

ESP

Evidence Synthesis Program

Benefits and Harms of Long-term Opioid Dose Reduction or Discontinuation in Patients with Chronic Pain

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August 2019

- Background on ESP & Evidence Synthesis Products
- Background on Opioid SOTA
- Overview of Topic
- Findings from August 2019 ESP Rapid Review
- Discussion and Questions

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Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend TEP members; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for report dissemination.

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National Pain Program, Specialty Care Services (10P11)

This report is based on research conducted by the Evidence Synthesis Program (ESP) Coordinating Center located at the **Portland VA Medical Center, Portland, OR**, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development.

The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs.

No investigators have any affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

The screenshot shows the website for the Evidence Synthesis Program (ESP) within the U.S. Department of Veterans Affairs. The header includes the VA logo, the text "U.S. Department of Veterans Affairs", a search bar for "Search HSR&D", and a "VA SITE MAP [A-Z]" link. A navigation menu contains links for Health, Benefits, Burials & Memorials, About VA, Resources, News Room, Locations, and Contact Us. The breadcrumb trail reads "VA » Health Care » HSR&D » Publications » Esp » Evidence Synthesis Program". The main heading is "Health Services Research & Development". A left sidebar lists various program areas like "About Us", "Research Impacts", "Research Topics", "Career Development Program", "Centers", "Cyberseminars", "For Managers", "For Researchers", "For Veterans", and "Funding". The main content area is titled "Evidence Synthesis Program" and "About the ESP Program". It describes the program as established in 2007, providing high-quality evidence synthesis to clinicians, managers, and policymakers. A blue "ESP Evidence Synthesis Program" logo is displayed. A list of benefits includes: "Develop clinical policies informed by evidence;", "Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and", and "Set the direction for future research to address gaps in clinical knowledge." On the right, there are three buttons: "View Published Reports", "Nominate an ESP Topic", and "ESP Reports in Progress". Below these is a "Subscribe to the ESP Report RSS feed" link with an RSS icon. A "TOPIC NOMINATION" section states "Nominations are currently being accepted." and provides instructions: "To nominate a topic, download and complete the".

