



Common Threads: Session 2
The State of Evidence-Based PAIN CARE
 Roger Chou, MD 35 Minutes →



Disclosures

- Funding from the U.S. Agency for Healthcare Research and Quality and the Centers for Disease Control and Prevention to conduct systematic reviews on pain treatments
- Board of Scientific Counselors, CDC National Centers for Injury Control and Prevention
- Author, CDC guideline on opioids for pain
- Author, UpToDate topics on low back pain
- No industry-related conflicts of interest

Session Learning Objective

01 | Demonstrate an understanding of current evidence related to interventions for chronic pain, including both pharmacologic and nonpharmacologic treatment options.

Background


Chronic pain (≥ 3 months) is common

- In 2016, 20.4% of U.S. adults had chronic pain
- 8% with high impact chronic pain
- Annual cost of \$560 to \$635 billion
- Leading cause of disability in the U.S.

Chronic pain is caused by a variety of conditions

Opioids often prescribed for chronic pain

- From 1999 and 2015
 - prescriptions for opioids for chronic pain more than tripled;
 - prescribing rates have leveled off and slightly declined
- From 1999 to 2014
 - more than 165,000 died from overdose related to prescription opioids;
- In 2021, there were about ~17,000



Background, Cont.

For the treatment of chronic pain:

Pharmacologic treatments include:	NSAIDs	Nonpharmacologic treatments include:	Exercise and other movement-based therapies
	acetaminophen		psychological/behavioral therapies
	antidepressants		complementary & integrative therapies
	antiseizure meds		mind-body interventions
	topicals		physical modalities
	As well as other pharmacologic treatments		and others

Background, Cont.

Three AHRQ-funded systematic reviews were conducted on treatments for chronic pain in 2019

- **Opioids:**
Update of 2014 AHRQ review
- **Nonopioid pharmacologic treatments:**
New review; duration of treatment at least 3 months
- **Nonpharmacologic treatments:**
Update of 2018 AHRQ review; restricted to trials that followed patients ≥1 m after completing therapy

Duration of follow-up categories	
Short-term follow-up	1 to <6m
Intermediate-term follow-up	6 to <12m
Long-term follow-up	≥12m

Results for pain reported on a 0-to-10 scale

Magnitude of Effect

	Small	Moderate	Large/Substantial
Pain	Mean difference (MD): 0.5 to <1.0 points on 0 to 10 scale, or equivalent	MD: 1 to <2 points on 0 to 10 scale, or equivalent	Effects greater than moderate
Function	MD: 5 to <10 points on 0 to 100 ODI 1 to <2 points on 0 to 24 RDQ, or equivalent Standardized mean difference (SMD): 0.2 to <0.5	MD: 10 to <20 points on ODI 2 to <5 points on RDQ, or equivalent SMD: 0.5 to <0.8	Effects greater than moderate

Efficacy of Opioid Treatments for Chronic Pain: Function and Pain Outcomes

Intervention	Function			Pain		
	Short-Term ES, SOE	Intermediate ES, SOE	Long-Term ES, SOE	Short-Term ES, SOE	Intermediate ES, SOE	Long-Term ES, SOE
Opioids vs. placebo	Small +++	No evidence	No evidence	Small +++	No evidence	No evidence
Opioids vs. nonopioids	None ++	No evidence	None ++	None ++	No evidence	None ++
Opioid + nonopioid vs. nonopioid	None +	No evidence	No evidence	None ++	No evidence	No evidence
Opioid + nonopioid vs. opioid alone	None +	No evidence	No evidence	None* ++	No evidence	No evidence

