Opioid Treatment Guidelines for Chronic Pain Part 3

Quantum Units Education
Affordable. Dependable. Accredited.

www.quantumunitsed.com

Appendix A: VA Signature Informed Consent

For the most current information on informed consent, see the VA National Center for Ethics in Health Care website (http://www.ethics.va.gov/).

Department of Veterans Affairs	Consent for Long-Term Opioid Therapy for Pain

A. IDENTIFICATION

1. Patient Name, Social Security Number, and Date of Birth:

Name: Last, First, Middle | Social Security Number | Date of Birth

2. Decision-making capacity:

☐ The patient HAS decision-making capacity (skip to item 3).

☐ The patient DOES NOT HAVE decision-making capacity. Enter surrogate name and relationship to the patient. (If the patient's surrogate is not established or available, refer to Handbook 1004.01 for guidance).

Name: Last, First, Middle | Relationship

3. Name of the treatment: Long-Term Opioid Therapy for Pain

4. Practitioner obtaining consent:

Name: Last, First, Middle

5. Supervising practitioner: (if applicable)

Name: Last, First, Middle

6. Additional practitioner(s) performing or supervising the treatment: (if not listed above)

B. INFORMATION ABOUT THE TREATMENT

7. Reason for long-term opioid therapy (diagnosis, condition, or indication):

8. Location of pain:

9. Goal(s) of long-term opioid therapy (e.g., pain score, functional abilities such as go back to work, climb stairs, walk short distances, sleep through the night, do daily household chores, start a light exercise program):

10. Name of current or initial opioid medication(s):

VA FORM MAY 2014 **10-0431c** Page 1

11. Brief description of the treatment:

Opioids are very strong medicines that may be used to treat pain. You may already be taking opioids. Or your provider may try to give you opioids to find out if they will help you. They may try them for a short time or continue them for the rest of your life. Your provider will learn more about your risks and side effects when you are trying the opioids. If the risks and side effects outweigh the benefits, your provider will stop the prescription.

If your provider continues your opioid prescription, the goals of your treatment may change over time. The names and doses of your opioids may also change. You will not need to sign another consent form for these changes. You may be asked to sign another consent form if you seek opioid pain care from another VA provider.

Your provider will monitor your prescription. This may include checking how often you refill and renew your prescription, counting pills, asking you about your symptoms, and testing your urine, saliva, and blood. If you do not take opioids responsibly, your provider may stop your prescription. For example, if you do not let your provider monitor how you are responding to the opioids or tell them if you are taking other drugs that may affect the safety or effectiveness of your opioid treatment, your provider may stop the prescription.

For your safety, your provider and pharmacist will monitor when you renew and refill your opioids within VA. Consistent with state law, they will also monitor this outside of VA. Most states have monitoring programs that track unsafe patterns of prescription drug use. VA and these programs may obtain and share information about you without your specific consent.

Your provider will review with you a Patient Information Guide called "Taking Opioids Responsibly" to make sure that you know how to take your medication safely. You will be given a copy of the guide so that you can use it as a reference

12. Potential benefits of the treatment:

Opioids -- when added to other treatments as part of your pain care plan -- may reduce your pain enough for you to feel better and do more. It is unlikely that opioids will eliminate your pain completely. It is possible that you may not receive any benefits from opioid therapy.

13. Known risks and side effects of the treatment:

Possible opioid side effects include:

- Sleepiness or "slow thinking"
- Mental confusion, bad dreams, or hallucinations
- Constipation
- Intestinal blockage
- Itching
- Sweating
- Nausea or vomiting
- Decreased sex hormones
- Irregular or no menstrual periods
- Depression
- Dry mouth that causes tooth decay
- Allergies

Other risks of opioid therapy:

- Withdrawal symptoms if you suddenly stop taking opioids, lower the dose of your opioids too quickly, or take a drug that reverses the effects of your opioids. Withdrawal symptoms are caused by physical dependence that is a normal result of long-term opioid therapy. Some common withdrawal symptoms are runny nose, chills, body aches, diarrhea, sweating, nervousness, nausea, vomiting, mental distress, and trouble sleeping.
- Sleep apnea (abnormal breathing pauses during sleep)
- Worsening of pain
- Impaired driving or impaired ability to safely operate machinery
- Tolerance, which means that you may need a higher dose of opioid to get the same pain relief, resulting in an increase in the likelihood of the other side effects and risks
- Addiction (craving for a substance that gets out of control). Some patients become addicted to opioids even when they take opioids as prescribed.
- Drug interactions (problems when drugs are taken together). Taking small amounts of alcohol, some over-the counter medications, some herbal remedies, and other prescription medications can increase the chance of opioid side effects.
- Risks in pregnancy:
  - ***Continued use of opioids during pregnancy can cause your baby to have withdrawal symptoms after birth and require your baby to stay in the hospital longer after birth.**
  - ***Stopping opioids <u>suddenly</u> if you are pregnant and physically dependent on opioids can lead to complications during pregnancy.**
  - ***Studies have not shown a clear risk for birth defects with opioid use in pregnancy. If there is an increased risk for birth defects in pregnancy with opioid use, it is likely small.**
- Death

VA FORM MAY 2014 **10-0431c** Page 2

14. Alternatives to the treatment:

You have the option not to take opioids. Other treatments can be used as part of your pain care plan. Alternatives include:

- Heat and cold therapy (heating pads, ice packs)
- Stretching
- Exercise
- Weight loss
- Massage
- Acupuncture
- Chiropractic
- Nerve Stimulation
- Relaxation or stress reduction training
- Physical therapy
- Occupational therapy
- Mental health treatment
- Self-care techniques
- Counseling and coaching
- Meditation
- Rehabilitation
- Non-opioid pain medicines (Non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants)
- Injections
- Specialist pain care
- Surgery
- Pain classes
- Support groups
- Attention to proper sleep

15. Additional Information:

16. Comments:

C. SIGNATURES

Practitioner obtaining consent:

- All relevant aspects of the treatment and its alternatives (including no treatment) have been discussed with the patient **(or surrogate) in language that s/he could understand. This discussion included the nature, indications, benefits, risks, side effects, monitoring, and likelihood of success of each alternative that was considered.**
- I have discussed all of the information contained in the education document "Taking Opioids Responsibly" with the patient (or surrogate).
- The patient (or surrogate) demonstrated comprehension of the discussion.
- I have given the patient (or surrogate) an opportunity to ask questions.
- I did not use threats, inducements, misleading information, or make any attempt to coerce the patient/surrogate to consent to this **treatment.**
- I have offered the patient (or surrogate) the opportunity to review and receive a printed copy of the consent form.
- If the patient is a woman of childbearing age (ages 15-50), I have discussed the patient's pregnancy status and pregnancy intentions.
  - **If the patient is not considering pregnancy, I have discussed (or referred the patient for) contraceptive counseling.**
  - **If the patient is considering pregnancy, I have discussed (or referred the patient for) preconception counseling.**

Signature _____ Date _____ Time _____

Patient or surrogate:

- I understand that to receive long-term opioids I must agree to my opioid treatment plan by signing this consent form.
- Someone has explained the treatment, what it is for, and how it could help me.
- Someone has explained things that could go wrong, including serious side effects and death, particularly if I do not take my medicine as prescribed.
- Someone has told me about other treatments that might be done instead, and what would happen if I have no treatment.
- I have discussed the information in the document "Taking Opioids Responsibly" with my provider.
- I understand the importance of:
  - **telling my provider about side effects.**
  - **telling my provider about changes in my pain and daily function.**
  - **getting my opioids from only my VA provider and no one else.**
  - **not giving away (or selling) my opioids to other people.**
  - **storing my opioids in a safe place away from children, family, friends, and pets.**
  - **safely getting rid of opioids I do not need.**
  - **not drinking alcohol or taking illegal street drugs when I am on opioids.**
  - **for women, telling my provider if I think I might be pregnant, know I am pregnant, or am planning to become pregnant.**

- I plan to use my medications responsibly, and take them as prescribed.
- I understand how to refill my opioid prescription or get a new prescription. I understand that my VA pharmacy may be closed on weekends, holidays, and after regular clinic hours. I understand that my provider might not give me early medication refills or replace doses that are lost or stolen.
- I understand that my provider may order urine or blood drug tests with my consent (separate from this consent). I understand that the results of these tests or my refusal to be tested may cause my provider to talk to me about changing my opioid treatment plan.
- I understand that I may have to stop opioids if my provider thinks that it is unsafe for me to continue.
- Someone has answered all my questions.
- Someone has given me information about how to contact the clinic, if there is a problem and who to call in an emergency.
- I know I may refuse or change my mind about having treatment. If I do refuse or change my mind, I will not lose my health care or any other VA benefits.
- I have been offered the opportunity to review and receive a copy of my consent form.
- I choose to have this treatment.

Signature	Date	Time

Witnesses: No witness is required if the patient or surrogate signs their name. Two witnesses are required only when the patient's signature is indicated with an "X" or some other identifying mark.

Witness Name (Please Print)		
Witness Signature	Date	Time
Witness Name (Please Print)		
Witness Signature	Date	Time

Appendix B: Urine Drug Testing

A. Benefits of Urine Drug Testing

Substance misuse in patients on LOT is more than 30% in some series.[107] The inaccuracies inherent to patient self-report coupled with the evident mortality and morbidity to the treated patients, their families, and others require additional methods to ascertain patient and public safety. UDT and confirmatory testing is an additional method of examining for patient substance misuse and adherence to the prescribed regimen as well as the development of trust within the provider-family-patient relationship. It is critical that the UDT and confirmatory testing be done in a timely, confidential, accurate, and easily available manner to assure the prescribers, patients, and public that safety, fairness, and trust are being addressed.

Within the VA, verbal informed consent is required prior to UDT. While a patient can decline to consent to UDT, a provider can factor that declination into their thinking about whether it is safe to continue with OT for that patient which is ultimately required if LOT is to be instituted/continued. For more information, see the VA National Center for Ethics in Health Care website (http://www.ethics.va.gov/).

B. Types of Urine Drug Testing

There are three main types of UDT currently being utilized in clinical settings: immunoassay, GCMS confirmatory testing, and liquid chromatography-mass spectrometry confirmatory testing. Immunoassay screening is inexpensive, fast and widely available. However, there are a number of drawbacks for using this test alone. There is a higher potential for false positives and negatives as well as lack of specificity of the actual opiate or benzodiazepine being tested. GCMS is highly sensitive and specific; however, it is expensive and time consuming. LCMS is less expensive than GCMS but more expensive than immunoassay. It can give a confirmation for a large number of medications, substances and drugs at one time and may be helpful in many patients at initiation of OT, periodically during OT, and following cessation of OT if SUD is a possibility. See Table B-1 through Table B-4 and Figure B-1 for more information.

Table B-1. Urine Toxicology Specimen Validity and Normal Characteristics of a Urine Sample [189-191]

Urine Toxicology Specimen Validity	Normal Characteristics of a Urine Sample
▪ Urine samples that are adulterated, substituted, or diluted may avoid detection of drug use ▪ Urine collected in the early morning is most concentrated and most reliable ▪ Excessive water intake and diuretic use can lead to diluted urine samples (creatinine<20 mg/dL) ▪ THC assays are sensitive to adulterants (e.g., eye drops)	Temperature within 4 minutes of voiding: 90-100°F
	pH: 4.5-8.0
	Creatinine: >20 mg/dL
	Specific gravity: >1.003
	Nitrates: <500 mcg/dL
	Volume: ≥30 mL

Abbreviations: °F: degrees Fahrenheit; dL: deciliter(s); mcg: microgram(s); mg: milligram(s); mL: milliliter(s); THC: tetrahydrocannabinol

Table B-2. Urine Toxicology Screening Federal Work Place Cut Off Values [189-195]

		Agent	Initial drug test level (immunoassay) (ng/mL)	Confirmatory drug test level (GCMS) (ng/mL)	Confirmatory test analyte	Detection Period after Last Dose (days)[1]
Extended UTS	Regular UTS	Marijuana metabolites	50	15	THCA	2-8 single use 20-30 chronic use[2]
		Cocaine metabolites	300	150	Benzyolyecgonine	1-3
		Opioid metabolites	2000[3]	2000[3]	Codeine Morphine 6-MAM	2-3 days opiates 3-5 minutes heroin 12-24 hr 6-MAM
		Oxycodone				2-4
		Amphetamines	1000	500	Amphetamine Methamphetamine MDMA, MDA, MDEA	1-3
		Methamphetamine	Incomplete data	500		3-4
		Benzodiazepines	300	200		3 short-acting 30 long-acting
		Barbiturates	300	200		1 short-acting 21 long-acting
		Methadone	300	200	EDDP	3-6
		Alcohol			EtG, EtS	12 hr

[1]Detection time for most drugs in urine is 1-3 days

[2]Long-term use of lipid-soluble drugs (THC, diazepam, ketamine) can be detected for a longer period of time

[3]Testing levels for opiates were raised from 300 ng/mL to 2000 ng/mL to reduce detection from foods containing poppy seeds

Abbreviations: 6-MAM: 6-monoacetylmorpine; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EtG: ethyl glucuronide; EtS: ethyl sulfate; GCMS: gas chromatography-mass spectrometry; hr: hour(s); MDA: 3,4-methylenedioxy-amphetamine; MDEA: 3,4-methylenedioxy-N-ethyl-amphetamine; MDMA: 3,4-methylenedioxy-methamphetamine; mL: milliliter(s); ng: nanogram(s); THC: tetrahydrocannabinol; THCA: delta-9-tetrahydrocannabinol-9-carboxylic acid; UTS: urine toxicology screening

Table B-3. Summary of Agents Potentially Contributing to False Positives [189-194]

Agent	Summary of Agents Potentially Contributing to False Positives		
Marijuana metabolites	▪ dronabinol ▪ efavirenz	▪ NSAIDs[1] ▪ proton pump inhibitors	▪ hemp foods: tea, oil[2]
Cocaine metabolites	▪ coca leaf teas	▪ topical anesthetics containing cocaine	
Opioid metabolites	▪ dextromethorphan ▪ fluoroquinolones ▪ levofloxacin	▪ ofloxacin ▪ poppy seeds ▪ poppy oil	▪ rifampin ▪ quinine
Amphetamines/ Methamphetamine (high rate of false positives)	▪ amantadine ▪ benzphetamine ▪ brompheniramine ▪ bupropion ▪ chlorpromazine ▪ desipramine ▪ dextroamphetamine ▪ doxepin ▪ ephedrine ▪ fluoxetine	▪ isometheptene ▪ isoxsuprine ▪ labetalol ▪ l-methamphetamine (OTC nasal inhaler) ▪ methylphenidate ▪ MDMA ▪ phentermine ▪ phenylephrine	▪ propanolamine ▪ promethazine ▪ pseudoephedrine ▪ ranitidine ▪ selegiline ▪ thioridazine ▪ trazodone ▪ trimethobenzamide ▪ trimipramine
Benzodiazepines	▪ oxaprozin	▪ sertraline	
Barbiturates	▪ ibuprofen	▪ naproxen	
Methadone	▪ chlorpromazine ▪ clomipramine ▪ diphenhydramine	▪ doxylamine ▪ ibuprofen ▪ quetiapine	▪ thioridazine ▪ verapamil
Alcohol	▪ mouthwash	▪ short-chain alcohols	▪ OTC cough products (isopropyl alcohol)

[1]Detection time for most drugs in urine is 1-3 days

[2]Long-term use of lipid-soluble drugs (THC, diazepam, ketamine) can be detected for a longer period of time

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; MDMA: 3,4-methylenedioxy-methamphetamine; OTC: over the counter; THC: tetrahydrocannabinol

Table B-4. Interpreting Urine Toxicology Screening [189-191,196]

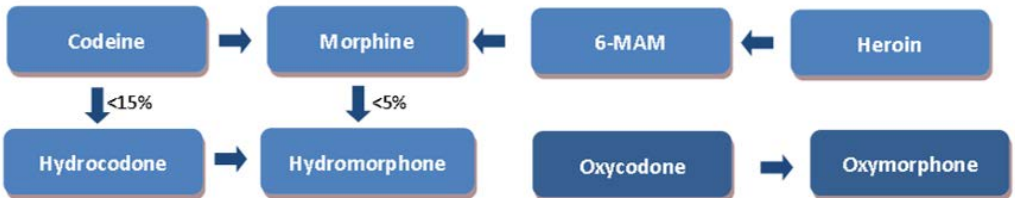
	Drug or Class	Expected Results	Considerations
Non-opioids	Alcohol	Alcohol	▪ Testing for ethanol metabolites, ethyl glucuronide or ethyl sulfate, can identify alcohol up to 80 hr after consumption
	Amphetamines	**Immunoassay** – Amphetamines, methamphetamines or MDMA **Confirmatory** – Amphetamines, methamphetamines or MDMA	▪ Immunoassay tests are highly cross-reactive; therefore confirmatory testing is required and can identify which amphetamine is present
	Benzodiazepines	**Immunoassay** – Unconjugated oxazepam or its metabolites **Confirmatory** – Alprazolam, diazepam, clonazepam, lorazepam, etc.	▪ Immunoassays for benzodiazepines have a 28% overall false negative rate ▪ Confirmatory testing is needed when use is expected or suspected (alprazolam, clonazepam and lorazepam often not detected by immunoassay)
	Barbiturates	**Immunoassay** – Barbiturates	▪ N/A
	Cocaine metabolites	**Immunoassay** – Cocaine or benzoylecgonine	▪ Cocaine's primary metabolite, benzoylecgonine, has low cross-reactivity with other substances and is highly predictive of cocaine use ▪ A positive result should be interpreted as recent exposure to cocaine
Opioids or "Opiates"-Natural (From Opium)	Codeine (Tylenol #2,3/4)	**Opiates Immunoassay** – Positive **Confirmatory** – Codeine, possibly morphine & hydrocodone	▪ Immunoassays for "opiates" are responsive to morphine and codeine but do not distinguish which ▪ Codeine is metabolized to morphine and small quantities of hydrocodone
	Morphine (Avinza, Embeda, MS Contin, Kadian)	**Opiates Immunoassay** – Positive **Confirmatory** – Morphine, possibly hydromorphone	▪ Immunoassays for "opiates" are responsive to morphine and codeine but do not distinguish which ▪ Morphine (<10%) may be metabolized to hydromorphone
	Heroin	**Opiates Immunoassay** – Positive **Confirmatory** – Heroin (6-MAM), morphine, possibly codeine	▪ 6-MAM is pathognomonic for heroin use, detection 12-24 hr ▪ Heroin is metabolized to morphine

	Drug or Class	Expected Results	Considerations
Opioids-Semisynthetic (Derived from Opium)	Hydrocodone (Lorcet, Lortab, Norco, Vicodin)	**Opiates Immunoassay** – Positive **Confirmatory** – Hydrocodone, possibly hydromorphone	▪ "Opiates" immunoassay may detect semisynthetic opioids ▪ hydrocodone >hydromorphone >oxycodone ▪ Negative result does not exclude use and confirmatory testing (GCMS) is required ▪ Hydrocodone is metabolized in small amounts to hydromorphone, both may be found in urine ▪ Oxycodone is metabolized to oxymorphone, both may be found in urine ▪ Hydromorphone and oxymorphone use does not result in positive screens for hydrocodone and oxycodone, respectively
	Hydromorphone (Dilaudid, Exalgo)	**Opiates Immunoassay** –May be positive **Confirmatory** – Hydromorphone	
	Oxycodone (Roxicet, OxyContin)	**Opiates Immunoassay** – May be positive **Oxycodone Immunoassay** – Positive **Confirmatory** – Oxycodone possibly oxymorphone	
	Oxymorphone (Opana)	**Oxycodone Immunoassay** – Positive **Confirmatory** – Oxymorphone	
Opioids – Synthetic (Man-made)	Buprenorphine	**Immunoassay** – Buprenorphine **LCMS, GCMS** – Buprenorphine, norbuprenorphine	▪ Current "opiates" immunoassays do not detect synthetic opioids ▪ Confirmatory testing (GCMS or LCMS) is needed
	Fentanyl	**GCMS** – Fentanyl, norfentanyl	
	Meperidine (Demerol)	**GCMS** – Normeperidine, possibly meperidine	
	Methadone (Methadose)	**Methadone Immunoassay** – Positive **GCMS** – Methadone, EDDP	

Note: Each facility may have its own order sets and lab policies and procedures. Contact your lab for additional details.

Abbreviations: 6-MAM: 6-monoacetylmorpine; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; GCMS: gas chromatography-mass spectrometry; LCMS: liquid chromatography-mass spectrometry; MDMA: 3,4-methylenedioxy-methamphetamine

Figure B-1. Opioid Metabolic Pathways [190-193]



Abbreviations: 6-MAM: 6-monoacetylmorpine

Appendix C: Diagnostic and Statistical Manual of Mental Disorders for Opioid Use Disorders

DSM-5 diagnostic criteria for OUD: A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the symptoms in Table C-1, occurring within a 12-month period.[197]

Table C-1: DSM-5 Diagnostic Criteria for OUD [197]

DSM-5 Diagnostic Criteria for OUD
1. Craving or strong desire or urge to use opioids
2. Recurrent use in situations that are physically hazardous
3. Tolerance
4. Withdrawal (or opioids are taken to relieve or avoid withdrawal)
5. Using larger amounts of opioids or over a longer period than initially intended
6. Persisting desire or unable to cut down on or control opioid use
7. Spending a lot of time to obtain, use, or recover from opioids
8. Continued opioid use despite persistent or recurrent social or interpersonal problems related to opioids
9. Continued use despite physical or psychological problems related to opioids
10. Failure to fulfill obligations at work, school, or home due to use
11. Activities are given up or reduced because of use

Table C-2: DSM-5 Diagnostic Criteria for Severity of OUD [197]

Severity of OUD	Number of Symptoms
Mild	Presence of 2-3 symptoms
Moderate	Presence of 4-5 symptoms
Severe	Presence of 6 or more symptoms

Appendix D: Drug Tables

A. Short-acting, Orally Administered Opioids

Table D-1: Use of Short-acting, Orally Administered Opioids in Adults [198]

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Codeine (alone or in combination with APAP or ASA) ▪ Codeine available as 15, 30 and 60 mg tablets ▪ Combination products vary in codeine content from 15 to 60 mg/dose unit	▪ 15 to 30 mg every 4 to 6 hr ▪ Initial dose based upon codeine component, maximum dose based upon non-opioid component	▪ Maximum APAP dose: 4000 mg/d (2000 mg/d in chronic alcoholics or in hepatic impairment) ▪ Analgesic ceiling effect occurs with codeine at doses >60 mg/dose ▪ Codeine alone is a weak analgesic; more effective alternatives are available (including codeine in combination with APAP or ASA)	15 to 30 30 to 60 4 to 6	▪ *Elderly or debilitated*: Use with caution ▪ *Hepatic dysfunction:* Conversion to active metabolite (morphine) may be reduced in patients with cirrhosis; avoid use in patients with liver disease ▪ *Renal dysfunction:* Use lower dosage or an alternative analgesic	▪ Codeine may be less effective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[2]) because of decreased conversion to the active metabolite, morphine ▪ CYP-2D6 ultra-rapid metabolizers[3] can have extensive conversion to morphine with increase in opioid-mediated effects

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Hydrocodone (in combination with APAP, ASA, or IBU) ▪ Combination products vary in hydrocodone content (2.5 to 10 mg per dosage unit)	▪ 5 to 10 mg every 6 hr (hydrocodone component) ▪ Initial dose based upon hydrocodone component ▪ Maximum dose based upon non-opioid component	▪ Maximum dose: • 60 mg/d (4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics or hepatic impairment) for hydrocodone + APAP combination OR • 37.5 to 50 mg/d (1000 mg/d IBU) for hydrocodone + IBU combination	10 to 20 60 to 100 4 to 8	▪ *Elderly or debilitated*: Use with caution; start with reduced dose (2.5-5 mg) of hydrocodone component ▪ *Hepatic dysfunction:* Use with caution	▪ Conversion to the active metabolite, hydromorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[2]) ▪ CYP-2D6 ultra-rapid metabolizers[3] can have extensive conversion to hydromorphone with potential increase in opioid-mediated effects
Hydromorphone ▪ Available as oral liquid 1 mg/ml, and 2, 4, and 8 mg tablets	▪ 2 mg every 4 to 6 hr ▪ May give an initial dose of 4 to 8 mg for severe pain	▪ There is no optimal or maximum dose of hydromorphone; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	15 to 30 30 to 60 3 to 4	▪ *Elderly or debilitated*: Use with caution, start at 25% to 50% of usual dose at low end of dosing range ▪ *Hepatic / Renal dysfunction*: Reduce initial dose for moderate impairment, more with severe impairment	

