*Summary of content (compiled by the engineering team) harvested from https://downloads.regulations.gov/CDC-2022-0024-0002/content.pdf.

Definitions

Essential elements for communication and discussion with patients before starting outpatient opioid therapy for acute pain include the following (Recommendation #1):

- Advise patients that short-term opioid use can lead to unintended long-term opioid use and the importance of working toward planned discontinuation of opioid use as soon as feasible, including a plan to appropriately taper opioids as pain resolves if opioids have been used around the clock for more than a few days (see Recommendation 6).
- Review communication mechanisms and protocols patients can use to inform clinicians of severe or uncontrolled pain and to arrange for timely reassessment and management.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder (see Recommendation 12) that can cause distress and inability to fulfill major role obligations at work, school, or home.
- Advise patients about common effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids. To prevent constipation associated with opioid use, advise patients to increase hydration and fiber intake and to maintain or increase physical activity as they are able. A cathartic (e.g., senna) with or without a stool softener or a laxative might be needed if opioids are used for more than a few days. To minimize withdrawal symptoms, clinicians should provide and discuss an opioid tapering plan when opioids will be used around the clock for more than a few days (see Recommendation 6). Limiting opioid use to the minimum needed to manage pain (e.g., taking the opioid only when needed if needed less frequently than every 4 hours and the prescription is written for every 4 hours as needed for pain) can help limit development of tolerance and therefore of withdrawal once opioids are discontinued.
- If formulations are prescribed that combine opioids with acetaminophen, advise patients of the risks of taking additional over-the-counter products containing acetaminophen. Acetaminophen can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic alcohol use or liver disease (American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009).
- To help patients assess when a dose of opioids is needed, explain that the goal is to reduce pain to make it manageable rather than to eliminate pain.
- Discuss effects that opioids might have on ability to safely operate a vehicle or other machinery, particularly when opioids are initiated or when other central nervous system depressants, such as benzodiazepines or alcohol, are used concurrently.

- Discuss increased risks for opioid use disorder, respiratory depression, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not taking more opioids or taking them more often.
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, non-prescribed or illicit drugs such as heroin, or other opioids (see Recommendations 8, 11).
- Discuss risks to household members and other individuals if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient, and that young children and pets are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (U.S. Food and Drug Administration, 2020a).
- Discuss planned use of precautions to reduce risks, including naloxone for overdose reversal (see Recommendation 8), and clinician use of prescription drug monitoring program information (see Recommendation 9).

Essential elements for communication and discussion with patients before starting opioid therapy include the following (Recommendation #2):

- Review available low-cost options for pain management for all patients, and particularly for low- income, underinsured, and uninsured patients. Review considerations related to access to care given the clinical oversight needed to initiate and continue opioid therapy and other treatments for pain.
- Be explicit and realistic about expected benefits of opioids, explaining that there is not robust evidence that opioids improve pain or function with long-term use, and that complete elimination of pain is unlikely.
- Emphasize improvement in function as a primary goal and that function can improve even when pain is not completely eliminated.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder that can cause distress and inability to fulfill major role obligations at work, school, or home.
- Advise patients about common effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids. To prevent constipation associated with opioid use, advise patients to increase hydration and fiber intake and to maintain or increase physical activity. A cathartic (e.g., senna) with or without a stool softener or a laxative might be needed.
- If formulations are prescribed that combine opioids with acetaminophen, advise patients of the risks of taking additional over-the-counter products containing acetaminophen. Acetaminophen can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages

in patients with chronic alcohol use or liver disease (American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009).

- Discuss effects that opioids might have on ability to safely operate a vehicle or other machinery, particularly when opioids are initiated, when dosages are increased, or when other central nervous system depressants, such as benzodiazepines or alcohol, are used concurrently. Discuss increased risks for opioid use disorder, respiratory depression, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not taking more opioids or taking them more often.
- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, non-prescribed drugs such as heroin, or other opioids.
- Discuss risks to household members and other individuals if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient, and that young children are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (U.S. Food and Drug Administration, 2020a).
- Discuss the importance of periodic reassessment to ensure that opioids are helping to meet patient goals and to allow opportunities for opioid dosage reduction and/or discontinuation and consideration of additional nonpharmacologic or nonopioid pharmacologic treatment options if opioids are not effective or are harmful.
- Discuss expectations for clinician and patient responsibilities to mitigate risks of opioid therapy and planned use of precautions to reduce risks, including naloxone for overdose reversal (see Recommendation 8), and clinician use of prescription drug monitoring program information (see Recommendation 9) and toxicology screening (see Recommendation 10).
- Consider whether cognitive status might interfere with management of opioid therapy and, if so, determine whether a caregiver can responsibly co-manage medication therapy. Discuss the importance of reassessing medication use over time with both the patient and caregiver (as appropriate).

