

# Long-Acting Opioid Analgesics

## Washington Drug Archive Report

Washington P&T Committee

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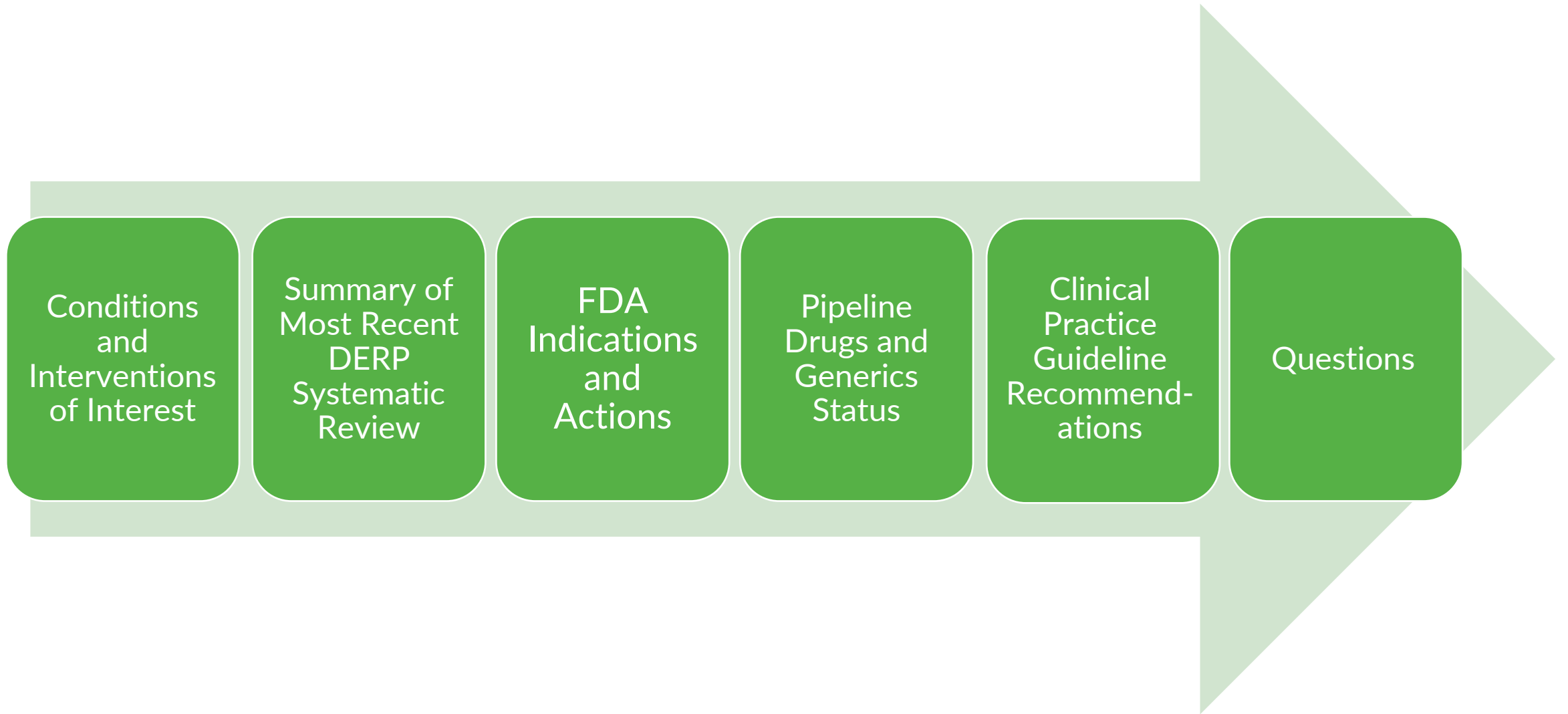


# Aim of Project

- The Drug Effectiveness Review Project (DERP) aims to present information to the Washington State Pharmacy and Therapeutics (P&T) Committee with topic reports on 9 drug classes that are candidates to be archived from active review by the Committee
- The 9 drug classes identified by the Washington Health Care Authority (HCA) as archive candidates are:
  - Anticoagulants
  - Antiemetics
  - Antiplatelets
  - Asthma controllers
  - Asthma quick relief drugs
  - **Long-acting opioids**
  - Overactive bladder drugs
  - PCSK9 inhibitors
  - Statins