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Morphine ▪ Available as oral solution (10 or 20 mg/5 ml, or 100 mg/5 ml for opioid-tolerant patients only) or as 15 or 30 mg tablets	▪ 10 to 30 mg every 4 hr	▪ There is no optimal or maximum dose of morphine; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	30 60 3 to 5	▪ *Elderly or debilitated*: Give with extreme caution; use lower dose ▪ *Hepatic dysfunction*: Use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 hr) and bioavailability is increased ▪ *Renal dysfunction*: Reduce dose or, if severe renal impairment exists, avoid use (see *Other Considerations*)	▪ M6G, an active metabolite, may accumulate in renal impairment ▪ M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Oxycodone (alone or in combination with APAP or ASA) ▪ Single-agent oxycodone available as oral solution 5 mg/5 ml, 20 mg/1 ml, and oral tablet 5, 10, 15, 20, and 30 mg ▪ Combination products vary in oxycodone content, 2.5 to 10 mg per dose unit	▪ 5 to 15 mg every 4 to 6 hr ▪ Initial dose based upon oxycodone component ▪ Maximum dose based upon non-opioid component	▪ For combination products, maximum dose is limited by APAP or ASA content (4000 mg/d for both; 2000 mg/d APAP in chronic alcoholics or patients with hepatic impairment) ▪ There is no optimal or maximum dose of oxycodone; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	10 to 15 30 to 60 3 to 6	▪ *Elderly or debilitated*: reduce dosage ▪ *Hepatic / Renal*: Use with caution; consider reducing dose and increasing frequency of dosing	▪ Conversion to the active metabolite, oxymorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[2])

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Oxymorphone ▪ Available as 5 or 10 mg tablets	▪ 5 mg every 4 to 6 hr	▪ There is no optimal or maximum dose of oxymorphone; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	30 to 45 N/A 4	▪ *Elderly or debilitated*: Use with caution and start at low end of dosing range; levels are increased 40% in patients ≥65 years ▪ *Hepatic dysfunction* • *Mild hepatic impairment:* Use cautiously, start at low end of dosing range • *Moderate and severe hepatic impairment:* Contraindicated ▪ *Renal dysfunction*: Bioavailability is increased 57-65% in moderate and severe impairment; start at lower doses and adjust slowly	▪ Food has been shown to increase peak levels of oxymorphone immediate-release by 38%; must be taken on an empty stomach at least 1 hr before or 2 hr after a meal ▪ Must NOT be taken concomitantly with alcohol; alcohol (240 ml of 4% to 40% ethanol) can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270% (demonstrated with ER oxymorphone)

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Tapentadol ▪ Available as 50, 75, or 100 mg tablets	▪ 50 mg every 4 to 6 hr	▪ Subsequent dose is 50, 75, or 100 mg every 4 to 6 hr, adjusted to analgesia and tolerability ▪ Second dose may be given 1 hr after the first dose if necessary ▪ Max recommended dose: 700 mg on first day, 600 mg on subsequent days ▪ Use tapentadol only under careful medical supervision at lowest effective dose ▪ Patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	N/A (rapid) 60 4 to 6	▪ *Elderly*: Consider starting at the lowest recommended dose ▪ *Hepatic dysfunction:* • *Mild hepatic impairment:* No dosage adjustment • *Moderate hepatic impairment:* Start at 50 mg and give subsequent doses at least 8 hr apart (max. 3 doses in 24 hr) • *Severe hepatic impairment:* Use is not recommended ▪ *Renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment ▪ *Respiratory dysfunction:* Use with caution because of respiratory depressant effects; consider non–mu opioid agonist analgesics	▪ Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration ▪ If used in combination with other CNS depressants, consider dose reduction of one or both agents ▪ Use with or within 14 days of MAOIs is contraindicated

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Tramadol (alone or in combination with APAP) ▪ Tramadol available as 50 mg tablet, or in tablet combination with APAP (325 mg APAP, 37.5 mg tramadol)	▪ 25 mg every morning	▪ May increase by 25 mg per day every 3 days to 100 mg tramadol/d (25 mg every 6 hr) ▪ Subsequent increments of 50 mg/d may then be made every 3 days to 200 mg/d (50 mg every 6 hr) ▪ After titration, may give 50 to 100 mg every 4 to 6 hr ▪ Maximum daily dose of tramadol: 400 mg/d ▪ Combination product: maximum 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics or in hepatic impairment	<60 ~120 to 240 6	▪ *Elderly or debilitated:* In elderly patients >75 years: give <300 mg/d in divided dose; use with caution in debilitated patients ▪ *Hepatic dysfunction:* Decrease dosage to 50 mg once every 12 hr in patients with cirrhosis ▪ *Renal dysfunction*: • *CrCl >30 ml/min:* No change in dose or frequency required • *CrCl <30 ml/min:* Increase dosing interval to 12 hr and decrease maximum daily dose to 200 mg ▪ *Dialysis patients*: Can receive their regular dose on the day of dialysis (<7% of a dose is removed by hemodialysis)	▪ Slower initiation and titration improves tolerability ▪ Inhibits reuptake of serotonin and norepinephrine; concomitant use with MAOIs or SSRIs may increase risk of seizures, serotonin syndrome ▪ Dose carefully or use another agent in patients on serotonergic agents ▪ Seizures reported within the recommended dosage range; increased risk above recommended dosage range and in patient with seizure disorder, history of seizures, in conditions with increased risk of seizures, or with other drugs that increase seizure risk; observe maximum dose limits ▪ Serious anaphylactoid reactions reported, often following first dose; patients with a history of anaphylactoid reaction to codeine and other opioids may be at increased risk

[1] Check local formulary for available formulations.

[2] CYP-2D6 Inhibiting Drugs: Antiarrhythmics (amiodarone, propafenone, quinidine [strong inhibitor]); analgesics (methadone [weak inhibitor], propoxyphene); antihistamines (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); histamine2 receptor antagonists (cimetidine); neuroleptics (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); protease inhibitors (ritonavir), quinine compounds (hydroxychloroquine, quinacrine, quinine); selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline), miscellaneous compounds (clomipramine, ketoconazole, ticlopidine)

[3] CYP-2D6 ultra-rapid metabolizers include 1% of Asian and Hispanic, 1-10% of Caucasians, 3% of African-Americans, and 16-28% of N. African and Arabic populations.

[4]Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone or equianalgesic dose of another opioid.

Abbreviations: APAP: acetaminophen; ASA: acetylsalicylic acid; CNS: central nervous system; CrCl: creatinine clearance; d: day(s); ER: extended-release; hr: hour(s); IBU: ibuprofen; LOT: long-term opioid therapy; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mg: milligram(s); min: minute(s); mL: milliliter(s); SSRIs: selective serotonin reuptake inhibitors

B. Long-acting/Extended-release Opioids

Table D-2. Use of Long-acting/Extended-release Opioids in Adults [198]

- Long-acting/ER opioids expose patients and other users to the risks of opioid misuse and OUD, which can lead to overdose and death, even when used at recommended dosages. Long-acting/ER opioids should be reserved for patients for whom alternative analgesic treatment options (e.g., non-opioid analgesics or immediate-release opioid analgesics) are ineffective, not tolerated, or provide inadequate control of pain. Assess each patient's risk prior to prescribing long-acting/ER opioids and institute risk mitigation strategies.
- The FDA has mandated that long-acting/ER opioids be subject to a structured Risk Evaluation and Mitigation Strategy (REMS) program to manage known or potential serious risks associated with their use (see http://www.er-la-opioidrems.com/IwgUI/rems/home.action).
- Most abuse deterrent technologies have been designed to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. In spite of these efforts, no opioid formulation prevents consumption of a large number of intact capsules or tablets, which continues to be the most common method of abuse.
- Long-acting/ER opioids should not be used for management of acute pain (with exception of oxycodone/acetaminophen ER tablets), as an as-needed medication, or on initiation of LOT (see Recommendation 13).

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine buccal film ▪ Available in strengths of 75, 150, 300, 450, 600, 750 and 900 mcg/film for twice daily administration	▪ 75 mcg once or twice daily for at least 4 days, then increase dose to 150 mcg every 12 hr ▪ There is potential for buprenorphine to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioid should be tapered to ≤30 mg MEDD before initiating buprenorphine	▪ After initial dosing, dosing changes as necessary can proceed in increments of 150 mcg every 12 hr, no more frequently than every 4 days ▪ Patients on prior dose of opioid 30 to 89 mg MEDD may initiate buprenorphine film at 150 mcg every 12 hr, 90 to 160 mg MEDD may initiate at 300 mcg every 12 hr; if prior opioid is >160 mg MEDD – consider an alternative analgesic ▪ Time to steady state ~3 days with every 12 hr dosing	▪ *Elderly:* Initiation at the low end of the dosing range is recommended ▪ *Renal dysfunction:* No dose adjustment recommended ▪ *Hepatic dysfunction:* Patients with severe hepatic impairment should have starting and titration doses reduced by half that of patients with normal liver function	▪ QTc prolongation reported with recommended doses of buprenorphine; maximum dose of 900 mcg every 12 hr established due to the potential for this adverse effect; avoid in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic drugs ▪ Buprenorphine buccal film is a potential treatment option for patients with significant renal impairment and those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of orally administered medications
Buprenorphine TDS ▪ Available in every 7 day patch formulation that delivers transdermal buprenorphine at the following rates: 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr	▪ In opioid-naïve or in patients on <30 mg MEDD of alternate agent: Initiate treatment with 5 mcg/hr patch ▪ There is potential for buprenorphine to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioid should be tapered to ≤30 mg MEDD before initiating buprenorphine; the 10 mcg/hr patch may then be initiated at the next dosing interval	▪ The maximum dose of buprenorphine TDS 20 mcg/hr may not provide adequate analgesia for patients requiring greater than 80 mg MEDD; an alternate analgesic should be considered ▪ Steady state achieved in ~3 days	▪ Dosage does not need to be adjusted in patients with mild or moderate hepatic impairment, renal impairment, or in the elderly ▪ Potential treatment option for patients with significant renal impairment or those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of oral medications	▪ Buprenorphine patch 10 mcg/hr is approximately equivalent to an oral MEDD of 18-28 mg; the 20 mcg/hr patch is approximately equivalent to a MEDD of 36-55 mg ▪ Dose of one 20 mcg/hr patch per week should not be exceeded due to risk of QTc prolongation ▪ Avoid use in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications ▪ Advise patients that application of external heat (e.g., hot baths, sunbathing, saunas, heating pads) increases maximum plasma concentration of buprenorphine and risk of fatal overdose

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Fentanyl TDS ▪ Available in every 3 day patch formulation that delivers transdermal fentanyl at the following rates: 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr	▪ Fentanyl TDS is contraindicated in non-opioid-tolerant patients ▪ Fentanyl TDS is contraindicated in the management of mild or post-operative pain, and as an "as-needed" analgesic ▪ The initial dose of fentanyl TDS in opioid-tolerant patients [2] is 25 mcg/hr, applied every 72 hr; the 12 mcg/hr dose has not been evaluated as an initial dose	▪ Fentanyl TDS must be used only on intact skin ▪ Dose change increments should be based on supplemental opioid doses, using a ratio of fentanyl TDS 12 mcg/hr for every 45 mg/24 hr of supplemental oral MEDD ▪ Dosing changes, as necessary, should occur at least 3 days after the initial dose; thereafter, not more often than every 6 days	▪ *Elderly:* Twice as sensitive to fentanyl as younger patients; avoid initiation at doses >25 mcg/hr unless patient is already taking >135 mg oral morphine or equivalent ▪ *Hepatic / Renal dysfunction:* Reduce dose by 50% in mild-moderate impairment and avoid use if impairment is severe ▪ *Patients with fever*: Increased body temperature may increase release of fentanyl from the TDS; monitor patients for opioid adverse effects and modify dosage as necessary	▪ Consider fentanyl TDS in patients with persistent, moderate-to-severe pain who cannot take oral ER morphine or oral ER oxycodone ▪ Avoid application of external heat sources (e.g., heating pads, electric blankets, heat lamps, saunas, hot tubs, hot baths, sunbathing, heated water beds) to the application site while the patch is worn as heat may increase release and speed absorption of fentanyl ▪ Using damaged or cut fentanyl TDS patches can lead to rapid release of the contents of the patch and fatal overdose ▪ Use of fentanyl TDS with CYP3A4 inhibitors[3] can result in increased fentanyl plasma concentrations, increased or prolonged opioid effects, including fatal respiratory depression; use extreme caution and frequent monitoring in patients receiving these combinations ▪ CYP 3A4 inducers may increase fentanyl clearance

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydrocodone ER ■ **ER tablets** contain 20, 30, 40, 60, 80, 100 or 120 mg hydrocodone for once daily administration ■ **ER capsules** contain 10, 15, 20, 30, 40 or 50 mg hydrocodone for every 12 hr administration	■ *Opioid-naïve patients:* 20 mg ER tablet once daily ■ *Opioid-naïve patients:* 10 mg ER capsule every 12 hr ■ *Opioid tolerant [2] patients:* Convert current opioid to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	■ *For opioid-experienced, both ER tablets and capsules:* Convert current opioid to equianalgesic hydrocodone dose then reduce that dose by 25%; initiate at nearest whole-tablet or capsule strength, rounding down as necessary ■ *For both tablets and capsules:* Dose change increments of 20 mg per day may be made every 3 to 7 days ■ Steady state achieved in ~3 days of dosing	■ *Elderly:* No significant pharmacokinetic differences ■ *Patients with renal impairment:* Hydrocodone plasma concentrations are increased in moderate or severe impairment; use low initial dose and monitor closely for adverse events such as excessive sedation and respiratory depression ■ *Patients with hepatic impairment:* no dosage adjustment is required in mild or moderate hepatic impairment; start with the lowest dose, 10 mg, in patients with severe hepatic impairment, and monitor closely	■ CYP3A4 inhibitors[3] may decrease clearance of hydrocodone, increase plasma concentrations, and increase risk of overdose; CYP3A4 inducers[4] may increase clearance and reduce opioid effect ■ Both ER tablets and ER capsules are formulated with polyethylene oxide which imparts ER properties ■ Hydrocodone ER tablets or capsules must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose ■ ER tablet has abuse deterrent labeling related to resistance to crushing and high viscosity when dissolved in aqueous solution ■ ER capsule has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydromorphone ER Tablets ▪ Available as 8, 12, 16, and 32 mg tablets for once daily administration	▪ Not indicated in opioid-naïve patients due to the risk of respiratory depression ▪ *Opioid tolerant*[2] *patients:* Convert current opioid to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	▪ Dosage adjustments may be made in increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia ▪ Steady state reached after 3 to 4 days of once-daily dosing	▪ *Elderly:* No specific guidance; monitor closely, particularly when initiating or titrating dosage ▪ *Patients with renal impairment:* Start patients with moderate impairment at 50% of usual dose, and patients with severe impairment at 25% of usual dose ▪ *Patients with hepatic impairment:* Start patients with moderate impairment at 25% of usual dose in non-impaired patients	▪ Hydromorphone ER tablets must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose ▪ Hydromorphone ER contains sulfites ▪ Hydromorphone ER has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Methadone ▪ Available as 5 and 10 mg tablets and oral solution, 5 or 10 mg/5 ml, for every 8 to 12 hr administration	▪ Should not be used for as-needed supplemental OT ▪ *Initial dose:* 2.5 to 5 mg orally every 8 to 12 hr; more frequent administration (every 6 hr) may be necessary during initiation to maintain analgesia ▪ START LOW AND GO SLOW ▪ See Appendix D for detailed dosing information including dosing recommendations in patients previously exposed to opioids ▪ Monitor patients carefully during initiation, conversions to and from other opioids, and dose titration	▪ Dose change increments of ▪ 2.5 mg every 8 hr may be made every 5 to 7 days ▪ Delayed analgesia or toxicity may occur because of drug accumulation after repeated doses, e.g., on days 2 to 5; if patient has excessive sedation during this timeframe, consider temporarily holding dose(s), lowering the dose, and/or slowing the titration rate ▪ Once a stable analgesic dose is reached, the dosing interval may be extended to every 8 to 12 hr or longer	▪ *Elderly or debilitated*: Consider reduced dosing in elderly or debilitated patients who may be more sensitive to opioid adverse effects ▪ *Hepatic dysfunction*: No dosage adjustments required in patients with stable chronic liver disease or mild-to-moderate hepatic dysfunction; avoid in severe liver disease ▪ *Renal dysfunction*: Methadone and its metabolites do not accumulate in patients with renal failure; however, dosage reduction by up to 50-75% is recommended in patients with CrCl <10 mL/min	▪ Prescribers of methadone should be thoroughly familiar with its complex pharmacokinetic and pharmacodynamic properties or consult a clinician with experience in dosing methadone ▪ Plasma half-life (22 to 128 hr short-term; 24 to 48 hr at steady-state) may be longer than the analgesic duration ▪ Methadone has little cross-tolerance with other opioids; therefore, even patients with a high degree of opioid tolerance may be at risk for overdose when switched to methadone ▪ Methadone is the only long-acting opioid available as an oral solution ▪ Methadone may be subject to drug interactions with agents that can influence CYP2B6 (e.g., ticlopidine) ▪ May prolong QTc intervals on ECG; risk of torsade de pointes; see Appendix D for detailed QTc monitoring information

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Morphine CR or SR ▪ Available in 15, 30, 60, 100, and 200 mg strengths for every 8 to 12 hr administration ▪ Morphine ER capsules available in 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, and 200 mg capsule strengths for once daily administration **Morphine and Naltrexone ER Capsule** ▪ Available as 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, and 100/4 capsule strengths (mg morphine/mg naltrexone) for once or twice-daily administration	▪ *Opioid-naïve patients:* Morphine CR or SR 15 mg every 8 to 12 hr ▪ Total daily increments of <30 to 40 mg/d may be made every 2 days ▪ *Opioid-naïve patients:* Morphine ER capsules are not indicated in opioid-naïve patients ▪ *Patients who are not opioid tolerant:* Start morphine ER at 30 mg daily, may adjust every 1 to 2 days ▪ *Opioid-naïve patients:* Initiate at the lowest dose, 20 mg/0.8 mg once daily ▪ *Opioid tolerant*[2] *patients:* Convert current opioid to equianalgesic daily dose of morphine; reduce the calculated amount by 33-50% for initial start dose (see Table D-3) ▪ Dose may be up titrated no more frequent than every other day	▪ Morphine CR or SR tablets should be swallowed whole, not broken, chewed, or crushed ▪ For patients who have difficulty swallowing, SR and ER capsules may be opened and the pellets may be sprinkled onto a small amount of soft food (for administration without chewing) or administered via 16F gastrostomy tube ▪ Steady state achieved with morphine ER within 24 to 36 hr ▪ Morphine/naltrexone must be swallowed whole or the contents of the capsules sprinkled on apple sauce; crushing, dissolving, or chewing pellets may cause a fatal overdose (particularly in the opioid-naïve patient) and the absorption of naltrexone could increase the risk of precipitating withdrawal in opioid tolerant patients ▪ Morphine/naltrexone: If once daily administration results in inadequate analgesia, may switch to twice daily dosing	*Information applies to all formulations of morphine listed* ▪ *Elderly:* Use with caution and at lower dose ▪ *Patients with renal dysfunction:* Bioavailability is increased and clearance is decreased; metabolites M3G and M6G accumulate significantly ▪ Reduce dose or, if severe renal impairment exists, avoid use ▪ *Patients with hepatic dysfunction:* Clearance decreases and half-life increases; M3G and M6G to morphine ratios are reduced; use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times	▪ Morphine SR is preferred first-line long-acting agent because of similar efficacy to other long-acting opioids, comparable safety profile, provider familiarity with use, and lower cost ▪ M6G, an active metabolite, may accumulate in renal impairment and contribute to excessive opioid effects ▪ M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia ▪ Morphine/naltrexone ER capsule has abuse deterrent labeling related to potential to precipitate withdrawal if drug is taken by other than oral route

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone ER ■ **Tablets** available in 10, 15, 20, 30, 40, 60, and 80 mg strengths for every 12 hr administration ■ **Capsules** available in 9, 13.5, 18, 27 and 36 mg strengths for every 12 hr administration	■ *Opioid-naïve patients:* 10 mg (tablets) or 9 mg (capsules) orally every 12 hr ■ *Opioid tolerant[2] patients:* Convert current opioid to equianalgesic daily dose of oxycodone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	■ *Dose change increments:* May increase to 20 mg (tablets) or 18 mg (capsules) every 12 hr after 1 or 2 days; thereafter, the total daily dose may be increased by 25-50% of the current dose every 1 or 2 days ■ ER tablets are not bioequivalent to ER capsules; 10 mg oxycodone HCl (ER tablet) = 9 mg oxycodone base (ER capsule) ■ Steady state achieved with tablets or capsules in 24 to 36 hr with repeat dosing	■ *Elderly*: Plasma concentrations of oxycodone are increased ~15% in the elderly; however, usual dosing and dosing intervals may be appropriate ■ *Patients with renal dysfunction*: Plasma concentrations of oxycodone are increased ~50% in patients with CrCl <60 ml/min; dose conservatively and adjust according to clinical situation ■ *Patients with hepatic dysfunction*: Reduce initial dose to 1/3 to 1/2 of the usual dose and monitor closely	■ Recommended for patients who experience intolerable, unmanageable adverse effects to long- acting morphine ■ Both ER tablets and ER capsules have abuse deterrent labeling related to resistance to abuse by intranasal and intravenous means ■ ER tablets should be swallowed whole, not broken, chewed, or crushed ■ ER capsules may be opened and sprinkled on soft food or administered via feeding tube

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone/APAP ER ▪ Available as tablets containing oxycodone 7.5 mg and APAP 325 mg for every 12 hr administration	▪ *Opioid-naïve patients:* May initiate therapy with the standard dose of 2 tablets every 12 hr ▪ A standard, single dose consists of 2 tablets totaling 15 mg oxycodone/650 mg APAP ▪ This is the only long-acting/ER opioid to have an acute pain indication	▪ The polyethylene oxide content causes the tablet to swell and become sticky when wet. This has the potential to cause obstruction of the airway or GI obstruction ▪ Steady state concentration of both components are reached within 24 hr of product initiation	▪ *Elderly:* Take precautions when determining the dosing amount and frequency in geriatric patients since a greater sensitivity to oxycodone may be observed in this patient population when compared to younger patients ▪ *Patients with renal or hepatic dysfunction:* Patients with renal dysfunction (CrCl <60 ml/min) or hepatic dysfunction should initiate therapy with 1 tablet every 12 hr and adjust as needed	▪ This long-acting/ER opioid is an exception to the REMS requirements due to the relatively low amount of oxycodone contained in each tablet ▪ Oxycodone/APAP ER tablets are formulated with PEO which is responsible for its ER in addition to labeled abuse deterrent properties ▪ Patients should be instructed not to pre-soak, lick, or otherwise wet tablets prior to swallowing and to take one tablet at a time with adequate water to insure complete and immediate swallowing

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxymorphone ER Tablets ▪ Available as 5, 7.5, 10, 15, 20, 30 and 40 mg tablets for every 12 hr administration	▪ *Opioid-naïve patients:* Initiate at 5 mg every 12 hr ▪ *Opioid tolerant[2] patients:* Convert current opioid to equianalgesic daily dose of oxycodone; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	▪ *Dose change increments:* May increase by 5 to 10 mg every 12 hr every 3 to 7 days ▪ Oxymorphone ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth ▪ Steady-state plasma levels are achieved after 3 days of multiple dose administration	▪ *Elderly:* Plasma drug levels are about 40% higher in elderly versus younger subjects; use caution, starting at the low end of dosing range and titrating slowly ▪ *Patients with renal dysfunction:* Bioavailability is increased by 57% in moderate impairment and by 65% in severe impairment; in patients with CrCl <50 mL/min, oxymorphone should be started with the lowest dose and titrated slowly ▪ *Patients with hepatic dysfunction:* Use with caution in patients with mild hepatic impairment, starting with lowest dose and titrating slowly ▪ Contraindicated in patients with moderate or severe hepatic impairment	▪ Must be taken on an empty stomach at least 1 hr before or 2 hr after a meal; food has been shown to increase peak levels of oxymorphone ER by 50% ▪ Must NOT be taken concomitantly with alcohol, which can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270%

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Tapentadol ER ▪ Available as tablets containing 50, 100, 150, 200, or 250 mg tapentadol for twice daily dosing	▪ *In opioid-naïve and non-tolerant patients:* Initiate therapy with 50 mg twice daily; use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression ▪ There are no established conversion ratios for conversion from other opioid to tapentadol ER; convert current opioid to an estimated equianalgesic daily dose of tapentadol; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	▪ *Dose change increments:* May increase dose by no more than 50 mg twice daily every 3 days ▪ *Maximum daily dose*: 500 mg daily ▪ Tapentadol ER tablets must be taken whole; crushing, chewing, or dissolving tablets will result in uncontrolled delivery of tapentadol and can lead to overdose or death ▪ Steady state is attained after the third dose (24 hr after the first twice daily multiple dose administration)	▪ *Elderly:* No dosing adjustment needed, consider starting at lowest recommended dosage ▪ *Patients with renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment ▪ *Patients with hepatic dysfunction:* Use not recommended in severe hepatic impairment	▪ Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration and cause fatal overdose ▪ Use with or within 14 days of MAOIs is contraindicated
Tramadol ER ▪ Available as 100, 200 and 300 mg tablets for once daily administration	▪ *Patients not currently on tramadol:* 100 mg once daily ▪ Converting from tramadol IR: Start at 24 hr dosage equivalent rounded down to closest 100 mg increment	▪ *Dose change increments:* May increase by 100 mg every 5 days based on analgesia and tolerability ▪ Maximum dose: 300 mg/day	▪ *Elderly:* Start at low end of dosing range; use particular caution, especially in patients >75 years ▪ *Renal dysfunction:* Avoid use if CrCl <30 ml/min ▪ *Hepatic dysfunction:* Avoid use in severe hepatic impairment (Child- Pugh Class C)	▪ Must be swallowed whole and must not be chewed, crushed, or split ▪ See warnings and precautions under Other Considerations for tramadol IR (Table D-1)

[1]Check local formulary for available formulations.

