KAISER PERMANENTE

Patients on Chronic Opioid Therapy for Chronic Non-Cancer Pain Safety Guideline

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Last guideline approval: July 2023

Guidelines are systematically developed statements to assist patients and providers in choosing appropriate health care for specific clinical conditions. While guidelines are useful aids to assist providers in determining appropriate practices for many patients with specific clinical problems or prevention issues, guidelines are not meant to replace the clinical judgment of the individual provider or establish a standard of care. The recommendations contained in the guidelines may not be appropriate for use in all circumstances. The inclusion of a recommendation in a guideline does not imply coverage. A decision to adopt any particular recommendation must be made by the provider in light of the circumstances presented by the individual patient.

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Interim Update January 2025

- Prescription naloxone 4 mg nasal spray has been discontinued by the manufacturer as December 2024. Over-the-counter (OTC) naloxone spray is now the only form available at KPWA.
- The preferred terminology of opioid equivalence has changed from MEDD (morphine equivalent daily dose) to MME (milligram morphine equivalent).

Major Changes as of July 2023

The following changes have been made to better align with current CDC guidance about opioid monitoring and to maximize harm reduction.

- The threshold dose for **higher-intensity** monitoring was lowered from 90 milligram morphine equivalent (MME) to **50 MME** per CDC guidelines, as increasing opioid doses above 50 MME provides minimal benefit in pain and function while sharply increasing the risk of respiratory depression and overdose death.
- The **lower-intensity** monitoring group attributes have been changed to taking an opioid dose **below 50 MME** and having an ORT-OUD score ≤ 2, with an absence of any of the risk factors listed in the high-intensity group.
- A new recommendation—"**lowest-intensity monitoring/persistent intermittent use**"—was added for patients who take low-dose opioids (below 50 MME) regularly **(3 or more prescriptions per year)** but less often than the strict definition of COT (70 out of 90 days).

Monitoring group	**Threshold dose**	**Prescription frequency**	**Other attributes**	**Monitoring**
Higher-intensity	50 MME or higher	Minimum 70-day supply in last 90 days/ 3 calendar months		*Minimum required:* Office or video visit and UDS every 3 months. (At least one visit per year must be in-office.)
Lower-intensity	< 50 MME	Minimum 70-day supply in last 90 days/ 3 calendar months	ORT-OUD score 2 or lower Absence of risk factors (see Table 1)	*Minimum required:* Office or video visit and UDS every 6 months. (At least one visit per year must be in-office.)
Lowest-intensity/ persistent intermittent use	< 50 MME	3+ opioid prescriptions per year (not including fractures or post-op) but < 70 out of 90 days	ORT-OUD score 2 or lower Use clinical judgment to increase monitoring intensity as needed.	Best practice: Office or video visit and UDS every 6–12 months. (At least one visit per year must be in-office.) *Minimum required:* Office visit and UDS at least every 12 months.

- The **MME conversion factors** for **hydromorphone, methadone, and tramadol** have been updated to be in alignment with 2022 CDC recommendations. See KP National Pharmacy MME Calculator.
- The list of risk factors indicating that a patient is at high risk of opioid-related harms (overdose or respiratory depression) has been updated:
    - **Mental health conditions** (depression, anxiety, PTSD): only considered to be a high-risk factor if the condition is active and not in remission.
    - **Age 65 and older**: only considered to be a high-risk factor if the patient has comorbidities such as renal or hepatic dysfunction.
    - **Age 25 or younger**: no evidence to support this as an independent risk factor; however, based on expert opinion/consensus, all patients age < 30 should be referred to Chronic Pain Consultative Services for consultation prior to beginning chronic opioid therapy (COT).

    - **BMI > 30**: no evidence to support this as an independent factor; however, these patients should be screened for obstructive sleep apnea, which is an independent risk factor.
- Patients on COT who are unable to taper and are not meeting criteria for opioid use disorder (OUD) may be referred to Chronic Pain Consultative Services to consider transitioning to buprenorphine as a safer alternative.
- Fentanyl testing is now a standard component of routine urine drug screening (UDS).
- Recommendations for follow-up after a non-fatal opioid overdose have been added.

Washington State Law

This guideline is in compliance with the State of Washington regulations WAC 246-919-850–985 on the use of opioids in the treatment of patients with chronic non-cancer pain.

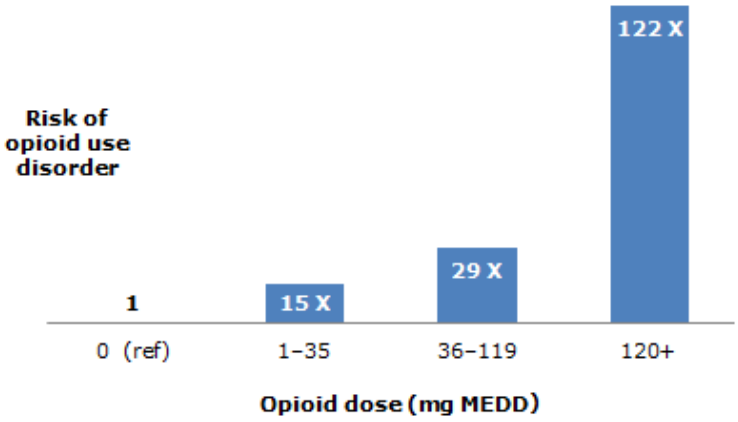
Introduction: Relationship Between Opioid Dose and Risk Levels

The use of chronic opioid therapy for chronic pain is not an evidence-based practice and is without established benefits that outweigh the considerable risks on a population level; therefore, it should occur only in very rare circumstances.

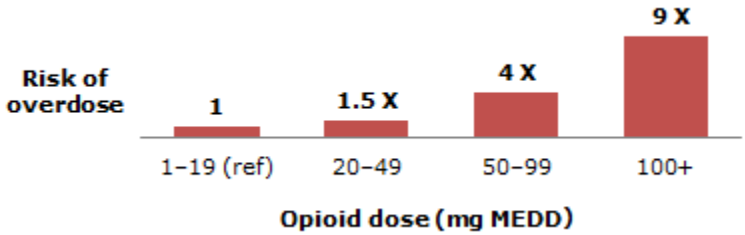
Best practice is to defer use of opioids by employing non-pharmacologic and non-opioid therapies first.

Serious opioid-related risks increase sharply with higher doses.

Opioid use disorder: A person taking a relatively low dose of prescribed opioids is **15 times** as likely to develop opioid use disorder as a person who has not been prescribed opioids. The risk continues to rise with escalating doses; at high doses (≥ 120 mg morphine equivalent daily dose [MEDD]) of opioids, the person's risk of developing OUD is **122 times** that of a person who has not been prescribed opioids. (Edlund 2014)



Opioid overdose: Similarly, a person taking ≥ 100 mg MEDD will be **9 times** as likely to overdose as a person taking < 20 mg MEDD. (Dunn 2010) Note that approximately 1 overdose in 7 is fatal.



Guideline Scope

Kaiser Foundation Health Plan of Washington has adopted the recommendations of the 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain and the National Permanente Medical Group Practice Recommendations for Improving Appropriate Opioid Prescribing and Reducing Potential for Harm (updated 2023).

This is a safety guideline. The recommendations in this guideline apply to adult patients who are **already on chronic opioid therapy (COT)** for the treatment of **chronic non-cancer pain.**

Chronic opioid therapy (COT) is daily or near-daily use of opioids for at least 90 days, often indefinitely. (Chou 2009). Additionally, COT is defined as a minimum 70-day supply of opioids dispensed in the previous 3 calendar months.

Chronic non-cancer pain means a state in which non-cancer pain persists beyond the usual course of an acute disease or healing of an injury, or that may or may not be associated with an acute or chronic pathologic process that causes continuous or intermittent pain over months or years (WAC 246-919-850–985).