Opioid use disorder is manifested by at least 2 out of 11 defined criteria occurring within a year (American Psychiatric Association, 2013) (Recommendation 12):

1. Taking opioids in larger amounts or over a longer period of time than intended
2. Having a persistent desire or unsuccessful attempts to reduce or control opioid use
3. Spending excess time obtaining, using or recovering from opioids
4. Craving for opioids
5. Continuing opioid use causing inability to fulfill work, home, or school responsibilities
6. Continuing opioid use despite having persistent social or interpersonal problems
7. Lack of involvement in social, occupational or recreational activities
8. Using opioids in physically hazardous situations

9. Continuing opioid use in spite of awareness of persistent physical or psychological problems
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect, or
    b. Markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome, or
    b. Opioids (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.

Note: Criteria 10 and 11 are not considered to be met for those taking opioids solely under appropriate medical supervision (American Psychiatric Association, 2013).

Recommendation categories

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

Category A recommendation

Applies to all persons; most patients should receive the recommended course of action.

Category B recommendation

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

Evidence type

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

Type 1 evidence

Randomized clinical trials or overwhelming evidence from observational studies.

Type 2 evidence

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

Type 3 evidence

Observational studies or randomized clinical trials with notable limitations.

Type 4 evidence

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

Determining Whether or Not to Initiate Opioids for Pain

Recommendation 1

Page 64 line 1459

Nonopioid therapies are effective for many common types of acute pain. Clinicians should only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient (recommendation category: B, evidence type: 3).

Implementation Considerations

- There is an important role for opioid therapy for acute pain related to severe traumatic injuries (including crush injuries and burns), invasive surgeries typically associated with moderate to severe postoperative pain, and other severe acute pain when NSAIDs and other therapies are contraindicated or likely to be ineffective.
- Opioids are not first-line therapy for many common acute pain conditions, including low back pain, neck pain, pain related to other musculoskeletal injuries (such as sprains, strains, tendonitis, bursitis), pain related to minor surgeries typically associated with minimal tissue injury and only mild postoperative pain (e.g., dental extraction), dental pain, kidney stone pain, and headaches including episodic migraine.
- When diagnosis and severity of acute pain are reasonably assumed to warrant the use of opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the lowest dose to achieve expected effects (see Recommendation 4) and for no longer than the expected duration of pain severe enough to require opioids (see Recommendation 6).
- Clinicians should maximize use of nonopioid pharmacologic (e.g., NSAIDs and/or acetaminophen) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization and/or exercise) therapies as appropriate for the specific condition and continue these therapies as needed once opioids are discontinued.
- Clinicians should prescribe and advise opioid use only as needed (e.g., hydrocodone 5 mg/acetaminophen 325mg, one tablet not more frequently than every 4 hours as needed for pain) rather than on a scheduled basis (e.g., one tablet every 4 hours) and

encourage and include an opioid taper if opioids will be taken around the clock for more than a few days (see Recommendation 6).
- If patients already receiving opioids in a long-term fashion require additional medication for acute pain, nonopioid medications should be used when possible, and if additional opioids are required (e.g., for superimposed severe acute pain), they should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient's baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days (see Recommendation 6).
- Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients meaningfully in decisions about whether to start opioid therapy.

Recommendation 2

Page 75 line 1729

Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the known risks and realistic benefits of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A, evidence type: 2).

Implementation Considerations

- To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis.
- Clinicians should use appropriate noninvasive, nonpharmacologic approaches to help manage chronic pain, such as exercise (aerobic, aquatic, and/or resistance exercises) or exercise therapy (a prominent modality in physical therapy) for back pain, fibromyalgia, and hip or knee osteoarthritis; weight loss for knee osteoarthritis; manual therapies for hip osteoarthritis; psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, and multidisciplinary rehabilitation for low back pain; mind- body practices (yoga, tai chi, qigong), massage, and acupuncture for neck pain; CBT, myofascial release massage, mindfulness practices, tai chi, qigong, acupuncture, and multidisciplinary rehabilitation for fibromyalgia; and spinal manipulation for tension headache.
- Low-cost options to integrate exercise include walking in public spaces or use of public recreation facilities for group exercise. Physical therapy can be helpful, particularly for patients who have limited access to safe public spaces or public recreation facilities for exercise or have not improved with low-intensity physical exercise.