*Drug class in **green** is presented in this report*

# Overview



# Chronic Pain: Definition & Epidemiology (slide 1 of 3)

- Chronic noncancer pain definition
  - Lasting at least 3 to 6 months
    - Example descriptions: aching, burning, shooting, squeezing, stiffness, stinging, throbbing sensations
- High-impact chronic pain is pain that results in serious restrictions to daily activities
- Types of noncancer chronic pain
  - Arthritis/joint pain, back or neck pain, headache, testicular pain, scar tissue pain, whole body muscle pain (e.g., fibromyalgia), neurogenic pain (i.e., damage to nerves/nervous system)

# Chronic Pain: Definition & Epidemiology (slide 2 of 3)

- In adults
  - Chronic pain is associated with
    - Medical conditions (depression, Alzheimer disease and other dementias, higher suicide risk, worsening chronic disease, substance misuse)
    - Poor quality of life
    - Societal concerns (reduced productivity, lost wages)
  - The percent of adults in the US with chronic pain increased since 2016, to nearly 21% in [2021](#)
    - Prevalence of high-impact chronic pain ranged from about 7% to 8% between 2019 and 2021
    - Populations with higher prevalence
      - Non-Hispanic American Indian or Alaska Native adults
      - Adults identifying as bisexual
      - Adults who are divorced or separated

# Chronic Pain: Definition & Epidemiology (slide 3 of 3)

- In children and adolescents
  - ❑ Chronic pain is associated with depression and anxiety, school absence, social isolation, and poor quality of life
  - ❑ 20% to over 50% and 5% to over 30% of all chronic pain in youth is attributed to headache and gastrointestinal disorders, [respectively](#)
- Factors associated with the [development](#) of chronic pain
  - ❑ Demographic factors (e.g., advanced age, socioeconomic status)
  - ❑ Lifestyle and behavior (e.g., smoking, sedentary behavior, poor nutrition)
  - ❑ Clinical (e.g., mental health conditions, surgical interventions, weight, sleep disorders, genetics)
  - ❑ Other (e.g., history of injury or abuse)

# Treatments for Chronic Noncancer Pain

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are first line for musculoskeletal pain
- [Nonpharmacological approaches](#) include acupuncture, physical/exercise therapy, massage, behavior therapy, and spinal manipulation in some situations
- Mixed results with steroid injections (back/spine)
- For chronic neuropathic pain, initial treatment often involves selected antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs]) or antiepileptic drugs (e.g., gabapentin), with adjunctive topical therapy when pain is localized
  - There is some evidence that [cannabis](#) can improve pain and function in adults with neuropathic pain
- If other interventions are unsuccessful, opioids are considered at the lowest effective dose, and for the shortest duration

# Summary of Most Recent DERP Products

Last Report	2015
Date Presented	September 2015
Report Title	<a href="#"><u>Long-Acting Opioid Analgesics</u></a>
Search Dates	From inception (most databases) through February 2015
Authors	Pacific Northwest Evidence-based Practice Center and CEbP researchers
<a href="#"><u>Scans/Surveillance</u></a> Since Last Report	
2017	<i>Long-Acting Opioid Analgesics Scan 3</i> • Search Dates: November 16, 2016, through November 20, 2017
2016	<i>Long-Acting Opioid Analgesics Scan 2</i> • Search Dates: October 2015 through November 16, 2016
2015	<i>Long-Acting Opioid Analgesics Scan 1</i> • Search Dates: December 2014 through November 2015



# PICOS of Most Recent DERP Report

- *Population*
  - Adults with chronic noncancer pain (continuous or recurring pain for at least 6 months)
- *Comparators*
  - Another listed intervention (head-to-head trials)
  - Short-acting opioids
- *Outcomes*
  - Pain intensity and pain relief
  - Function
  - Adverse events (AEs; specific AEs, serious AEs, withdrawal due to AEs)
- *Study Designs*
  - Randomized controlled trials, comparative effectiveness reviews