The Centers for Disease Control and Prevention has found insufficient evidence to determine the long-term benefits of opioid therapy for chronic pain and has found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent. (CDC 2022)

Outside the scope of this guideline are:

- Indications for opioid prescribing
- Initiation of opioid prescribing
- General recommendations for the treatment of chronic non-cancer pain

This guideline does **not** apply to patients receiving palliative, hospice, or other end-of-life care.

Expectations for Kaiser Foundation Health Plan of Washington Providers

Using protocols and standard documentation, Kaiser Foundation Health Plan of Washington aims to minimize practice variation in the management of patients on chronic opioid therapy for chronic non-cancer pain, which will improve patient safety, ensure compliance with Washington State law, and ultimately increase both patient and provider satisfaction.

- ✓ Patients on COT shall be **risk-stratified** to the highest appropriate category by the prescribing clinician and have **regular COT monitoring visits** that include standard components.
- ✓ Patients on COT shall **receive all chronic pain management prescriptions from one physician and one pharmacy** wherever possible. Clinicians treating a patient on COT are expected to clarify—both among themselves and with the patient—which clinician holds primary prescribing responsibility. See "Opioid prescribing procedures," p. 15.
- ✓ Physicians prescribing opioids for chronic non-cancer pain shall have a one-time completion of **at least 1 hour of continuing medical education regarding best practices in the prescribing of opioids.**
- ✓ All DEA-registered physicians are required to take a **one-time 8-hour continuing education training on treating and managing patients with opioid or other substance use disorders,** including the appropriate clinical use of all FDA-approved drugs for the treatment of a substance use disorder. See KPWA Continuing Medical Education for more information and qualifying activities.

Managing Chronic Opioid Therapy (COT)

Risk stratification, intensity of monitoring, and frequency of visits

The intensity of monitoring is determined by the "patient attributes" in Table 1. Patients should be placed in the **highest-intensity group for which they meet at least one of the criteria.** For example, patients taking benzodiazepines should be in the high-intensity monitoring group even if they are on a relatively low dose of opioids.

All patients on COT should have a monitoring visit every 3 to 6 months (depending on risk level) either **in person or by video,** including at least one in-person visit annually. (Telephone and secure messaging conversations are no longer considered monitoring visits.)

Patients on COT may be at increased risk of opioid overdose and death from respiratory depression. **Recommend OTC naloxone as a preventive rescue medication for patients (and their family members)** who are taking opioid therapy ≥ 40 MME or have other risk factors for opioid overdose as defined in Table 1 (p. 6). See "Naloxone as preventive rescue medication," p. 15.

"Table 1. Opioid therapy patient monitoring groups" is on the following page.

Table 1. Opioid therapy patient monitoring groups		
Monitoring group	**Patient attributes**	**Monitoring visit and urine drug screening (UDS) frequency**

High-intensity (chronic use)	**Elevated risk factors for opioid overdose**
	• Taking ≥ 50 milligram morphine equivalent (MME)
	Note: For patients taking ≥ 120 mg MME, referral to a pain specialist [1] is required.
	• Taking methadone or fentanyl
	• Taking sedative-hypnotic drugs (benzodiazepines, Z-drugs), [2] carisoprodol or other muscle relaxants concurrently
	• Taking gabapentinoids currently (see 2019 FDA warning [3])
	• Using alcohol or marijuana concurrently [4]
	• History of overdose [5]
	• Legal issues related to substances (e.g., DUI)
	• ORT-OUD score ≥ 3
	• Active mental health conditions: depression, anxiety, substance use disorder, PTSD
	• Medical conditions: sleep apnea, cardiac disease, pulmonary disease, renal insufficiency, hepatic insufficiency, osteoporosis, pregnancy, history of falls
	• Illicit substance use: other opioids, other people's opioid prescriptions, heroin, illicit use of prescription drugs and fentanyl
	• Repeated aberrant behaviors, such as:
	  ○ Frequent early refill requests
	  ○ Escalating dose without consulting with physician
	  ○ Multiple emergency room/urgent care presentations for opioid treatment
	  ○ Getting opioids from multiple prescribers
	  ○ Lost or stolen medications
	  ○ Sharing medications with others
	  ○ Disruptive behavior
	  ○ Not taking as prescribed
		Minimum requirement: Office or video visit at least every 3 months; at least one visit per year must be in-office.
		
		UDS required at least every 3 months.

Lower-intensity (chronic use)	• Taking < 50 MME and no high-intensity risk factors • Low score ORT-OUD score ≤ 2 • Compliant with pain treatment plan	Minimum requirement: Office or video visit at least every 6 months; at least one visit per year must be in-office. UDS required at least every 6 months.
Lowest-intensity (persistent intermittent use)	• Taking low-dose opioids (< 50 MME) regularly (3 or more prescriptions per year) but less often than the strict definition of COT (70 out of 90 days)	Best practice: Office or video visit and UDS every 6-12 months; at least one visit per year must be in-office. Minimum requirement: Office visit and UDS at least every 12 months.

1 Pain specialist: See https://app.leg.wa.gov/wac/default.aspx?cite=246-919-945.

2 See the Benzodiazepine and Z-Drug Safety Practice Resource and this 2016 FDA Safety Warning on the risks of combining benzodiazepines with opioids.

3 See 2019 FDA Safety warning.

4 Per National Permanente Medical Group 2019 Clinician Practice Recommendations for Opioid Prescribing (updated 2023), COT should not be initiated in patients currently using alcohol or marijuana, and tapering should be considered in patients using COT concurrently with either of these substances.

5 Patients who experience nonfatal opioid overdose should receive naloxone, be evaluated for suicidal ideation and OUD, have their opioid dosage reduced (or discontinued) with shorter prescription durations combined and more frequent monitoring visits.

The chronic opioid therapy monitoring visit: standard components

Steps listed apply to every COT monitoring visit, except *where noted.*

Every monitoring visit is an opportunity to improve safety for patients on COT and to consider adjusting the Opioid Care Plan—including tapering or discontinuation of opioid therapy—based on changes in the patient's conditions or comorbidities.

For a patient's **initial** COT monitoring visit (ongoing or new start), use SmartPhrase ***.opioidvisit,*** which includes all steps required at the initial visit.

For a patient's **follow-up** COT monitoring visits, use either ***.opioidvisit*** or ***.opioidfollowup*** (synonym ***.opioidmini***), which includes just the steps that are required at all visits.

Consider using the CHRONICPAIN SmartSet, which incorporates all aspects of the visit, including screening, documentation, care plan, and referral orders.

1

Screening for contradictions and conditions affecting opioid risk

History

Physical exam *– initial visit*

1. Medical screening, history, and physical exam

Use of opioid medications is **contraindicated** in patients with

- Known opioid use disorder (see "Recognizing opioid use disorder," p. 9)
- History of opioid overdose

Screen for medical issues that affect opioid risk (e.g., pulmonary, cardiac, renal or hepatic disease; obstructive sleep apnea [using the Epworth Sleepiness Scale]; pregnancy risk; severe obesity; history of falls). See "Tapering or discontinuing opioids," p. 10.

Obtain/review **patient history.**

At the patient's initial COT monitoring visit, conduct a ***physical exam.***

2

Pain and function assessment

PEG Tool
and
Oswestry Disability Index (optional)

2. Pain and function assessment

Continuation of COT should be considered only when the benefits outweigh the risks. AMDG defines clinically meaningful improvement in function as an improvement in pain **and** function of at least 30% as compared to the start of treatment or in response to a dose change.

To assess patients' ongoing response to COT, use the **PEG (Pain/Enjoyment/General function) Tool** available as the SmartPhrase **.pegscore**. The PEG Tool is also available as a KP HealthConnect documentation flowsheet, review flowsheet, and secure message.