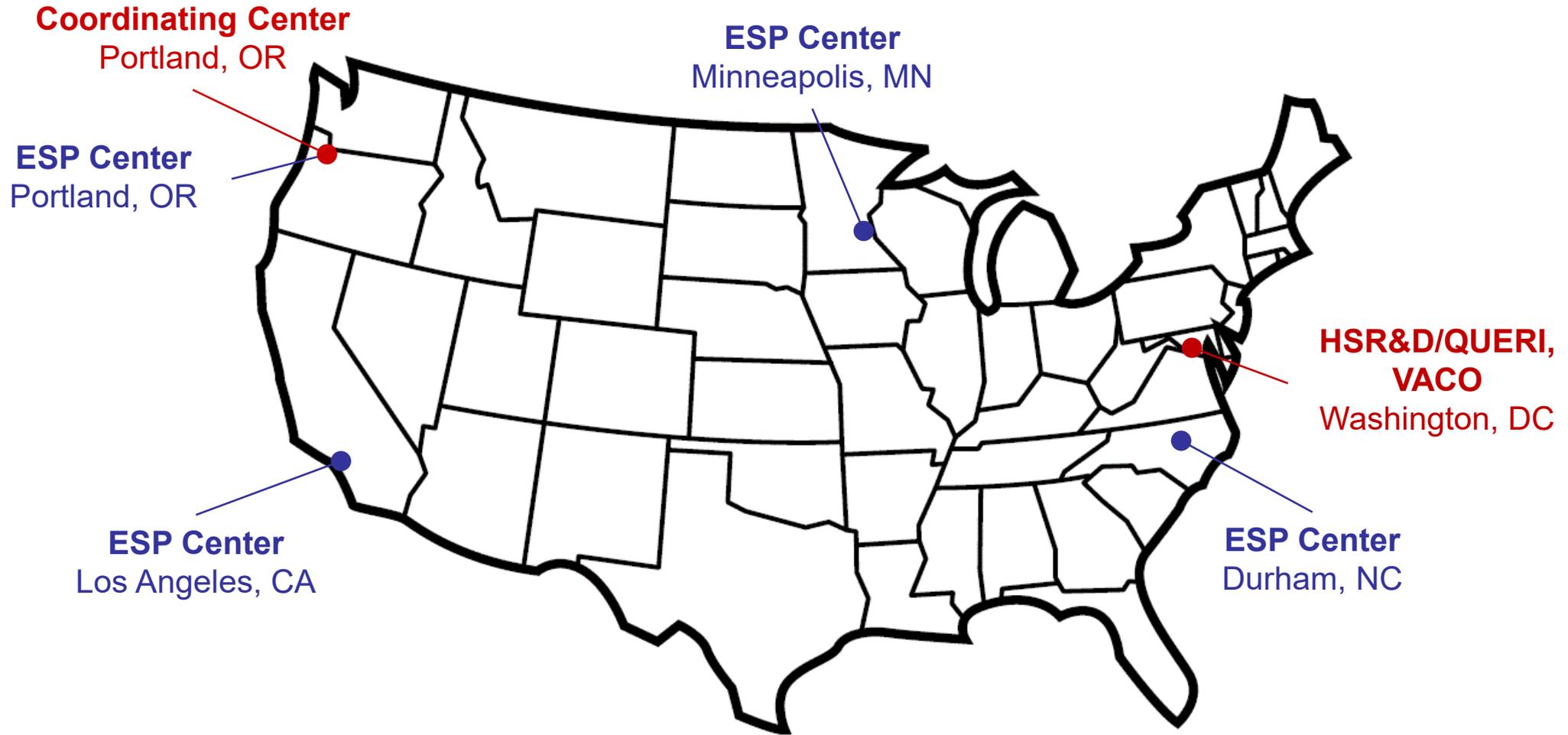
Mission: To make high-quality evidence synthesis available to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans.



“ESP reports are a terrific resource to inform policy decisions. They are methodologically rigorous and available [upon] request.”

<https://www.hsrd.research.va.gov/publications/esp/>

ESP Center Locations



Our Reports Help VA With



Range of Products for Different Needs

| | Speed (product within 4 months) | Fully follows all SR steps | Critical appraisal of evidence | External peer review |
|----------------------|---------------------------------|----------------------------|--------------------------------|----------------------|
| Systematic review | | ✓ | ✓ | ✓ |
| Scoping review | * | | | * |
| Evidence map | | | * | ✓ |
| Rapid evidence brief | ✓ | | ✓ | ✓ |
| Evidence assist | ✓ | | ✓ | |
| Evidence compendium | ✓ | | | |
| Evidence inventory | ✓ | | | |

* Possible on a case-by-case basis

Standard Systematic Review (9-12 months)

Comprehensive synthesis using the most methodologically rigorous process. Reviews several broad, overarching key questions.

Scoping Review (4-12 months)

Descriptive overview that identifies gaps and overlap in key concepts and highlights specific and/or unique features of interest.

Evidence Map (9-12 months)

User-friendly visual figure or graph and interpretive summary of a broad research field that provides quick access to questions and answers that previous research has addressed and identifies gaps that are important for VHA.

Rapid Evidence Brief (2-4 months)

Detailed report that generally follows, but streamlines, accepted systematic review methods and PRISMA reporting guidelines.

Evidence Assist™ (1-4 months)

Consultative memorandum with flexible format.

Evidence Compendium (1-2 months)

Brief summary of key features, data abstraction, and bibliography, organized by key features (eg, key question, study design, population, etc).

Evidence Inventory (1-4 weeks)

Bibliography organized by key features (eg, key question, study design, population, etc).