# PICOS of Most Recent DERP Report

- *Interventions*

Name	Brand Name	Formulation	Mechanism	FDA Approval Date
Buprenorphine	Butrans	ER transdermal film	Opioid partial agonist	June 10, 2010
Fentanyl	Duragesic <sup>a</sup>	ER transdermal film	Opioid agonist	August 7, 1990
Hydrocodone bitartrate	Hysingla ER	ER oral tablet	Opioid agonist	November 20, 2014
	Zohydro ER <sup>a</sup>	ER oral capsule	Opioid agonist	October 25, 2013
Hydromorphone	Exalgo <sup>a</sup>	ER oral tablet	Opioid agonist	May 1, 2010
Levorphanol	Generic only	Oral tablet	Opioid agonist	1953
Methadone	Dolophine <sup>a</sup>	Oral tablet	Opioid agonist	1947
	Methadose <sup>a</sup>	Oral route	Opioid agonist	1973
Morphine sulfate	Kadian <sup>a</sup>	ER oral capsule	Opioid agonist	July 3, 1996
	MS-Contin	CR oral tablet	Opioid agonist	May 29, 1987
Morphine sulfate + naltrexone	Embeda <sup>a</sup>	ER oral capsule	Opioid agonist + opioid antagonist	August 13, 2009
Oxycodone	Oxycontin	ER oral tablet	Opioid agonist	April 5, 2010
Oxycodone HCl + naloxone	Targiniq ER <sup>a</sup>	ER oral tablet	Opioid agonist + opioid antagonist	July 23, 2014
Oxymorphone	Opana ER <sup>a</sup>	ER oral tablet	Opioid agonist	June 22, 2006
Tapentadol	Nucynta ER	ER oral tablet	Opioid agonist	August 25, 2011

Note: <sup>a</sup> Brand discontinued as of November 9, 2023.

Abbreviations. CR: controlled release; ER: extended release; FDA: US Food and Drug Administration; HCl: hydrochloride.

## Key Questions in Most Recent DERP Report

- What are the comparative effectiveness and harms of different long-acting opioids (**KQ1 & KQ3**) and of long-acting versus short-acting opioids (**KQ2 & KQ4**) in adults with chronic noncancer pain?
- Are there differences in outcomes for long-acting opioids (**KQ5**) or for short-acting opioids (**KQ6**) across patient subpopulations?

# Summary of Findings in Most Recent DERP Report (slide 1 of 2)

- 2015 report
  - 25 head-to-head studies included cumulatively since original report through 2015 update
    - 18 head-to-head trials, 7 trials with short-acting opioids as comparator
- Summary of key findings (effectiveness)
  - Tapentadol resulted in greater reduction in pain intensity with knee osteoarthritis than oxycodone in 2 studies; some greater improvement with back pain in 1 study
  - No difference in pain relief with hydromorphone versus oxycodone
  - Generally, no difference in efficacy between long-acting and short-acting opioids
    - Insufficient evidence to assess differential efficacy between long-acting opioids, and between long- and short-acting opioids

## Summary of Findings in Most Recent DERP Report (slide 2 of 2)

- Summary of key findings (harms)
  - Tapentadol ER resulted in fewer withdrawals due to AEs and fewer specific AEs than oxycodone
  - Long-acting morphine resulted in fewer withdrawals due to AEs than transdermal fentanyl (but with more constipation)
  - A large cohort study found a lower mortality rate with methadone than with long-acting morphine
  - No difference in safety outcomes between
    - Hydromorphone osmotic release oral system (OROS) and oxycodone sustained release (SR)
    - Oxymorphone and long-acting oxycodone
    - Morphine ER and long-acting oxycodone; morphine ER and SR
    - Hydromorphone ER and oxycodone
    - Morphine + naltrexone and morphine ER
  - Insufficient evidence to assess differential safety risks between long-acting opioids, and between long- and short-acting opioids

