist	2-4	3-4
Oxycodone	Agonist	3-5	4-6
Hydrocodone	Agonist	3-5	4-6
Hydromorphone	Agonist	2-6	2-3
Oxymorphone	Agonist	2-6	2-3
Methadone	Agonist	22	6-12
Fentanyl	Agonist	3-5	1-2
Buprenorphine	Partial Agonist	36	4-12
Tramadol	Weak Agonist	6-7	4-6h

A Review of Opioid Guidelines to Help Pharmacists Curb the Opioid Epidemic

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1. Complete and mail entire page. SCPhA members can take journal CE for free; $15 for non-members. Check must accompany test. You may also complete the test and submit payment online at www.scrx.org.
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EVALUATION (circle the appropriate response)

1. Did the article achieve the stated objects?	(Note at all)	1	2	3	4	5	(Completely)
2. Overall evaluation of the article?	(Poor)	1	2	3	4	5	(Excellent)
3. Was the information relevent to your practice?	(No)	1	2	3	4	5	(Yes)

4. How long did it take you to read the article and complete the exam? _____

CE credit will ONLY be awarded when a submitted test is accompanied by completing the evaluation above or online at www.scrx.org.

SELF-ASSESSMENT QUESTIONS

1. Calculate the number of Morphine Milliequivalents in the following prescription.
Percocet® 5-325mg 2 tablets by mouth every 6 hours.
   a. 40mg
   b. 50mg
   c. 60mg
   d. 70mg

2. In regard to naloxone, the opioid antagonist responsible for reversing the effects of opioid overdose, and the prescription in question 1, what recommendation, if any, would you make?
   a. Offer naloxone because the MME is greater than 50 MME/ day.
   b. There is no indication for naloxone because the MME is less than 50 MME/day.
   c. There is no indication for naloxone because the MME does not exceed 90 MME/day.
   d. Naloxone is not helpful for patients on Percocet®.

3. Long-term opioid use often begins with treatment of acute pain. The recommended max day supply to be deemed sufficient enough to cover acute pain is:
   a. 3 days
   b. 10 days

c. 14 days
d. 30 days

4. When is an appropriate follow-up time to assess benefits and harms of opioids for a patient initiated on 30 MME/day of hydrocodone?

a. 3 days
b. 2 weeks
c. 8 weeks
d. 6 months

5. When is an appropriate follow-up time to assess benefits and harms of opioids for a patient initiated on 65 MME/day of oxycodone?

a. 3 days
b. 2 weeks
c. 8 weeks
d. 6 months

6. A patient comes to the pharmacy with a prescription for oxycodone 15mg every 4 hours daily with the following medication profile. At your counseling session with the patient you state they are now at an increased risk for ____ due to the interaction with oxycodone and the _____ on the medication profile. This interaction is associated with a _____ increased risk of the adverse effect of concern.

1. Amlodipine 5mg daily
2. Alprazolam 0.5mg twice daily
3. Metformin 1000mg twice daily

a. Orthostatic hypotension; amlodipine; twofold
b. Respiratory depression; alprazolam; twofold
c. Respiratory depression; alprazolam; fourfold
d. Constipation; metformin; fourfold

7. For a patient chronically on MS Contin® 30 mg 3 times daily, who wishes to decrease their dependence, which of the following is the most reasonable and practical initial step of a taper regimen? Of note, the patient has tried to taper their dosage in the past, but experienced significant diarrhea. He also has no history of opioid abuse or misuse.

a. MS Contin 30 mg, 1 tablet twice daily
b. MS Contin 40 mg, 1 capsule twice daily
c. Kadian® 80 mg, 1 capsule daily
d. Kadian® 20 mg, 1 capsule 3 times daily

8. A prescription for Suboxone® 2 mg/0.5 mg daily comes through your pharmacy, prescribed by Jason Simmons, MD. Dr. Simmons's DEA number is FS1257218. Which of the following should be your response?

a. Fill the prescription as is since the DEA is valid and the prescriber is authorized to write for Suboxone®
b. Do not fill the prescription as the recommended starting dose is 8 mg/0.5 mg daily
c. Do not fill the prescription as the provider is not properly registered with SAMHSA
d. Do not fill the prescription as the DEA number is invalid; contact appropriate authorities to report fraud