- **Background:** In September 2019, VA HSR&D will hold a State of the Art Conference (SOTA) on *Effective Management of Pain and Addiction: Strategies to Improve Opioid Safety*
- **Goals:**
 - Assess current VA burden and clinical practice
 - Review state of the evidence and relevance to VA population
 - Where evidence is sufficient, define consensus
 - Where evidence is conflicting or limited, define research agenda
 - Make practice or policy recommendations where consensus exists but is at odds with practice

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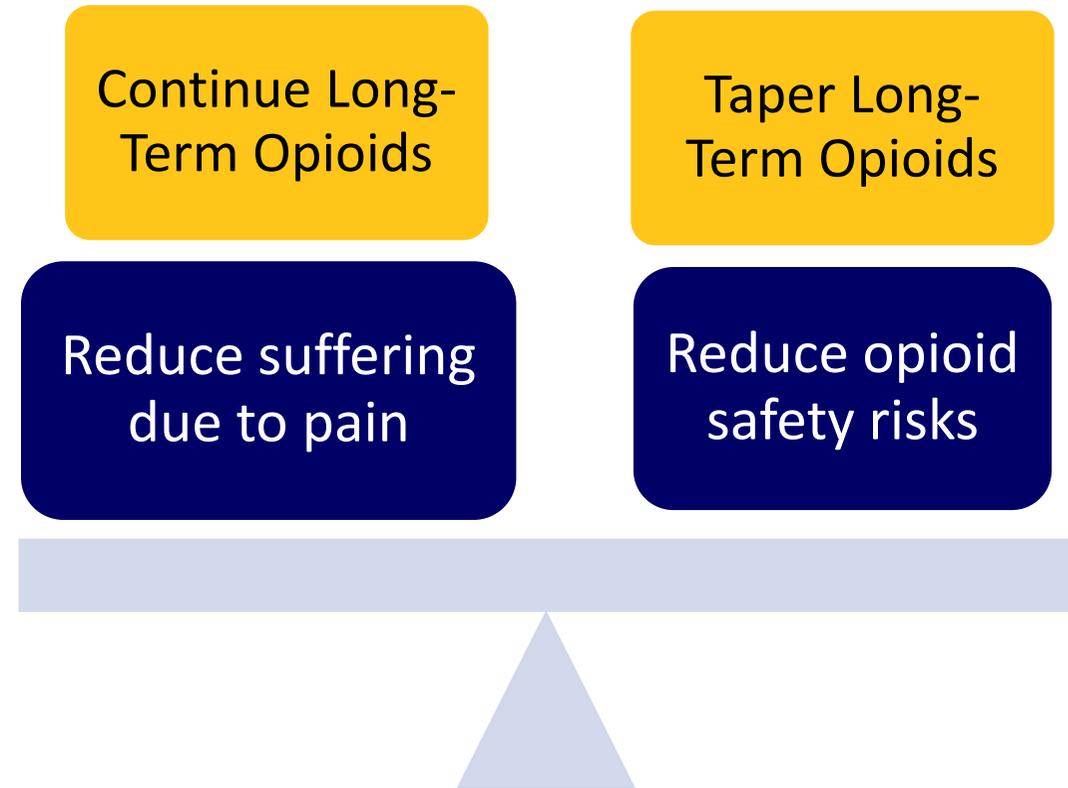
Workgroup 1: Managing Opioid Use Disorder

Workgroup 2: Long-term Opioid Therapy and Tapering

Workgroup 3: Managing Co-Occurring Pain and Substance Use Disorders

The Problem: A Difficult Balance

- Evolving crisis of morbidity, mortality, and misuse due to opioids
- VA/DoD and CDC guidelines recommend considering LTOT tapers when risks > benefits
- Patients with chronic pain on long-term opioid therapy (LTOT) and the providers who care for them are at the center of a difficult balance



- Emphasize shared decision-making regarding LTOT tapers
- Individualize taper speeds and suggest gradual tapers with pauses in the tapering process as needed
- Similar approaches are recommended by the American Academy of Family Physicians, the Washington State Agency Medical Directors' Group, and the Oregon Pain Guidance Clinical Advisory Group



The NEW ENGLAND
JOURNAL of MEDICINE June 13, 2019

Perspective

No Shortcuts to Safer Opioid Prescribing

Deborah Dowell, M.D., M.P.H., Tamara Haegerich, Ph.D., and Roger Chou, M.D.