## Summary of Findings in Most Recent Surveillance (slide 1 of 2)

- Cumulative from last report through most recent 2017 scan
  - 1 new drug
    - Buprenorphine hydrochloride (brand name Belbuca, buccal film; approved October 2015)
  - 5 new formulations of previously approved drugs
    - Vantrela ER (new brand of hydrocodone bitartrate ER tablet; approved January 2017)
    - Arymo ER (new brand of morphine sulfate ER tablet; approved January 2017)
    - Troxyca ER (new brand of oxycodone hydrochloride + naltrexone ER capsule; approved August 2016)
    - Xtampza (new brand of oxycodone ER capsule; approved April 2016)
    - MorphaBond (new brand of morphine sulphate ER tablet; approved October 2015)
  - 6 new studies
    - 4 new comparative effectiveness systemic reviews, 2 new head-to-head trials

## Summary of Findings in Most Recent Surveillance (slide 2 of 2)

- Cumulative from last report through most recent 2017 scan (cont.)
  - New boxed warnings (issued December 2016)
    - For all drugs except for levorphanol and methadone
      - Concomitant use with benzodiazepines or other central nervous system (CNS) depressants may result in profound sedation, respiratory depression, coma, and death
    - Buprenorphine (Butrans)
      - Risk of neonatal opioid withdrawal syndrome
    - Fentanyl patch (Duragesic)
      - Risk of increased fentanyl absorption with application of external heat
    - Hydrocodone bitartrate (Zohydro ER)
      - Risks of interaction with alcohol
    - Oxymorphone (Opana)
      - Risk of addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, interaction with alcohol

# New FDA Drugs and Actions Since Most Recent DERP Report

- **New drugs**

- The 6 new drugs/formulations identified in the scans through 2017 (see slide 13)
- No new drugs since last scan

- **New indications**

- No new indications for long-acting opioids for chronic noncancer pain

- **New boxed warnings**

- The new boxed warnings identified in the surveillance (1 for multiple agents for risks of combined use with CNS depressants, and 4 other warnings; see slide 14)
- 1 new boxed warning for all included long-acting opioids, September 2018
  - Risk Evaluation and Mitigation Strategy (REMS) required by the FDA to ensure that benefits of opioid analgesics outweigh risks of addiction, abuse, and misuse



# FDA-Approved Indications (slide 1 of 2)

- Indications as of January 23, 2024

Generic Name (Brand Name)	Moderate to Severe Chronic Pain for Which Alternative Treatments Are Inadequate	Severe Pain in Opioid Tolerant Patients for Which Alternative Treatments Are Inadequate	Detoxification Treatment of Opioid Addiction	Maintenance Treatment of Opioid Addiction, Adjunct to Other Social and Medical Services
Buprenorphine ( <a href="#">Butrans</a> )	√			
Buprenorphine HCl ( <a href="#">Belbuca</a> ) <sup>a</sup>	√			
Fentanyl ( <a href="#">Duragesic</a> ) <sup>b</sup>		√		
Hydrocodone bitartrate ( <a href="#">Hysingla ER</a> , <a href="#">Zohydro ER</a> ) <sup>b</sup> , <a href="#">Vantrela ER</a> ) <sup>a,b</sup>	√			
Hydromorphone ( <a href="#">Exalgo</a> ) <sup>b</sup>		√		
Levorphanol	√			
Methadone ( <a href="#">Dolophine</a> ) <sup>b</sup> , <a href="#">Methadose</a> ) <sup>b</sup>	√ (not an indication for Methadose)		√	√

Note. <sup>a</sup> Newly approved since last report; <sup>b</sup> Brand discontinued as of November 2023.  
Abbreviations. ER: extended release; HCl: hydrochloride.