Abbreviations: SOE=strength of evidence

Effect size: None or small, moderate, or large favoring intervention A

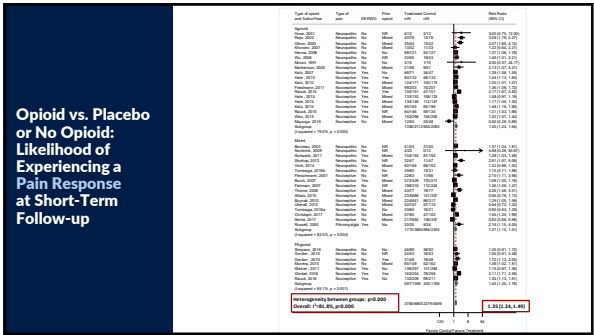
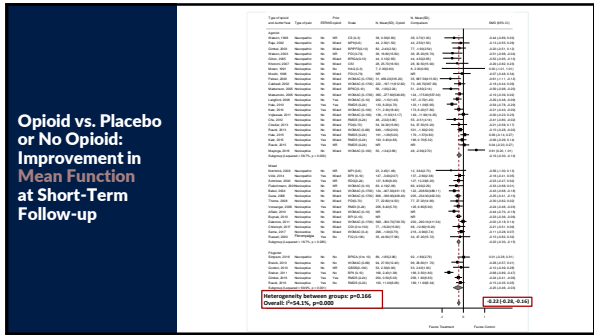
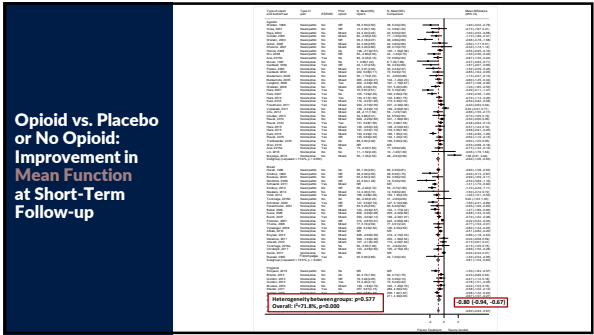
SOE: + = low, ++ = moderate, +++ = high

* The effect was statistically significant but below the threshold for small

Opioid vs. Placebo or No Opioid

Outcome	Studies (k), Sample Size (N)	Pooled Estimate*	I ²	SOE
Pain Intensity (continuous)	k=70 N=19,486	MD -0.80 point (95% CI, -0.94 to -0.67)	72%	High
Pain response (dichotomous)	k=43 N=12,351	RR 1.35 (95% CI, 1.24 to 1.49) ARD 15% (95% CI, 11% to 19%)	82%	High
Function	k=43 N=12,297	SMD -0.22 (95% CI, -0.28 to -0.16)	54%	High
SF-36 physical health status	k=22 N=7,875	MD 1.65 points (95% CI, 1.09 to 2.1)	0%	High
SF-36 mental health status	k=20 N=7,456	MD -0.52 point (95% CI, -1.45 to 0.41)	64%	High
Sleep quality	k=24 N=6,590	SMD -0.25 (95% CI, -0.33 to -0.19)	0%	Moderate
Depression Severity	k=8 N=1,079	SMD 0.00 (95% CI, -0.22 to 0.18)	40%	Moderate

*In stratified analyses, effects on pain were slightly higher for neuropathic pain (vs. musculoskeletal pain), opioid dose 50-90 MED/day (vs. <50 MED/day), enriched enrollment randomized withdrawal design (vs. non-ERW), for studies published in or after 2007, and for crossover design (vs. parallel group); and for pain and function at 1-3-month follow-up (vs. 3-6-month follow-up).

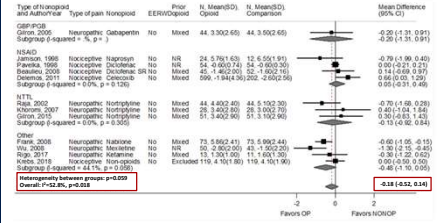


Opioid vs. Nonopioid

Outcome*	Studies (k) / Sample Size (N)	Pooled Estimate	I ²	SOE
Pain intensity (continuous)	k=12 N=1,879	MD -0.18 point (95% CI, -0.52 to 0.14)	53%	Moderate
Pain response (dichotomous)	k=11 N=2,646	RR 1.06 (95% CI, 0.88 to 1.32)	75%	Moderate
Function	k=9 N=1,694	SMD 0.05 (95% CI, -0.10 to 0.17)	12%	High
SF-36 physical health status	k=6 N=1,423	MD -1.80 points (95% CI, -5.45 to -0.12)	11%	Moderate
SF-36 mental health status	k=6 N=1,427	MD -0.63 points (95% CI, -4.27 to 0.91)	38%	Moderate
Sleep quality	k=6 N=1,454	SMD 0.01 (95% CI, -0.14 to 0.12)	0%	Moderate
Depression severity	k=7 N=748	SMD 0.05 (95% CI, -0.09 to 0.22)	0%	Moderate
Anxiety severity	k=3 N=414	SMD 0.00 (95% CI, -0.62 to 0.36)	0%	Low

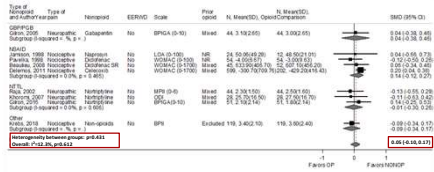
*No interactions between nonopioid type and effects on any outcome. 1 trial found stepped therapy with opioids associated with no difference vs. stepped therapy initiated with nonopioid therapy in BPI interference at 12 months (3A vs. 3B, MD 0.1, 95% CI, -0.3 to 0.7), but opioid therapy stepped care was associated with higher BPI pain intensity (4C vs. 3A, MD 0.5, 95% CI, 0.0 to 1.0).