- To improve pain management and reduce medication use and associated risks, health insurers and health systems should increase access to noninvasive, nonpharmacologic therapies with evidence for effectiveness.
- Clinicians should review FDA-approved labeling including boxed warnings and weigh benefits and risks before initiating treatment with any pharmacologic therapy.
- When patients affected by osteoarthritis have an insufficient response to nonpharmacologic interventions such as exercise for arthritis pain, topical NSAIDs can be used in patients with a single or few joints near the surface of the skin (e.g., knee). In patients with osteoarthritis pain in multiple joints or incompletely controlled with topical NSAIDs, duloxetine or systemic NSAIDs can be considered.
- NSAIDs should be used at the lowest dose and duration needed and should be used with caution, particularly in patients with cardiovascular comorbidities, chronic renal failure, or previous gastrointestinal bleeding.
- When patients with chronic low back pain have had an insufficient response to nonpharmacologic approaches such as exercise, clinicians can consider NSAIDs or duloxetine for patients without contraindications.
- Tricyclic, tetracyclic, and SNRI antidepressants, selected anticonvulsants (pregabalin, gabapentin enacarbil, oxcarbazepine), and capsaicin and lidocaine patches can be considered for neuropathic pain.
- Duloxetine and pregabalin are FDA-approved for the treatment of diabetic peripheral neuropathy, and pregabalin and gabapentin are FDA-approved for treatment of post-herpetic neuralgia.
- In patients with fibromyalgia, tricyclic (amitriptyline) and SNRI antidepressants (duloxetine and milnacipran), NSAIDs (topical diclofenac), and specific anticonvulsants (pregabalin and gabapentin) are used to improve pain, function, and quality of life. Duloxetine, milnacipran, and pregabalin are FDA-approved for the treatment of fibromyalgia.
- Patients with co-occurring pain and depression might be especially likely to benefit from antidepressant medication (see Recommendation 8).
- Opioids should not be considered first-line or routine therapy for subacute or chronic pain. This does not mean that patients should be required to sequentially “fail” nonpharmacologic and nonopioid pharmacologic therapy or be required to use any specific therapy before proceeding to opioid therapy. Rather, expected benefits specific to the clinical context should be weighed against risks before initiating therapy. In some clinical contexts (e.g., serious illness in a patient with poor prognosis for return to previous level of function, contraindications to other therapies, and clinician and patient agreement that the overriding goal is patient comfort), opioids might be appropriate regardless of previous therapies used. In other situations, (e.g., headache or fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used.
- Opioid therapy should not be initiated without consideration by the clinician and patient of an “exit strategy” to be used if opioid therapy is unsuccessful.

- Before opioid therapy is initiated for subacute or chronic pain, clinicians should determine jointly with patients how effectiveness will be evaluated and establish treatment goals.
- Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy. Clinicians should avoid rapid tapering or abrupt discontinuation of opioids (see Recommendation 5).
- 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.
- Clinicians should review available low-cost options for pain management for all patients, and particularly for low-income, underinsured and uninsured patients.
- Clinicians should ensure that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients in decisions about whether to start opioid therapy.

Opioid Selection and Dosage

Recommendation 3

Page 91 line 2141

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

Implementation Considerations

- Clinicians should not treat acute pain with ER/LA opioids or initiate opioid treatment for subacute or chronic pain with ER/LA opioids, and clinicians should not prescribe ER/LA opioids for intermittent or as needed use.
- ER/LA opioids should be reserved for severe, continuous pain. Some ER/LA opioids should be considered only for patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) of immediate-release opioids daily for at least 1 week.
- When changing to an ER/LA opioid for a patient previously receiving a different immediate- release opioid, clinicians should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance.
- Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or hepatic dysfunction because decreased clearance of medications among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations.
- Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate- release opioids in combination with ER/LA

opioids is preferable, given the potential increased risk for adverse events, including respiratory depression and overdose.
- Methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients, including assessing risk for QT prolongation and considering electrocardiographic monitoring, should consider prescribing methadone for pain.
- Only clinicians who are familiar with the dosing and absorption properties of the ER/LA opioid transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

Recommendation 4

Page 95 line 2256

When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest dosage to achieve expected effects. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients (recommendation category: A, evidence type: 3).