[2]Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone or equianalgesic dose of another opioid.

[3]CYP3A4 inhibiting agents include: ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil

[4] CYP3A4 inducing agents include: carbamazepine, phenobarbital, phenytoin, primidone, rifampin

Abbreviations: APAP: acetaminophen; CR: morphine controlled; CrCl: creatinine clearance; CYP2B6: cytochrome P450 2B6; CYP3A4: cytochrome P450 3A4; ECG: electrocardiogram; ER: extended-release; GI: gastrointestinal; HCl: hydrochloride; hr: hour(s); IR: immediate release; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mcg: microgram(s); MEDD: morphine equivalent daily dose; mg: milligram(s); min: minute(s); mL: milliliter(s); OT: opioid therapy; PEO: polyethylene oxide; TDS: transdermal system; QTc: the heart rate's corrected time interval from the start of the Q wave to the end of the T wave; REMS: Risk Evaluation and Mitigation Strategy; SR: sustained release

C. Morphine Milligram Equivalent Doses

Table D-3: Morphine Milligram Equivalent Doses for Commonly Prescribed Opioids[33]

Morphine Milligram Equivalent Doses (MME)	
Opioid Agent	**Conversion Factor**
Codeine[1]	0.15
Tapentadol[2]	0.4
Morphine	1
Hydrocodone	1
Oxycodone	1.5
Oxymorphone	3
Hydromorphone	4

- All doses in mg/d except for fentanyl.
- Multiply the daily dosage for each opioid by the conversion factor to determine the equianalgesic dose in MME. Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics.
- Do not use the calculated dose in MME to determine the doses to use when converting one opioid to another. When converting opioids, the new opioid is typically dosed at substantially lower than the calculated MME dose (33-50% less) to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics.
- Use particular caution with fentanyl because it is dosed in mcg/hr instead of mg/d, and absorption is affected by heat and other factors.
- See Table D-2 for conversion guidance for buprenorphine-containing agents.

[1]When converting from weak opioid analgesics to more potent opioids, use the recommended initial doses of the new opioid for opioid-naïve patients.

[2]The conversion factor estimate for tapentadol is based upon μ-receptor agonist activity in animal models where tapentadol has been shown to be 2-3 times less potent than morphine.

Abbreviations: d: day(s); hr: hour(s); mcg: microgram(s); mg: milligrams; MME: morphine milligram equivalent dose

D. Methadone Dosing Guidance

a. Summary

- Methadone is not a first-line agent for the treatment of chronic pain.[33] It is an alternative long-acting opioid analgesic that may be useful in managing pain severe enough to require continuous daily treatment for which alternative treatment options are inadequate.
- In general, as with other opioids, methadone should be used as one aspect of a comprehensive pain management plan, as agreed upon by the practitioner and the patient.
- Methadone should be initiated and adjusted by, or in consultation with, a practitioner who has the relevant knowledge and expertise;[33] if a provider with clinical experience is not available, then another long-acting opioid may be used until such consultation is obtained.
- The general principles utilized in the dosing of methadone are different than those of other opioids; these differences are due to methadone's unique pharmacokinetic and pharmacodynamic properties and include, but are not limited to:
  - Dose titration should occur after at least 5-7 days on a designated dose (in the large majority of cases)
  - Careful consideration must be given to potential drug interactions and to the potential for QT prolongation
- Methadone is considered to be safe in patients with renal and/or hepatic impairment but should be used with caution in end-stage disease cases of these conditions.
- There are a number of methods available that use conversion ratios to initiate or titrate methadone; no single method is considered superior to others. Titration should be based on patient response and not solely based on equianalgesic dosing tables.
- Monitoring ECG for QTc interval prolongation is recommended based upon certain clinical scenarios.

b. Overview

Methadone is indicated for persistent, moderate-to-severe chronic pain in patients requiring continuous, around-the-clock opioid administration over an extended time. Methadone's pharmacokinetic properties are complex and incompletely documented.[199,200] It has a long elimination half-life that has wide inter-patient variability (mean or median half-life, depending on subject type, ranges from 3-128 hr) [201-214] and does not reflect duration of analgesia.[210,215] Initially, methadone duration of analgesia ranges from 4-6 hr; however, with repeated dosing, duration of analgesia can extend to 8-12 hr. Accordingly, while initial dosing may require more frequent administration (three times per day [TID]) to achieve adequate analgesia,[216,217] once steady-state levels are established, reducing dosing frequency to two times per day (BID) can be considered. In elderly and frail patients, consideration may be given to starting with BID dosing. Also, as a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. It may take ten days for plasma levels to stabilize; thus, as a general rule, dose titration should not be more frequent than every 5-7 days.[218] Patients should be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased.[33] Once stable dosing is established, follow-up can be as clinically warranted.

While methadone is an alternative to ER morphine or oxycodone for treatment of moderate-to-severe pain, a number of authors have cautioned about the complexities of dosing and suggested the drug be prescribed by practitioners with relevant experience, in an adequately monitored setting.[33,216,217,219-225] Significant toxicity has occurred particularly when doses were increased too frequently, conversion doses were too high, or dosing intervals too close.[222,226-228]

In 2014, a methadone safety guideline was developed by the American Pain Society and College of Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, which made recommendations for safer prescribing of methadone.[169] Table D-4 outlines baseline and monitoring recommendations based on categorization of patients for risk of QTc prolongation. Palliative care patients with the goal of comfort care may require less vigilance with ECG monitoring.

Table D-4: Baseline and Monitoring Recommendations Based on Categorization of Patients for Risk of QTc Prolongation [169]

Category	Baseline ECG	Follow Up ECGs[1]	Action
Patients with risk factors for QTc prolongation, any prior QTc >450, or history of syncope	Obtain baseline ■ ECG within last 3 months is sufficient ■ Strong recommendation ■ Low quality evidence	■ 2-4 weeks after initiation ■ With significant dose increases ■ When methadone dose reaches 30-40[2] mg/d ■ When methadone dose reaches 100 mg/d[2] ■ When new risk factors arise or signs or symptoms of suggestive arrhythmia	■ Avoid use if QTc >500 ms[3] ■ Consider alternative to methadone for QTc 450-500[3] ■ Evaluate and correct reversible causes of QTc prolongation
Patients not known to be at higher risk of QTc prolongation	Consider baseline ■ ECG within the last 12 months is sufficient ■ Weak recommendation ■ Low quality evidence	■ When methadone dose reaches 30-40[2] mg/d ■ When dose reaches 100 mg/d[2] ■ When new risk factors arise or signs or symptoms of suggestive arrhythmia	■ Avoid use if QTc >500 ms[3] ■ Consider alternative to methadone for QTc 450-500[3] ■ Evaluate and correct reversible causes of QTc prolongation

[1]Consider obtaining yearly ECGs once a stable dose is reached.

[2]Doses this high are not recommended for chronic pain and are typically observed only for patients receiving methadone for MAT for OUD.

[3]For patients on stable doses of methadone in whom a prolonged QTc has been noted (QTc >450 ms), consider tapering the dose of methadone and repeating the ECG. Other QT prolonging medications should be evaluated and cardiology specialty care should be consulted for expert opinion.

Abbreviations: d: day(s); ECG: electrocardiogram; MAT: medication assisted treatment; ms: millisecond(s); mg: milligram(s); OUD: opioid use disorder; QTc: QTc interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave)

Special caution is recommended with concurrent benzodiazepines and drugs that prolong the QT interval.[229]

Methadone is primarily metabolized by CYP450 2B6 to inactive/nontoxic metabolites.[230-236] CYP2B6 is a highly polymorphic gene[237] and may help to explain why the pharmacokinetics of methadone can be extremely variable from individual to individual. Currently, it is unclear whether cytochrome P450 3A has

any influence on methadone metabolism and caution is encouraged when using drugs that interact with both enzymes.

c. Dosing Strategies

The dosing recommendations listed below (in Table D-5) are provided to offer guidance on using methadone in the treatment of patients with chronic pain, particularly when converting from another opioid to methadone. The use of methadone for pain should be done in the context of a pain clinic or with assistance of local pain management experts, including healthcare providers or pharmacists, who have experience with methadone's use. If such resources are not readily available, other long-acting opioids should be considered (e.g., morphine sustained action [SA], or oxycodone SA).

Various methadone dosing strategies have been employed [224,238,239] and methods are still evolving. Older, prospective studies found no evidence to support the superiority of one dosing strategy over another.[220,240,241] The lack of prospective and comparative studies concerning methadone dosing strategies highlights the need to carefully individualize the dosing regimen of methadone.

For opioid tolerant patients, a number of different equianalgesic dose ratio tables can be used to determine the dose of methadone.[220,223,242-245] This VA/DoD OT CPG includes one of the more conservative equianalgesic dose ratio tables as a reference for providers to discuss and/or consider (Table D-3).[245] Local subject matter experts may prefer, or be more familiar with, other accepted (evidence-based) equianalgesic dose ratio tables. No equianalgesic dose ratio table is considered superior and all have similar limitations. When converting to methadone, lower MEDDs have lower conversion ratios than higher MEDDs. As compared to lower MEDDs, higher MEDDs may convert to smaller methadone doses than one might expect. For example, 60 mg MEDD would be ~15 mg of methadone/day (a ratio of ~4:1); whereas 180 mg MEDD would be ~22.5 mg/day (a ratio of ~8:1). Methadone dose conversion is not a linear process. Furthermore, while the equianalgesic dose ratio tables account for cross-tolerance,[218] some subject matter experts feel the calculated methadone dose should be further decreased for incomplete cross-tolerance, especially for patients on higher MEDDs. [169,246]

Table D-5: Dosing Recommendations for Patients Receiving Codeine Preparations or No Previous Opioids [247,248]

Dosing Strategy	Initial Methadone Dose	Increments	Comments
Gradual titration (For CNCP and situations necessitating less frequent monitoring)	2.5 mg every 12 hr or 8 hr	2.5 mg every 12 hr or 8 hr, no more often than every 5 to 7 d	As a general rule, *start low and go slow*
Faster titration (For cancer pain and situations where frequent monitoring is possible)	2.5-5 mg every 8 hr	2.5 to 5 mg every 8 hr as often as every third day	

Note: All doses refer to oral administration
Abbreviations: CNCP: chronic non-cancer pain; d: day(s); hr: hour(s); mg: milligram(s)

Table D-6: Equianalgesic Dose Ratios [245,246]

Morphine Dose (mg/d)	<30	31-99	100-299	300-499	500-999	1000-1200	>1200
Morphine: Methadone	2:1	4:1	8:1	12:1	15:1	20:1	Consult

Note: The conversion ratio increases as the morphine equivalent dose increases [33,220-222,249]
Abbreviations: d: day(s); mg: milligram(s)

The equianalgesic dose ratio is only one component of the process for appropriate dosing of methadone and other opioids. Once the dose is determined, there are two different methods to make the switch: a rapid conversion method and a stepwise/phased conversion. Again, no one conversion method has been determined to be superior to the others.

- For rapid conversion, the previous opioid is discontinued and the calculated methadone dose is started on day one.
- For the stepwise/phased conversion, the dose of the previous opioid is decreased by 1/3 and replaced with 1/3 of the calculated methadone dose (given in three divided doses). Then the previous opioid dose is decreased by an additional 1/3 and the methadone dose is increased by 1/3. Finally, the remaining 1/3 of the previous opioid dose is discontinued and the methadone dose is increased to the initial calculated dose. This can be done over several days or weeks.[218,250]

For breakthrough pain, a short-acting opioid preparation (e.g., acetaminophen with hydrocodone, oxycodone with or without acetaminophen, or immediate-release morphine) may be used until steady state is achieved (i.e., 5-7 days). As-needed methadone has also been used in a palliative care setting;[224,238,240] however, it is generally discouraged to avoid drug accumulation. It is important to note that use of breakthrough pain medications in patients with CNCP is controversial. If opioid medications for breakthrough pain are indicated, following titration to a stable methadone dose in CNCP patients, they should be used sparingly.[241]

d. Converting from Methadone to Oral Morphine

Switching from methadone to another opioid is not simply the reverse process; the equianalgesic dose ratio tables previously mentioned are not bi-directional and cannot be used in reverse (i.e., the morphine to methadone conversion ratio may not be the same as the methadone to morphine ratio).[251] There is no widely accepted conversion strategy for switching from methadone to another opioid. A proposed safe and conservative approach is a 1:3 methadone to morphine ratio (10 mg methadone/day = 30 mg oral morphine/day).[218] However, literature suggests patients may end up on as high as 1:4.7 methadone to morphine ratio (10 mg methadone = 47 mg morphine).[252]

e. Special Patient Populations

Patients 65 years and older may have decreased clearance of methadone.[212] Dosage adjustments do not appear necessary in patients with stable chronic liver disease; in addition, methadone and its metabolites do not accumulate in patients with renal failure.[253] However, two prospective studies on methadone dosing strategies excluded patients with liver or renal disease,[220,240] thus caution should

be observed when dosing methadone in these populations. Dosage adjustments may be necessary in patients with end-stage liver or renal disease.

f. Patient Education

Discuss the following information with patients prior to and during treatment with methadone:[243]

- Methadone must be taken only as directed. Patients should never take extra doses without getting approval from the prescriber.
- Taking methadone as frequently as other opioids may produce a fatal overdose.
- Patients should use other CNS depressants (especially benzodiazepines) with caution and only as directed by a healthcare provider.
- Patients should only use methadone in combination with other opioids as prescribed by a healthcare provider.
- The use of illicit drugs and/or alcohol with methadone may be fatal.
- Pain relief builds gradually and usually takes 5-7 days to see the full effects of a particular dose.
- Patients should tell all medical providers that they are taking methadone. Adding medications or changing dosing of other medications can affect methadone and should be coordinated with the methadone prescriber.
- Patients should avoid activities requiring mental alertness or coordination (such as driving or using machinery) until the effects of methadone are realized, typically a week or longer.
- Patients should rise slowly from a sitting/supine position, as methadone may cause dizziness.
- Methadone, like other opioids, can cause significant constipation. Patients should take a prescribed laxative as directed.
- Patients should report any of the following symptoms immediately and/or seek urgent/emergent care: dizziness or lightheadedness, irregular heartbeat (palpitations), falls or near falls, chest pain/pressure, and shortness of breath.
- Patients should avoid abrupt discontinuation of methadone without first consulting a healthcare provider.

Appendix E: Evidence Review Methodology

A. Developing the Scope and Key Questions

The CPG Champions, along with the Work Group, were tasked with identifying KQs to guide the systematic review of the literature on LOT. These questions, which were developed in consultation with the Lewin Team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table E-1 provides a brief overview of the PICOTS typology.

Table E-1. PICOTS [254]

P	Patients, Population, or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions, Work Group, and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Due to resource constraints, all developed KQs were not able to be included in the systematic review. Thus, the Champions and Work Group determined which questions were of highest priority, and those were included in the review. Table E-4 contains the final set of KQs used to guide the systematic review for this CPG.

a. Population(s)

Adults 18 years or older with chronic cancer or non-cancer pain treated in any clinical setting were covered in this systematic review.

b. Intervention(s)

Table E-2 lists the interventions that were covered in this systematic review. The interventions are listed according to the KQs they address.

Table E-2. Key Question Specific Interventions

Question	Interventions
1	Patients with a co-occurring medical or psychological condition on the following opioids: ■ Buprenorphine ■ Codeine ■ Hydrocodone ■ Hydromorphone ■ Morphine ■ Oxycodone ■ Oxymorphone ■ Tapentadol ■ Tramadol ■ Fentanyl ■ Methadone
2	Opioid dosage Length of opioid use Other risk factors (others may be included)[255] ■ Age ■ Days with physical healthcare visits ■ Degree of pain ■ Gender ■ History of sexual abuse ■ History of abuse (including emotional, physical, or cyber bullying) or domestic violence ■ History of SUD—Self or familial ■ Marital status ■ Mental disorders ■ Non-opioid substance abuse ■ Race ■ Social status ■ Work status
3	See list of opioids under KQ1; non-pharmacological interventions
4	See list of opioids under KQ1; non-pharmacological interventions

Question	Interventions
5	Short-acting opioids ■ Codeine ■ Fentanyl ■ Hydrocodone (only in combination with acetaminophen and ibuprofen) ■ Hydromorphone ■ Morphine sulfate (tablet/liquid) ■ Oxycodone (alone or in combination with acetaminophen, ibuprofen, or aspirin) ■ Oxymorphone ■ Tramadol Long-acting/ER opioids ■ Buprenorphine transdermal system ■ Fentanyl transdermal system ■ Hydrocodone bitartrate ER capsules/tablets ■ Hydromorphone hydrochloride ER tablets ■ Methadone hydrochloride tablets ■ Morphine sulfate and naltrexone ER capsules ■ Morphine sulfate ER capsules/tablets ■ Oxycodone hydrochloride and naloxone hydrochloride ER tablets ■ Oxycodone hydrochloride ER tablets ■ Oxymorphone hydrochloride ER tablets ■ Tapentadol ER oral tablets ■ Transdermal, buccal, sublingual, or pumps See main list of opioids. ■ Abuse deterrent formulations ■ Buprenorphine/Naloxone ■ Morphine/Naltrexone ■ OROS hydromorphone (Osmotic ER Oral delivery System) ■ Oxycodone Controlled Release ■ Oxymorphone ■ Additional medications ■ Tramadol and other dual-mechanism opioids ■ Buprenorphine ■ Methadone
6	Opioid therapy plus other psychoactive medications such as CNS depressants/antidepressants, non-opioid analgesics, benzodiazepines, stimulants, muscle relaxers, medical marijuana, Z-drugs (e.g., Zolpidem [Ambien], Eszopiclone [Lunesta], Zaleplon [Sonata]), and over-the-counter sleep medications (e.g., diphenhydramine hydrochloride or doxylamine succinate)

Question	Interventions
7	Naloxone rescue with one form of naloxone Informed consent Use of written informed consent (previously called contracts) Risk assessment instruments Opioid management plans Patient education UDT PDMP Monitoring instruments More frequent monitoring Pill counts Use of abuse–deterrent formulations Diversion prevention interventions (e.g., properly securing drugs, medication take back programs, public health education) Pharmacogenetic testing Random call-backs Compliance with other therapies Case management Periodic check of state databases Needle exchange programs
8	Treatment with at least one of the following: ▪ Buprenorphine (with or without naloxone) ▪ Methadone ▪ Injectable/oral naltrexone ▪ Medical Management ▪ Contingency Management ▪ Individual Drug Counseling ▪ Motivational interviewing ▪ Motivational Enhancement Therapy ▪ Other motivational approaches
9	One tapering strategy or schedule

c. Comparator(s)

Table E-3 lists the comparators of interest to this systematic review. The comparators are listed by the KQ they address.

Table E-3. Key Question Specific Comparators

Question	Comparators
1	Patients without a co-occurring medical or mental health condition on LOT
2	Comparison groups that vary by LOT dosage and length of opioid use, other factors
3	No OT (including placebo) or other pain management strategies Other modalities: ■ Non-opioid medications (e.g., non-steroidal including compounded topical preparations) ■ Physical interventions (e.g., physical therapy, active/passive exercise, ultrasound stimulation, chiropractic, osteopathic manipulation therapy) ■ Behavioral/mental health interventions EXAMPLES: • CBT • Dialectical behavior therapy (DBT) • Mindfulness • Acceptance and commitment therapy (ACT) ■ Complementary and alternative interventions EXAMPLES: • Acupuncture • Chiropractic interventions
4	No OT (including placebo) or other pain management strategies Other modalities: ■ Non-opioid medications (e.g., non-steroidal including compounded topical preparations) ■ Physical interventions (e.g., physical therapy, active/passive exercise, ultrasound stimulation, chiropractic, osteopathic manipulation therapy) ■ Behavioral/ mental health interventions (e.g., CBT, ACT, mindfulness, DBT) ■ Complementary and alternative interventions
5	Long-acting opioid drugs or combination short and long-acting drugs (See list) Other route of administration/delivery alternatives Non abuse-deterrent formulations Other opioids No use of buprenorphine No use of methadone
6	Opioid therapy alone
7	No mitigation strategy or other mitigation strategy
8	No treatment for OUD or other treatment for OUD
9	Different tapering strategy or schedule

d. Outcomes

For the treatment and management questions (KQ 3–9), the following outcomes were of interest in the systematic review:

- Pain relief
- Quality of life
- Cognitive/functional status
- Mortality
- Opioid abuse/misuse

- Adverse events
  - SUD
  - Aberrant use
  - Overdose
  - Non-pain use of opiates
  - Abuse
  - Addictions
  - Cardiovascular events
  - Respiratory depression
  - Gastrointestinal complications (including constipation)
  - Endocrinological complications (including impotence)
  - Weight gain
  - Cognitive performance
  - Psychiatric decompensation
  - Psychological symptoms (e.g., depression, loss of libido, nightmares)
  - Headaches
  - Suicide
  - Accidents (including falls)
  - Infections
  - Increased risk of HIV and Hepatitis A, B, and C
  - Loss to follow-up/medical care

e. Timing

The timing considered in the systematic review was 12 weeks for studies looking at the efficacy of OT, and any follow-up for studies reporting on the safety of OT.

f. Setting

The setting considered in the systematic review was primary care.