Opioid vs. Nonopioid: Improvement in Mean Pain at Short-Term Follow-up



Note: Nonspecific pain refers to musculoskeletal condition

Opioid vs. Nonopioid: Improvement in Mean Function Short-Term Follow-up

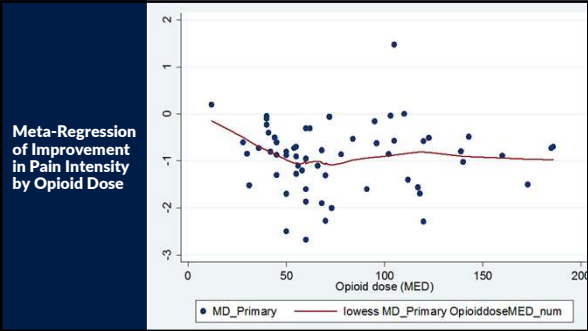


Opioid vs. Placebo or No Opioid

Outcome	Studies (k) / Sample Size (N)	Pooled Estimate	I ²	SOE
Discontinuation due to AEs	k=6 N=1,864	RR 2.26 (95% CI, 1.87 to 2.75) ARD 10% (95% CI, 7% to 12%)	72%	High
Serious AEs	k=37 N=13,030	RR 1.21 (95% CI, 0.87 to 1.71)	37%	Moderate
Nausea	k=6 N=11,718	RR 2.66 (95% CI, 2.17 to 2.88) ARD 24% (95% CI, 12% to 17%)	50%	High
Vomiting	k=9 N=17,388	RR 3.57 (95% CI, 2.98 to 4.34) ARD 7% (95% CI, 6% to 9%)	15%	High
Constipation	k=58 N=13,351	RR 3.28 (95% CI, 2.96 to 3.92) ARD 44% (95% CI, 11% to 17%)	21%	High
Somnolence	k=52 N=17,458	RR 2.97 (95% CI, 2.44 to 3.66) ARD 9% (95% CI, 7% to 12%)	48%	High
Dizziness	k=53 N=14,396	RR 2.66 (95% CI, 2.37 to 2.99) ARD 8% (95% CI, 6% to 10%)	0%	High
Pruritus	k=30 N=11,454	RR 3.51 (95% CI, 2.47 to 5.16) ARD 7% (95% CI, 4% to 10%)	50%	High
Headache	k=48 N=17,405	RR 1.06 (95% CI, 0.95 to 1.17)	0%	High

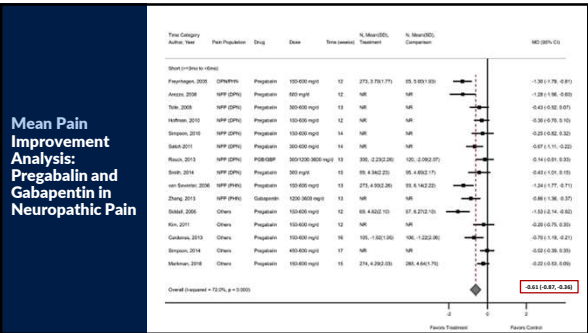
Opioid vs. Placebo or No Opioid, Cont.

Outcome	Number of Studies	Main Findings	SOE
Opioid abuse, dependence, or addiction	2 cohort studies	Association between opioid use and increased risk of opioid abuse, dependence, or addiction	Low
Overdose events	2 cohort studies	Association between opioid use and increased risk of overdose events	Low
All-cause mortality	1 cohort study	Long-acting opioids associated with increased risk of all-cause mortality vs. nonopioid medications	Low
Risk of fracture	5 observational studies	Association between opioid use and risk of fracture and risk of falls, though differences were not statistically significant in all studies and estimates decreased with longer duration of opioid use in some studies	Low
Risk of falls	3 observational studies	Association between opioid use and increased risk of MI	Low
Myocardial infarction	2 observational studies	Association between opioid use and increased risk of MI	Low
Use of ED medications	1 cross-sectional study	Long-term opioid use associated with increased risk for use vs. nonuse	Low
Attempted suicide/self-harm	1 cohort study	No association between any long-term opioid use and increased risk of attempted suicide/self-harm	Low
Opioid abuse, dependence, or addiction	2 cohort studies	Association between opioid use and increased risk of opioid abuse, dependence, or addiction	Low