## FDA-Approved Indications (slide 2 of 2)

- Indications as of January 23, 2024

Generic Name (Brand Name[s])	Moderate to Severe Chronic Pain for Which Alternative Treatments Are Inadequate	Severe Pain in Opioid- Tolerant Patients for Which Alternative Treatments Are Inadequate	Serious Neuropathic Pain Associated with Diabetic Peripheral Neuropathy in Adults for Which Alternative Treatments Are Inadequate
Morphine-sulfate ( <a href="#">Kadian<sup>b</sup></a> , <a href="#">MS-Contin</a> , <a href="#">Arymo ER<sup>a,b</sup></a> , <a href="#">Morphabond<sup>a,b</sup></a> )	√		
Morphine-sulfate + naltrexone (Embeda <sup>b</sup> )	√		
Oxycodone ( <a href="#">Oxycontin</a> , <a href="#">Xtampza<sup>a</sup></a> )	√ (In adults only for Oxycontin)	√ (In patients 11 years and older for Oxycontin)	
Oxycodone HCl + naloxone ( <a href="#">Targiniq ER<sup>b</sup></a> , <a href="#">Troxyca ER<sup>a,b</sup></a> )	√		
Oxymorphone ( <a href="#">Opana ER<sup>b</sup></a> )	√		
Tapentadol ( <a href="#">Nucynta ER</a> )	√		√

Note. <sup>a</sup> Newly approved since last report; <sup>b</sup> Brand discontinued since last report.  
Abbreviations. ER: extended release; HCl: hydrochloride.

# Pipeline Therapies

- **1 new pipeline therapy**

- Dinalbuphine sebacate (LT1001)

- Extended-release injection; kappa-agonist/partial mu-antagonist analgesic
    - In phase 3 trials for postsurgery indications (haemorrhoidectomy, cholecystectomy, and bariatric surgery pain management)
    - Expected to compete with other long-acting opioids if approved

# Generic Drug Status & Brand Discontinuations (slide 1 of 2)

Name	Generic Availability	Status
Buprenorphine	Yes	Already available as generic with last report
Buprenorphine HCl	No	Estimated date of earliest generic launch, January 2027
Fentanyl	Yes	Already available as generic with last report <ul style="list-style-type: none"> <li>• Duragesic brand discontinued</li> </ul>
Hydrocodone bitartrate	<b>Yes</b>	<b><i>Hysingla ER and Zohydro ER formulations newly indicated as available as generics since last report</i></b> (but not clear across all sources) <ul style="list-style-type: none"> <li>• Zohydro ER brand discontinued</li> <li>• Vantrela ER brand discontinued, and formulation does not appear available as generic</li> </ul>
Hydromorphone	<b>Yes</b>	<b><i>New generic available since last report</i></b> <ul style="list-style-type: none"> <li>• Exalgo brand discontinued</li> </ul>
Levorphanol	Yes	Available only as generic with last report
Methadone	Yes	Already available as generic with last report <ul style="list-style-type: none"> <li>• Dolophine brand discontinued</li> <li>• Methadose tablet discontinued, but oral suspension formulations appear available</li> </ul>

Abbreviations. ER: extended release; HCl: hydrochloride.

## Generic Drug Status & Brand Discontinuations (slide 2 of 2)

Name	Generic Availability	Status
Morphine sulfate	Yes	Kadian and MS-Contin brand formulations indicated as available as generics <ul style="list-style-type: none"> <li>• Kadian brand discontinued</li> <li>• Arymo ER and MorphaBond brands discontinued, and formulations do not appear available as generics</li> <li>• MS-Contin brand availability unclear</li> </ul>
Morphine sulfate + naltrexone	No	Potential for future generic availability unclear <ul style="list-style-type: none"> <li>• Embeda brand discontinued</li> </ul>
Oxycodone	Yes	<ul style="list-style-type: none"> <li>• <b>Oxycontin brand formulation indicated as new generics since last report</b> (status somewhat unclear)</li> <li>• Xtampza brand formulation estimated earliest possible generic launch, September 2033</li> </ul>
Oxycodone HCl + naloxone	No	Potential for future generic availability unclear <ul style="list-style-type: none"> <li>• Targiniq ER and Troxyca ER brands discontinued</li> </ul>
Oxymorphone	Yes	<b>Generic available, likely new since last report</b> <ul style="list-style-type: none"> <li>• Opana ER brand discontinued</li> </ul>
Tapentadol	No	Estimated earliest possible generic launch, June 2025

Abbreviations. ER: extended release; HCl: hydrochloride.