For longitudinal tracking of a patient's progress towards functional goals, consider using the **Oswestry Disability Index** (available in KP HealthConnect).

3

Prescription monitoring

PDMP database

3. Prescription monitoring

Check the patient's record in the Washington State Prescription Drug Monitoring Program database every time controlled substances are prescribed to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk.

4

Opioid risk assessment – initial visit

Opioid Risk Tool (ORT-OUD)

4. Opioid risk assessment (initial visit only)

*At the patient's initial COT monitoring visit, use the updated Opioid Risk Tool (ORT-OUD) to assess the risk of developing opioid use disorder (OUD) when taking long-term opioids. The ORT-OUD is a validated tool recommended by the Washington State AMDG. A score of **3 or higher** indicates a high risk of developing OUD.*

5

Psychological comorbidity screening

Annual Mental Health Questionnaire

5. Psychological comorbidity screening

Screen the patient for depression, suicidal ideation, alcohol use, drug use, PTSD, and anxiety using the Annual Mental Health Questionnaire. Both sides of the questionnaire—including the additional questions on the second page—are **required** for patients on COT, regardless of whether the PHQ-2 screen is positive. Screening for mental health issues is part of adult standard care.

6

Urine drug screening

Higher-intensity monitoring requires UDS at least every 3 months (every visit)

Lower-intensity monitoring requires UDS at least every 6 months

Lowest-intensity (persistent intermittent use) monitoring requires UDS at least every 6–12 months

6. Urine drug screening (UDS)

UDS provides objective data regarding patients who are managing chronic pain and can be used to directly improve patient safety. For their safety, it is important that patients take opioids as prescribed, and this test helps assess whether they are doing that. UDS should also be ordered when seeing patients already on COT who are new to the health plan and have no record of recent UDS.

UDS is legally required, and its routine use helps to ensure that all patients on COT are treated equitably.

UDS is for medical purposes only. KPWA does not collect samples for use in a court of law or for workplace testing.

Clinicians should have a discussion with the patient before the UDS that includes:

- The purpose of testing
- What will be screened for
- What results the patient expects
- Prescriptions or any other drugs the patient has taken
- Time and dose of last dose of opioids
- Actions that may be taken based on the results of the screen
- Possibility of cost to the patient

Patients should be notified that the results will become part of their permanent medical record. Unexpected UDS results must be discussed with the patient; the care plan should be reevaluated **only** after unexpected positive and negative results have been confirmed by laboratory testing and after the patient has had the opportunity to discuss the results with the prescribing clinician.

For more detailed information on urine drug screening, see Drug Screening Ordering & Interpretation (SharePoint).

7

Care plan

.avsopioidcareplan
Care Plan AVS

7. Care plan

Use **.avsopioidcareplan** at every visit to:

- Ensure the patient's treatment plan includes all components required by Washington State opioid legislation (https://app.leg.wa.gov/wac/default.aspx?cite=246-919-850). **The physician shall use a written agreement that outlines the patient's responsibilities for opioid therapy.** (Note: The legislation does not specify that a paper copy or patient signature is needed.)
- Serve as informed consent and documentation for chronic opioid therapy.

8

Documentation and coding

.opioidvisit
(initial and follow-up visits)

.opioidfollowup
(follow-up visits only)

8. Documentation and coding

For a patient's **initial** COT monitoring visit (ongoing or new start), use SmartPhrase ***.opioidvisit,*** which includes all steps required at the initial visit.

For a patient's **follow-up** COT monitoring visits, use either ***.opioidvisit*** or ***.opioidfollowup*** (synonym ***.opioidmini***), which includes just the steps that are required at all visits.

When documenting an encounter with a patient on COT, providers should include diagnosis codes for **both** the condition being treated with opioid medications **and** the long-term opioid treatment itself:

- **Diagnosis code for underlying condition, and**
- **Z79.891 Long-term (current) use of opioid analgesic**

When COT monitoring is the main reason for the visit, **Z79.891** should be used as the primary diagnosis, with the underlying condition as a secondary diagnosis. Conversely, when managing the underlying condition is the main reason for the visit—for example, when ordering physical therapy for a patient with chronic back pain—providers should document the **underlying condition** (chronic back pain) as the primary diagnosis, and Z79.891 as a secondary diagnosis.

In the rare instances that providers are treating a patient with both a health problem requiring opioid therapy and a concurrent opioid use disorder, documentation should be clear that the opioids are being used to treat the indicated health problem and not as a treatment for the opioid use disorder. (For patients with an existing or suspected opioid use disorder, see "Recognizing opioid use disorder," p. 9.)

Recognizing opioid use disorder

It is not uncommon for patients on COT to develop opioid use disorder (OUD) during their treatment. OUD can be unmasked during the tapering process: consultation with Pain Team is recommended in this situation. Whenever OUD is suspected, use the DSM-5 criteria (below) during a conversation with the patient that ideally includes a family member or other observer, or contact the Mental Health and Wellness Mind Phone (1-888-844-4662) for a consultation if unsure how to proceed.

All providers with a DEA registration that includes Schedule III medications can prescribe buprenorphine for treatment of opioid use disorder in outpatient settings. Methadone to treat OUD can only be prescribed at a federally licensed methadone clinic. See the KPWA Opioid Use Disorder Diagnosis and Treatment Guideline for more information.

Tapering and Discontinuing Opioids

General principles

1. Any time the risks of continued opioid therapy are found to outweigh its benefits, opioid medications should be tapered and possibly discontinued. The decision to taper is the provider's; however, developing the care plan is an opportunity for shared decision-making with the patient and family.
2. Taper planning must be individualized based on the patient's clinical needs, indication for taper, readiness for taper, and ability to comply with the care team's tapering instructions, and on the provider's clinical judgement.
    - Determine initial step of taper and document rationale in medical record.
    - Consider referral to the Pain Team for help with dosing complicated tapers, when considering transitioning to buprenorphine, or any time that tapering fails.
    - **Do not reverse a taper.** A temporary pause in tapering may be indicated to mitigate side effects. There is a high risk of unintentional overdose when returning to a previous dose since opioid tolerance decreases quickly when tapering. Patients should be counseled about these risks and have naloxone on hand during a taper.
    - Taper planning should be collaborative to the extent possible between provider and patient/family. Areas for shared decision-making can include tapering rate, choice of which medication to taper first, and any other aspects of planning where patient input is appropriate.
    - Consider using the BRAVO protocol (see p. 12) to support conversations about tapering.
3. Assess the patient's response to the initial dose reduction in the first 1 to 4 weeks.
4. Reassess taper weekly to monthly based on patient's response, and prior to each subsequent dose reduction.
5. Recommend OTC naloxone for any patient at risk for overdose.
6. Some special populations, such as pregnant patients or patients with mental health comorbidities, may require alternative approaches to opioid tapers.
7. For questions before initiating or during an opioid taper, please see the Referral Criteria, p. 18.