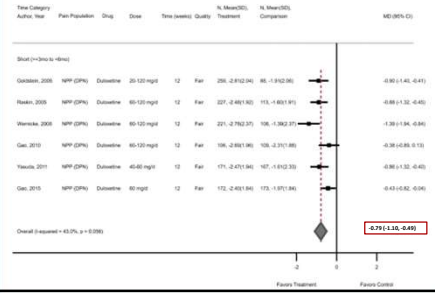


Non-Opioid Medications

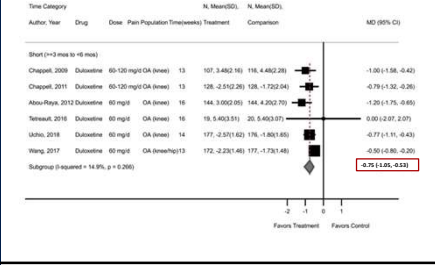
	SNRI	Pregabalin or gabapentin	NSAIDs
Neuropathic pain	MD -0.61 (-0.87 to -0.36)	MD -0.79 (-1.10 to -0.49)	--
Fibromyalgia	MD -0.61 (-0.79 to -0.48)	MD -0.60 (-0.80 to -0.36)	--
Osteoarthritis	MD -0.75 (-1.05 to -0.53)	--	MD -0.71 (-0.82 to -0.61)
Low back pain	MD -0.50 (-0.71 to -0.29)	--	--



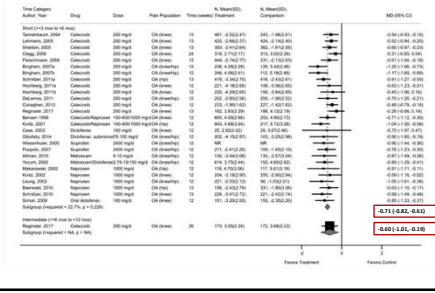
Mean Pain Improvement Analysis: SNRI Duloxetine in Neuropathic Pain



Mean Pain Improvement Analysis: SNRI Duloxetine in Osteoarthritis



Mean Pain Improvement Analysis: NSAIDs in Osteoarthritis



Nonpharmacologic therapies: "Active" chronic LBP interventions vs. usual care, waitlist, attention control, placebo

Intervention	Function			Pain		
	Short-Term ES, SOE	Intermediate ES, SOE	Long-Term ES, SOE	Short-Term ES, SOE	Intermediate ES, SOE	Long-Term ES, SOE
Exercise	slight +	none +	none +	slight ++	moderate +	moderate +
Psychological: CBT primarily	slight ++	slight +	slight ++	slight ++	slight ++	slight ++
Mind-Body Practices: Yoga	slight ++	slight +	no evidence	moderate +	moderate ++	no evidence
Mindfulness Practices: MBSR	none +	none +	none +	slight ++	slight +	none +
Multidisciplinary Rehabilitation	slight +	slight +	none +	slight ++	slight ++	none +

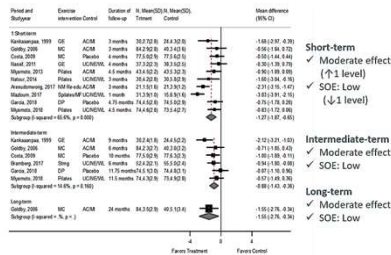
Nonpharmacologic therapies:
"Passive" chronic LBP interventions vs. usual care, waitlist, attention control, placebo

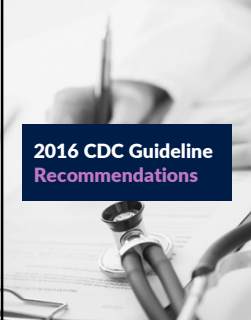
Intervention	Function			Pain		
	Short-Term ES, SOE	Intermediate ES, SOE	Long-Term ES, SOE	Short-Term ES, SOE	Intermediate ES, SOE	Long-Term ES, SOE
Physical Modalities: Ultrasound	insufficient evidence	no evidence	no evidence	none +	no evidence	no evidence
Physical Modalities: Low Level Laser	slight +	none +	no evidence	moderate +	none +	no evidence
Manual Therapies: Spinal Manipulation	slight +	slight +	no evidence	none +	slight ++	no evidence
Manual Therapies: Massage	slight ++	none +	no evidence	slight ++	none +	no evidence
Manual Therapies: Traction	none +	no evidence	no evidence	none +	no evidence	no evidence