# Clinical Practice Guidelines (slide 1 of 4)

- Treatment of chronic noncancer pain
  - Assess and determine type of pain
    - Nociceptive (damage or disease of musculoskeletal/nonneural tissue)
    - Neuropathic (damage or disease of nerve tissue)
    - Nociplastic (activation of pain receptors with no evidence of nerve damage)
  - Address sleep disturbance
  - First-line interventions include nonpharmacologic approaches
    - Exercise therapy (e.g., physical therapy, tai chi, yoga, motor control exercises)
    - Psychoeducational interventions (e.g., cognitive behavioral therapy, patient education)
    - Mind-body therapies (e.g., mindfulness, stress reduction, meditation)
    - Other physical interventions (e.g., acupuncture, massage, chiropractic manipulation, diet, transcutaneous electrical nerve stimulation [TENS])
  - Pharmacologic interventions for patients with inadequate pain relief from optimized nonpharmacologic approaches

# Clinical Practice Guidelines (slide 2 of 4)

- Pharmacologic management of chronic noncancer pain
  - Nociceptive pain
    - First line: treatment: NSAIDs + nonpharmacological approaches
      - Topical NSAIDs for localized arthritis/superficial joint pain
    - Second-line: antidepressant (duloxetine) or antiseizure medication
    - Opioids only if benefits outweigh risks
    - Injectable corticosteroids for osteoarthritis typically not recommended
  - Neuropathic/nociplastic/centralized pain
    - First line treatment: tricyclic or tetracyclic antidepressants (TCAs), SNRIs, or antiseizure medications, with adjunctive topical therapy if pain localized
      - Consider combination therapies if needed
    - Opioids considered only as second- or third-line option (could be considered earlier if with severe pain, episodes of severe pain)

# Clinical Practice Guidelines (slide 3 of 4)

- Pharmacologic management of chronic noncancer pain (cont.)
  - Opioids
    - Long-term use not recommended; immediate-release opioids should be prescribed first
    - Reserve for patients:
      - With low risk for substance abuse
      - With persistent pain despite ongoing multimodal treatment
      - Who are expected to, and informed of, likely need to remain continuously on opioids long-term
    - US Department of Veterans Affairs (VA) and Department of Defense (DoD) highlight additional risks for younger age [groups](#)



# Clinical Practice Guidelines (slide 4 of 4)

- Pharmacologic management of chronic noncancer pain (cont.)
  - Opioids (cont.)
    - If indicated, use lowest dose for shortest period of time
      - Consider restricting dose (e.g., < 50 to < 90 mg morphine equivalents) for patients beginning opioid [therapy](#); some recommendations for titration until effective
      - Continue to monitor for substance use disorders and other risks during use
    - VA/DoD recommends buprenorphine over full opioid agonists
    - Methadone use only if failure of other opioid therapy by trained [staff](#)
  - Infusion therapies (ketamine, lidocaine) may be options for certain patients

# Key Clinical Practice Guidelines

Focus	Date	Title of Guideline
American College of Physicians (ACP)		
Low back pain	2017	<a href="#">Low Back Pain: Practice Guidelines</a>
American Society of Interventional Pain Physicians (ASIPP)		
Safe prescription for noncancer pain	2017	<a href="#">Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain</a>
Canadian Guidelines: Canadian Medical Association and Health Canada		
Opioid for chronic pain	2017	<a href="#">Canadian Guideline for Opioid Therapy and Chronic Noncancer Pain</a>
Canadian Guidelines: Centre for Effective Practice Management		
Noncancer pain	2018	<a href="#">Management of Chronic Noncancer Pain</a>
Centers for Disease Control and Prevention (CDC)		
Prescribing opioids	2022	<a href="#">Clinical Practice Guidelines for Prescribing Opioids for Pain</a>
US Department of Veterans Affairs/Department of Defense (VA/DoD)		
Opioids for chronic pain	2022	<a href="#">Use of Opioids in the Management of Chronic Pain</a>

Questions?