For Immediate Release:

April 09, 2019

Statement From:

Deputy Director for Regulatory Programs - About the Center for Drug Evaluation and Research
Douglas Throckmorton MD

“Recently, the FDA has received reports of serious harm, including serious withdrawal symptoms, uncontrolled pain and suicide, in patients who are physically dependent on opioid pain medicines when these medicines are suddenly discontinued or when the dose is reduced too quickly, often without adequate patient communication, follow-up or support.”



Annals of Internal Medicine

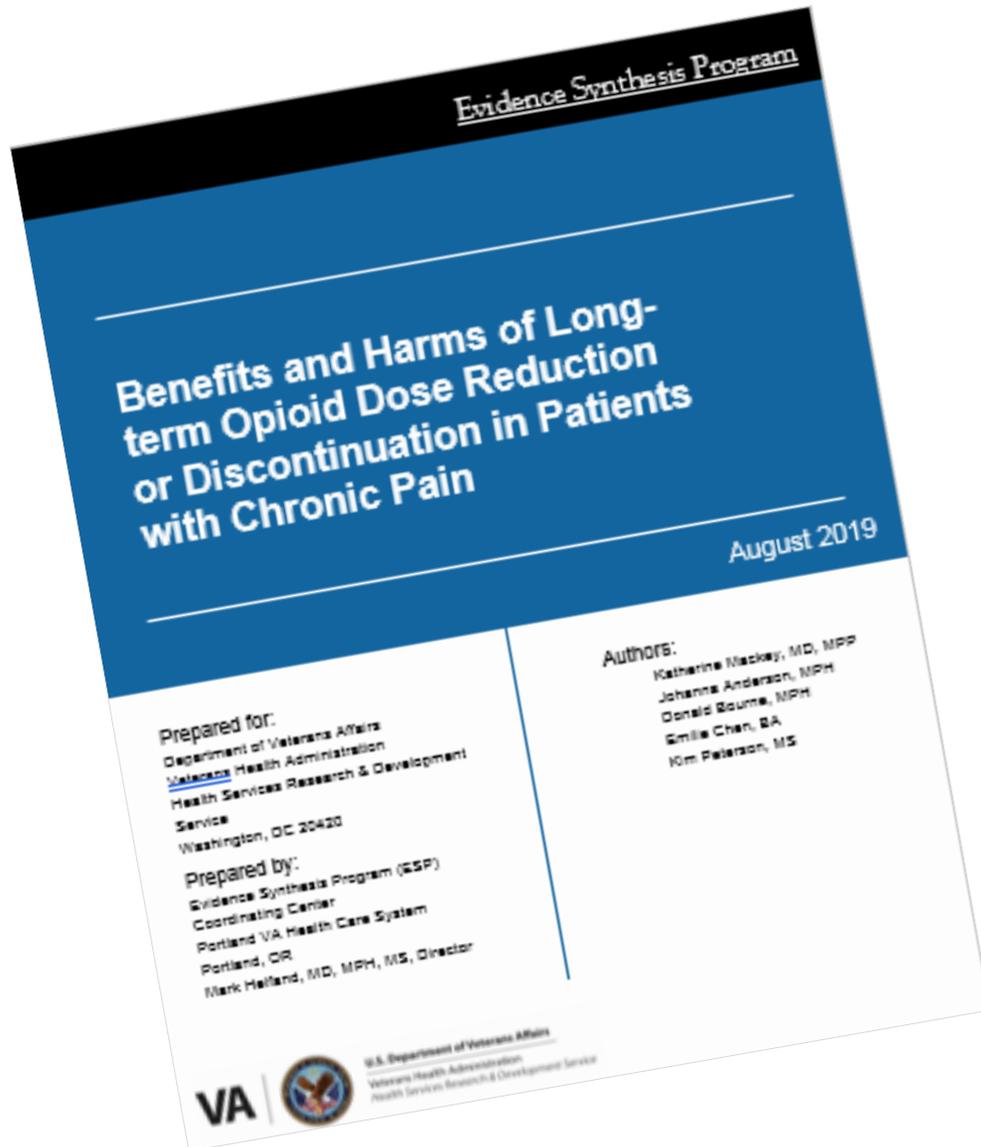
REVIEW

Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy A Systematic Review

Joseph W. Frank, MD, MPH; Travis I. Lovejoy, PhD, MPH; William C. Becker, MD; Benjamin J. Morasco, PhD; Christopher J. Koenig, PhD; Lilian Hoffecker, PhD, MLS; Hannah R. Dischinger, BS; Steven K. Dobscha, MD; and Erin E. Krebs, MD, MPH

- Included 40 studies of patient outcomes following LTOT tapers
- Most studies fair- or poor-quality
- Inconclusive evidence on the impact of LTOT tapers on pain severity, pain-related function, quality of life, withdrawal symptoms, substance abuse, and adverse effects

- Synthesize evidence on LTOT dose reduction and discontinuation for a broader range of outcomes and with an emphasis on evidence most relevant and applicable to VHA populations
- Identify evidence gaps



Full-length report available on ESP website:
<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>

Key Question 1: Among patients prescribed long-term opioid therapy for chronic pain, what are the benefits and harms of opioid dose reduction or discontinuation?