Nonpharmacological therapies:
"Active" and "Passive" chronic LBP interventions vs. exercise

Intervention	Function			Pain		
	Short-Term ES, SOE	Intermediate ES, SOE	Long-Term ES, SOE	Short-Term ES, SOE	Intermediate ES, SOE	Long-Term ES, SOE
ACTIVE						
Mind-Body Practices: Yoga	none +	none +	no evidence	slight +	none +	no evidence
Mind-Body Practices: Qigong	none +	slight favoring exercise	no evidence	slight favoring exercise	none +	no evidence
Multidisciplinary Rehabilitation	slight +	slight ++	none +	slight ++	slight ++	none +
PASSIVE						
Physical Modalities: Low-Level Laser Therapy	no evidence	none +	no evidence	no evidence	slight +	no evidence
Manual Therapies: Spinal Manipulation	none +	none +	no evidence	none +	slight +	no evidence
Manual Therapies: Massage	no evidence	none +	no evidence	no evidence	none +	no evidence

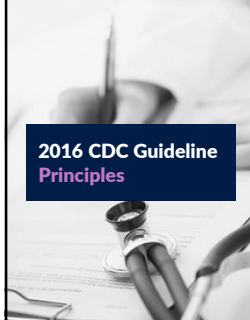
Chronic LBP Pain:
Exercise vs. usual care, attention control, placebo





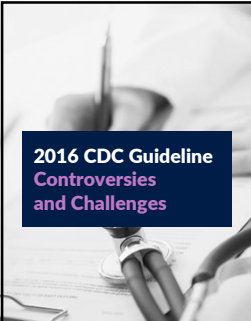
2016 CDC Guideline Recommendations

- 12 recommendations in 3 areas
 - When to initiate or continue opioids
 - Opioid selection, dosage, duration, follow-up, and discontinuation
 - Assessing risk and addressing the harms of opioid use
 - All recommendations category A (strong) except 1 recommendation category B (conditional) on urine drug testing
- All evidence for recommendations
 - type 3 (RCTs with notable limitations, or observational studies), or
 - type 4 (RCTs with major limitations, or observational studies with notable limitations/clinical experience)
 - except 1 category 2 (RCTs with limitations or strong observational studies) on treatment for OUD



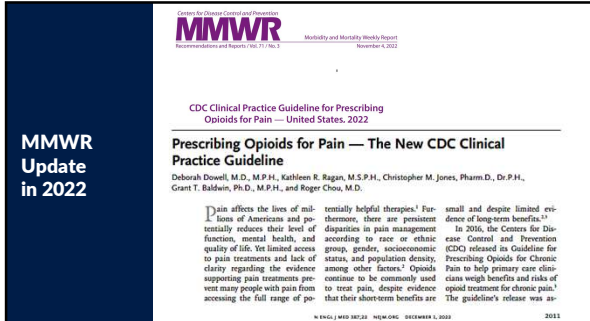
2016 CDC Guideline Principles

- Judicious use of opioids for chronic pain based on individualized risk assessment; nonopioid therapies preferred
- Treatment goals including impact on function as well as pain
- Risk mitigation strategies: Initiation, dose, selection of opioids, co-prescribing, urine drug toxicology, prescription drug monitoring programs, naloxone
- Continuation of opioids based on periodic re-assessment
- Taper or discontinue if benefits don't outweigh harms
- For acute pain, use doses and amount necessary (usually <3 days; rarely >7 days)



2016 CDC Guideline Controversies and Challenges

- Guideline applied to populations it was not intended for
- Guideline interpreted as prohibiting opioids for chronic pain
- Application of inflexible dose thresholds
 - "...carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine mg equivalents (MME)/day...avoid increasing dosage to ≥90 morphine mg equivalents (MME)/day or carefully justify a decision to titrate dose to ≥90 MME."
 - "...empathically review benefits and risks of continued high-dosage therapy...For patients who agree to taper opioids...clinicians should collaborate with the patient on a tapering plan."
- Harms of "forced" tapering and optimal methods for tapering
- Duration parameters for acute pain may be too short for some situations
- Dose and duration thresholds arbitrary



MMWR Update in 2022

Center for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
 Recommendations and Reports 71(1) No. 1
 November 4, 2022

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


Prescribing Opioids for Pain — The New CDC Clinical Practice Guideline

Deborah Dowell, M.D., M.P.H., Kathleen R. Ragan, M.S.P.H., Christopher M. Jones, Pharm.D., Dr.P.H., Grant T. Baldwin, Ph.D., M.P.H., and Roger Chou, M.D.