Clinical indications for opioid tapering

Table 2. Clinical indications and methods for individualized tapering of opioid therapy	
Examples of indications	**Taper methods**
• Consider for patients taking high-dose, long-acting opioids for many years, with no aberrant behaviors, **who do not have other indications as below.**	**SLOWEST** 2–5% every 4–8 weeks
• Function and pain are not improved, or • Tolerance has developed with long-term opioid prescription, or • Comorbid conditions or other factors increase risk of complications), or • Patient requests taper.	**SLOW: Most common method** 5–10% every 4–8 weeks
• Medication adverse effects indicate risks are greater than benefits, or • Morphine equivalent daily dose exceeds recommended threshold of 90 MME, or • Comorbid conditions increase risk of complications, or • Pain is resolved.	**MODERATE** 10% per week
• Urine drug screen is consistent with substance abuse concerns, or UDS does not show presence of opioids, or • Patient's behavior suggests possible misuse or diversion of medication. Such behaviors might include: ○ Selling prescription drugs ○ Forging prescriptions ○ Stealing or borrowing drugs ○ Frequently losing prescriptions ○ Aggressive demand for opioids ○ Injecting oral/topical opioids ○ Unsanctioned use of opioids, including fentanyl ○ Unsanctioned dose escalation ○ Concurrent use of illicit drugs ○ Getting opioids from multiple prescribers ○ Recurring emergency department visits for chronic pain management ○ Non-adherence to opioid treatment plan ○ Overdose event [1]	**RAPID** 20–50% first dose, then 10–20% per day Refer patient for chemical dependency or addiction counseling. (See Referral Criteria, p. 18.) See Treating opioid withdrawal symptoms, p. 14.
• If patient is not at risk of withdrawal and is not currently taking an opioid (e.g., negative UDS, patient states no longer taking), no taper is needed. • Do not resume previous opioid medication.	**TAPER NOT NEEDED** Consider mental health support. Provide withdrawal medication if indicated. See Treating opioid withdrawal symptoms, p. 14.
[1] Patients who experience nonfatal opioid overdose should receive naloxone, be evaluated for suicidal ideation and OUD, and have their opioid dosage reduced (or discontinued) with shorter prescription durations combined and more frequent monitoring visits.	

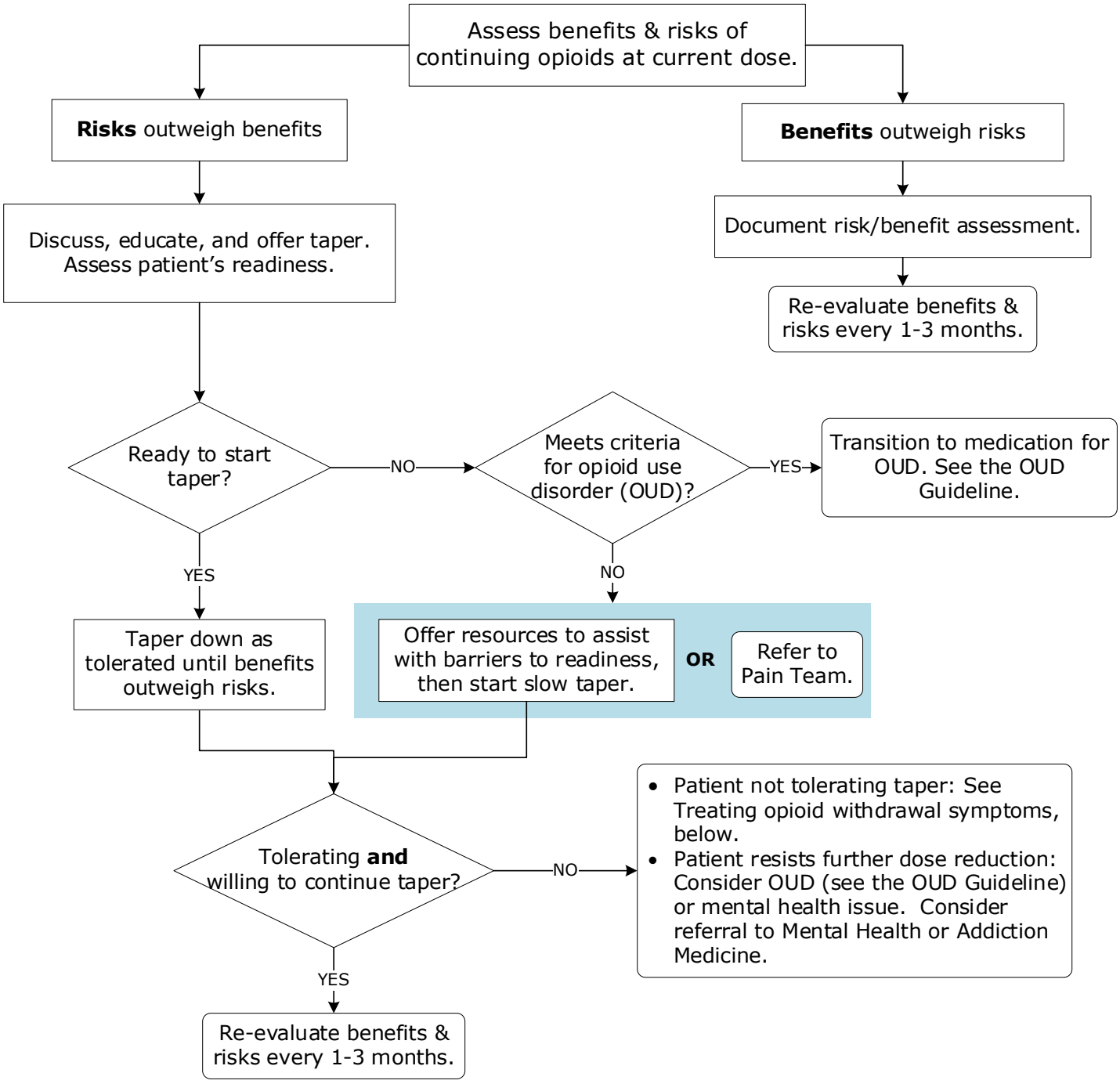
BRAVO Protocol: how to taper patients off of chronic opioid therapy

The BRAVO protocol was developed to help providers implement a compassionate approach to opioid tapering while also maintaining a therapeutic alliance. It is a helpful approach when tapering opioids, especially with complex chronic pain patients.

https://content.tts.org/content/Refresher2018/files/G-09_Lembke.pdf

B	Broaching the Subject • Schedule enough time with your patient to have a discussion on this difficult topic • Anticipate the patient's strong emotional reaction • Identify the feelings, normalize those feelings, and express empathy with the concerns the patient may have
R	Risk-Benefit Calculator • When assessing benefits, weigh the patient's pain relief against their functionality • Involve family members for more objective views on a patient's opioid use • Track common risks such as tolerance and opioid-induced hyperalgesia • Include all of these factors when discussing reasons for tapering off opioids
A	Addiction Happens • Addiction is defined by the "Four C's": out of Control use, Compulsive use, Craving, and Continued use • Dependence happens when the body relies on a drug to function normally • Dependence and addiction are not equivalent
V	Velocity Matters – and So Does Validation • Go slowly, take the necessary time to ease your patients down on their doses • Let the patient be involved when deciding how much to decrease and at what time • It is OK to take breaks in lowering the dosage • Never go backwards; your patient's tolerance will increase and progress will be lost
O	Other Strategies for Coping with Pain – teach patients these 3 Dialectical Behavioral Therapy (DBT) practices • STOP: **S**top. **T**ake a breath. **O**bserve internal and external experiences and **P**roceed mindfully. • Opposite Action Skills: acting opposite to a negative emotional urge in the service of pursuing values goals. • Radical Acceptance: accepting reality as it is and not as we wish it to be.

Opioid Tapering Flowchart



Adapted from Health and Human Services. Available at https://content.tts.org/content/Refresher2018/files/G-09_Lembke.pdf

Treating opioid withdrawal symptoms

When opioids are rapidly discontinued (see Table 2, above) or stopped immediately, withdrawal symptoms can occur. The typical time course for symptom development depends on the particular opioid used by the patient.

- Short-acting opioids (e.g., heroin or oxycodone): Withdrawal symptoms begin 8–12 hours after last use and peak 48–72 hours after last use.
- Long-acting opioids (e.g., methadone or buprenorphine): Withdrawal symptoms begin more gradually, with a few symptoms in the first 24–48 hours, a peak in symptoms 3–5 days after last use, and some symptoms continuing for up to a few weeks.

While opioid withdrawal is unpleasant, it is not dangerous to patients. Medications for withdrawal symptoms are in Table 3.