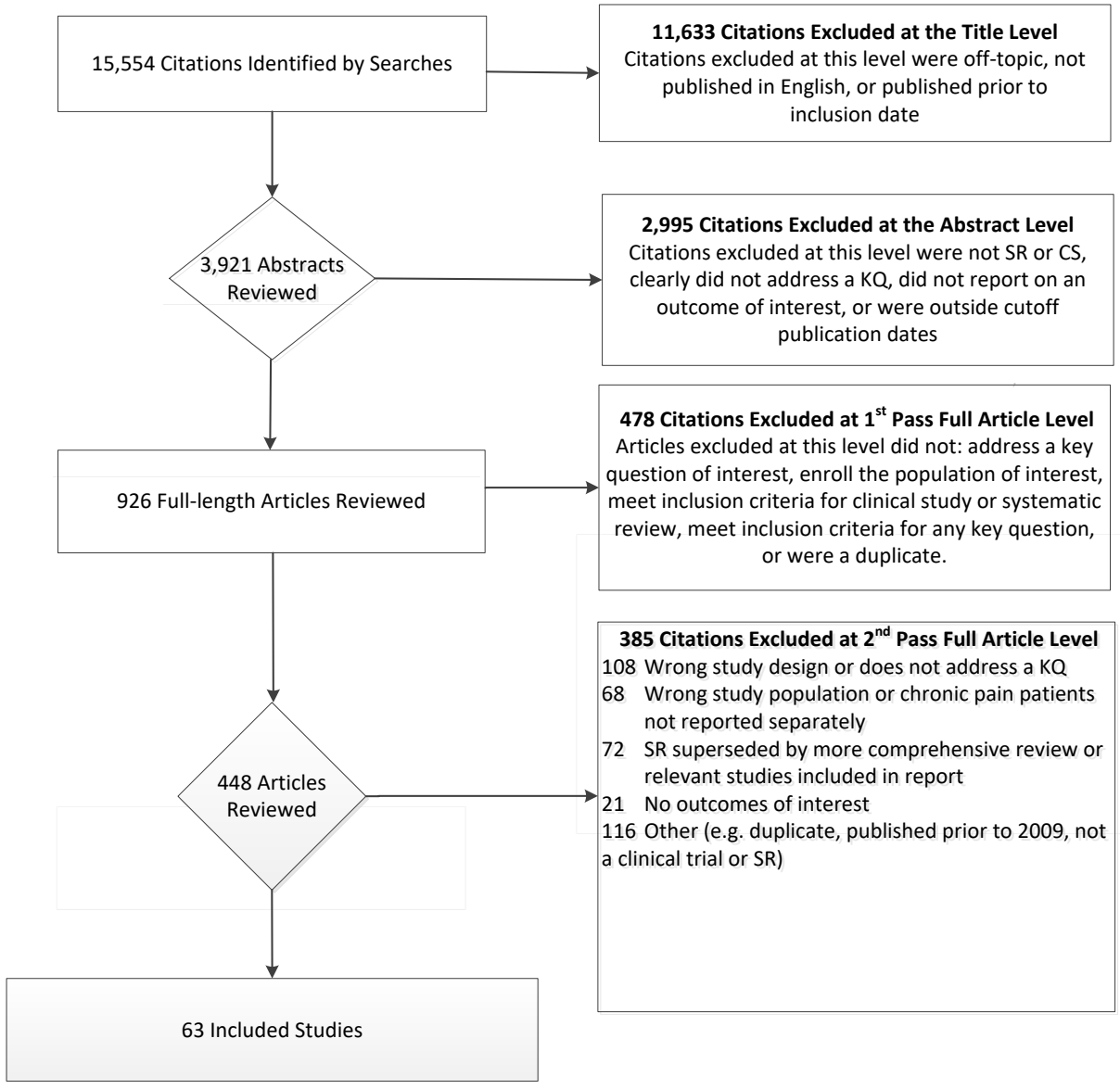
B. Conducting the Systematic Review

Extensive literature searches using the search terms and strategy included in Appendix J identified 15,554 citations potentially addressing the KQs of interest to this evidence review. Of those, 11,633 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, not a full-length article). Overall, 3,921 abstracts were reviewed with 2,995 of those being excluded for the following reasons: not a systematic review or clinical study (CS), did not address a KQ of interest to this review, did not enroll a population of

interest, or published prior to March 1, 2009. A total of 926 full-length articles were reviewed. Of those, 478 were excluded at a first pass review for the following: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for CS or systematic review, not meeting inclusion criteria for any KQ, or being a duplicate. A total of 448 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 385 were ultimately excluded. Reasons for their exclusion are presented in Figure E-1 below.

Overall, 63 articles addressed one or more of the KQs and were considered as evidence in this review. Table E-4 indicates the number of studies that addressed each of the questions.

Figure E-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

At the face-to-face meeting, sub-questions of KQs 3 and 4 were added assessing the safety and effectiveness of non-invasive treatments for chronic pain in patients not receiving OT. Searches to address these sub-questions were highly targeted to include systematic reviews only. Searches of EMBASE, PubMed, and PsycINFO were conducted through April 20, 2016. Five systematic reviews were included in the evidence base. Additionally, one systematic review was identified through hand searches of the literature and was also included in the final evidence base.

During the drafting process, two additional searches were performed. An additional search was added assessing the safety and effectiveness of take-home naloxone kits, a sub-question of KQ 7. Searches to address this intervention were highly targeted to include systematic reviews assessing use of take-home naloxone. Searches of EMBASE, PubMed, and PsycINFO were conducted through October 5, 2016. Two systematic reviews were included in the evidence base.

An additional sub-question assessing the need for follow-up after the prescription of opioids for acute pain was added to KQ 2 and an additional search was conducted. Searches to address this sub-question were broad, but the selection criteria were highly targeted to focus on prospective studies assessing risks associated with acute opioid use to treat acute pain. Searches of EMBASE, PubMed, and PsycINFO were conducted through December 20, 2016. Four retrospective cohorts and one secondary data analysis were included in the evidence base. Additionally, four studies already included in the evidence base for KQ 2 were used to inform the sub-question.

Table E-4. Evidence Base for Key Questions

Question Number	Question	Number and Type of Studies
1	What is the evidence that the following medical or mental health conditions are absolute or relative contraindications of prescribing long-term opioid therapy (LOT)? ■ Active pursuit of compensation ■ Centralized pain conditions such as fibromyalgia ■ Chronic obstructive pulmonary disease ■ Cognitive impairment ■ Depression ■ Headache ■ Gastrointestinal (GI) motility problems (e.g., toxic megacolon, GI pain syndromes, narcotic bowel syndrome) ■ Immune status changes ■ Inability to participate in comprehensive treatment plan ■ Incarceration (history of) ■ Hepatic, renal, or pulmonary disease ■ Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed) ■ Osteoporosis ■ Personality disorders ■ Posttraumatic stress disorder ■ Sleep disorders ■ Substance use disorders (SUD) (current or history of) ■ Suicidality ■ Traumatic brain injury ■ Use of medical marijuana ■ QT prolongation	12 cohort studies 1 case-cohort study 1 nested case-control study
2	What factors increase the risk of developing misuse or opioid use disorder (OUD) when considering LOT? a) What are the risks for long-term use associated with acute use of opioids in treating acute pain?	14 cohort studies 1 case-cohort study 1 nested case-control study 1 secondary data analysis
3	What is the comparative effectiveness of LOT versus other treatment modalities? a) What is the comparative effectiveness of LOT versus no opioid therapy or other treatment modalities for patients with a history of or current SUD? b) What is the effectiveness of non-pharmacological interventions in patients with chronic pain?	7 systematic reviews and 17 RCTs
4	What is the safety of LOT versus other treatment modalities? a) What is the safety of LOT versus other treatment modalities for patients with a history of or current SUD? b) What is the safety of non-pharmacological interventions in patients with chronic pain?	

Question Number	Question	Number and Type of Studies
5	What is the comparative effectiveness and safety of various opioid formulations? a) Immediate-release/short-acting opioids compared to ER/long-acting opioids b) Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps c) Abuse deterrent formulations compared to non-abuse deterrent formulations d) Tramadol and other dual-mechanism opioids e) Buprenorphine f) Methadone	2 systematic reviews and 7 RCTs
6	Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to opioid therapy alone?	1 RCT 1 prospective comparison trial 1 post-hoc pooled analysis 1 retrospective cohort study
7	What is the comparative effectiveness of different risk mitigation strategies for patients either on LOT or being considered for LOT? a) Does this differ for patients with history of or current SUD? b) Does this differ for patients with mental health comorbidities? c) Does this differ for patients with medical comorbidities? d) What is the safety and effectiveness of take-home naloxone kits?	3 systematic reviews 1 prospective cohort study 1 retrospective database study
8	What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a) Do outcomes vary by severity of OUD?	1 systematic review and 2 RCTs
9	What is the safety and effectiveness of different tapering strategies and schedules?	1 RCT 1 prospective cohort study
Total Evidence Base (Note, some papers were used for more than one KQ)		**63 Studies**

a. Criteria for Study Inclusion/Exclusion

i. General Criteria

- Clinical studies or systematic reviews published on or after March 1, 2009 to January 18, 2016. For sub-questions of KQs 3 and 4, systematic reviews published through April 20, 2016 were included. For a sub-question of KQ 7, systematic reviews published through October 5, 2016 were included. For a sub-question of KQ 2, clinical studies or systematic reviews published through December 20, 2016 were included. If multiple systematic reviews addressed a KQ, the most recent and/or comprehensive review was selected. Systematic reviews were supplemented with clinical studies published subsequent to the systematic review.
- Studies must have been published in English.
- Publication must have been a full CS or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length clinical studies were not accepted as evidence.

- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted (see Key Question Specific Criteria below).
- Study must have reported on an outcome of interest. Study must have enrolled a patient population in which at least 80% of patients were receiving OT for chronic pain of at least 12 weeks' duration (except for the sub-question of KQ 2a pertaining to risks associated with acute opioid use in acute pain, and KQ 7d on naloxone rescue). If the percentage is less than 80%, then data must have been reported separately for this patient subgroup.
- For outcomes measuring treatment effectiveness, patients must have been followed for at least 12 weeks.
- For KQ specific criteria, in the event that one or more KQs did not have sufficient evidence from the study designs specified below, lower-level evidence was evaluated for that KQ(s). Lower-level evidence was considered on a question-by-question basis.

ii. Key Question Specific Criteria

- For KQ 1, acceptable study designs included systematic reviews, RCTs, or prospective cohort studies that statistically compared outcomes for patients with chronic pain and a co-occurring medical or mental health condition on OT to patients with chronic pain and no additional medical or mental health condition on OT. Large retrospective database studies (200 patients minimum) that performed multivariate statistical analyses of the effect of co-occurring conditions on patient outcomes were also acceptable.
- For KQ 2, acceptable study designs included systematic reviews, RCTs, or prospective cohort studies that statistically compared outcomes for patients with chronic pain and differences in potential risk factors for developing opioid misuse or OUD. For LTOT, large retrospective database studies (200 patients minimum) that performed multivariate statistical analyses of the effect of risk factors on patient outcomes were also acceptable. For KQ 2a, studies were limited to prospective study design.
- For KQs 3-6, 8, and 9, acceptable study designs included systematic reviews of RCTs and/or individual RCTs.
- For KQ 7, acceptable study designs included systematic reviews of RCTs, individual RCTs, or nonrandomized comparative studies.

b. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table E-5, below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in Appendix J.

Table E-5. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Bibliographic Databases		
The Cochrane Central Register of Controlled Trials (CENTRAL)	11/24/15	Wiley
The Cochrane Database of Methodology Reviews (Methodology Reviews)	11/24/15	Wiley

Name	Date Limits	Platform/Provider
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	11/24/15	Wiley
Database of Abstracts of Reviews of Effects	11/24/15	Wiley
EMBASE (Excerpta Medica)	12/20/16	Elsevier
Health Technology Assessment Database (HTA)	11/24/15	Wiley
MEDLINE/PreMEDLINE	12/20/16	OVIDSP
PsycINFO	12/21/16	OVIDSP
PubMed (In-process and Publisher records)	12/20/16	NLM
Gray Literature Resources		
AHRQ	11/30/15	AHRQ
Healthcare Standards database	11/30/15	ECRI Institute
National Guideline Clearinghouse™	11/30/15	AHRQ
National Institute of Health and Clinical Excellence	11/30/15	NHS

C. Convening the Face-to-face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group on April 5-8, 2016. These experts were gathered to develop and draft the clinical recommendations for an update to the 2010 OT CPG. Lewin presented findings from the evidence review of KQs 1-9 in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group was charged with interpreting the results of the evidence review, and asked to categorize and carry forward recommendations from the 2010 OT CPG, modifying the recommendations as necessary. The members also developed new clinical practice recommendations not presented in the 2010 OT CPG, based on the 2016 evidence review. The subject matter experts were divided into two smaller subgroups at this meeting.

As the Work Group drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

In addition to developing recommendations during the face-to-face meeting, the Work Group also revised the 2010 OT CPG algorithm to reflect the new and amended recommendations. They discussed the available evidence as well as changes in clinical practice since 2010, as necessary, to update the algorithm.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[68]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences

- Other implications, as appropriate, e.g.,:
  - Resource Use
  - Equity
  - Acceptability
  - Feasibility
  - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for LOT, conducted by ECRI, assessed the confidence in the quality of the evidence base and assigned a rate of “High,” “Moderate,” “Low,” or “Very Low.”

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients’ perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term “values” has the closest connotation to these processes. For others, the connotation of “preferences” best captures the notion of choice. In general,

values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values, concerns, and preferences of patients and empowering them or their surrogates to make decisions consistent with patient goals of care becomes even more important. A recommendation can be described as having "similar values," "some variation," or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practically of the recommendation.

The framework below (Table E-6) was used by the Work Group to guide discussions on each domain.

Table E-6. Evidence to Recommendation Framework

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	
▪ Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? ▪ Are the desirable anticipated effects large? ▪ Are the undesirable anticipated effects small? ▪ Are the desirable effects large relative to undesirable effects?	Benefits outweigh harms/burden Benefits slightly outweigh harms/burden Benefits and harms/burden are balanced Harms/burden slightly outweigh benefits Harms/burden outweigh benefits
Confidence in the quality of the evidence	
▪ Is there high- or moderate quality evidence that answers this question? ▪ What is the overall certainty of this evidence?	High Moderate Low Very low
Values and preferences	
▪ Are you confident about the typical values and preferences and are they similar across the target population? ▪ What are the patient's values and preferences? ▪ Are the assumed or identified relative values similar across the target population?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	
▪ Are the resources worth the expected net benefit from the recommendation? ▪ What are the costs per resource unit? ▪ Is this intervention generally available? ▪ Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? ▪ Is there lots of variability in resource requirements across settings?	Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains.[68] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.[256] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician, or they may be qualified with an explanation about the issues that would lead decisions to vary.

E. Recommendation Categorization

a. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether or not they were based on an updated review of the evidence. If evidence had been reviewed, recommendations were categorized as "New-added," "New-replaced," "Not changed," "Amended," or "Deleted."

"Reviewed, New-added" recommendations were original, new recommendations that were not in the 2010 OT CPG. "Reviewed, New-replaced" recommendations were in the previous version of the guideline, but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as "Reviewed, Not changed" were carried forward from the previous version of the CPG unchanged.

To maintain consistency between 2010 recommendations, which were developed using the USPSTF methodology, and 2017 recommendations, which were developed using the GRADE methodology, it was necessary to modify the 2010 recommendations to include verbiage to signify the strength of the recommendation (e.g., "We recommend," "We suggest"). Because the 2010 recommendations inherently needed to be modified at least slightly to include this language, the "Not changed" category was not used. For recommendations carried forward to the updated CPG with review of the evidence and slightly modified wording, the "Reviewed, Amended" recommendation category was used. This allowed for the wording of the recommendation to reflect GRADE methodology as well as for any other non-substantive (i.e., not clinically meaningful) language changes deemed necessary. The evidence used to support these

recommendations was carried forward from the previous version of the CPG and/or was identified in the evidence review for the update.

Recommendations could have also been designated "Reviewed, Deleted." These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

b. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without a systematic review of the evidence. Due to time and budget constraints, the update of the OT CPG could not review all available evidence on management of LOT, but instead focused its KQs on areas of new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated systematic review of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the previous version of the CPG. These recommendations were categorized as "Not reviewed." If evidence had not been reviewed, recommendations could have been categorized as "Not changed," Amended," or "Deleted."

"Not reviewed, Not changed" recommendations refer to recommendations from the previous version of the OT CPG that were carried forward unchanged to the updated version. The category of "Not reviewed, Amended" was used to designate recommendations that were modified from the 2010 CPG with the updated GRADE language, as explained above.

Recommendations could also have been categorized as "Not reviewed, Deleted" if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (e.g., population, care setting, treatment, condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2017 version of the guideline are noted in the Recommendations. The categories for the recommendations from the 2010 OT CPG are noted in Appendix H.

c. Recommendation Categories and Definitions

For use in the 2017 OT CPG, a set of recommendation categories was adapted from those used by the United Kingdom National Institute for Health and Clinical Excellence (NICE).[72,73] These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2010 OT CPG. The categories and definitions can be found in Table E-7.

Table E-7. Recommendation Categories and Definitions

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012) [72] and Garcia et al. (2014) [73]
Abbreviation: CPG: clinical practice guideline

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2010 OT CPG to support the amended "carried forward" recommendations. The Work Group also considered tables, appendices, and other sections from the 2010 OT CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithm, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14-20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in Peer Review Process. After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials, which included a provider summary, pocket card, and a patient summary. The final 2017 OT CPG was submitted to the EBPWG in February 2017.

Appendix F: Patient Focus Group Methods and Findings

A. Methods

On December 14, 2015, as part of the effort to update this CPG, the VA and DoD Leadership, along with the OT CPG Work Group, held a patient focus group at the Washington DC VA Medical Center. Focus group participants included six patients and two family caregivers. One additional family caregiver was interviewed separately at a later date.

The aim of the focus group and interview was to further the understanding of the perspectives of patients receiving LOT within the VA and/or DoD healthcare systems, as these patients are most affected by the recommendations put forth in the updated OT CPG. The focus group and interview explored patient perspectives on a set of topics related to management of OT in the VA and DoD healthcare systems, including knowledge of OT and other pain treatment options, delivery of care, and the impact of and challenges with LOT.

Participants for the focus group were recruited from the pain clinics at the Walter Reed National Military Medical Center and the Washington DC VA Medical Center. Patient focus group participants were not intended to be a representative sample of VA and DoD patients who have experienced LOT. However, recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the guideline development process. Patients were not incentivized for their participation or reimbursed for travel expenses.

The OT CPG Champions and Work Group developed a set of questions to help guide the focus group and interview. The facilitator from Lewin led the discussion using interview questions prepared by the Work Group as a general guide to elicit the most important information from the patients regarding their experiences and views about their treatment and overall care. Given the limited time and the range of interests and expressiveness of the participants, not all of the listed questions were addressed.

At the time of the focus group, three patients were receiving care in the DoD healthcare system, two patients were receiving care in the VA healthcare system, and one patient was receiving care from a private pain center. Some of these patient participants had transitioned between multiple care settings, including from VA to DoD, from DoD to VA, and from a governmental healthcare setting to a private healthcare setting. Two patients stated that they were currently on LOT for pain. Four patients stated that they had previously been on LOT, but have since transitioned to other treatments for pain.

The following concepts are aspects of care that are important to patients and family caregivers that emerged from the focus group discussion and the interview. Each of these themes was an important and needed aspect of participants' healthcare.

B. Patient Focus Group Findings

Using shared decision making, consider all treatment options and develop treatment plan based on the balance of risks, benefits, and patient-specific goals, values, and preferences

- Identify patient-specific goals associated with LOT (main goals of these focus group participants included returning to work, minimizing pain, maintaining a functional life, avoiding invasive medical procedures, and getting off opioids)
- Discuss and consider all pain management options (non-pharmacotherapy and non-opioid pharmacotherapy) prior to starting LOT; do not default to prescribing opioids
- Use shared decision making to develop an individualized treatment plan; discuss pros and cons (e.g., benefits, risks, side effects) of each treatment option (including non-opioid treatment options) in conjunction with each patient's goals, priorities, values, and preferences
- Maintain focus on patient goals throughout treatment, including any changes in those goals over time

Modify treatment based on patient response, considering patient-specific goals, values, and preferences

- Be prepared to adjust or otherwise change treatment (e.g., tapering opioids) subject to patient response, preferences, and changes in priorities and goals; convey this flexibility and support the patient and support him/her during the change in treatment
- Do not continue to prescribe opioids when patients express reluctance to take them or do not adhere; continue to understand patient needs and preferences and adapt treatment accordingly
- Take time to develop a thorough understanding of patient needs and capabilities; develop an individualized treatment plan; be accountable for adverse outcomes
- Even after LOT is initiated, continue to discuss and consider all pain management options (non-pharmacotherapy and non-opioid pharmacotherapy)
- Carefully consider side effects during monitoring and adjust treatment in order to minimize side effects (e.g., depression, weight gain, headaches, nightmares, problems with intimacy, paresthesias) pursuant to individual patient preferences

Involve family caregivers in accordance with patient preferences and maintain open, trusting, and respectful relationship with patients and family caregivers

- Foster family, including family caregiver, involvement in shared decision making and support in accordance with patient preferences and in a way that is beneficial to the patient
- Always treat patients and family, including family caregivers, with respect and support
- Build and maintain trust, respect, and support in relationship with the patient and family, including family caregivers
- Ensure the patient has the capability to engage in shared decision making; recognize that patients who are in pain or who are taking opioids or other powerful medications may be in

suboptimal condition to make informed decisions on their own and may benefit from involvement of knowledgeable family members, including family caregivers

Educate patients regarding treatment plan, alternative treatment options, and monitoring

- Clinicians should be proactive and responsive in providing necessary clinical information in a manner comprehensible to patients and family caregivers; acknowledge that patients will seek and acquire information from other sources (especially the Internet) and encourage patient proactivity
- When prescribing opioids, provide in-depth and patient-specific education on medication (e.g., side effects, dosing, administration, storage, safety, disposal, take back programs) during medical visits in conjunction with distributing or otherwise enabling access to educational materials
- Provide necessary information regarding changes in treatment; discuss tapering and risks of self-tapering as necessary; recognize and address the challenges for patients on OT, including tapering
- Explain/provide education to patients as to why doctors use monitoring practices such as UDT when patients are using opioids; do not simply order the tests without such explanation

Within and between healthcare systems, work with appropriate providers to ensure continuity of high quality care

- Consult with other providers (e.g., psychologists, physical therapists) and patient advocates as appropriate, especially when patients express the need for more information or other clinical support
- Provide seamless transitions in opioid treatment and other pain management within and between VA, DoD, and any other healthcare systems; patients should not have to encounter abrupt changes in treatment regimens moving from one system to another or have to "start all over" when moving to another system
- Continue transformation of pain management

Organize treatment to encourage patient adherence and participation

- Facilitate appointment scheduling for days and times that fit the patient's needs (e.g., try to avoid patient work days where possible, schedule multiple provider appointments on same day rather than multiple days)
- Facilitate prescription refills and patient visits for refills in a way that fits the patient's needs, lifestyle, and schedule, while maintaining safe prescribing practices

Acknowledge and minimize effects of potential medical error and take action to prevent future medical error

- Acknowledge instances of potential medical error or other instances in which patient outcomes from previous medical procedures were less than desirable or expected (including experiences

of adverse events) and the consequences for the patient; consider these experiences when developing treatment plans

- Report potential medical errors that may have been experienced by patients and take action to prevent future medical error

Appendix G: Evidence Table

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
1.	a) We recommend against initiation of long-term opioid therapy for chronic pain. b) We recommend alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments. c) When pharmacologic therapies are used, we recommend non-opioids over opioids.	None None None	[80-83,85] **Additional References:** [3,26,84]	a) Strong against b) Strong for c) Strong for	Reviewed, New-replaced
2.	If prescribing opioid therapy for patients with chronic pain, we recommend a short duration. Note: Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits.	None	[86-89] **Additional References:** [132]	Strong for	Reviewed, New-replaced

[15] The 2010 VA/DoD OT CPG used the USPSTF evidence grading system (http://www.uspreventiveservicestaskforce.org). Inclusion of more than one 2010 Grade indicates that more than one 2010 CPG recommendation is covered under the 2016 recommendation. The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. "None" indicates that the 2017 OT CPG recommendation replaced or amended a 2010 OT CPG recommendation for which there was no grade. "N/A" indicates that the 2017 OT CPG recommendation was a new recommendation, and therefore does not have an associated 2010 Grade.