Pain affects the lives of millions of Americans and potentially reduces their level of function, mental health, and quality of life. Yet limited access to pain treatments and lack of clarity regarding the evidence supporting pain treatments prevent many people with pain from accessing the full range of potentially helpful therapies.¹ Furthermore, there are persistent disparities in pain management according to race or ethnic group, gender, socioeconomic status, and population density, among other factors.² Opioids continue to be commonly used to treat pain, despite evidence that their short-term benefits are small and despite limited evidence of long-term benefits.^{3,4}

In 2016, the Centers for Disease Control and Prevention (CDC) released its Guideline for Prescribing Opioids for Chronic Pain to help primary care clinicians weigh benefits and risks of opioid treatment for chronic pain.⁵ The guideline's release was as-

WEEKLY MORBIDITY AND MORTALITY REPORT
 THE NEW ENGLAND JOURNAL OF MEDICINE



Comparison to 2016 Guidelines

- General approach (judicious, individualized use of opioids for chronic pain with close monitoring and risk mitigation) unchanged
- Emphasis on general principles in recommendations, rather than specific levels/doses, to avoid inflexible application
- Additional guidance on tapering, including emphasis on slower tapers and strategies to mitigate harms and increase success
- Additional guidance on the use of opioids for acute pain and the need for re-assessment in patients receiving opioids for 1 to 3 months (subacute pain)
- Addition of guiding principles to facilitate equitable/individualized implementation of recommendations

Guiding Principles

- 1 Appropriately assess and treat pain independent of whether opioids are part of a treatment regimen.
- 2 Recommendations are voluntary and are intended to support, not supplant, individualized, person-centered care.
- 3 Utilize a multimodal & multidisciplinary approach to pain management.
- 4 Do not misapply the guideline beyond its intended use.
- 5 Address and reduce health inequities, ensure affordable and appropriate access.

Conclusions

- Opioids associated with improved pain and function vs. placebo but increased risk of harms that appears dose-dependent.
- Little difference between opioids vs. nonopioids in pain or function.
- Evidence on alternative opioid dosing strategies, tapering, and risk mitigation is limited.
- Several nonopioid medications associated with short-term benefits vs. placebo for various chronic pain conditions, but increased risk of withdrawal due to AE.
- Several nonpharmacologic interventions associated with benefits on pain or function beyond the course of therapy for specific chronic pain conditions; most effects sizes are small; evidence for "active" vs. "passive" interventions may inform treatment selection.
- Benefits of all therapies for chronic pain are small, with limited data on longer-term outcomes.
- The subsequent series of three updates did not change the main conclusions.
- 2022 CDC guideline retains a judicious, individualized approach to the use of opioids but attempts to reduce misapplication by focusing on general principles rather than specific levels/parameters.

Knowledge Check

Which of the following statements about opioid therapies for chronic pain is true?

- A Opioids are associated with no benefits versus placebo.
- B Opioids are associated with benefits that appear similar to nonopioid medications.
- C Opioids are associated with small long-term benefits versus placebo.
- D There is a consistent association between increasing opioid dose and larger benefits.
- E Opioids are associated with greater benefits than exercise.

Knowledge Check

Which of the following statements about opioid therapies for chronic pain is true?

- A Opioids are associated with no benefits versus placebo. **X**
- B Opioids are associated with benefits that appear similar to nonopioid medications. **✓**
- C Opioids are associated with small long-term benefits versus placebo. **X**
- D There is a consistent association between increasing opioid dose and larger benefits. **X**
- E Opioids are associated with greater benefits than exercise. **X**

References

SESSION TWO

1. AHRQ review on nonpharmacological therapies: <https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/research>
2. AHRQ review on nonopioid therapies: <https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research>
3. AHRQ review on opioid treatments: <https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research>
4. 2022 CDC guideline on opioids for pain: Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guidelines for Prescribing Opioids for Pain—United States, 2022. *MMWR Recomm Rep* 2022;71:1-95
5. SPACE trial: Krebs EE et al. Effect of opioid vs. nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain. The SPACE randomized clinical trial. *JAMA* 2018;319: 872-82.