Table 3. Medications used to treat symptoms during gradual opioid taper

Target symptoms	Medication	Dosing
Hypertension, tremors, sweats, anxiety, restlessness	Clonidine [1]	0.1 mg three times daily as needed
Anxiety, restlessness	Hydroxyzine [2] or Diphenhydramine [2]	25 mg every 6 hours as needed
Insomnia	Hydroxyzine [2] or Diphenhydramine [2]	25–50 mg daily at bedtime as needed
Nausea/vomiting	Promethazine [2]	25 mg every 6 hours as needed
	Metoclopramide [2]	10 mg every 6 hours as needed
Dyspepsia	Calcium carbonate	500 mg 1–2 tabs every 8 hours as needed
	Mylanta, Milk of Magnesia	Follow package instructions.
Pain, fever	Acetaminophen (Tylenol)	500 mg every 4 hours (not to exceed 3 g/24 hours)
	Ibuprofen	400 mg every 4 hours as needed
Diarrhea	Loperamide [2]	4 mg initially, then 2 mg every loose stool as needed; maximum 16 mg/day
Muscle spasm	Methocarbamol [2]	1,000 mg every 6 hours as needed

[1] Clonidine is not FDA-approved for this use, although evidence supports use in this setting. This guideline recommends clonidine as the first-line agent, as it is effective in many patients. As a non-opioid treatment option, it is readily available statewide and does not have extra restrictions on prescribing. Monitor blood pressure and pulse. Dosing of clonidine depends on whether patient is acutely withdrawing or gradually being tapered.

[2] These are high-risk medications for the elderly. Please consider alternatives for patients aged 64 and older.

Minimizing Risks When Continuing to Prescribe Opioids

This guideline seeks to balance the appropriate use of opioid therapy in chronic non-cancer pain against its potential harms.

- Opioid therapy is continued only when the expected benefits—such as reduced pain and clinically meaningful improvement in function (as measured with the PEG Tool)—are expected to outweigh the risks of overdose, opioid use disorder, and other opioid-related harms.
- Opioid therapy is prescribed at the lowest necessary dose and for the shortest duration.
- Clinicians who manage patients on COT are skilled and knowledgeable in the principles of opioid prescribing, tapering, and discontinuing opioid medication, and in the assessment and management of risks associated with opioid use, such as the development of opioid use disorder.
- Clinicians who manage patients on COT routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary treatment as needed and available, and other non-opioid therapies. Pain is a normal sensation. Acceptance of chronic pain and focus on functional goals improves quality of life.
- The Centers for Disease Control and Prevention has found insufficient evidence to determine the long-term benefits of opioid therapy for chronic pain, and has found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent. (Dowell 2016)

Over the counter naloxone as preventive rescue medication

Naloxone is an opioid antagonist that may be used to reverse the symptoms of opioid overdose (including respiratory depression) after a known or suspected opioid overdose. *Naloxone does not replace emergency medical care.*

Naloxone is strongly encouraged as a preventive rescue medication for patients (and their family members) who are taking opioid therapy ≥ 40 MME or have other risk factors for opioid overdose as defined in Table 1, p. 6. Although naloxone is available over-the-counter, patient education is still recommended.

Counsel family members or other personal contacts who are in a position to assist the patient who is at risk of opioid-related overdose.

Resources

Pharmacy patient handout on naloxone nasal spray (SharePoint). Use SmartPhrase **.avsnaloxone**.
Opioid overdose prevention education: www.stopoverdose.org

Opioid prescribing procedures

Chronic non-cancer pain patients should receive all chronic pain management prescriptions from one physician and one pharmacy whenever possible. Clinicians involved in treating a patient on COT are expected to clarify—both among themselves and with the patient—which clinician holds primary responsibility for prescribing. Cross-coverage by another Primary Care provider is included as an extension of the primary prescribing clinician.

Before writing a prescription:

- Calculate and document the total milligram morphine equivalent (MME); doing this can help assess the magnitude of seemingly small incremental dosage changes over time. See “Milligram morphine equivalent,” below.
- Calculate and document the total acetaminophen dose, including prescribed and over-the-counter.

When writing prescriptions, provide explicit directions:

- Provide specific patient instructions (e.g., schedule for taking).
- Avoid range dosing. For example, instead of “1–2 tablets every 4–6 hours,” use “1 tablet every 6 hours.”
- Order medication in multiples of 7 days and include “to last __ days.”
- Consider setting up refills on Tuesday through Thursday so that they don’t fall on a Monday or Friday, when patients and/or providers are more likely to be on vacation.

Do not initiate extended-release/long-acting opioid medication in opioid-naïve patients.

Do not prescribe extended-release/long-acting opioid medication on an as-needed basis.

- Food and Drug Administration (FDA) labels state that extended-release and long-acting opioid analgesics are indicated "for the management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate." The labels emphasize first considering potentially less-addictive measures.
- Limitations of use: Due to the greater risks of overdose and death with extended-release formulations, their use should be reserved for patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, are not tolerated, or provide inadequate or insufficient pain management. (FDA news release 2013)
- For patients aged 65 years and older, short-acting opioids are preferable, as metabolism of medications slows with age. (AMDG 2015)

Milligram morphine equivalent (MME)

KPWA has adopted the updated MME conversion factors for hydromorphone, methadone, and tramadol, in accordance with 2022 CDC recommendations and KP National Pharmacy.

The new conversion factors (see Table 4) have been incorporated into KPWA HealthConnect allowing for automatic MME calculation for all opioid orders.

Equianalgesic dosing and cross-tolerance

All conversions between opioids are estimates generally based on "equianalgesic dosing" (ED). Patient response to these EDs can vary widely, due primarily to genetic factors and incomplete cross-tolerance. **It is recommended that, after the appropriate conversion dose is calculated, it be reduced by 25–50% to ensure safety.**

- Reduce opioid dose by 30–50% to accommodate for unknown cross-tolerance and titrate to goal.
- The wide variation among individuals is multifactorial and poorly understood.
- Incomplete cross-tolerance can lead to greater than anticipated potency in a new opioid, even in the same class of analgesic.
- Monitor clinical response and adverse effects.

Table 4. Milligram morphine equivalent (MME) for selected opioids
Reference dose is 30 mg morphine

Opioid	Conversion factor
Codeine	0.15
Fentanyl transdermal	2.4
Hydrocodone	1.0
Hydromorphone	5.0
Methadone	4.7
Morphine (reference)	1.0
Oxycodone	1.5
Oxymorphone	3.0
Tapentadol	0.4
Tramadol	0.2

Approaches that are not recommended

Buprenorphine used as pain control

Use of buprenorphine (film or patch) or Suboxone (buprenorphine/naloxone) is not recommended for the treatment of chronic pain due to lack of evidence of safety and efficacy. However, based on emerging evidence, transition to buprenorphine for pain control may be considered as a means of harm reduction for patients who are unable to taper. Referral to the Pain Team is required before making this transition.

Note: Patients who are currently taking buprenorphine or Suboxone for pain control should not be abruptly stopped. These patients should be referred to Addiction & Recovery Services for OUD evaluation prior to tapering.

Cannabinoids (THC/CBD)

There is insufficient evidence from high-quality studies to determine that any cannabis-based products are effective in reducing pain in patients with chronic non-cancer pain or in increasing the rates of opioid discontinuation. There is limited low-quality evidence suggesting that cannabis-based products may reduce pain in patients with neuropathic pain, however the effect was minimal to moderate.

Adverse effects of cannabis include higher risk of cognitive impairment, headache, nasopharyngitis, nausea, somnolence, and dizziness. KP National 2019 Clinician Practice Recommendations for Opioid Prescribing (updated 2023) advises avoiding using opioids in patients who choose to use marijuana.