[16] The evidence column indicates studies that support each recommendation. For new recommendations, developed by the 2016 guideline Work Group, the literature cited corresponds directly to the 2016 evidence review. For recommendations that have been carried over from the 2010 VA/DoD OT CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the evidence column indicates "additional evidence," which can refer to either 1) studies that support the recommendation and which were identified through the 2016 evidence review, or 2) relevant studies that support the recommendation, but which were not systematically identified through a literature review.

[17] Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

[18] Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
3.	For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies (see Recommendations 7-9), assessment for opioid use disorder, and consideration for tapering when risks exceed benefits (see Recommendation 14).	None	[86-89] **Additional References:** [132]	Strong for	Reviewed, New-replaced
4.	a) We recommend against long-term opioid therapy for pain in patients with untreated substance use disorder. b) For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, we recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering (see Recommendation 14 and Recommendation 17).	None	[59,61,66,86,87]	a) Strong against b) Strong for	Reviewed, Amended
5.	We recommend against the concurrent use of benzodiazepines and opioids. Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate (see Recommendation 14 and the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders).	N/A	[66] **Additional References:** [90,91]	Strong against	Reviewed, New-added
6.	a) We recommend against long-term opioid therapy for patients less than 30 years of age secondary to higher risk of opioid use disorder and overdose. b) For patients less than 30 years of age currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits (see Recommendation 14 and Recommendation 17).	None	[58,59,62,86-88,92,94] **Additional References:** [93,95-98]	a) Strong against b) Strong for	Reviewed, New-replaced

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
7.	We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include: ■ Ongoing, random urine drug testing (including appropriate confirmatory testing) ■ Checking state prescription drug monitoring programs ■ Monitoring for overdose potential and suicidality ■ Providing overdose education ■ Prescribing of naloxone rescue and accompanying education	None None None None None None B B	[61,99,100,107-109,114] **Additional References:** [24,33,53,101-106,110-113,115-122]	Strong for	Reviewed, New-replaced
8.	We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary.	None None	[61,123-128] **Additional References:** [129-131]	Strong for	Reviewed, Amended
9.	We recommend evaluating benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months.	None None None None B	**Additional References:** [132]	Strong for	Reviewed, New-replaced
10.	If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits. Note: There is no absolutely safe dose of opioids.	None	[58,59,66,87,133,136] **Additional References:** [134,135]	Strong for	Reviewed, New-replaced
11.	As opioid dosage and risk increase, we recommend more frequent monitoring for adverse events including opioid use disorder and overdose. Note: ■ Risks for opioid use disorder start at any dose and increase in a dose dependent manner. ■ Risks for overdose and death significantly increase at a range of 20-50 mg morphine equivalent daily dose.	None	[58,59,66,87,133,136] **Additional References:** [134,135]	Strong for	Reviewed, New-replaced

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
12.	We recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain. Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation (see Recommendations 14 and 15).	None	[58,59,66,87,133,136] **Additional References:** [134,135]	Strong against	Reviewed, New-replaced
13.	We recommend against prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy.	None	[140,141,143,144,146,149-159,163,165] **Additional References:** [10,137-139,142,145,147,148,160,162,164,166-169]	Strong against	Reviewed, New-replaced
14.	We recommend tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits. Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.	N/A	**Additional References:** [10,137,170-175]	Strong for	Reviewed, New-added
15.	We recommend individualizing opioid tapering based on risk assessment and patient needs and characteristics. Note: There is insufficient evidence to recommend for or against specific tapering strategies and schedules.	N/A	**Additional References:** [10,137,170-175]	Strong for	Reviewed, New-added
16.	We recommend interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior.	None None None None None	[114,176]	Strong for	Reviewed, New-replaced
17.	We recommend offering medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder. Note: See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.	None None None	**Additional References:** [177-182]	Strong for	Reviewed, New-replaced

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
18.	a) We recommend alternatives to opioids for mild-to-moderate acute pain. b) We suggest use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain. c) If take-home opioids are prescribed, we recommend that immediate-release opioids are used at the lowest effective dose with opioid therapy reassessment no later than 3-5 days to determine if adjustments or continuing opioid therapy is indicated. Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.	N/A	[58,59,183-188]	a) Strong for b) Weak for c) Strong for	Reviewed, New-added

Appendix H: 2010 Recommendation Categorization Table

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
1	A	1	A trial of opioid therapy is indicated for a patient with chronic pain who meets all of the following criteria: a. Moderate to severe pain that has failed to adequately respond to indicated non-opioid and non- drug therapeutic interventions b. The potential benefits of opioid therapy are likely to outweigh the risks (i.e., no absolute contraindications) c. The patient is fully informed and consents to the therapy d. Clear and measurable treatment goals are established	None	Not reviewed, Deleted	
1	A	2	The ethical imperative is to provide the pain treatment with the best benefit-to-harm profile for the individual patient.	None	Not reviewed, Deleted	

[19] The first three columns indicate the location of each recommendation within the 2010 OT CPG.

[20] The 2010 Recommendation Text column contains the wording of each recommendation from the 2010 OT CPG.

[21] The 2010 VA/DoD OT CPG used the U.S. Preventive Services Task Force (USPSTF) evidence grading system. http://www.uspreventiveservicestaskforce.org The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. "None" indicates there was no grade assigned to the recommendation in the 2010 OT CPG.

[22] The Category column indicates the way in which each 2010 OT CPG recommendation was updated.

[23] For recommendations that were carried forward to the 2010 OT CPG, this column indicates the new recommendation(s) to which they correspond.

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade1[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
1	B	1	A comprehensive patient assessment should be completed to identify clinical conditions that may interfere with the appropriate and safe use of opioid therapy (OT). The comprehensive assessment should include: a. Medical History • Age, Sex • History of present illness, including a complete pain assessment (see Annotation C) • History of injury if applicable • Past Medical and Surgical history • Past Psychiatric history (including depression, anxiety, other emotional disorders, risk of suicide including family history and previous suicidal attempts) • Medications (including current and past analgesics, their effectiveness, side effects, and tolerability, as well as drugs that may interact with opioid therapy) • Substance use history (personal, family, peer group) • Family history • Social history (including employment, cultural background, social network, marital history, and legal history, other behavioral patterns (i.e. impulse behaviors)) • Review of systems • Allergies • Abuse (sexual, physical and mental) b. Physical examination • A general examination • A pain-focused musculoskeletal and neurologic examination • Mental Status Examination (MSE) (Including level of alertness, ability to understand and follow instruction, and suicidal ideation) c. Review of diagnostic studies and assessments d. Evaluation of occupational risks and ability to perform duty	None	Not reviewed, Deleted	
1	B	2	Information from the pain history and physical exam should be reviewed to ensure that the patient has had an adequate therapeutic trial of non-opioid medication therapies.	None	Not reviewed, Deleted	
1	B	3	A urine drug test (UDT) (also referred to as urine drug screen (UDS)) should be used to screen for the presence of illegal drugs, unreported prescribed medication, or unreported alcohol use prior to starting therapy. [B]	B	Reviewed, Deleted	
1	B	4	Patients on chronic opioid therapy should be assessed for suicide risk at onset of therapy and regularly thereafter. High suicide risk is a relative contraindication for OT.	None	Reviewed, Amended	Recommendation 8

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
1	B	5	Opioid therapy should be used only after careful consideration of the risks and benefits.	None	Reviewed, New-replaced	Recommendation 1 Recommendation 2 Recommendation 3
1	C	1	Pain intensity should be evaluated at each visit.	None	Not reviewed, Deleted	
1	C	2	Intensity of pain should be measured using a numeric rating scale (0-10 scale) for each of the following: • current pain, • least pain in last week • "usual" or "average" pain in last week	None	Not reviewed, Deleted	
1	C	3	The patient's response to current pain treatments should be assessed using questions such as: • "What is your intensity of pain after taking (use of) your current treatment/medication?" • "How long does your pain relief last after taking your treatment/medication?" • "How does taking your treatment/medication affect your functioning?" (Note: some interventions may temporarily increase pain, so it may not be appropriate to ask these questions.)	None	Not reviewed, Deleted	
1	C	4	Other attributes of pain should be assessed as part of the comprehensive pain assessment: • Onset and duration, location, radiation, description (quality), aggravating and alleviating factors, behavioral manifestations of pain, and impact of pain • Temporal patterns and variations (e.g., diurnal, monthly, seasonal) • Current and past treatments for pain • Patient's expectations for pain relief	None	Not reviewed, Deleted	
1	C	5	If possible, determine the type of pain: • Differentiate between nociceptive and neuropathic pain • Consider further evaluation if needed (such as imaging, Electro Diagnostic Studies (EDS) or consultation) • Ask specifically whether the patient suffers from headache	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
1	C	6	Assessment of function, to obtain a baseline, should include: (Consistent evaluation tool is helpful in providing evaluation of response to opioid therapy over time): • Cognitive function (attention, memory, and concentration) • Employment • Enjoyment of life • Emotional distress (depression and anxiety) • Housework, chores, hobbies, and other day to day activities • Sleep • Mobility • Self-care behaviors • Sexual function	None	Not reviewed, Deleted	
1	C	7	Information from the pain history and physical exam should be reviewed to ensure that the patient has had an adequate trial of non-opioid therapy.	None	Not reviewed, Deleted	
2	D	1	Opioid therapy trial should NOT be initiated in the following situations (absolute contraindications): a. Severe respiratory instability b. Acute psychiatric instability or uncontrolled suicide risk c. Diagnosed non-nicotine Substance Use Disorder (DSM-IV criteria) not in remission and not in treatment d. True allergy to opioid agents (cannot be resolved by switching agents) e. Co-administration of drug capable of inducing life-limiting drug-drug interaction f. QTc interval > 500 millisecond for using methadone g. Active diversion of controlled substances (providing the medication to someone for whom it was not intended) h. Prior adequate trials of specific opioids that were discontinued due to intolerance, serious adverse effects that cannot be treated, or lack of efficacy	None	Reviewed, Amended	Recommendation 4

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
2	D	2	Opioid therapy trial can be initiated with caution in the following situations. Consider consultation with appropriate specialty care to evaluate if potential benefits outweigh the risks of therapy. a. Patient receiving treatment for diagnosed Substance Use Disorder (DSM-IV criteria). (See Annotation P1) b. Medical condition in which OT may cause harm: • Patient with obstructive sleep apnea not on CPAP • Patients with central sleep apnea (See Annotation P2) • Chronic pulmonary disease (mild-moderate asthma, COPD) • Cardiac condition (QTc interval 450-500 milliseconds) that may increase risk of using methadone • Known or suspected paralytic ileus • Respiratory depression in unmonitored setting c. Risk for suicide or unstable psychiatric disorder d. Complicated pain • Headache not responsive to other pain treatment modalities e. Conditions that may impact adherence to OT: • Inability to manage opioid therapy responsibly (e.g., cognitively impaired) • Unwillingness or inability to comply with treatment plan • Unwillingness to adjust at-risk activities resulting in serious re-injury • Social instability • Mental Health disorders	None	Reviewed, Deleted	
2	D	3	Consider consultation with an appropriate specialist if legal or clinical problems indicate need for more intensive care related to opioid management. (See Annotation E – Indications for consultation).	None	Not reviewed, Deleted	
2	E	1	Refer to an Advanced Pain provider, or interdisciplinary pain clinic or program for evaluation and treatment a patient with persistent pain and any of the following conditions: a. Complex pain conditions or polytrauma b. Significant medical comorbidities that may negatively impact opioid therapy c. Situation requires management beyond the comfort level of the primary provider	None	Not reviewed, Deleted	
2	E	2	Refer to SUD Specialty Provider for evaluation and treatment patient whose behavior suggests addiction to substances (excluding nicotine).	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
2	E	3	Consider consultation with a SUD specialist to evaluate the risk of recurrent substance abuse or to assist with ongoing management.	None	Reviewed, New-replaced	Recommendation 16
2	E	4	Refer to Behavioral Health Specialty for evaluation and treatment a patient with any of the following conditions: a. Psychosocial problems or comorbidities that may benefit from behavioral disease/case management b. Uncontrolled, severe psychiatric disorders or those who are emotionally unstable c. Patients expressing thoughts or demonstrating behaviors suggestive of suicide risk	None	Not reviewed, Deleted	
2	E	5	Refer patients with significant headache to a neurologist for evaluation and treatment.	None	Not reviewed, Deleted	
2	E	6	Consider consultation with occupational health specialty if patient's occupation requires a high level of cognitive function.	None	Not reviewed, Deleted	
2	F	1	The clinician should assess the ability of the patient being considered for opioid therapy to be able to adhere to treatment requirements, as these patients are likely to do well and benefit from OT.	None	Not reviewed, Deleted	
2	F	2	The appropriateness of opioid therapy as a treatment modality for chronic pain and the level of risk for adverse outcomes should be determined based on the initial and ongoing assessment of the patient.	None	Not reviewed, Deleted	
2	F	3	For patients with history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors, initiation of a trial of OT in the primary care setting should only be considered if more frequent and stringent monitoring can be provided. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist.	None	Not reviewed, Deleted	
2	F	4	Young patients (less than 25 years old) are at higher risk for diversion and abuse and may benefit from more stringent monitoring.	None	Reviewed, New-replaced	Recommendation 6
2	F	5	The clinician should consider referring patients who have unstable co-occurring disorders (substance use, mental health illnesses, or aberrant drug related behaviors) and who are at higher risk for unsuccessful outcomes (see Annotation E).	None	Not reviewed, Deleted	
2	G	1	Involve the patient and family/caregiver in the educational process, providing written educational material in addition to discussion with patient/family.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
2	G	2	Discuss the opioid pain care agreement (OPCA) in detail, and reinforce in subsequent visits (See Annotation H).	None	Reviewed, New-replaced	Recommendation 7
2	G	3	Provide, and document in the medical record, patient education on the following topics: • General Information: goals and expectations, addiction, tolerance, physical dependency, withdrawal symptoms • Patient responsibilities: prescriptions, adherence to treatment plan, obtaining medications from a single prescriber (or clinic) and single pharmacy, pain diary, feedback to the provider • Legal Issues • Instruction on how to take medication: importance of consistent dosing and timing, interaction with other drugs • Prophylactic treatment of adverse effects and management of constipation • Discussion of an individualized comprehensive care plan that may include, in addition to OT, physical therapy, occupational therapy, cognitive-behavioral therapy, acupuncture, manipulation, complementary and alternative medicine, other non-pharmacologic therapies, and other non-opioid agents.	None	Reviewed, New-replaced	Recommendation 7
2	H	1	Discuss a trial of opioid therapy with the patient, and obtain the patient's informed consent in a shared decision-making discussion. Document the informed consent discussion.	None	Not reviewed, Deleted	
2	H	2	Review and discuss a written Opioid Pain Care Agreement (OPCA) with the patient who is expected to receive daily opioid therapy for the treatment of chronic pain. The signed agreement can serve as documentation of an informed consent discussion. (For a sample agreement, see Appendix C)	None	Reviewed, New-replaced	Recommendation 7