Implementation Considerations

- When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest dosage to achieve expected effects.
- For patients not already taking opioids, the lowest dose to achieve expected effects can be determined using product labeling as a starting point with calibration as needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency (see Recommendation 8).
- The lowest starting dose for opioid-naïve patients is often equivalent to a single dose of approximately 5 to 10 MME or a daily dosage of 20-30 MME/day.
- Risks of opioid use, including risk for overdose and overdose death, increase continuously with dosage, and there is no single dosage threshold below which risks are eliminated.
- If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage and should generally avoid dosage increases when possible.
- Many patients do not experience benefit in pain or function from increasing opioid dosages to ≥50 MME/day but are exposed to progressive increases in risk as dosage increases. Therefore, before increasing total opioid dosage to ≥50 MME/day, clinicians should pause and carefully reassess evidence of individual benefits and risks. If a

decision is made to increase dosage, clinicians should use caution and increase dosage by the smallest practical amount.
- Additional dosage increases beyond 50 MME/day are progressively more likely to yield diminishing returns in benefits relative to risks to patients as dosage increases further. Clinicians should carefully evaluate a decision to further increase dosage based on individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to risks with previous dosage increases, other treatments and effectiveness, and patient values and preferences.
- The recommendations related to opioid dosages are not intended to be used as an inflexible, rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient decision making. Further, these recommendations apply specifically to starting opioids or to increasing opioid dosages, and a different set of benefits and risks applies to reducing opioid dosages (see Recommendation 5).

Recommendation 5

Page 101 line 2393

For patients already receiving higher opioid dosages, clinicians should carefully weigh benefits and risks and exercise care when reducing or continuing opioid dosage. If risks outweigh benefits of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual clinical circumstances of the patient, to appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue, such as warning signs of impending overdose, e.g., confusion, sedation, or slurred speech, opioid therapy should not be discontinued abruptly, and clinicians should not abruptly or rapidly reduce opioid dosages from higher dosages (recommendation category: B, evidence type: 4).

Implementation Considerations

- Clinicians should consider tapering to a reduced opioid dosage, or tapering and discontinuing opioid therapy, and discuss these approaches with patients prior to initiating changes, when risks outweigh benefits (potentially including avoiding risks of tapering) of continued opioid therapy.
- Patient agreement and interest in tapering is likely to be a key component of successful tapers.
- For patients agreeing to taper to lower opioid dosages as well as for those remaining on higher opioid dosages, clinicians should establish goals with the patient for continued opioid therapy (see Recommendations 2 and 7) and maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

- Clinicians should collaborate with the patient on the tapering plan, including patients in decisions such as how quickly tapering will occur and when pauses in the taper may be warranted.
- Clinicians should follow up frequently (at least monthly) with patients engaging in opioid tapering.
- When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used.
- Tapers can be completed over several months to years depending on the opioid dosage and should be individualized based on patient goals and concerns. Longer durations of previous opioid therapy might require longer tapers.
- Tapers of 10% per month or slower are likely to be better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for a year or longer).
- Significant opioid withdrawal symptoms can signal the need to further slow the taper rate.
- 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 should not be reversed without careful assessment of benefits and risks of increasing opioid dosage or without maximizing nonopioid treatments for pain and addressing behavioral distress.
- Once the smallest available dose is reached, the interval between doses can be extended.
- Goals of the taper may vary—some patients might achieve discontinuation; others might attain a reduced dosage. If the clinician has determined with the patient that the ultimate goal of tapering is discontinuing opioids, opioids may be stopped when taken less frequently than once a day.
- Clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal.
- Clinicians should advise patients that there is an increased risk for overdose on abrupt return to a previously prescribed higher dose, caution that it takes as little as a week to lose tolerance, provide opioid overdose education, and offer naloxone.
- Clinicians should remain alert to signs of anxiety, depression, and opioid misuse or opioid use disorder (see Recommendations 8 and 12) that might be revealed by an opioid taper and provide treatment or arrange for management of these co-morbidities.
- Clinicians should closely monitor patients who are unable to taper and who continue on high- dose or otherwise high-risk opioid regimens (e.g., opioids prescribed concurrently with benzodiazepines) and should work with patients to mitigate overdose risk (e.g., by providing overdose education and naloxone—see Recommendation 8).
- Clinicians can use periodic and strategic motivational questions and statements to encourage movement toward appropriate therapeutic changes and functional goals.