Adverse effects of opioids

Serious adverse effects may include:

- **Slowed breathing (respiratory depression) that can cause death.** This is more likely for patients who:
    - Have sleep apnea or chronic lung disease,
    - Are on higher opioid doses,
    - Take more medicine than prescribed,
    - Have renal or hepatic impairment, or
    - Use any of the following at any time while taking prescribed opioids: alcohol, other prescription medicines (such as sleep aids, muscle relaxants, and tranquilizers), or street drugs.

  See also “Over the counter naloxone as preventive rescue medication,” p. 15.

- **Sedation (sleepiness and sluggishness)** can cloud patients’ judgment and slow their reaction time, putting them at increased risk for falls and accidents while driving, using tools, or operating heavy equipment. Driving while on opioids may be considered driving under the influence (DUI).
- **Babies born to mothers taking opioids will be dependent on opioids at birth.** Women who are trying to get pregnant should not take opioids. Women who become pregnant while taking opioids should consult with their physician to make a plan regarding their medication.
- **Physical dependence, tolerance, or addiction to opioids**. Patients with *physical dependence* will experience withdrawal if they stop suddenly. Patients with *tolerance* need to take more of the medicine to get the same effect. Patients with *addiction* are not able to control their use of opioids even if they want to, which may result in harmful outcomes. See “Recognizing opioid use disorder,” p. 9.

Common adverse effects may include:

- Constipation
- Depression
- Fatigue
- Itching (a side effect and not an allergic reaction)
- Nausea or vomiting
- Decreased sex drive (decreased testosterone)
- Low blood pressure
- Difficulty with urination
- Insomnia
- Increased sensitivity to pain (hyperalgesia)
- Impaired immune system

Referral Criteria

Table 5. Referral recommendations for patients on COT for chronic non-cancer pain	
Specialty	**Reason for referral**

Mental Health Crisis Team (833-378-2774)	• Contact urgently to assess patients with **suicidal ideation.**
	• Can provide short-term therapy:
	  ○ To help patients develop better coping skills for chronic pain
	  ○ For mild to moderate depression

Mind Phone Consultation	• Always an option for recommendations related to diagnostic assessment or mental health medication treatment.
Mental Health & Wellness Referral	• Primary treatment with psychotherapy (individual or group) for moderate to severe mental health conditions • Severe depressive or anxiety disorders which have not responded to trials of two or more SSRI/SNRIs • Patients with complex presentation and diagnostic uncertainty (e.g., possible bipolar disorder) • Any condition with severe symptoms, elevated suicide risk, and/or psychosis
Addiction & Recovery Services Referral (may be virtual/telephonic consultation)	• Co-occurring non-opioid substance use disorder • Suspected opioid use disorder with diagnostic uncertainty • Urine drug screen positive for alcohol, sedative, cocaine or methamphetamine use • Patient request for help with addiction • Consideration of a new start of medication treatment for OUD, including methadone, naltrexone, or buprenorphine (Suboxone) treatment • Concern about substance use disorder • Difficulty adhering to opioid care plan • Problematic use of medications other than opioids • Taking Suboxone from an outside provider for OUD • Difficulty tolerating opioid taper • Inheriting patient established on buprenorphine for chronic pain
Pain Specialist [1]	**Pain specialty consultation is *required* for:** • **Taking over 120 MME or dose increase to 120 MME or higher per day** **Consider pain specialty consultation if any of the following:** • Taking > 90 MME • Taking Suboxone from an outside provider for chronic pain • Help with tapering/discontinuing opioid medication • Taking long-term opioids (more than 1 year) • Previous failed attempt to taper • Patients on fentanyl or methadone (these tapers can be complex)
[1] Pain specialists may include rheumatologists, neurologists, and anesthesiologists. See WAC-246-919-945 for more information.	

Preventing Conversion from Acute to Chronic Opioid Therapy: General Principles

There is no evidence to support the use of ever-increasing doses of opioids for non-cancer pain. There is now evidence that this leads to harm. (See National Permanente Medical Group 2019 Practice Recommendations [updated 2023].)

The best way to minimize chronic opioid use is to minimize acute opioid prescribing. Sixty percent of patients who take opioids for 3 months are still taking them 5 years later. (AMDG 2015)

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than that needed for the expected duration of pain severe enough to require opioids. (CDC 2022)

For acute, subacute, and perioperative prescribing, general principles from the AMDG guideline are listed here. Refer to the full AMDG guideline for more detailed recommendations.

Acute phase (0–6 weeks post episode of pain or surgery)

- Check the Washington State Prescription Drug Monitoring Program (PDMP) before prescribing.
- Don't prescribe opioids for non-specific back pain, headaches, or fibromyalgia.
- Prescribe the lowest necessary dose for the shortest duration.
- Three days or less will often be sufficient; more than 7 days will rarely be needed.
- Opioid use beyond the acute phase is rarely indicated.
- **Required:** Use **.ACUTEOPIOIDTREATMENT** for documentation when prescribing or offering an acute opioid prescription.

Subacute phase (6–12 weeks post episode of pain or surgery)

- Don't continue opioids without clinically meaningful improvement in function and pain.
- Screen for comorbid mental health conditions and risk for opioid misuse using validated tools.
- Recheck the PDMP and administer a baseline urine drug test if you plan to prescribe opioids beyond 6 weeks.

Perioperative (preoperative through time of hospital discharge)

- Refer to the 2018 AMDG Supplemental Guidance on Prescribing Opioids for Postoperative Pain.
- Evaluate thoroughly preoperatively: Check the PDMP and assess for risk for over-sedation and difficult-to-control pain.
- Tapering opioids is not required before surgery, but avoid escalating the dose before surgery. Set appropriate expectations with patients that their pain management needs will be met following surgery, with the understanding that they will return to their preoperative dose (or less) following surgery.
- Discharge with acetaminophen, NSAIDs, or very limited supply (2–3 days) of short-acting opioids for some minor surgeries.
- For patients on chronic opioids, taper to preoperative doses or lower within 6 weeks following major surgery.

Special populations

- Pregnant women: Counsel women before and during pregnancy about maternal, fetal, and neonatal risks.
- Elderly patients: For older adults, initiate opioids at a 25–50% lower dose than for younger adults.
- Adolescents and children: Avoid prescribing opioids for most chronic pain problems.
- Cancer survivors: Rule out recurrence or secondary malignancy for any new or worsening pain.

Evidence Summary

The Chronic Opioid Therapy Safety Guideline was developed using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis.

As part of our improvement process, the Kaiser Permanente Washington guideline team is working towards developing new clinical guidelines and updating the current guidelines every 2–3 years. To achieve this goal, we are adapting evidence-based recommendations from high-quality national and international external guidelines, if available and appropriate. The external guidelines should meet several quality standards to be considered for adaptation. They must: be developed by a multidisciplinary team with no or minimal conflicts of interest; be evidence-based; address a population that is reasonably similar to our population; and be transparent about the frequency of updates and the date the current version was completed.

In addition to identifying the recently published guidelines that meet the above standards, a literature search was conducted to identify studies relevant to the key questions that are not addressed by the external guidelines.

External guidelines eligible for adapting/adopting

2022 CDC: Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022

2022 VA/DoD Clinical Practice Guideline. (2022). Use of Opioids in the Management of Chronic Pain Work Group. Washington, DC: U.S. Government Printing Office. Version 4 May 2022

2021 American College of Obstetricians and Gynecologists' Committee on Clinical Consensus—Obstetrics. Pharmacologic stepwise multimodal approach for postpartum pain management: ACOG clinical consensus no. 1

2020 The American Society of Addiction Medicine (ASAM) NATIONAL PRACTICE GUIDELINE For the Treatment of Opioid Use Disorder 2020 Focused Update

2020 American Academy of Pediatrics Clinical Report. Guidance for the Clinician in Rendering Pediatric Care

2018 Washington State Agency Medical Directors Group (AMDG). Prescribing Opioids for Postoperative Pain – Supplemental Guidance.