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
2	H	3	The responsibilities during therapy, of the provider and the patient, should be discussed with the patient and family. A discussion of patient responsibilities should be patient-centered and address the following issues : • Goals of therapy -- Partial pain relief and improvement in physical, emotional, and/or social functioning • The requirement for a single prescribing provider or treatment team • The limitation on dose and number of prescribed medications • Proscription against the patient changing dosage without discussing with provider • Monitoring patient adherence - discuss the role of random urine drug testing, the use of "pill counts" • A prohibition on use with alcohol, other sedating medications, or illegal drugs without discussing with provider • Agreement not to drive or operate heavy machinery until abatement of medication-related drowsiness • Responsibility to keep medication safe and secure • Prohibition of selling, lending, sharing or giving any medication to others • Limitations on refills: only by appointment, in person, and no extra refills for running out early (exceptions should be considered on an individual basis) • Compliance with all components of overall treatment plan (including consultations and referrals) • Adverse effects and safety issues such as the risk of dependence and addictive behaviors • The option of sharing information with family members and other providers, as necessary, with the patient's consent • Need for periodic re-evaluation of treatment • Reasons for stopping opioid therapy • Consequences of non-adherence with the treatment agreement.	None	Reviewed, Deleted	
2	H	4	Patient’s refusal to sign an agreement as part of the initial and ongoing assessments of the patient’s ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Table 2, Annotation F). The prescription of therapy, in such cases, should be based on the individual patient and the benefits versus harm involved with therapy. The rationale for prescribing opioids without a signed agreement should be documented.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
2	I	1	The treatment plan should be individually tailored to the patient's circumstances and to the characteristics of the patient's pain.	None	Not reviewed, Deleted	
2	I	2	Consider the use of other treatment approaches (such as supervised therapeutic exercise, biofeedback, or cognitive behavior approaches), which should be coordinated with the opioid therapy.	None	Reviewed, New-replaced	Recommendation 1
2	I	3	Consider establishing a referral and interdisciplinary team approach, if indicated.	None	Not reviewed, Deleted	
2	I	4	Establish a follow-up schedule to monitor treatment and patient progress.	None	Not reviewed, Deleted	
2	I	5	The treatment plan and patient preferences should be documented in the medical record.	None	Not reviewed, Deleted	
3	K1	1	Chronic pain is often a complex biopsychosocial condition. Clinicians who prescribe OT should routinely integrate psychotherapeutic interventions, functional optimization, interdisciplinary therapy, and other adjunctive non-opioid pain therapies.	None	Not reviewed, Deleted	
3	K1	2	Provide written and verbal education to the patient about the specific medication, anticipated adverse effects, dosing and administration, possible excessive sedation and symptoms of opioid withdrawal.	None	Not reviewed, Deleted	
3	K1	3	With patient consent, obtain a urine drug test (UDT) prior to initiating an OT trial and randomly at follow-up visits to confirm the appropriate use of opioids. A patient can refuse urine drug testing. The provider should take into consideration a patient's refusal to undergo urine drug testing as part of the ongoing assessment of the patient's ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Annotation F, Table 2).	None	Reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
3	K1	4	There is no evidence to recommend for or against the selection of any specific opioid: a. Using a shared decision-making process, select a specific opioid formulation, based on experience and knowledge that matches the individual's needs and specific medical conditions b. Consider patient preference, and agent that allows administration by the least invasive route c. Consider the ease of drug administration, patient's prior experience with, and level of tolerance to opioid medications, potential risk for misuse, abuse patterns, and local formulary guidance d. Transdermal fentanyl should be avoided in opioid naïve patients.	None	Reviewed, New-replaced	Recommendation 13
3	K1	5	Start the opioid therapy trial with a low dose and with one medication at a time.	None	Not reviewed, Deleted	
3	K1	6	Initiate a bowel regimen to prevent and treat constipation, which is anticipated with all opioids.	None	Not reviewed, Deleted	
3	K1	7	For continuous chronic pain, an agent with a long duration of action, such as controlled-release morphine or methadone is recommended.	None	Not reviewed, Deleted	
3	K1	8	Alternatively, short-acting opioids can be started, and later converted to long acting opioids. (See Annotation K2 - Titration)	None	Not reviewed, Deleted	
3	K1	9	Treatment of continuous chronic pain should be initiated with opioids on a defined and scheduled basis.	None	Not reviewed, Deleted	
3	K1	10	For episodic chronic pain, consider short-acting opioids (such as morphine, oxycodone, or hydrocodone), trying one medication at a time on a PRN (as needed) basis. Long-acting opioids should not be used on a PRN basis.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
3	K1	11	When using methadone: a. Inform patients of the arrhythmia risk b. Ask patients about heart disease, arrhythmia, and syncope c. Obtain an electrocardiogram (ECG) to measure the QTc interval before starting methadone and once the dose is stabilized (maintenance phase). Measure the QTc annually thereafter if the patient history is positive for risk factors for prolonged QTc interval, or has known prolonged QTc interval. Perform additional electrocardiography if the methadone dosage exceeds 100 mg/day, or if the patient has unexplained syncope or seizures d. If the QTc interval is greater than 450ms, but less than 500ms, reevaluate and discuss with the patient the potential risks and benefits of therapy, and the need for monitoring the QTc more frequently e. If the QTc interval exceeds 500 ms, discontinue or taper the methadone dose and consider using an alternative therapy. Other contributing factors, such as drugs that cause hypokalemia, or QT prolongation should be eliminated whenever possible f. Be aware of interactions between methadone and other drugs that may prolong QTc interval, or slow the elimination of methadone, and educate patients about drug interaction.	None	Not reviewed, Deleted	
3	K2	1	Maintain close communication with patients and families, explicitly discussing the criteria for evaluating the effects of analgesic medications; doing so can help in defusing the anxiety that often accompanies visits to the physician.	None	Not reviewed, Deleted	
3	K2	2	Ask the patient to keep records of the time and dose of medication, the degree of pain relief, and the occurrence of adverse effects.	None	Not reviewed, Deleted	
3	K2	3	Documentation is essential, and should demonstrate the evaluation process—including consultation, prescriptions, and periodic review of patient status. Any change and consequent patient response should be documented in the record.	None	Not reviewed, Deleted	
3	K2	4	Follow up with the patient in no longer than 2 to 4 weeks after dosage modifications, or other treatment adjustments, basing the frequency of follow-up on the clinical situation (also see Annotation K3 – Maintenance Phase).	None	Reviewed, Deleted	
3	K2	5	Assess the patient for changes in biopsychosocial and spiritual domains but especially the diagnosis, trajectory of disease, and effect of adjuvant therapies.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
3	K2	6	As with initial opioid selection and dosing, titration should be individualized according to the patient's age, health status, previous exposure to opioids, level of pain, comorbidities, potential drug interactions, the particular opioid formulation, the level (setting) of care, attainment of therapeutic goals, and predicted or observed harms.	None	Not reviewed, Deleted	
3	K2	7	If necessary, the daily dose may be increased by 25%-100% at a time. In general, smaller increments are appropriate for elderly or frail patients, those with likely low opioid tolerance, and patients experiencing unsatisfactory pain relief in the presence of some adverse effects. Larger increments may be used in patients with severe uncontrolled pain or likely high level of opioid tolerance. If the new dose is well tolerated but ineffective, additional increases in dose can be considered.	None	Not reviewed, Deleted	
3	K2	8	To ensure that the full effect from a dosage change has been manifested, and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every five half-lives. In the case of methadone, upward dosage titration should not occur more frequently than every 7 days and perhaps longer (e.g., every 1 to 2 months), and only if there is no problem with daytime sedation, taking into consideration that there is wide interpatient variability in half-lives and responsiveness. (See Appendices E1 and F)	None	Not reviewed, Deleted	
3	K2	9	If possible, titrate only one drug at a time while observing the patient for additive effects. Maintain patients on as few medications as possible to minimize drug interactions and adverse events. Discontinue medications, especially adjuvant medications, which do not add substantially to patient function or comfort. Continue close assessment of patients prescribed multiple centrally acting/psychoactive medications.	None	Not reviewed, Deleted	
3	K2	10	If a medication provides less than satisfactory pain reduction despite increasing the dose as tolerated to a reasonable level (less than 200 mg/day morphine equivalent), evaluate for potential causes such as nonadherence and drug interactions (see Appendix E, Table E6– Drug Interactions), and consider changing to an alternate opioid medication.	None	Not reviewed, Deleted	
3	K2	11	Medication may be increased until limited by adverse effects or clear evidence of lack of efficacy. If a high dose of medication (greater than 200 mg/day morphine equivalent) provides no further improvement in function, consider consultation rather than further increasing the dose.	None	Not reviewed, Deleted	
3	K2	12	During the titration phase, reasonable supplemental (rescue) doses of a short acting opioid may be considered. (See Annotation K-4-Supplemental Dosing)	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
3	K2	13	Consider one or more of the following adjustments in therapy when there is an apparent loss of analgesic effect a. Further optimize adjuvant therapies b. Re-titrate the dose • Increase dose by 25-100%. • Do not increase the dose more frequently than every 5 half lives (for methadone or fentanyl no more than once a week), to ensure that the full effect from a dosage change has been manifested and to avoid potential toxicity due to rapid accumulation of a drug • If possible, titrate only one drug at a time, while observing the patient for additive effects. Inappropriate or ineffective medications should be tapered while titrating an appropriate pharmacologic regimen • Medication may be increased until treatment goals are met, intolerable adverse effects occur, or there is clear evidence of lack of efficacy c. Rotate to another opioid • Rotation between opioids may help to improve efficacy, reduce side effects and reduce dose escalation in some patients who are receiving long-term opioid therapy • Rotate to another agent based on equianalgesic table and titrate (see Appendix E, Table E6 for conversion factors) d. Refer or consult with advanced pain care (pain or palliative care specialist/pharmacist) • If the dose of opioid is large (more than 200mg/day morphine equivalent) • If opioid induced hyperalgesia or opioid tolerance is suspected e. Discontinue Opioid Therapy (See Annotation X).	None	Not reviewed, Deleted	
3	K2	14	For a patient with continuous pain, an agent with a long duration of action, such as controlled-release morphine or methadone, is recommended.	None	Not reviewed, Deleted	
3	K2	15	If short-acting opioids are effective and well tolerated, it may be possible to achieve equivalent pain relief with fewer daily doses of the medication by substituting an equivalent dose of long-acting opioid medication (such as methadone, morphine CR, oxycodone CR, or transdermal fentanyl). These long- acting medications may provide steadier serum levels and smoother pain control. They can be supplemented with doses of short-acting medication to control pain exacerbation.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
3	K2	16	The conversion to a long-acting opioid should be based on an equianalgesic conversion (see Appendix E, Table E3 for conversion factors) and consideration of the incomplete cross-tolerance between opioids. To allow for incomplete cross-tolerance, in most cases, the starting conversion dose should be 50% to 67% of the calculated equianalgesic dose. A notable exception to this general rule is methadone, which has relatively little cross-tolerance with other opioids and should be started at a conversion dose that is based on the previous morphine- equivalent dose. Inexperienced clinicians should consult with an expert before initiating methadone; even in an opioid tolerant patient (see Appendix E, Table E-3, and Appendix F Methadone Dosing Recommendations).	None	Not reviewed, Deleted	
3	K2	17	Base the method of rotating opioids on the clinical situation. Either of the following two methods may be used: a. Step-wise Rotation: Reduce the old opioid dose by 25% to 50% decrements and replace the amount removed with an equianalgesic conversion dose of the new opioid. This method may be preferable when switching large doses of opioids. A disadvantage of this method is that the causative opioid(s) of new or worsening adverse effects during rotation would be difficult to identify. b. Single-step Rotation: Stop the old opioid and start the new opioid in an equianalgesic conversion dose. This method may be preferable when the old agent must be stopped immediately because of a hypersensitivity reaction. A disadvantage of this method is that pain may worsen if the new agent has a delayed peak analgesic effect (e.g., methadone) while the old agent has a relatively short offset of effects.	None	Not reviewed, Deleted	
3	K3	1	Maintain the lowest effective and well-tolerated dose. The optimal opioid dose is the one that achieves the goals of pain reduction and/or improvement in functional status and patient satisfaction with tolerable adverse effects.	None	Reviewed, New-replaced	Recommendation 10 Recommendation 11 Recommendation 12
3	K3	2	Recognize that the dose may need to be titrated up or down on basis of the patient's current biopsychosocial situation. (See Annotation K2 – Titration Phase)	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
3	K3	3	Assess patients at least every 1 to 6 months based on the following: a. Individualize and adjust visit frequencies based on patient characteristics, comorbidities, level of risk for potential drug misuse (i.e., diversion, addiction, abuse, and aberrant drug-related behavior), type of pain, and type and dose of opioids. No specific visit frequency applies to all patients b. Select a frequency that allows close follow-up of the patient's adverse effects, pain status, and appropriate use of medication c. The patient should be able to request an early evaluation d. Any change in the efficacy of the maintenance dose requires a face to face encounter for assessment prior to modifying therapy	None	Reviewed, Deleted	
3	K3	4	Monthly renewal of the prescription for opioid medication can be facilitated by: a. Phone call, email, or mail-in requests; and/or b. A structured program (e.g., opioid renewal clinic) staffed by advanced care providers (e.g., pharmacists, nurse practitioners, PA-Cs, psychologists, RNs) with appropriate co-signatures	None	Not reviewed, Deleted	
3	K3	5	In addition to the maintenance opioid analgesic, supplemental doses of short-acting opioids may be considered. (See Annotation K4 – Supplemental Therapy)	None	Not reviewed, Deleted	
3	K3	6	Assess and re-educate patient's adherence with safely storing opioid medications.	None	Not reviewed, Deleted	
3	K4	1	Evaluate worsening or new pain symptoms to determine the cause and the best treatment approach.	None	Not reviewed, Deleted	
3	K4	2	Encourage the use of non-pharmacologic modalities (e.g., pacing activities, relaxation, heat, cognitive behavioral therapy).	None	Reviewed, New-replaced	Recommendation 1
3	K4	3	Carefully evaluate the potential benefits, side effects, and risks when considering supplemental opioids.	None	Not reviewed, Deleted	
3	K4	4	Consider supplemental short-acting opioid, non-opioid, or a combination of both agents on an as- needed basis.	None	Not reviewed, Deleted	
3	K4	5	Avoid the use of rapid-onset opioids as supplemental opioid therapy in chronic pain, unless the time course of action of the preparation matches the temporal pattern of pain intensity fluctuation.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
3	K4	6	Avoid use of long-acting agents for acute pain or on an as-needed basis in an outpatient setting.	None	Not reviewed, Deleted	
3	K4	7	When using combination products, do not exceed maximum recommended daily doses of acetaminophen, aspirin, or ibuprofen.	None	Not reviewed, Deleted	
3	K4	8	Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence.	None	Not reviewed, Deleted	
3	K4	9	Whenever possible, use the same opioid for supplemental therapy as the long-acting opioid to avoid confusion about the cause of any adverse effects that may develop.	None	Not reviewed, Deleted	
3	K4	10	When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10-15%, the every four hourly equivalent, or 1/6th of the total daily opioid dose, as needed.	None	Not reviewed, Deleted	
3	K4	11	Use rescue short-acting opioids to assist with pain management during the titration process and to help determine the long-term daily opioid dose.	None	Not reviewed, Deleted	
3	K4	12	Do not use routinely for chronic pain. If necessary, use breakthrough pain therapy sparingly.	None	Not reviewed, Deleted	
3	K4	13	Consider adjusting the long-acting opioid regimen if pain exacerbations are interfering with patient function due to severity, frequency, or diurnal variations in pain intensity.	None	Not reviewed, Deleted	
3	K4	14	Educate and reassure patient, emphasizing realistic expectations about limitations of chronic opioid therapy, the normal cyclic nature of chronic pain, and the importance of pacing activities.	None	Not reviewed, Deleted	
3	K4	15	Consider providing preemptive analgesia for preventing incident pain e.g., 8 to 12 doses per month of short-acting opioid preparation.	None	Not reviewed, Deleted	
3	L	1	When writing a prescription for opioid therapy, be certain to record the name of the drug, the strength, the number of dosage units (written numerically and in text) and how the drug is to be taken. (In the case of methadone, indicate on the prescription that it is for pain as opposed to detoxification).	None	Not reviewed, Deleted	
3	L	2	Follow local regulations.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
4	M1	1	Evaluate patient for opioid adverse effects: constipation, nausea, vomiting, headache, dyspepsia, pruritus, dizziness, tiredness, dry mouth, sweating, hyperalgesia, sexual dysfunction, and sedation.	None	Not reviewed, Deleted	
4	M1	2	Many adverse effects spontaneously resolve with continued administration and development of tolerance. Consider individual levels of tolerability to different opioid agents.	None	Not reviewed, Deleted	
4	M1	3	If not already done, anticipate and consider preventive treatment for common adverse effects, particularly constipation and nausea.	None	Not reviewed, Deleted	
4	M1	4	Keep in mind that slowly titrating the opioid dose, modifying the dosage regimen, treating symptoms, and rotating the opioid agents may successfully treat most adverse effects.	None	Not reviewed, Deleted	
4	M1	5	Consider evaluation of possible drug-to-drug interactions with other medications that have been prescribed for the patient (see Appendix E: Drug Table E4 – Drug Interactions).	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
4	M2	1	At every visit and telephone contact for opioid renewal, assess and document adherence with appropriate use of opioid analgesics, and any evidence of misuse, abuse, or addiction. a. Evaluate how and when the patient is taking medication, use of other medications including nonprescription and herbal preparations, and use of alcohol and illicit drugs b. Screening aids such as random pill counts, adherence checklists, or instruments such as the Screener and Opioid Assessment for Patients with Pain (SOAPP), may be used to assist the provider in assessing adherence c. With patient consent, obtain a Urine Drug Test (UDT) before initiating opioid therapy trial and randomly at follow-up visits to confirm the appropriate use of opioids (See Annotation M3) d. Assess and document adherence to other components of the treatment plan, such as follow up with referrals, tests, and other therapies e. Assess patients for behaviors that are predictive of addiction including repeated minor variations in adherence that may indicate an increased likelihood of addiction or serious non-adherence f. Assess patient's adherence and reeducate regarding the importance of safely storing opioid medications g. Assess and document patient motivation and barriers to adherence	None	Reviewed, New-replaced	Recommendation 7 Recommendation 9
4	M2	2	Based on the clinical assessment the provider should determine whether aberrant behavior is present and respond with appropriate action.	None	Not reviewed, Deleted	
4	M2	3	If the clinician is not sure of the meaning of the behavior, more frequent clinic visits, addiction or mental health specialist consultations, or periodic drug screens might be employed.	None	Reviewed, New-replaced	Recommendation 7 Recommendation 9
4	M2	4	When aberrant behaviors are present, providers should not stigmatize or judge patients but instead simply inform the individual that the behavior is unsafe and needs evaluation and adjustment in treatment through increased structure and monitoring or referral.	None	Not reviewed, Deleted	
4	M2	5	A continuing pattern of repeated episodes of non-adherence following treatment changes designed to maximize adherence should increase prescriber concerns and consideration of potential cessation of opioid therapy.	None	Reviewed, New-replaced	Recommendation 9

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
4	M2	6	Consider involving family members or significant others in identifying solutions to non-adherence and in monitoring future adherence when possible. This may include a change in the patient's living situation that would provide greater structure (e.g., nursing home, assisted living facility), potentially enhance compliance, and reduce nonadherence	None	Not reviewed, Deleted	
4	M3	1	Inform patients that drug testing is a routine procedure for all patients starting or on opioid therapy, and is an important tool for monitoring the safety of their treatment.	None	Reviewed, New-replaced	Recommendation 7
4	M3	2	With patient consent, obtain a UDT in all patients prior to initiation of OT. [B]	B	Reviewed, New-replaced	Recommendation 7
4	M3	3	With patient consent monitor all patients on OT with periodic random UDTs to confirm adherence to the treatment plan. Increase the frequency of UDTs based on risk level for aberrant drug-related behaviors and following each dose increase. [B]	B	Reviewed, New-replaced	Recommendation 7
4	M3	4	Take into consideration a patient's refusal to take a UDT as part of the ongoing assessment of the patient's ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Annotation F).	None	Not reviewed, Deleted	
4	M3	5	When interpreting UDT results take into account other clinical information (e.g., past SUD, other risk factors, aberrant drug-related behaviors, and other conditions indicating risk.)	None	Not reviewed, Deleted	
4	M3	6	Understanding of lab methods for drug testing and reporting are necessary to interpret UDT results (i.e., screen versus confirmatory test, substances tested, cut-off levels for tests). Maintain a close working relationship with the clinical laboratory to answer any questions about the UDT or for confirming the results.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
4	M4	1	Evaluate and assess the patient for the following problems or other indications for consultation or referral: a. Patient with complex pain conditions b. Patient with significant medical comorbidities that may negatively impact opioid therapy c. Patient with significant concurrent psychiatric illnesses d. Patient who is unable to tolerate increased pain or physical withdrawal symptoms arising from opioid tapering when OT is being discontinued e. Opioid induced hyperalgesia or opioid tolerance suspected (i.e., pain increases or changes while on chronic stable opioid dosing and with an unchanged underlying medical condition causing the pain) f. Patient with conditions requiring management beyond the expertise level of the primary provider	None	Not reviewed, Deleted	
4	M5	1	Evaluate pain intensity at each visit. a. Intensity of pain should be measured in the following manner using a Numeric Rating Scale (NSR) (0 to 10) and include the following: • Current pain • Least pain in last week • "Usual" or "Average" pain in the last week b. The patient's response to current pain medications should be assessed each visit using questions such as: • "What is your intensity of pain after taking your current treatment/medication?" • "How long does your pain relief last after taking your medication?"	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
4	M5	2	Evaluate pain-related function using objective documentation whenever possible, such as physical therapy progress notes, employment records, exercise diaries, family reports, clinician observations (e.g., walking distance), or validated instruments or NRS rating scales on a monthly basis during the titration phase and every six months after the patient is on stable opioids. Assessment of function may include: • Employment • Enjoyment of life • Emotional distress (depression and anxiety) • Housework, chores, hobbies, and other day to day activities • Sleep • Mobility • Self-care behaviors • Sexual function	None	Not reviewed, Deleted	
4	M5	3	Assess overall patient satisfaction with pain therapy at each visit	None	Not reviewed, Deleted	
4	M5	4	Emphasis should be given to capitalizing on improved analgesia by gains in physical and social function; opioid therapy should be considered complementary to other analgesic and rehabilitative approaches.	None	Not reviewed, Deleted	
5	N1	1	Adverse effects can usually be minimized through the use of low starting doses, slow titration rates, prophylactic and symptomatic treatments, and specific patient education provided at initiation of therapy.	None	Not reviewed, Deleted	
5	N1	2	Symptomatic treatment should be augmented with slow dosage titration, dose modification, and/or opioid rotation to minimize the adverse effects as follows: a. Titrate slowly, temporarily reducing or holding doses if necessary, or modify the dosage regimen to allow the patient to develop tolerance to the adverse effects b. If these measures fail to minimize the adverse effects, consider rotating to another opioid agent	None	Not reviewed, Deleted	
5	N1	3	If adverse effects are unmanageable and therapy is a greater detriment than benefit as determined by discussion with the patient and family, opioid therapy should be discontinued.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
5	N1	4	Initial bowel regimens should generally consist of a bowel stimulant and a stool softener as well as general measures, such as increased fluid intake, increased dietary fiber, and adequate exercise.	None	Not reviewed, Deleted	
5	N1	5	Routinely initiate a stimulant-based bowel regimen at commencement of chronic opioid therapy.	None	Not reviewed, Deleted	
5	N1	6	If the initial regimen is inadequate, mild hyperosmotic, saline, and emollient laxatives may be added.	None	Not reviewed, Deleted	
5	N1	7	If possible, reduce or discontinue other drugs that may cause or contribute to constipation.	None	Not reviewed, Deleted	
5	N1	8	Bulk-producing laxatives, such as psyllium and polycarbophil, are not recommended and are relatively contraindicated as they may exacerbate constipation and lead to intestinal obstruction in patients with poor fluid intake.	None	Not reviewed, Deleted	
5	N1	9	Assess patients for constipation symptoms at every office visit.	None	Not reviewed, Deleted	
5	N1	10	Consider prophylactic antiemetic therapy at initiation of therapy.	None	Not reviewed, Deleted	
5	N1	11	Rule out other causes of nausea, and/or treat based on cause including a. Stimulation of chemoreceptor trigger zone: dopamine or serotonin antagonist b. Slowed GI motility: metoclopramide c. Nausea associated with motion: dimenhydrinate or scopolamine.	None	Not reviewed, Deleted	
5	N1	12	Rule out an allergic reaction.	None	Not reviewed, Deleted	
5	N1	13	Itching may resolve spontaneously despite continuation of opioid therapy. If the itching does not spontaneously resolve, consider treatment with antihistamines.	None	Not reviewed, Deleted	
5	N1	14	Rule out other causes.	None	Not reviewed, Deleted	
5	N1	15	Reduce dose (with or without addition of a co-analgesic). Excessive sedation within the first few days of initiating opioids may require temporarily holding one or two doses and restarting at a lower dose to prevent respiratory depression.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
5	N1	16	Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced.	None	Not reviewed, Deleted	
5	N1	17	If the above measures fail to relieve sedation adequately, consider rotating to another opioid agent.	None	Not reviewed, Deleted	
5	N1	18	Consider adding caffeine or a prescription psychostimulant medication.	None	Not reviewed, Deleted	
5	N1	19	Rule out other causes.	None	Not reviewed, Deleted	
5	N1	20	Consider reducing or stopping (tapering) the dose.	None	Not reviewed, Deleted	
5	N1	21	Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced.	None	Not reviewed, Deleted	
5	N1	22	Rotate opioid agent.	None	Not reviewed, Deleted	
5	N1	23	If patient continues to deteriorate during titration phase and presents with symptoms of delirium, opioid therapy should be discontinued.	None	Not reviewed, Deleted	
5	N1	24	If patient develops increased confusion or major cognitive changes (delirium) during the maintenance phase, consider hospitalization to investigate the cause and to continue treatment safely.	None	Not reviewed, Deleted	
5	N1	25	Ask all patients on opioids for chronic pain about symptoms of opioid-induced endocrinopathy (i.e. hypogonadism) on each visit.	None	Not reviewed, Deleted	
5	N1	26	If opioid-induced endocrinopathy symptoms are present, , and not accounted for by another disorder or illness (e.g., depression, chronic disease), laboratory evaluation and consultation with an endocrinologist should be considered	None	Not reviewed, Deleted	
5	N1	27	Insufficient data exists to recommend routine laboratory screening for endocrinopathy in asymptomatic patients on OT.	None	Not reviewed, Deleted	
5	N1	28	There is insufficient evidence to make recommendations regarding OT and immune dysfunction.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
5	N1	29	Consider monitoring bone density in patients at risk for osteoporosis (See Table 6: Risk Factors for Osteoporosis), as patients with fractures associated with hypogonadism often have no other symptoms associated with hypogonadism.	None	Not reviewed, Deleted	
5	N2	1	If a medication causes unmanageable adverse effects, consider changing to an alternate opioid medication.	None	Not reviewed, Deleted	
5	N2	2	When therapy is a greater detriment than benefit as determined in consultation with the patient and family, opioid therapy should be discontinued.	None	Not reviewed, Deleted	
5	N3	1	Address safety issues immediately and apply legal mandates as appropriate.	None	Not reviewed, Deleted	
5	N3	2	Dangerous or illegal behaviors may require immediate cessation of the opioid therapy with consideration of appropriate treatment of potential withdrawal symptoms.	None	Not reviewed, Deleted	
5	N3	3	Document and refer to behavior health specialty those patients demonstrating behaviors suggestive of suicide.	None	Reviewed, Amended	Recommendation 8
5	N3	4	For a patient with evidence of diversion or dangerous or suicidal behavior the clinician should discontinue OT, refer as appropriate for emergency psychiatric evaluation, and flag the chart.	None	Not reviewed, Deleted	
5	N3	5	Consider notifying law enforcement about suspected criminal behaviors such as prescription fraud or diversion. Consult with counsel prior to doing so to clarify current confidentiality laws and regulations (e.g., VA /military police, risk manager, and/or regional counsel).	None	Not reviewed, Deleted	
5	N3	6	Carefully document the details of the situation in the clinical record, or not, as advised by risk management and/or legal counsel.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
5	N4	1	Consider adjustment of the initial treatment agreement, with emphasis upon specific adherence issues that have been identified; a more structured approach may be required. Possible responses to minor nonadherence might include: a. Reviewing, discussing, and restating the treatment plan b. Reviewing the written opioid treatment agreement and incorporating any needed revisions c. Recommending consultation with a pain, addictions, or behavior health specialist d. Administration of medications under supervision or with the assistance of others e. Change of medication, medication dose, or amount dispensed f. More frequent clinic contacts (telephonic, physician extenders, or clinic visits) g. Instituting periodic or random urine toxicology screens	None	Reviewed, New-replaced	Recommendation 9
5	N4	2	Consider setting up a grievance procedure with the patient.	None	Not reviewed, Deleted	
5	N4	3	Consider involving family members or significant others in identifying solutions to non-adherence and in monitoring future adherence when possible. This may include change in the patient's living situation that would provide greater structure (e.g. nursing home, assisted living facility) and might enhance compliance and reduce nonadherence.	None	Not reviewed, Deleted	
5	N5	1	Consider consultation with, or referral to, a behavioral health specialist if exacerbation of an underlying psychotic disorder is an issue, if the nonadherent behaviors may be due to changes in mood or increased suicidality, or if there is evidence of increased and poorly controlled anger and tendency to violent behaviors (see Annotation O2).	None	Not reviewed, Deleted	
5	N5	2	Consider referral to an addiction specialist if the nonadherent behaviors are those associated with possible addiction (see Annotation O1).	None	Reviewed, New-replaced	Recommendation 16
5	N5	3	Patients presenting with persistent or troublesome aberrant behavior who do not respond to intervention by primary care should be referred for evaluation and management of OT to a more structured care environment (e.g., Pharmacy Pain Management Clinic / Opioid Renewal Pain Care Clinic/ Pain Medicine Clinic).	None	Reviewed, New-replaced	Recommendation 16
5	N5	4	If such programs are not available, consider continuing OT with increased frequency of monitoring and screening, performing a comprehensive behavioral assessment, and addressing co-morbidities.	None	Reviewed, New-replaced	Recommendation 16