- Clinicians have a responsibility to provide or arrange for coordinated management of patients' pain and opioid-related problems, including opioid use disorder. **Clinicians should not abandon patients.**
- Payers, health systems, and state medical boards should not use this clinical practice guideline to set rigid standards related to dose or duration of opioid therapy, and should ensure that policies based on cautionary dosage thresholds do not result in rapid tapers or abrupt discontinuation of opioids, and that policies do not penalize clinicians for accepting new patients who are using prescribed opioids for chronic pain, including those receiving high doses of opioids.
- While Recommendation 5 specifically refers to patients using long-term, high-dose opioid therapy for subacute or chronic pain, many of the principles in these implementation considerations and supporting rationale, including communication with patients, pain management and behavioral support, and slower taper rates, are also relevant when discontinuing opioids in patients receiving shorter durations and/or lower-dosages (see also Recommendations 6 and 7).

Clinicians should consider tapering to a reduced opioid dosage, or tapering and discontinuing opioid therapy, and discuss with these approaches with patients prior to initiating changes when:

- The patient requests dosage reduction or discontinuation
- Pain improves and might indicate resolution of an underlying cause
- When opioid therapy has not meaningfully reduced pain or improved function
- The patient has been treated with opioids for a prolonged period (e.g., years), and current benefit-risk balance is unclear (e.g., decreased positive effects due to tolerance, symptoms such as reduced focus or memory that might be due to opioids)
- The patient is receiving higher opioid doses without evidence of benefit from the higher dose The patient experiences side effects that diminish quality of life or impair function
- There is current evidence of opioid misuse
- The patient experiences an overdose or other serious event (e.g., an event leading to hospitalization or injury) or has warning signs for an impending event such as confusion, sedation, or slurred speech
- The patient is receiving medications (e.g., benzodiazepines) or has medical conditions (e.g., lung disease, sleep apnea, liver disease, kidney disease, fall risk, advanced age) that increase risk for adverse outcomes

Opioid Duration and Follow-up

Recommendation 6

Page 115 line 2742

When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids (recommendation category: A, evidence type: 4).

Implementation Considerations

- Nontraumatic, nonsurgical acute pain can often be managed without opioids (see Recommendation 1).
- Opioids are sometimes needed for treatment of acute pain (see Recommendation 1). When the diagnosis and severity of acute pain warrant use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. For many common causes of nontraumatic, nonsurgical pain, when opioids are needed, a few days or less are often sufficient, and shorter courses can minimize the need to taper opioids to prevent withdrawal symptoms at the end of a course of opioids. However, durations should be individualized based on the clinical circumstances of the specific patient.
- Clinicians should generally avoid prescribing additional opioids to patients “just in case” pain continues longer than expected.
- For postoperative pain related to major surgery, procedure-specific opioid prescribing recommendations are available with ranges for amounts of opioids needed (based on actual use and refills and on consensus).
- To minimize unintended impact on patients with an unexpectedly prolonged duration of severe acute pain, clinicians, practices, and health systems should have mechanisms in place to provide timely re-evaluation for 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. In particular, clinicians, practices, and health systems should ensure all patients can access and afford additional evaluation and treatment, as needed, to minimize disparities across patients based on access to and affordability of care and refills.
- Longer durations of opioid therapy are more likely to be needed when the mechanism of injury is expected to result in prolonged severe pain (e.g., severe traumatic injuries).
- Patients should be evaluated at least every 2 weeks if they continue to receive opioids for acute pain.
- If opioids are continued for a month or longer, clinicians should refer to recommendations on subacute and chronic pain for follow-up (Recommendation 7) and tapering (Recommendation 5).
- If patients already receiving long-term opioids require additional opioids for superimposed severe acute pain (e.g., major surgery), opioids should be continued only for the duration of pain severe enough to require additional opioids, returning to the patient’s baseline opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were used around the clock for more than a few days.
- If opioids are prescribed continuously (around the clock) for more than a few days for acute pain, clinicians should prescribe a taper to minimize withdrawal symptoms on discontinuation of opioids.
- Taper durations might need to be adjusted depending on the duration of the initial opioid prescription (see supporting rationale for this recommendation for additional details).
- Tapering plans should be discussed with the patient prior to hospital discharge and with clinicians coordinating the patient’s care as an outpatient. For tapering considerations

when patients have taken opioids continuously for longer than one month, see Recommendation 5.