2017 American Society of Interventional Pain Physicians (ASIPP) Guidelines Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain.

2015 Washington State Agency Medical Directors Group (AMDG). Interagency Guideline on Prescribing Opioids for Pain.

2014 World Health Organization 2014: Community management of opioid overdose

Note: The vast majority of the evidence is adopted from the 2022 CDC: Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022.

Key questions

1. **In patients with chronic pain who are on high-dose opioid therapy, not meeting criteria for opioid use disorder, and unable to taper, what is the safety and efficacy of switching them to buprenorphine versus continuing the use of high-dose opioid?**

   From the CDC 2022 guideline:

   "For patients who choose to taper, but are unable to, clinicians can reassess for opioid use disorder and offer buprenorphine treatment or refer for buprenorphine or methadone treatment if criteria for opioid use disorder are met. Even without a diagnosis of opioid use disorder, transitioning to buprenorphine for pain also can be considered because of reduced risk for overdose with buprenorphine compared with risk associated with full

agonist opioids. It is also found it to be effective in preventing return to drug use (Recommendation 5 category: B; evidence type: 4)."

To date, there is no new published evidence that would change or add to the CDC recommendation.

2. In patients on chronic opioid therapy (COT) for chronic pain, what are the benefits and risks of including fentanyl testing in their periodic urine drug tests (UDT) to detect aberrant behavior?

There is insufficient published evidence on the benefits and risks of including fentanyl testing in the periodic urine drug tests (UDT) to detect aberrant behavior in patients on chronic opioid use.

3. In patients on COT who have experienced a nonfatal drug overdose with treatment, what is the optimal follow-up care for preventing additional nonfatal or fatal overdoses?

- There is insufficient published evidence from randomized controlled trials (RCTs) or well-conducted prospective cohort studies to determine the optimal follow-up care for an initial opioid overdose to prevent future nonfatal or fatal overdose events.
- There is insufficient high-quality evidence to determine the effectiveness of the different guideline recommendations and various strategies/policies used by different states and agencies for the prevention of secondary fatal or nonfatal opioid overdose in patients on COT who had experienced an initial nonfatal drug overdose.
- The various strategies recommended by different guidelines and agencies and/or investigated for secondary prevention were mainly based on or consensus opinion, retrospective observational studies, and/or indirect evidence.
- The published literature indicates that the emergency department (ED) is a critical entry point for the primary and secondary prevention of overdose. As explained by Houry and colleagues, 2018, "ED provides the opportunity to improve opioid prescribing, respond to overdoses with overdose education and naloxone distribution, engage patients in motivational interviewing, initiate treatment for opioid use disorder, and improve surveillance efforts in collaboration with health departments."
- Other recommendations, strategies and/or policies include the following:

Treatment

- Treatment with buprenorphine or methadone.
- Starting medication-assisted treatment (MAT) in the hospital.
- Encouraging patient to obtain OTC naloxone and making it available for home use.
- Training the opioid users and their household members on using naloxone in the event of overdose.

Patient education/motivational interviewing

- Patient education on the benefits versus the harms of opioid use, and the increased risk associated with overdose.
- Providing education on safe opioid storage and disposal.

Handoff/referral

- Quick handoff of the patient to mental health services in their community.
- Connecting the patient to a social support network.
- Linking patients to an outpatient treatment program that can maintain individuals on medication for OUD (MOUD), buprenorphine, methadone, or naltrexone.

Screening/Monitoring

- Screen for suicidal ideation.
- Urine drug testing for fentanyl and fentanyl analogues.
- Increasing frequency of monitoring.
- Post-ED follow-up telephone calls.

4. In patients on COT, what are the risks associated with each of the following conditions, variables, or risk factors, and at what level of severity and/or dose or frequency when applicable?

From the CDC 2022 guideline:
"Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone (Recommendations category A; evidence type: 4)."

Overall, there is very limited evidence to determine the effects of patient demographics and comorbidities on risk for opioid-related harms. According to the AHRQ evidence review (Chou 2020) the risk factors likely to increase opioid-related harms, and the recommended strategies to reduce the associated risk, were based on observational studies and expert opinion**.**

4.1. Are patients with obstructive sleep apnea (OSA) more vulnerable to the respiratory depressant effects of opioids compared with patients who do not suffer from OSA?

The published literature mainly investigated the association of o*pioid use* with the development of obstructive and central sleep apnea, i.e., *opioid-induced sleep apnea.*

Fewer studies investigated the adverse effects of opioid use in patients with OSA sleep apnea.

A review article (Freire 2022) explained that the presence of OSA increases the risk of opioid-induced respiratory depression. Opioids affect control of breathing and impair upper airway function, causing central apneas, upper airway obstruction, and hypoxemia during sleep. They added that, even if the relationship between opioids and central sleep apnea is proven, the question of whether opioids can aggravate OSA remains unanswered. While several reports have shown a high prevalence of OSA and nocturnal hypoxemia in patients receiving a high dose of opioids, other studies did not find a correlation between opioid use and obstructive events.

4.2. Are patients aged ≥ 65 years on COT at higher risk of adverse effects compared to younger individuals?

- The review conducted recently for AHRQ (Chou 2020) did not find sufficient direct evidence on opioid-related outcomes in older adults prescribed opioids or having opioid-related disorders. The reviewers concluded that more research is needed to determine which factors may predict clinically important, patient-centered, opioid-related outcomes.
- Literature search for more evidence published after the AHRQ report did not identify any studies that would change the recommendation.
- The more recent published studies only provide low-quality indirect evidence suggesting that opioid use in older adults may be associated with an increased rate of CVD events and an increased risk of traumatic brain injury.

4.3. What is the risk associated with the use of opioid therapy during pregnancy to the mother, fetus, and/or newborn child?

From the CDC 2022 guideline:

"Opioid exposure during pregnancy is associated to poor health for both mothers and babies; OUD has been linked to maternal death, poor fetal growth, preterm birth, stillbirth, specific birth defects, and neonatal abstinence syndrome. The effects of prenatal opioid exposure on children over time are largely unknown."

The search for more recent studies on the risk of opioid use in pregnant women identified only observational study-based health records or databases. The great majority evaluated the effect of opioid use during pregnancy on the neonate and do not add or change the CDC guideline conclusions.

- Moderate-quality evidence from a recent meta-analysis (Marchand 2022) of studies on neonatal outcomes in marijuana-exposed pregnancies suggests that maternal opioid use during pregnancy may be associated with multiple risks to the fetus or newborn, including preterm birth, lower gestational age, lower weight at birth, neonatal abstinence syndrome, and an increased rate of admission to the neonatal intensive care

unit. It is, however, hard to determine if some of these risks to the newborn (e.g., preterm birth) are related to the opioid use or to indications for its use.
- Low-quality evidence from one observational study (Bowie 2022) suggests an association between the exposure of a fetus to opioid analgesics in the first trimester and a small but increased risk of congenital anomalies.

4.4. Are individuals with substance use disorder at higher risk of developing adverse effects when treated with COT?

From the CDC 2022 guideline:

"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 (e.g., offering naloxone… and increasing frequency of monitoring)."

- The CDC 2022 guideline recommendations were based on earlier observational studies and expert opinion.
- No new studies that provide a causal association were identified.

4.5. What is the risk of using COT in patients with anxiety, depression, or other mental health conditions?

From the 2022 CDC guideline:

"Patients with mental health conditions including depression might be at higher risk than other patients for opioid use disorder and drug overdose. Additional caution and increased monitoring might lessen the increased risk for overdose among patients with depression. In addition, patients with anxiety disorders and other mental health conditions are more likely to receive benzodiazepines, which can exacerbate opioid-induced respiratory depression and increase risk for overdose."