Key Question 2: Do the benefits and harms of opioid dose reduction or discontinuation vary by:

- Patient characteristics
- Patient engagement in tapering
- LTOT regimen
- Tapering characteristics

Population: Adults prescribed long-term opioids (≥ 3 months) for chronic pain (excluding patients receiving palliative care, treatment for cancer-related pain, or undergoing surgery)

Intervention: Dose reduction or discontinuation (excluding studies of chronic pain interventions not explicitly designed to lower opioid doses)

Comparator: Any

Outcomes: Pain severity, pain-related function, quality of life, patient satisfaction, healthcare utilization, opioid withdrawal symptoms, substance use, opioid overdose, suicidal ideation and suicidal self-directed violence

Timing, Setting, Study Design: Any

- **Search:** MEDLINE, PsycINFO, Cochrane databases and other sources (January 1, 2017 - March 15, 2019) and consulted with experts
- **Study selection:** Based on eligibility criteria
- **Data abstraction:** Study characteristics and results
- **Critical appraisal:** Use of standardized tools
- **Quality control:** Assessments first completed by one reviewer and checked by at least one additional reviewer. Disagreements resolved by consensus.
- **Peer Review:** Topic and methodological experts commented, responses are publicly available

Methodological Limitations

Precision

Consistency

Directness

HIGH

We are very confident that the true effect lies close to that of the estimate of the effect