Recommendation 7

Page 120 line 2884

Clinicians should evaluate benefits and risks with patients within 1 to 4 weeks of starting opioid therapy for subacute or chronic pain or of dose escalation. Clinicians should evaluate benefits and risks of continued therapy with patients every 3 months or more frequently (recommendation category: A, evidence type: 4).

Implementation Considerations

- In addition to evaluating benefits and risks of opioids before starting opioid therapy (see Recommendation 2), clinicians should evaluate patients to assess benefits and risks 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, given increased risk for overdose within the first 2 weeks of treatment, or when total daily opioid dosage is ≥50 MME/day. (Note: Overdose risk is doubled across multiple studies for dosages of 50 to <100 MME/day relative to <20 MME/day - see Recommendation 4).
- Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone, given the variable half-life of this drug (see Recommendation 3) and the potential for drug accumulation during initiation and during upward titration of dosage.
- An initial follow-up interval closer to 4 weeks can be considered when starting immediate-release opioids at a dosage <50 MME/day.
- Clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, at least every 3 months.
- Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy (see Recommendation 2).
- Clinicians should re-evaluate patients who are at higher risk for opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a history of overdose, taking ≥50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months.
- To minimize unintended impact on patients with challenges in accessing or affording follow-up visits, practices, and health systems should work to ensure all patients can access and afford follow-up evaluation.
- In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other context makes follow-up visits challenging), follow-up assessments that allow the clinician to communicate with and observe the patient through telehealth modalities may be conducted.

- At follow-up, clinicians should review patient perspectives and goals, determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function; whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events or has signs of opioid use disorder.
- Clinicians should ensure that treatment for depression, anxiety, or other psychological co- morbidities is optimized.
- Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced. If risks outweigh benefits of continued opioid therapy (e.g., if patients do not experience meaningful, sustained improvements in pain and function compared with prior to initiation of opioid therapy; if patients are taking higher-risk regimens [e.g., dosages ≥50 MME/day or opioids combined with benzodiazepines] without evidence of benefit; if patients believe benefits no longer outweigh risks; if patients request dosage reduction or discontinuation; or if patients experience overdose or other serious adverse events), clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible, using principles from Recommendation 5.
- Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

Assessing Risk and Addressing Harms of Opioid Use

Recommendation 8

Page 125 line 3017

Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone when factors that increase risk for opioid overdose are present (recommendation category: A, evidence type: 4).

Implementation Considerations

- Clinicians should offer naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients with sleep-disordered breathing, patients taking higher dosages of opioids (e.g., ≥50 MME/day), patients taking benzodiazepines with opioids (see Recommendation 11), and patients at risk for returning to a high dose to which they have lost tolerance (e.g., patients undergoing tapering or recently released from prison).
- Practices should provide education on overdose prevention and naloxone use to patients and offer to provide education to members of their households.

- Naloxone co-prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists or through standing orders for naloxone at pharmacies.
- Resources for prescribing naloxone in primary care and emergency department settings can be found through Prescribe to Prevent at http://prescribetoprevent.org; additional resources are at https://samhsa.gov.
- In part because of concerns about cost of naloxone and access for some patients, this recommendation specifies that naloxone should be "offered" to patients. Clinicians, health systems, and payers should work to ensure patients can access naloxone, a potentially lifesaving treatment.
- Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing when possible to minimize risks for opioid overdose.
- When making decisions about whether to initiate opioid therapy for pain during pregnancy, clinicians and patients together should carefully weigh benefits and risks. For pregnant people already receiving opioids, clinicians should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 5).
- For pregnant people with opioid use disorder, medications for opioid use disorder (buprenorphine or methadone) have been associated with improved maternal outcomes and should be offered (see Recommendation 12).
- Clinicians should use additional caution and increased monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or hepatic insufficiency and for patients aged ≥65 years and should implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.
- Clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed.
- Clinicians should ask patients about their drug and alcohol use.
- Clinicians should use PDMP data (see Recommendation 9) and toxicology screening (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose.
- Clinicians should provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 2) and ensure that patients are provided or receive effective treatment for substance use disorders when needed (see Recommendation 12).
- Although substance use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. See "Pain management for patients with opioid use disorder" section of Recommendation 12 for additional considerations specific to patients with pain and opioid use disorder.
- If clinicians consider opioid therapy for chronic pain for patients with substance use disorder, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and

incorporate strategies to mitigate risk into the management plan, such as offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing frequency of monitoring (see Recommendation 7).