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
6	O1	1	Consider consultation or referral to addiction specialty for evaluation and treatment in the following conditions: a. Demonstration of behaviors suggesting addiction to prescribed opioids or substance use disorders b. Patients with a significant chronic, or substantiated pain, who develop addiction behaviors in the context of chronic opioid therapy c. Uncontrolled substance use disorder (excluding nicotine) d. Behaviors characteristic of compulsive drug use (addiction) to either opioids or other drugs or alcohol should be referred to an addiction specialty e. Complex conditions who manifest behaviors characteristic of addiction with multiple co- occurring psychiatric disorders f. Need for tapering of opioids or unable to tolerate tapering after discontinuation of OT.	None	Reviewed, New-Replaced	Recommendation 16
6	O1	2	Consider consultation with a SUD specialist to evaluate the risk of recurrent substance abuse or to assist with ongoing management.	None	Reviewed, New-replaced	Recommendation 17
6	O1	3	Refer patient for psychosocial treatments specific to prescription medication addiction/abuse. These can include addiction counselors comfortable with such topics, and self-help organizations (Pills Anonymous/PA, the National Chronic Pain Outreach association, and other similar organizations).	None	Not reviewed, Deleted	
6	O2	1	Consider referral to a Pain Medicine Specialist in the following situations: a. Patient with complex pain conditions or polytrauma b. Patient with significant medical comorbidities that may negatively impact opioid therapy c. Patient who is unable to tolerate increased pain or physical withdrawal symptoms arising from opioid tapering when OT is being discontinued d. Opioid induced hyperalgesia or opioid tolerance is suspected e. High dose of medication (greater than 200 mg/day morphine equivalent) provides no further improvement in function f. Patient requiring management beyond the expertise of the primary provider	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
6	O2	2	Consider Referral to/consultation with a Behavioral Health Provider for evaluation and treatment in the following conditions: a. Exacerbation of an underlying psychotic disorder b. Uncontrolled, severe psychiatric disorder or those who are emotionally unstable c. Demonstration of high-risk behaviors suggestive of suicide ideation d. Psychosocial problems or comorbidities that may benefit from disease or case management e. Adverse behavioral or cognitive effects of OT f. Co-occurring trauma related conditions (mTBI, TBI, PTSD)	None	Not reviewed, Deleted	
7	P	1	Schedule follow-up visits at least every 2-4 weeks after any change in medication regimen and at least once every 1-6 months for the duration of the therapy (maintenance).	None	Not reviewed, Deleted	
7	P	2	Assess at each visit: a. Comfort (degree of analgesia) b. Opioid-related adverse effects c. Functional status (physical and psychosocial) d. Adherence to opioid treatment agreement and other aspects of treatment plan e. Obtain laboratory studies (especially liver or kidney function screens), and/or order drug screens as indicated f. Use of self-report instruments (diary, opioid log) may be helpful but should not be required.	None	Not reviewed, Deleted	
7	P	3	Documentation is essential and the medical record for each encounter should specifically address comfort, function, adverse-effects, and treatment plan adherence.	None	Not reviewed, Deleted	
8	Q	1	Opioid therapy should be tapered off and discontinued if any of the following situations occur: a. The medication fails to show partial analgesia with incremental dose titration b. Trials with different agents provide inadequate analgesia c. There is other evidence that the pain may not be opioid responsive d. Real or potential harms outweigh real or potential benefits e. Patient request.	None	Not reviewed, Deleted	
8	Q	2	Consider decreasing the opioid dose when pain level decreases in stable patients. (See Annotation X – Tapering)	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
8	R	1	Document, and offer referral to addiction specialty for patients demonstrating behaviors suggesting addiction to prescribed opioids or substance use disorders.	None	Reviewed, New-replaced	Recommendation 17
8	R	2	Discuss pharmacotherapy options with all patients with opioid and/or alcohol dependence.	None	Reviewed, New-replaced	Recommendation 17
8	R	3	If there are clearly unsafe or illegal behaviors, opioid prescribing should stop immediately and withdrawal should be addressed.	None	Not reviewed, Deleted	
8	S	1	Attempt to maintain contact with any patient who withdraws from treatment due to a disagreement.	None	Not reviewed, Deleted	
8	S	2	Refer patients with comorbid psychiatric disorders to appropriate mental health providers.	None	Not reviewed, Deleted	
8	S	3	Identify and document any co-occurring disorders (CODs) in patients with substance use disorders; a. Psychiatric history, including symptoms and their relation to substance use, current and past diagnoses, treatments and providers b. Infectious diseases (HIV, Hepatitis C, sexually transmitted disease) c. For patients using nicotine offer and recommend tobacco use cessation treatment d. Medical CODs that may be related to or affected by substance use (e.g., diabetes, cardiovascular disease, digestive disorders, skin infections, respiratory disorders, dementia, cerebrovascular disease)	None	Not reviewed, Deleted	
8	S	4	Individuals with SUD should be assessed for any significant, unmet psychosocial needs or situational stressors. These include but are not limited to: a. Inadequate or no housing b. Financial difficulties, especially if unable to meet basic needs c. Problematic family relationships or situations (including caregiver burden or domestic violence) d. Poor social support e. Religious and spiritual problems f. Occupational problems g. Difficulties with activities of daily living or instrumental activities of daily living	None	Not reviewed, Deleted	
8	T	1	Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
8	T	2	For those patients who are at high risk of aberrant behaviors (parasuicidal acts, dealing/selling medications, or those with severe impulse control disorders), tapering opioid in a primary care setting is not appropriate and those patients should be referred to an addiction or pain specialist with expertise dealing with difficult cases.	None	Not reviewed, Deleted	
8	T	3	Patients with complicated withdrawal symptoms should be referred to a pain specialist or a center specializing in withdrawal treatment.	None	Not reviewed, Deleted	
8	T	4	Patient being tapered due to development of addiction should be referred for SUD treatment. Opioid detoxification in a primary care setting followed by ongoing substance use treatment may be appropriate.	None	Not reviewed, Deleted	
8	U	1	Complete evaluation of treatment, comorbidity, psychological condition, and other relevant factors should be completed prior to the initiation of the taper.	None	Not reviewed, Deleted	
8	U	2	Clear written and verbal instructions should be given to patients/family to educate them about the slow taper protocol that will minimize abstinence (withdrawal) syndromes.	None	Not reviewed, Deleted	
8	U	3	Patients who are unable to tolerate the taper as described should be considered for referral to, or consultation with, a pain specialist, substance use specialist or other expert.	None	Not reviewed, Deleted	
8	U	4	Withdrawal management for addicted patients is not part of this guideline. Refer to the VA/DoD Guideline for the Management of Substance Use Disorders.	None	Not reviewed, Deleted	
8	V	1	Do not abandon a patient under any circumstances.	None	Not reviewed, Deleted	
8	V	2	Maintain contact with any patient who withdraws from treatment due to a disagreement.	None	Not reviewed, Deleted	
8	V	3	Refer patients with comorbid psychiatric disorders to appropriate mental health providers.	None	Not reviewed, Deleted	
9	W	1	Use caution when using opioids in patients with history of substance use disorders. [B]	B	Reviewed, Deleted	
9	W	2	Use an integrated treatment approach addressing both pain [B] and SUD issues with appropriate information sharing. [C]	C	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
9	W	3	Patients on opioid agonist therapy for DSM-IV diagnosis of opioid dependence who have a co- occurring chronic pain disorder should be treated for pain considering the following options: a. Use non-pharmacologic interventions b. Use other non-opioid pharmacologic treatment modalities c. Cautious use of opioid therapy by using another opioid agonist with slow titration and careful communication with the SUD opioid agonist therapy prescribers. [B]	B	Reviewed, Deleted	
9	W	4	Perform urine drug testing as an adjunctive tool at regular intervals. [B]	B	Reviewed, New-replaced	Recommendation 9
9	W	5	Management of OT in patients on sublingual (SL) buprenorphine (with or without naloxone) for DSM-IV diagnosis of opioid dependence: a. SL buprenorphine is FDA-approved for treatment of opioid dependence and can only be prescribed by a qualified and DEA-waivered physician for this purpose b. Patients on SL buprenorphine should not receive full agonist opioids concomitantly for routine pain control c. Nonopioid and nonpharmacologic strategies for pain management should be maximized In the event of anticipated pain (i.e., an elective procedure or surgery) SL buprenorphine should be stopped for 48 hr before the scheduled event e. For unanticipated pain (trauma, emergency surgery or procedure) the care team managing the acute pain should be notified that the patient is prescribed SL buprenorphine and when the last dose was taken.	None	Not reviewed, Deleted	
9	X	1	Be vigilant for sleep apnea during OT. If clinical suspicion exists for the presence of sleep apnea in a patient on OT, sleep study should be considered. [B].	B	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
9	X	2	Patients on OT who present with sleep disorder confirmed by a sleep study should be assessed for the appropriateness of continuing OT and should be evaluated for the risks (based on the severity of the sleep-disordered breathing) versus benefits of OT. If OT is continued, it should be titrated cautiously. Patients found to have sleep-disordered breathing should be followed with a repeated sleep study. [C]	C	Not reviewed, Deleted	
9	X	3	Patient with abnormal sleep study should be educated about the significant additional risks including breathing disruption, and instructed to avoid alcohol, or any CNS-depressant medication. [A]	A	Not reviewed, Deleted	
9	X	4	The type of sleep apnea should be evaluated to determine if it is obstructive or central. CPAP may worsen central sleep apnea. [D]	D	Not reviewed, Deleted	
9	X	5	Patients with sleep apnea who are on OT may benefit from a reduction in the dose of their opioids.	None	Not reviewed, Deleted	
9	X	6	Discontinuation of opioid therapy should be considered if the sleep apnea is severe or life threatening.	None	Not reviewed, Deleted	
9	X	7	Consider more careful monitoring of OT in patients treated with methadone and/or benzodiazepines. [B]	B	Not reviewed, Deleted	

Appendix I: Participant List

Elizabeth (Liz) Rees Atayde, RN, MSN, FNP, CCM, CPHM Nursing, Medical Management Medical Management Consultant/CPG Coordinator U.S. Army Medical Command Fort Sam Houston, TX	LTC Robert Brutcher, PharmD, PhD Pharmacy Deputy Director, Department of Pharmacy Walter Reed National Military Medical Center/ Defense Health Agency Bethesda, MD
Michael O. Chaffman, PharmD, BCPS Pharmacy National PBM Clinical Pharmacy Program Manager, Veterans Health Administration Pharmacy Benefits Management Services Hines, IL	Corinne K. B. Devlin, MSN, RN, FNP-BC Family Nurse Practitioner Chief, Office of Evidence Based Practice U.S. Army Medical Command Clinical Performance Assurance Directorate Fort Sam Houston, TX
Karen Drexler, MD Substance Use Disorders, Psychiatry National Mental Health Program Director, Substance Use Disorders Mental Health Services, VA Central Office Atlanta, GA	LTC William Grief, MD Family Medicine, Pain Medicine Chief, Department of Pain Management Madigan Army Medical Center Joint Base Lewis-McChord, WA
James Hardin, LCSW-C, MAC Social Work Chief, Addiction Treatment Services Walter Reed National Military Medical Center Bethesda, MD	Connie Kurihara, RN Pain Management Research Nurse Walter Reed National Military Medical Center Bethesda, MD
Franz Macedo, DO Pain Medicine, Physical Medicine and Rehabilitation Medical Director, Comprehensive Pain Center Minneapolis VA Medical Center Minneapolis, MN	Aram Mardian, MD Family Medicine, Primary Care Chief, Chronic Pain Wellness Program Phoenix VA Health Care System Phoenix, AZ
Anthony J. Mariano, PhD Pain Psychology Director, Pain Psychology, VISN 20 Pain Medicine and Functional Rehabilitation Center VA Puget Sound Healthcare System Seattle, WA	CDR Marisol Martinez, PharmD, MBA Pharmacy Clinical Pharmacy Analyst U.S. Public Health Service Defense Health Agency Pharmacy Operations Division San Antonio, TX
Capt Erick C. Messler, PhD Psychology Director of Psychological Health Malmstrom Air Force Base, MT	Ilene Robeck, MD Internal Medicine, Addiction Medicine, Mental/Behavioral Health Co-Chair, National Primary Care Pain Champions Initiative Director of Virtual Pain Care, Richmond VA Medical Center Richmond, VA

Jack Rosenberg, MD, FASAM (Champion) Pain Medicine, Anesthesiology, Addiction Chair, National Pain Guidelines Group Member, National Pain Management Strategy Coordinating Committee Co-Physician Pain Lead, VISN 10 Staff Physician, Ann Arbor VA Medical Center Ann Arbor, MI	Friedhelm Sandbrink, MD Pain Medicine, Neurology, Clinical Neurophysiology Chief, Pain Management Program, Department of Neurology, Washington DC VA Medical Center Deputy National Program Director for Pain Management, Specialty Care Services, VHA Washington, DC
LTC Jason Silvernail DPT, DSc, FAAOMPT Physical Therapy Chief, Physical Therapy Service Walter Reed National Military Medical Center/ Defense Health Agency Bethesda, MD	Maria Silveira, MD, MA, MPH Palliative Care, Geriatrics Clinical Scientist, Geriatric Research Education Clinical Center, Ann Arbor VA Medical Center Ann Arbor, MI
Christopher Spevak, MD, MPH, JD (Champion) Pain Medicine, Addiction Medicine Director, Prescription Medication Misuse Program Deputy Director, Wounded Warrior and NCRP Initiatives Walter Reed National Military Medical Center/ Defense Health Agency Bethesda, MD	Nancy Wiedemer, MSN, RN, ANP-BC Nursing, Primary Care, Pain Medicine Pain Management and Opioid Safety Lead for VISN 4 Pain Management Coordinator, Corporal Michael Crescenz VA Medical Center, Philadelphia
CAPT Necia Williams, MD Pain Medicine, Anesthesiology Command Surgeon Marine Special Operations Command Camp Lejeune, NC	

Appendix J: Literature Review Search Terms and Strategy

A. Topic-specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Table J-1. EMTREE, Medical Subject Headings (MeSH), PsycInfo, and Keywords

Concept	Controlled Vocabulary	Keywords
Patient population		
Chronic Pain	**EMBASE** 'chronic disease'/exp 'chronic inflammatory pain'/exp 'chronic pain' 'pain'/exp **MeSH** exp chronic disease/ exp pain/ **PsycINFO** Exp chronic illness/ exp chronic pain/ exp pain/	chronic Chronic adj3 pain* Chronic NEXT/3 pain* Long?term NEXT/3 pain* months pain weeks year*
Chronic Opioid Use	**EMBASE** 'analgesic agent'/exp 'codeine'/de 'drug therapy'/lnk 'fentanyl'/de 'morphine'/de 'narcotic agent'/exp 'narcotics'/exp 'narcotic drugs'/exp 'opiate'/de 'opiates'/exp **MeSH** Chronic pain/drug therapy exp analgesics, opioids exp narcotics **PsycINFO** exp analgesic drugs exp narcotics exp narcotic drugs exp opiates	Analgesic* COT 'chronic NEXT/1 opi* NEXT/1 therapy' 'chronic opi* therapy' codeine Fentanyl heroin Hydrocodone Hydromorphone Long?term Methadone months morphine narcotic* Opi* Oxycodone Oxycontin Oxymorphone percocet Tapentadol Tramadol Vicodin weeks Year*

Concept	Controlled Vocabulary	Keywords
KQ 1 **Contraindications** What is the evidence that the following medical or mental health conditions are absolute or relative contraindications of prescribing LOT? ■ Active pursuit of compensation ■ Centralized pain conditions such as fibromyalgia ■ Chronic obstructive pulmonary disease ■ Cognitive impairment ■ Depression ■ Headache ■ GI motility problems (e.g., toxic megacolon, GI pain syndromes, narcotic bowel syndrome) ■ Immune status changes ■ Inability to participate in comprehensive treatment plan ■ Incarceration (history of) ■ Hepatic, renal, or pulmonary disease ■ Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed) ■ Osteoporosis ■ Personality disorders ■ Posttraumatic stress disorder ■ Sleep disorders ■ SUD (current or history of)—include specific disorders and appropriate key words in search ■ Suicidality ■ Traumatic brain injury ■ Use of medical marijuana ■ QT prolongation	**EMBASE** 'drug contraindication'/exp 'drug interaction'/exp 'drug safety'/exp **MeSH** analgesics, opioid/contraindications Polypharmacy/ **PsycINFO** Drug interactions/ Polypharmacy/ Safety/	Cardiovascular CNS COPD Compensation* Contraindication* depression Fibromyalgia gastrointestinal Headache* Heart immune Liver Lung Obstructive Osteoporosis (personality or cognitive or mental or neuro*) adj3 (disorder* or disease* or illness*)) Post?traumatic stress PTSD Respiratory Sleep Substance adj2 (abuse OR misuse) Substance use disorder SUD Suicide suicidality TBI Traumatic brain

Concept	Controlled Vocabulary	Keywords
KQ 2 **Risk factors for the continuum of misuse or OUD** What factors increase the risk of developing misuse or OUD when considering LTOT? a) What are the risks for long-term use associated with acute use of opioids in treating acute pain?	**EMBASE** 'analgesic agent abuse'/exp 'bullying'/exp 'opiate addiction'/exp 'opioid-related disorders'/exp 'risk'/exp 'sexual abuse'/exp **MeSH** 'bullying'/ 'domestic violence'/exp 'risk assessment'/exp 'substance-related disorders'/exp **PsycINFO** Exp addiction/ Exp at risk populations/ Exp codependency/ Exp drug abuse/ Exp drug addiction/ Exp drug overdoses/ Exp illegal drug distribution/ Exp risk assessment/ Exp risk factors Exp risk perception/	Abuse Acute Addict* Assess* Bully Bullying Day* dependency Disorder* Early Initial New New onset Overdose* Predict* Risk* Short term violence

Concept	Controlled Vocabulary	Keywords
KQ 3 AND KQ 4 **Effectiveness of LTOT** What is the comparative effectiveness of LTOT versus other treatment modalities? a) What is the comparative effectiveness of LTOT versus other treatment modalities for patients with a history of or current SUD? b) What is the effectiveness of non-pharmacological interventions in patients with chronic pain? **Safety of LTOT** What is the safety of LTOT versus other treatment modalities? a) What is the safety of LTOT versus other treatment modalities for patients with a history of or current SUD? b) What is the safety of non-pharmacological interventions in patients with chronic pain?	**EMBASE** 'adverse drug events'/exp 'adverse drug reaction'/exp 'adverse drug reaction'/lnk 'drug overdose'/exp 'patient safety'/exp 'prescription drugs'/exp 'side effect'/lnk 'side effect'/de 'treatment outcome'/de **MeSH** 'analgesics, opioid'/*adverse effects 'prescription drugs'/adverse effects 'quality of life' 'risk' 'side effect'/de 'treatment outcome' **PsycINFO** *quality of life/ "side effects (drug)"/ *treatment outcomes/ Drug overdose/*prevention & control	Aberrant NEXT/3 behavior* Absence absent Abuse Accident* 'ade' Addict* adverse 'adverse drug events' Adverse NEXT/1 effect* Anxiety cardiac cardiovascular cognitive complication depression Disorder* Diversion effective effectiveness Fall Falls Harm* Misuse Mood Outcome* Overdose* 'pain relief' Pain NEXT/2 relief Pain NEXT/3 reliev* poison* 'quality of life' QOL Safety 'side effect*' Sleep s

Concept	Controlled Vocabulary	Keywords
KQ 5 **Effectiveness of different opioid formulations** What is the comparative effectiveness and safety of various opioid formulations? a) Immediate-release/short-acting opioids compared to ER/long-acting opioids b) Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps c) Abuse deterrent formulations compared to non-abuse deterrent formulations d) Tramadol and other dual-mechanism opioids e) Buprenorphine f) Methadone	**EMBASE** 'short acting analgesic agent'/exp **MeSH** 'analgesics, short-acting' **PsycINFO** *drug therapy	Abuse-deterrent controlled 'controlled release' extended 'extended release' Formulation immediate 'immediate release' LA 'long?acting' Medication Medicine Pill* Prescription* SA 'short?acting' (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)) Sustained

Concept	Controlled Vocabulary	Keywords
KQ 6 **Added benzodiazepines** Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to OT alone?	**EMBASE** 'antidepressant agent'/exp 'benzodiazepine' 'benzodiazepine derivative'/exp 'hypnotic sedative agent'/exp 'narcotic analgesic agent'/exp 'non prescription drug' 'prescription drug' **MeSH** 'patient safety' 'polypharmacy'/exp 'safety' **PsycINFO** exp analgesic drugs/ Exp anesthetic drugs/ Exp anticonvulsive drugs/ Exp antidepressant drugs/ Exp antiemetic drugs/ Exp antihistaminic drugs/ Exp antihypertensive drugs/ exp benzodiazepines/ exp cns depressant drugs/ drug therapy/sh *hypnotic drugs/ Insomnia.id. Major depression.id. Exp polypharmacy/ Schizophrenia.id. Exp sedatives/ Exp self medication/	Ambien 'anti depressant' Antidepressant* Anti-depressant' Benzodiazepine* 'eszopiclone' Hypnotic* lunesta OTC 'over-the-counter' 'over the counter' prescription* polypharmacy psychoactive* sonata stimulant* 'z drug' 'z drugs' 'zaleplon' 'zolpidem'

Concept	Controlled Vocabulary	Keywords
KQ 7 **Risk mitigation strategies** What is the comparative effectiveness of different risk mitigation strategies for patients either on LTOT or being considered for LTOT? a) Does this differ for patients with history of or current SUD? b) Does this differ for patients with mental health comorbidities? c) Does this differ for patients with medical comorbidities? d) What is the safety and effectiveness of take-home naloxone kits?	**EMBASE** 'naloxone'/exp 'opiate addiction'/exp 'patient education'/exp 'prescription drug diversion'/exp 'risk reduction'/exp 'substance abuse'/exp 'urinalysis'/exp **MeSH** 'contracts' 'drug monitoring' exp 'patient compliance'/ exp 'risk'/ **PsycINFO** exp addiction/ Exp client education/ exp drug abuse/ drug abuse.sh. exp drug addiction/ opiates.id. exp monitoring/ exp naloxone/ exp patient compliance/ Exp prescription drugs/ Exp risk assessment/ Exp risk evaluation and mitigation strategy/ Exp risk perception/ Exp treatment compliance/ Exp urinalysis/	Abuse Addict* agreement 'call back' Call-back Compliance comply consent contract database diversion divert doctor Detect* Diversion Divert Misuse Mitigat* Monitor* naloxone Naloxone NEXT/2 rescue office Pill NEXT/2 count physician primary Precaution* Query Recall Rescue Risk* Risk NEXT/5 reduc* Risk NEXT/5 mitigat* Screen* surveillance Test* Urin*

Concept	Controlled Vocabulary	Keywords
KQ 8 **Treatment of OUD** What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a) Do outcomes vary by severity of OUD?	**EMBASE** 'acceptance and commitment therapy'/exp 'addiction'/exp 'analgesic agent abuse'/exp 'cognitive therapy'/exp 'drug abuse'/exp 'drug dependence'/exp 'narcotic analgesic agent'/exp 'narcotic dependence'/exp 'opiates'/exp 'opiate addiction'/exp 'psychotherapy'/exp 'support group'/exp **MeSH** 'analgesics, opioid'/exp 'cognitive therapy'/exp 'counseling'/exp 'motivational interviewing'/ 'narcotics'/exp 'substance abuse detection'/exp 'substance-related disorders'/exp **PsycINFO** exp addiction/ Exp adjunctive treatment/ Exp cognitive therapy/ Exp counseling/ exp drug abuse/ drug abuse.sh. exp drug addiction/ exp drug dependence/ electrosleep treatment/ exp motivational interviewing/ exp opiates/ opiates.id. Exp prescription drugs/ Exp psychotherapy/ Exp support group/ Exp treatment/ Exp treatment compliance/ Exp treatment effectiveness evaluation/ Exp treatment outcomes/	aberrant Abuse Addict* Behavioral buprenorphine Cognitive Contingency 'contingency management' Counsel* counseling drug interview* methadone misuse motivation* naltrexone therapy treat* treatment

Concept	Controlled Vocabulary	Keywords
KQ 9 **Tapering** What is the safety and effectiveness of different tapering strategies and schedules?	**EMBASE** 'analgesia'/exp 'clinical protocol'/exp 'dose response'/exp 'drug administration'.exp 'drug therapy'/lnk 'pain management'/exp **MeSH** 'clinical protocols'/exp 'drug administration schedule'/exp **PsycINFO** exp analgesic drugs/ Exp drug dosages/ Exp pain management/	Adjust* administration Decrease* Dose Dosing plan protocol Reduc* Schedule Strategy strategies Taper* Titrat*

B. Search Strategies

Table J-2. MEDLINE/PSYCINFO (presented in OVID syntax)