MODERATE

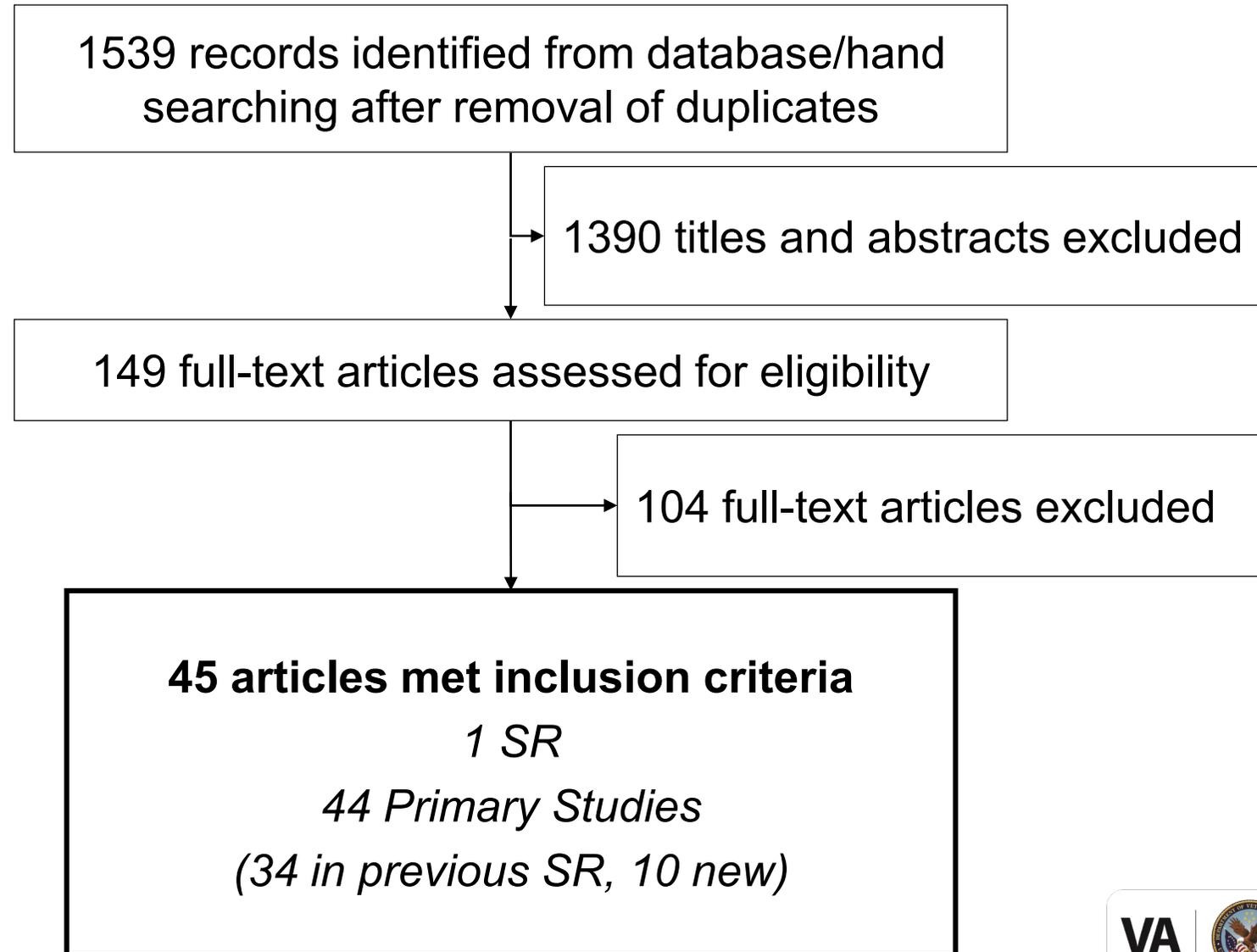
We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