- If patients experience nonfatal opioid overdose, clinicians should evaluate for opioid use disorder and treat or arrange treatment if needed. Clinicians should work with patients to reduce opioid dosage and to discontinue opioids when indicated (see Recommendation 5) and should ensure continued close monitoring and support for patients prescribed or not prescribed opioids.
- If clinicians continue opioid therapy in patients with prior opioid overdose, they should discuss increased risks for overdose with patients, carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone and increasing frequency of monitoring (see Recommendation 7).

Recommendation 9

Page 135 line 3299

When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, 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 combinations that put the patient at high risk for overdose (recommendation category: B, evidence type: 4).

Implementation Considerations

- Ideally, PDMP data should be reviewed before every opioid prescription for acute, subacute, or chronic pain. This is recommended in all jurisdictions where PDMP availability and access policies, as well as clinical practice settings, make this practicable (e.g., clinician and delegate access permitted).
- At a minimum, during long-term opioid therapy, PDMP data should be reviewed before an initial opioid prescription and then every 3 months or more frequently. The recommendation category B acknowledges variation in PDMP availability and circumstances. However, because PDMP information can be most helpful when results are unexpected, and to minimize bias in application, clinicians should apply this recommendation when feasible to all patients rather than differentially based on assumptions about what they will learn about different patients.
- Clinicians should use specific PDMP information about medications prescribed to their patient in the context of other clinical information, including their patient's history, physical findings, and other relevant testing, in order to help them communicate with and protect their patient.

- Clinicians should review PDMP data specifically for prescription opioids and other controlled medications patients have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or combinations (e.g., opioids combined with benzodiazepines) that put the patient at high risk for overdose.
- PDMP-generated risk scores have not been validated against clinical outcomes such as overdose and should not take the place of clinical judgment. Clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of prescription opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendations 1 and 2], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendations 8 and 12]).
- Clinicians should take actions to improve patient safety:
    - Discuss information from the PDMP with their patient and confirm that the patient is aware of any additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).
    - Discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving prescription opioids from more than one clinician or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines; see Recommendation 11) and offer naloxone (see Recommendation 8).
    - Use extreme caution when prescribing opioids and benzodiazepines concurrently, appreciating that some patient circumstances warrant prescribing of these medications concomitantly. Clinicians should communicate with others managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care (see Recommendation 11).
    - Consider the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 4). Buprenorphine should not be counted in the total MME/day in calculations given its opioid partial agonist properties that confer a ceiling effect on respiratory depression. If patients are found to be receiving high total daily dosages of opioids, discuss safety concerns with the patient, consider in collaboration with the patient if tapering to a safer dosage is warranted (see Recommendation 5), and offer naloxone (see Recommendation 8).
    - Discuss safety concerns with other clinicians who are prescribing controlled substances for their patient. Ideally, clinicians should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other clinicians to improve the patient's safety.
    - Screen for substance use and discuss concerns with their patient (see Recommendations 8 and 12).

    - If clinicians believe their patient might be diverting (sharing or selling prescription opioids and not taking them), consider toxicology testing to assist in determining whether prescription opioids can be discontinued without causing withdrawal (see Recommendations 5 and 10). A negative toxicology test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should consider other possible reasons for this test result, such as false negative results or misinterpretation of results (see Recommendation 10).

Recommendation 10

Page 139 line 3421

When prescribing opioids for subacute or chronic pain, clinicians should consider toxicology testing to assess for prescribed medications as well as other prescribed and non-prescribed controlled substances (recommendation category: B, evidence type: 4).

Implementation Considerations

- Clinicians should not dismiss patients from care based on a toxicology test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids or other drugs from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.
- Prior to starting opioids and periodically during opioid therapy, clinicians should consider toxicology testing to assess for prescribed opioids as well as other prescription and nonprescription controlled substances that increase risk for overdose when combined with opioids, including nonprescribed and illicit opioids and benzodiazepines.
- Clinicians, practices, and health systems should aim to minimize bias testing and should not apply this recommendation differentially based on assumptions about what they will learn about different patients.
- Predicting risk is challenging, and currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use or substance use disorder. Rather, clinicians should consider toxicology screening results as potentially useful data, in the context of other clinical information, for all patients, and consider toxicology screening whenever its potential problems can be mitigated.
- Clinicians should explain to patients that toxicology testing will not be used to dismiss patients from care and is intended to improve their safety.
- Clinicians should explain expected results (e.g., presence of prescribed medication and absence of drugs, including non-prescribed controlled substances, not reported by the patient) and ask patients about use of prescribed and other drugs and whether there might be unexpected results.
- Toxicology screening can be performed with a relatively inexpensive presumptive immunoassay panel that tests for opiates as a class, benzodiazepines as a class, and several non-prescribed substances.