"Psychological distress frequently interferes with improvement of pain and function in patients with chronic pain; therefore, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ-9 or PHQ-4) to support assessment for anxiety, posttraumatic stress disorder (PTSD), and depression might help clinicians improve overall pain treatment outcomes…. Clinicians should ensure that treatment for depression and other mental health conditions as well as treatment for pain is optimized, consulting with behavioral health specialists when needed. Treatment for depression can improve pain symptoms and depression and might decrease overdose risk. For treatment of chronic pain in patients with depression, clinicians should consider using tricyclic or SNRI antidepressants for analgesic as well as antidepressant effects if these medications are not otherwise contraindicated."

- The CDC 2022 guideline recommendations were based mainly on the results of earlier retrospective observational studies.
- The literature search did not identify any more recent studies that would provide additional and/or stronger evidence to determine a causal association on the risk of COT in patients with anxiety, depression, or other mental conditions.

4.6. What are the harms of using COT in patients with a previous overdose?

From the CDC 2022 guideline:
"Previous opioid overdose is associated with substantially increased risk for future nonfatal or fatal opioid overdose. Yet, a cohort study (Larochelle 2016) of commercially insured patients found that opioids were dispensed to 91% of patients who had a previous overdose; a substantial percentage experienced a repeated opioid overdose, with a cumulative incidence at 2 years of 17% among patients receiving ≥ 100 MME/day, 15% among those prescribed 50–100 MME/day, 9% among those prescribed no opioids.

"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… and should ensure continued close monitoring and support for patients prescribed or not prescribed opioids. If clinicians continue opioid therapy in patients with previous 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 offering naloxone… and increasing frequency of monitoring…"

- The literature search did not identify any new studies that would add to the CDC 2022 guideline recommendations.

4.7. Are individuals on COT at higher risk of fractures compared to those who are not opioid users?

- The literature search identified three meta-analyses with overlapping studies (Yue 2020, Ping 2017, Tenz 2015) that examined the association between fractures, mainly hip fracture, and the use of opioids. The meta-analyses included cohort and case control studies. No RCTs were identified or included in any of the three meta-analyses.
- Fair evidence suggests an association between opioid use and increased risk of fractures overall and for hip fractures.

4.8. What are the harms associated with COT in patients with chronic kidney disease (CKD)?

- There is insufficient high-quality published evidence on the harms of COT in patients with renal insufficiency.
- Low-quality evidence from a recent systematic review and meta-analysis of observational studies (Lambourg 2022) showed that opioid use in patients with CKD was associated with an increased risk of death (HR=1.61; 95% CI, 1.12–2.31), hospitalization with higher opioid doses (HR=1.38; 95% CI, 1.32–1.45), and fractures (1.51; 95% CI, 1.16–1.96) in patients undergoing dialysis.
- Low-quality evidence from two review articles (Zhuo 2021, Owsiany 2019) also of observational studies suggest that harms associated with opioid use in older adults with CKD included severe fatigue, nausea, vomiting, tremors, myoclonus, agitation, confusion, cognitive dysfunction, and decreased renal function.

4.9. What are the harms associated with COT in patients with hepatic insufficiency?

Low-quality evidence suggests that opioid prescriptions may be associated with the risk of incident hepatic encephalopathy in adult patients with liver cirrhosis and no recent decompensation.

4.10. What are the harms associated with COT in patients with cardiovascular disease?

A recent meta-analysis (Pratama 2022) of RCTs and observational studies assessed the clinical efficacy and harms of morphine use in patients with acute heart failure (AHF) and chronic heart failure (CHF). The results of the analysis suggest that opioids were harmful to patients with AHF, with no benefits observed for any clinical outcome studied. However, patients with stable CHF NYHA II/III showed improvement in their exercise outcomes after morphine administration.

4.11. What are the harms associated with COT in patients with osteoporosis?

- The literature search did not identify any study that directly examined the effect of chronic opioid use in patients with osteoporosis.
- The association of opioid use with the risk of falls and hip fracture was discussed earlier.

4.12. What are the harms associated with COT in severely obese patients?

There is insufficient published evidence to determine the harms associated with COT in severely obese patients.

4.13. What are the harms associated with COT in marijuana users?

There is insufficient published evidence to determine the risk associated with the concomitant use of marijuana and opioids in patients with non-cancer pain.

4.14. What are the harms associated with COT in individuals younger than 25 years?

The literature search did not identify any study that directly examined the effect of chronic opioid use in adolescents or young adults.

Citations for external guidelines reviewed

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CDC guideline categories of evidence

- Type 1 (randomized clinical trials or overwhelming evidence from observational studies; equivalent to AHRQ high strength of evidence),
- Type 2 (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies; equivalent to AHRQ moderate strength of evidence),
- Type 3 (observational studies, or randomized clinical trials with notable limitations; equivalent to most AHRQ low strength of evidence ratings),
- Type 4 (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations; equivalent to AHRQ low strength of evidence with serious limitations).
- When no studies were available or the evidence was too limited to estimate effects, evidence was assessed as insufficient.

CDC grading of recommendations (Using GRADE working group method)

- **Category A recommendations**
  The evidence is higher quality, a balance of desirable relative to undesirable effects is greater, resources and costs are lower, and recommendations are less sensitive to differences in values and preferences. Category A recommendations typically apply to all persons in the group addressed in the recommendation and indicate a course of action that can be followed in most circumstances.
- **Category B recommendations**
  Indicate that the recommendation might not apply to all persons in the group addressed in the recommendation; therefore, different choices will be appropriate for different patients, and decisions should be made based on the patient's circumstances. For category B recommendations, clinicians must help patients arrive at a decision consistent with patient values and preferences and specific clinical situations (shared decision-making).

Guideline Development Process and Team

Development process

This guideline was adapted from externally developed evidence-based guidelines and organizations that establish the community standards for chronic opioid therapy for chronic non-cancer pain. The guideline team reviewed additional evidence using an evidence-based process, including systematic literature search, critical appraisal, and evidence synthesis. For details, see Evidence and References.

This edition of the guideline was approved for publication by the Guideline Oversight Group in July 2023.

Team

The following specialties were represented on the development and/or update team: addiction and recovery services, clinical laboratory, family medicine, nursing, pain team, patient safety, pharmacy, population health, residency, and urgent care.

Clinician lead: John Dunn, MD, MPH, Medical Director, Knowledge & Implementation
Guideline coordinator: Avra Cohen, MN, RN, Clinical Improvement & Prevention
Clinical expert: Stacy Lundstedt, MD, Medical Director, Controlled Substance Policy and Safety

DeNelle Ballenger, RN, Nursing Education and Practice
Karen Birmingham, PharmD, Patient Safety
Melanie Edwards, RN, Quality Improvement Consultant
Scott Ekin, MD, Urgent Care Quality Medical Program Director
Megan Kavanagh, Patient Engagement, Clinical Improvement & Prevention
Annie Links, MD, Interim Medical Director, Patient Safety
Ed Lojeski, DO, Pain Team
Kim Painter, MD, Medical Director, Special Populations
Shannon Phibbs, MD, Family Medicine, Pain Clinic
Mena Raouf, PharmD, BCPS, Coordinator Pharmacy Clinical Programs
Nadia Salama, MD, PhD, Clinical Epidemiologist, Clinical Improvement & Prevention
Shaun Smith, MD, Addiction and Recovery Services
Ann Stedronsky, Clinical Publications, Clinical Improvement & Prevention
Melissa Sturgis, PharmD, Coordinator Pharmacy Clinical Programs
Amanda Teblunthuis, MD, Resident
Min Xu, MD, PhD, Medical Director, Laboratory