Set Number	Concept	Search Statement
1	Chronic pain	*exp chronic pain/ OR (exp pain/ AND (chronic OR long?term)) OR (exp chronic illness/ AND pain?)
2		Chronic adj3 pain?.ti,ab.
3	Combine	1 OR 2
4	LTOT	exp analgesic drugs/ or exp narcotics/ or exp narcotic drugs/ or exp opiates/
5		(opioid* or opiod* or opiate* or oposal or opon or narcotic*).mp. OR (morphine or codeine or fentanyl).mp.
6		(Oxymorphone or tapentadol or methadone or fentanyl or hydrocodone or oxycodone or codeine or morphine or hydromorphone or tramadol).mp.
7	Combine	4 OR 5 OR 6
8	Combine chronic pain and LTOT	3 AND 7
9	Contraindications (KQ1)	(Contraindication or COPD or cardiovascular or respiratory or obstructive or lung or fibromyalgia or headache or heart or liver or sleep or osteoporosis or CNS or immune or gastrointestinal).mp.
10		(medic* adj1 marijuana).mp. or ("post?traumatic stress" or PTSD).mp. or traumatic brain.mp. or TBI.ti,ab. or (substance adj2 abuse).mp. or (substance adj2 misuse).mp. or (depression or suicide or suicidality).mp. or ((personality or cognitive or mental or neuro*) adj3 (disorder* or disease* or illness*)).mp.
11		9 OR 10
12	Workers compensation	exp litigation/ or exp workers' compensation insurance/ or lawsuit.mp. or litigation.mp. exp insurance/ or insurance claim.mp. or exp disability evaluation/ or exp malingering/ or malingering.mp.
13		(worker adj2 compensation).mp. or litigation.ti. or lawsuit.ti. or claim*.ti. or disability*.ti. or compensation.ti. or malinger*.ti.
14	combine	11 OR 12 OR 13

Set Number	Concept	Search Statement
15	Combine with chronic pain and LTOT	8 AND 14
16	Risk of misuse (KQ2)	Exp drug abuse/ or exp addiction/ or exp codependency/ or exp drug addiction/ or exp drug overdoses/ or exp illegal drug distribution/
17		16 AND (opi* or narcotic* or hydrocodone or vicodin or oxycodone or oxycontin or percocet or heroin or methadone or morphine or codeine or analgesic*).mp.
18		((opi* or narcotic* or hydrocodone or vicodin or oxycodone or oxycontin or percocet or heroin or methadone or morphine or codeine or analgesic*) adj2 (addict* or abuse or misuse or disorder* or diversion)).mp.
19		Risk*.mp. or exp risk assessment/ or exp risk perception/ or exp at risk populations/ or exp risk factors/
20		17 OR 18
21	Combine risk and abuse	19 AND 20
22	Combine with chronic pain and LTOT	8 AND 21
23	Effectiveness and Safety of LTOT (KQs 3 and 4)	exp "Side Effects (Drug)"/ or exp "side effects (treatment)"/ or exp "complications (disorders)"/
24		exp Suicide/ or exp Major Depression/ or exp Attempted Suicide/ or exp Drug Abuse/ or exp Drug Overdoses/ or exp Drug Addiction/ or exp Safety/ or overdose.mp. or adverse events.mp. or drug addiction.mp.
25		Exp pain management/ or (pain adj2 (reliev* or relief)) or exp Quality of Life/ or quality of life.mp. or exp treatment outcomes/ or outcomes.mp.
26		((adverse adj1 event*) or (adverse adj1 effect*) or (aberrant adj3 behavior*)).mp. or (overdose* or diversion or addict* or abuse or accident* or complication* or absence or absent or falls or fall or depression or anxiety or mood or sleep or cardiovascular or cardiac or cognitive).ab,ti.
27		((work or occupation* or job) adj3 (injur* or accident or absence or performance)).mp. or exp safety/ or exp occupational safety/ or exp accidents/ or exp job performance/ or exp employee absenteeism/ or exp cognitive processes/ OR exp cognitive impairment/
28		exp driving behavior/ or exp drivers/ or exp risk taking/ or exp risk perception/ or exp highway safety/ or exp motor traffic accidents/ or exp motor vehicles/ or exp transportation accidents/ or exp motor traffic accidents/ or (accident* or crash or collison or wreck).mp. or ((drive or driving or car* or traffic or vehicle*) and (safe* or accident* or crash* or wreck* or impair* or risk* or collison*)).mp.
29	Combine	23 OR 24 OR 25 OR 26 OR 27 OR 28
30	Combine with LTOT	7 AND 29
31	Formulations (KQ5)	(*drug therapy/ or (prescription* or medication or medicine or pill*).mp. AND opi*
32		'immediate release' OR 'extended release' OR 'short acting' OR shortacting OR sa OR 'long acting' OR longacting OR la OR 'controlled release' OR (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)).mp.
33		(formulation* or short?act* or long?act* or immediate or extended or controlled or sustained or abuse-deterrent or (abuse adj1 deterrent)).mp.

Set Number	Concept	Search Statement
34		(opiate* or opioid).ti. and (formulation* or short?act* or long?act* or immediate or extended or controlled or sustained).mp.
35	Combine	(31 AND (32 OR 33)) OR 34
36	Combine with LTOT	7 AND 35
37	Added benzodiazepines (KQ6)	benzodiazepine*.mp. or exp benzodiazepines/
38		*hypnotic drugs/ or exp analgesic drugs/ or exp anesthetic drugs/ or exp anticonvulsive drugs/ or exp antiemetic drugs/ or exp antihistaminic drugs/ or exp antihypertensive drugs/ or exp benzodiazepines/ or exp cns depressant drugs/ or exp sedatives/ or exp antidepressant drugs/ or exp nonprescription drugs/ or exp self medication/ or exp prescription drugs/ or exp polypharmacy/
39		(insomnia or chronic pain or schizophrenia or major depression).id. and drug therapy.sh.
40		(zolpidem or zaleplon or eszopiclone or ambien or lunesta or sonata or benzodiazepine* or antidepressant* or anti-depressant* or stimulant* or 'z drug' or 'z drugs' or hypnotic* or psychoactive*).mp.
41		(over-the-counter or 'over the counter' or OTC).mp or (prescription* or prescribed).ab,ti. Or polypharmacy.mp.
42		((medication* or medicine) and (multiple or concomitant or several)).mp.
43	Combine	37 OR 38 OR 39 OR 40 OR 41 OR 42
44	Combine with chronic pain and LTOT	8 AND 43
45	Risk mitigation for addiction (KQ7)	exp opiates/ or exp drug addiction/ or exp prescription drugs/ or exp drug abuse/ or exp addiction/ OR (opiates.id and drug abuse.sh.)
46		((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol)).mp.
47	Combine opiate addiction or misuse	45 OR 46
48	Mitigation strategies	urin* adj7 (screen* OR test* OR detect* OR anal* OR monitor*) OR exp urinalysis/ or exp drug usage screening/
49		Count OR 'call back' OR database OR query OR compliance OR contract* OR agreement OR consent OR recall OR surveillance OR call-back OR monitor* OR (‘pill count’ OR pill count).mp.
50		(naloxone adj2 rescue).mp.
51		'patient compliance'/exp OR (patient:ab,ti AND (compliance:ab,ti OR comply:ab,ti))
52		Exp treatment compliance/ or (patient and (compliance or comply)).ab,ti.
53		((office OR doctor OR primary) adj3 (visit* OR appointment* OR check*)).mp. OR (exp opiates/ AND exp monitoring/)
54		Exp client education/ or patient education.mp. OR patient NEXT/3 (aware* OR educat*)
55		(opi* adj5 (contract OR contracts OR agreement)).mp.
56	Combine mitigation strategies	48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55

Set Number	Concept	Search Statement
57	Risk	Exp risk assessment/ or exp risk perception/ or (risk* adj7 (mitigate* OR reduc*)).mp. or (risk evaluation and mitigation strategy).mp.
58	Combine addiction, mitigation, and risk	47 AND 56 AND 57
59	Combine addiction, mitigation, and risk with LTOT	7 AND 58
60	Treatment of OUD (KQ8)	((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol)).mp.
61	Opiate addiction or misuse	exp opiates/ or exp drug addiction/ or exp prescription drugs/ or exp drug abuse/ or exp addiction/ OR (opiates.id and drug abuse.sh.)
62		(exp drug abuse/ or exp drug dependence/ or exp drug addiction/ or aberrant.ti. or aberrant.ab.) and (exp opiates/ or opioid*.mp. or oxymorphone.mp. or tapentadol.mp. or methadone.mp. or fentanyl.mp. or hydrocodone.mp. or oxycodone.mp. or codeine.mp. or morphine.mp. or hydromorphone.mp. or tramadol.mp. or analgesic*.mp.)
63	Counseling	Exp psychotherapy/ OR exp cognitive therapy/ OR exp counseling/ OR exp support group/ OR exp motivational interviewing/ exp Adjunctive Treatment/ or exp Treatment Compliance/ or exp Treatment/ or exp Treatment Effectiveness Evaluation/ or (treat or treatment or therap* or counsel*s).ab,ti.
64		counsel OR counseling OR ((cognitive OR contingency OR drug OR behavioral OR motivational) adj2 (counseling OR therapy)) OR motivation* adj1 interview* OR (buprenorphine OR naloxone OR naltrexone OR methadone) OR contingency management.mp.
65	Combine addiction	60 OR 61 OR 62
66	Combine counseling	63 OR 64
67	Combine LTOT and addiction and counseling	7 AND 65 AND 66
68	Tapering (KQ9)	(exp analgesia/ or exp analgesic drugs/ or exp pain management/) AND exp drug dosages/
69		((dose or dosing) and (protocol* or administration or plan* or schedule* or strategy or strategies)).mp.
70		(taper* or decrease* or reduc* or adjust* or titrat* or dosing or dose*).mp.
71		((taper* or decrease* or reduc* or adjust* or titrat* or dosing or dose*) and (protocol* or administration or plan* or schedule* or strategy or strategies)).mp.
72	Combine tapering sets	68 OR 69 OR 70 OR 71
73	Combine tapering and chronic pain and LTOT	8 AND 72
74	Combine all final sets	15 OR 22 OR 30 OR 36 OR 44 OR 59 OR 67 OR 73
75	Apply limits	limit 74 to (human and english language and yr="2009 - 2016")
76	Apply publication type limits	75 AND (trial* or study or studies or method* or review* or analysis or compar* or random* or systematic*).mp.
77		limit 75 to ("0100 journal" or "0110 peer-reviewed journal" OR “journal article”)

Set Number	Concept	Search Statement
78		75 AND (exp clinical trials/ or exp cohort analysis/ or exp followup studies/ or exp longitudinal studies/ or ((compar* or comparison or comparative) and trial*).ab,ti.
79	Combine final sets	76 OR 77 OR 78

OVID syntax:

* (within or following a term) = truncation character (wildcard)

.ab. = limit to abstract

ADJn = search terms within a specified number (n) of words from each other in any order

exp/ = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.ti,ab. = limit to title and abstract fields

Table J-3. EMBASE/Medline Search Strategies Conducted using EMBASE Syntax

Set Number	Concept	Search Statement
1	Chronic pain	'chronic pain'/exp OR (chronic OR 'long term') NEXT/2 pain*
2		'chronic inflammatory pain'/de OR (chronic NEXT/3 pain*):ab,ti.
3	Combine sets for chronic pain	1 OR 2
4	LTOT	'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de
5		opioid* OR opiod* OR opiate* OR oposal OR opon OR narcotic*
6		'morphine'/de OR 'codeine'/de OR 'fentanyl'/de
7		Oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol
8		'pain'/exp AND 'drug therapy'/lnk AND opi*
9	Combine sets for opioids	4 OR 5 OR 6 OR 7 OR 8
10	Combine with chronic	9 AND (chronic:ti OR 'cot':ti OR chronic NEXT/1 opi* NEXT/1 therapy OR longterm:ti OR 'long term':ti OR months:ab,ti OR year*:ab,ti)
11	Combine chronic pain with LTOT	3 AND 10
12	Contraindications (KQ1)	'drug contraindication'/exp OR 'drug interaction'/exp OR 'drug safety'/exp OR 'analgesics, opioid/contraindicaitons'

Set Number	Concept	Search Statement
13		Compensation* OR contraindication* OR copd OR cardiovascular OR respiratory OR 'chronic obstructive' OR lung OR fibromyalgia OR headache* OR heart OR liver OR sleep OR osteoporosis OR cns OR immune OR gastrointestinal OR medic* NEAR/1 marijuana OR 'post-traumatic stress' OR ptsd OR 'traumatic brain' OR tbi OR 'substance use disorder' OR sud OR depression OR suicide OR suicidality OR (personality OR cognitive OR mental OR neuro*) NEXT/3 (disorder* OR disease* OR illness*)
14	Combine contraindications	12 OR 13
15	Combine contraindications with chronic pain and LTOT	11 AND 14
16	Risk of misuse (KQ2)	('opiate addiction'/exp OR 'analgesic agent abuse'/exp OR 'opioid-related disorders'/exp) AND ('risk'/exp OR risk*:ab,ti)
17		'risk'/exp OR (risk* AND (predict* OR assess*))
18		(opi* OR narcotic* OR hydrocodone OR vicodin OR oxycodone OR oxycontin OR percocet OR heroin OR methadone OR morphine OR codeine OR analgesic*) NEXT/2 (addict* OR abuse OR misuse OR disorder OR diversion)
19	History of abuse	'domestic violence'/exp OR 'sexual abuse'/exp OR 'bullying'/exp OR bully OR bullying OR (domestic OR spous* OR child* AND (abuse OR violence))
20	Risk of opioid addiction	17 AND (18 OR 19)
21	Combine risk sets	16 OR 20
22	Combine risk of misuse with chronic pain and LTOT	11 AND 21
23	Effectiveness and Safety of LTOT (KQs 3 and 4)	'adverse drug events' OR 'ade' OR overdose OR diversion OR misuse OR addict* OR abuse OR adverse NEXT/1 event OR adverse NEXT/1 effect* OR accident* OR absence OR absent OR falls OR fall OR depression OR anxiety OR mood Or overdose* OR poison* OR death OR harm* OR disorder* OR sleep OR aberrant NEXT/3 behavior* OR complication* OR cardiovascular OR cardiac OR cognitive
24		'quality of life'/exp OR 'quality of life' OR qol OR pain NEXT/2 relief OR pain NEXT/2 reliev* OR ‘pain relief’
25		'prescription drugs'/exp AND ('adverse drug reaction'/lnk OR 'side effect'/lnk)
26		'treatment outcome'/de OR 'side effect'/de OR 'adverse drug reaction'/exp OR ‘drug overdose’/ OR ‘adverse outcome’/exp OR ‘opiate addiction’/exp OR 'patient safety'/exp OR safety OR effectiveness OR effective OR outcome*
27	Combine sets for safety	23 OR 24 OR 25 OR 26
28	Combine with chronic pain and LTOT	11 AND 27
29	Formulations (KQ5)	'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de
30		opioid* OR opiod* OR opiate* OR oposal OR opon OR narcotic* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol
31		'morphine'/de OR 'codeine'/de OR 'fentanyl'/de
32		'pain'/exp AND 'drug therapy'/lnk AND opi*

Set Number	Concept	Search Statement
33	Combine sets for opioids	29 OR 30 OR 31 OR 32
34		'immediate release' OR 'extended release' OR 'short acting' OR shortacting OR sa OR 'long acting' OR longacting OR la OR 'controlled release' OR (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)) OR 'short acting analgesic agent'/exp OR (abuse-deterrant AND formula*)
35		33 AND 34
36		'opiate'/exp OR 'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de OR morphine OR oxycodone OR oxymorphone OR opi* AND (controlled OR sustained OR extended)
37	Opioid formulations	35 OR 36
38	Combine with chronic pain and LTOT	11 AND 37
39	Added benzodiazepines (KQ6)	'benzodiazepine derivative'/exp OR 'benzodiazepine' OR benzodiazepine* OR 'antidepressant agent'/exp OR 'hypnotic sedative agent'/exp OR 'narcotic analgesic agent'/exp OR 'benzodiazepine derivative'/exp OR 'zolpidem'/exp OR 'zaleplon'/exp OR 'eszopiclone'/exp
40		'zolpidem' OR 'zaleplon' OR 'eszopiclone' OR ambien OR lunesta OR sonata OR benzodiazepine* OR antidepressant* OR 'anti-depressant' OR 'anti depressant' OR stimulant* OR 'z drug' OR 'z drugs' OR hypnotic* OR psychoactive*
41		prescription* AND (otc OR 'over the counter') AND (multiple* OR added OR additional OR several OR concomitant)
42		'prescription drug'/exp AND 'non prescription drug'/exp OR 'polypharmacy'/exp
43	Combine medicine sets	38 OR 39 OR 40 OR 41
44		'treatment outcome'/de OR 'side effect'/de OR 'adverse drug reaction'/exp OR 'patient safety'/exp OR safety OR effectiveness OR effective OR outcome*
45	Combine with outcomes	42 AND 43
46	Combine with chronic pain and LTOT	11 AND 45
47	Risk mitigation for addiction (KQ7)	'opiate addiction'/exp OR 'substance abuse'/exp OR 'drug monitoring'/exp OR 'prescription drug diversion'/exp OR ((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol))
48		urin* NEXT/7 (screen* OR test* OR detect* OR anal* OR monitor*) OR 'urinalysis'/exp
49		pill NEXT/2 count OR 'call back' OR database OR query OR compliance OR contract* OR agreement OR consent OR recall OR surveillance OR call-back OR monitor* OR naloxone NEXT/2 rescue
50		'patient compliance'/exp OR (patient:ab,ti AND (compliance:ab,ti OR comply:ab,ti))
51		'patient education'/exp OR patient NEXT/3 (aware* OR educat*)
52		(office OR doctor OR primary) NEXT/3 (visit* OR appointment* OR check*)
53		'contracts'/exp OR opi* NEXT/5 (contract OR contracts OR agreement)

Set Number	Concept	Search Statement
54		Risk* NEXT/7 (mitigate* OR reduc*) OR 'risk'/exp OR 'risk reduction'/exp OR 'risk evaluation and mitigation strategy' OR 'naloxone'/exp OR naloxone OR rescue OR precaution*
55	Combine risk mitigation strategies	47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54
56	Combine with chronic pain and LTOT	11 AND 55
57	Treatment of OUD (KQ8)	addict* OR abuse OR misuse OR disorder AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol) OR 'opiate use disorder'
58		'opiate addiction'/exp OR 'analgesic agent abuse'/exp OR ('drug abuse'/exp OR 'drug dependence'/exp OR 'narcotic dependence'/exp OR 'addiction'/exp OR aberrant:ti OR aberrant:ab AND ('narcotic analgesic agent'/exp OR 'opiates'/exp OR opioid* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol OR analgesic*))
59		'psychotherapy'/exp OR 'cognitive therapy'/exp OR 'counseling'/exp OR 'acceptance and commitment therapy'/exp OR 'support group'/exp OR 'motivational interviewing'/exp
60		counsel OR counseling OR (cognitive OR contingency OR drug OR behavioral OR motivational) NEAR/2 (counseling OR therapy) OR 'contingency management' OR motivation* NEAR/1 interview* OR buprenorphine OR naloxone OR methadone
61	Combine opioid addiction set	57 OR 58
62	Combine counsel set	59 OR 60
63	Combine with chronic pain and LTOT	11 AND 61 AND 62
64	Tapering (KQ9)	'pain management'/exp OR 'analgesia'/exp AND ('drug administration'/exp OR 'clinical protocol'/exp)
65		'dose response'/exp OR ((dose OR dosing) AND (protocol* OR administration OR plan* OR schedule* OR strategy OR strategies))
66		(taper* OR decrease* OR reduc* OR adjust* OR titrat* OR dosing OR dose*) AND (protocol* OR administration OR plan* OR schedule* OR strategy OR strategies)
67	Combine tapering sets	64 OR 65 OR 66
68	Combine with chronic pain and LTOT	11 AND 67
69	Combine all final sets	15 OR 22 OR 28 OR 38 OR 46 OR 56 OR 63 OR 68
70	Apply limits	69 AND [2009-2016]/py AND [English]/lim AND [humans]/lim
71	Apply unwanted publication types	70 NOT ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)
72	Apply trials hedge	71 AND (random*:ab,ti OR trial* OR control* OR cohort OR compar*:ab,ti OR prospective OR retrospective OR series OR review* OR study OR studies OR method* OR analysis OR systematic*:ab,ti)

Set Number	Concept	Search Statement
73		71 AND ('clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'longitudinal study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial'/de OR 'comparative study'/exp OR 'methodology'/exp)
74		71 AND ('meta analysis'/de OR 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'outcomes research'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR 'systematic review'/de OR 'meta? analysis':ab,ti OR 'systematic review':ab,ti)
75	Combine	72 OR 73 OR 74

EMBASE.com Syntax:

* (within or following a term) = truncation character (wildcard)

:ab = limit to abstract

:ab,ti = limit to abstract and title

NEAR/n = search terms within a specified number (n) of words from each other in any order

/exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

:it. = limit to publication type

:ti. = limit to title

Appendix K: Abbreviation List

Abbreviation	Definition
^{o}F	degrees Fahrenheit
AAAP	American Academy of Addiction Psychiatry
AAPM	American Academy of Pain Medicine
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immunodeficiency syndrome
AMA	American Medical Association
AOR	adjusted odds ratio
APAP	acetaminophen
APTA	American Physical Therapy Association
ARR	adjusted risk ratio
ASA	acetylsalicylic acid
ASAM	American Society of Addiction Medicine
BID	two times per day
BPI	Brief Pain Inventory
CARF	Commission on Accreditation of Rehabilitation Facilities
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CENTRAL	The Cochrane Central Register of Controlled Trials
CI	confidence interval
CNCP	chronic non-cancer pain
CNS	central nervous system
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
COR	contracting officer's representative
CPG	clinical practice guideline
CS	clinical study
DATA 2000	Drug Addiction Treatment Act of 2000
DEA	Drug Enforcement Administration
dL	deciliter(s)
DoD	Department of Defense
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBPWG	Evidence-Based Practice Work Group
ECG	electrocardiogram
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EMR	electronic medical record
FDA	Food and Drug Administration
FY	fiscal year
GCMS	gas chromatography- mass spectrometry

Abbreviation	Definition
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
HR	hazard ratio
hr	hour
IOM	Institute of Medicine
IRR	incidence rate ratios
KQ	key question
LCMS	liquid chromatography-mass spectrometry
LOT	long-term opioid therapy
m	meter(s)
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MAOI	monoamine oxidase inhibitor
MAT	medication assisted treatment
mcg	microgram(s)
MDA	3,4-methylenedioxy-amphetamine
MDEA	3,4-methylenedioxy-N-ethyl-amphetamine
MDMA	3,4-methylenedioxy-methamphetamine
MEDD	morphine equivalent daily dose
MeSH	Medical Subject Headings
mg	milligram(s)
MHS	Military Health System
mL	milliliter(s)
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
OEF	Operation Enduring Freedom
OEND	Opioid Overdose Education and Naloxone Distribution
OIF	Operation Iraqi Freedom
OR	odds ratio
OSI	Opioid Safety Initiative
OTC	over the counter
OTRR	Opioid Therapy Risk Report
OUD	opioid use disorder
PDMP	Prescription Drug Monitoring Program
PICOTS	population, intervention, comparison, outcome, timing, and setting
PPACA	Patient Protection and Affordable Care Act

Abbreviation	Definition
PRN	as needed
PTSD	posttraumatic stress disorder
QTc interval	the heart rate's corrected time interval from the start of the Q wave to the end of the T wave
RCT	randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategy
SA	sustained action
SAMHSA	Substance Abuse and Mental Health Services Administration
SE	standard error
SL	sublingual
SMART	Specific, Measurable, Action Oriented, Realistic, Timed
SNRIs	serotonin-norepinephrine reuptake inhibitors
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
STORM	Stratification Tool for Opioid Risk Mitigation
SUD	substance use disorders
THC	tetrahydrocannabinol
THCA	delta-9-tetrahydrocannabinol-9-carboxylic acid
TID	three times per day
U.S.	United States
UDT	urine drug testing (or urine drug test)
USPSTF	United States Preventive Services Task Force
UTS	urine toxicology screening
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

The Opioid Therapy for Chronic Pain Work Group.
(2017, February).
VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain.
Department of Veterans Affairs, Department of Defense.