- The use of confirmatory testing can add substantial costs and should be based on the need to detect specific opioids, such as those that are being prescribed, and those that cannot be identified on standard immunoassays or on the presence of unexpected toxicology test results.
- Clinicians should be familiar with the drugs included in toxicology screening panels used in their practice and should understand how to interpret results for these drugs. For example, a positive “opiates” immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but does not detect synthetic opioids and might not detect semisynthetic opioids. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive.
- Restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of toxicology testing.
- Clinicians may wish to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results with the patient.
- Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted.
- Clinicians should use unexpected results to improve patient safety (e.g., change pain management strategy [see Recommendation 2], carefully weigh benefits and risks of reducing or continuing opioid dosage [see Recommendation 5], re-evaluate more frequently [see Recommendation 7], offer naloxone [see Recommendation 8], offer or refer for substance use disorder treatment [see Recommendation 12], all as appropriate).

Recommendation 11

Page 145 line 3579

Clinicians should use extreme caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants (recommendation category: B, evidence type: 3).

Implementation Considerations

- Although there are circumstances when it might be appropriate to prescribe opioids to a patient who is also prescribed benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should use

extreme caution when prescribing opioids and benzodiazepines concurrently. In addition, clinicians should consider whether benefits outweigh risks of concurrent use of opioids with other central nervous system depressants (e.g., muscle relaxants, non-benzodiazepine sedative hypnotics, potentially sedating anticonvulsant medications such as gabapentin and pregabalin).

- Clinicians should check the PDMP for concurrent controlled medications prescribed by other clinicians (see Recommendation 9) and should consider involving pharmacists as part of the management team when opioids are co-prescribed with other central nervous system depressants.
- In patients receiving opioids and benzodiazepines long-term, clinicians should carefully weigh the benefits and risks of continuing therapy with opioids and benzodiazepines and discuss with patients and other members of the patient's care team.
- Risks of concurrent opioid and benzodiazepine use are likely to be greater with unpredictable use of either medication, with use of high-dose opioids and high-dose benzodiazepines in combination, or with use with other substances including alcohol (as compared to long-term stable use of low-dose opioids and low-dose benzodiazepines without other substances).
- In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing.
- Buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system.
- If risks are determined to outweigh benefits of continuing opioid and benzodiazepine therapy at current dosages and a decision is made to taper, it might be safer and more practical to taper opioids first. There can be greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and tapering opioids can be associated with anxiety (see Recommendation 5).
- Clinicians should taper benzodiazepines gradually prior to discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death. The rate of tapering should be individualized.
- If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific antidepressants or other nonbenzodiazepine medications approved for anxiety should be offered.
- Clinicians should communicate with clinicians managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

Recommendation 12

Page 149 line 3680

Clinicians should offer or arrange treatment with medication for patients with opioid use disorder (recommendation category: A, evidence type: 1).

Implementation Considerations

- Although stigma can reduce the willingness of individuals with opioid use disorder to seek treatment, opioid use disorder is a chronic, treatable disease from which people can recover and continue to lead healthy lives.
- If clinicians suspect opioid use disorder, they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems.
- Clinicians should assess for the presence of opioid use disorder using DSM-5 criteria.
- For patients meeting criteria for opioid use disorder, particularly if moderate or severe, clinicians should offer or arrange for patients to receive treatment with medication for opioid use disorder.
- Clinicians should not dismiss patients from their practice because of opioid use disorder because this can adversely affect patient safety and could represent patient abandonment.
- Medication treatment of opioid use disorder has been associated with reduced overdose and overall mortality. Identification of opioid use disorder represents an opportunity for a clinician to initiate potentially life-saving interventions, and it is important for the clinician to collaborate with the patient regarding their safety to increase the likelihood of successful treatment.
- For pregnant people with opioid use disorder, medication therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered.
- Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office- based buprenorphine or naltrexone treatment provider, or from an opioid treatment program certified by SAMHSA to provide methadone or buprenorphine for patients with opioid use disorder.
- All clinicians, and particularly clinicians prescribing opioids in communities without sufficient treatment capacity for opioid use disorder, should obtain a waiver to prescribe buprenorphine.
- Clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community and should work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.
- Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and opioid use disorder require ongoing pain management that maximizes benefits relative to risks.