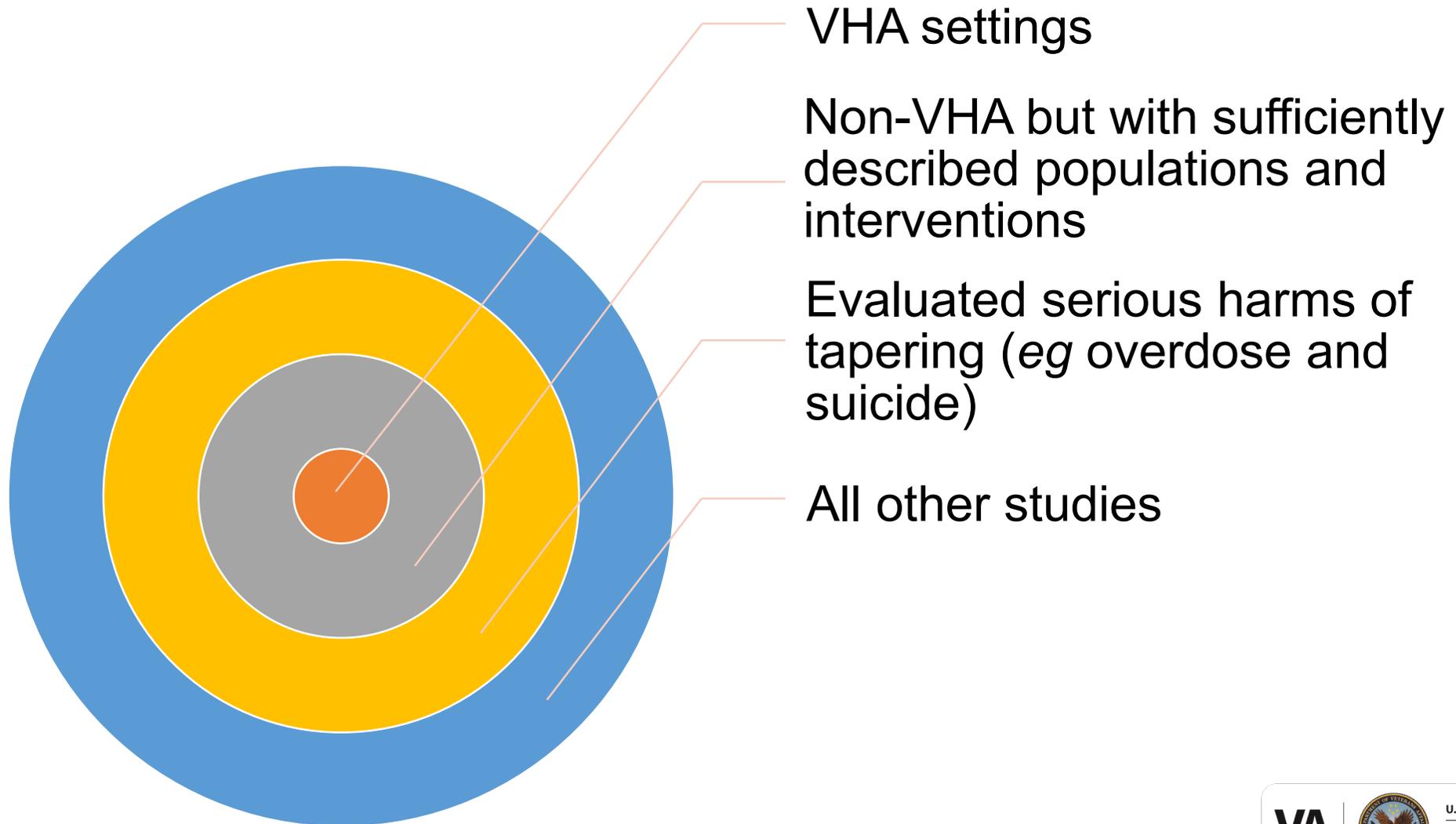
LOW

Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

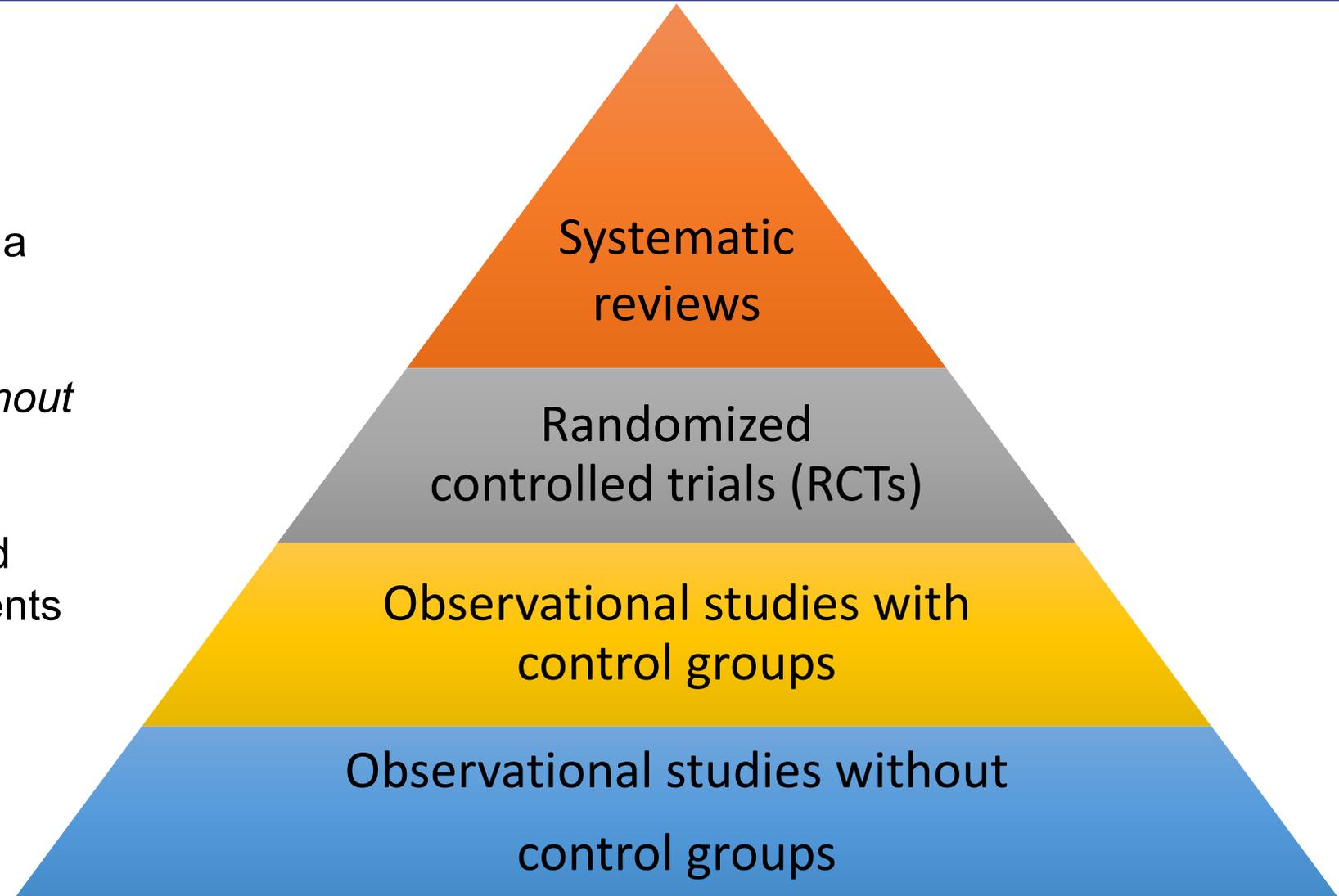
VERY LOW

We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

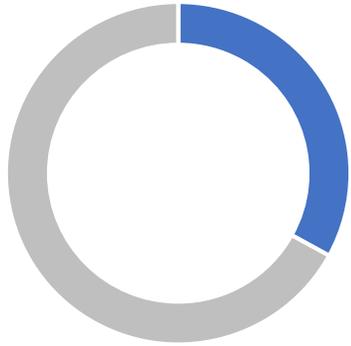




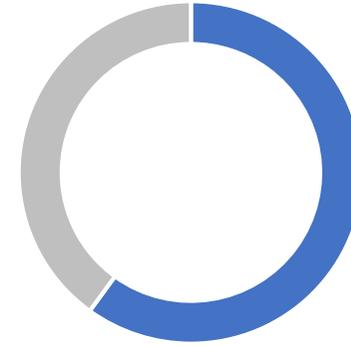
- 2 RCTs
- 2 Observational studies *with* a control group
- 11 Observational studies *without* a control group
- Remaining studies either had low applicability to VHA patients or care settings or included patients or interventions that were not well-described



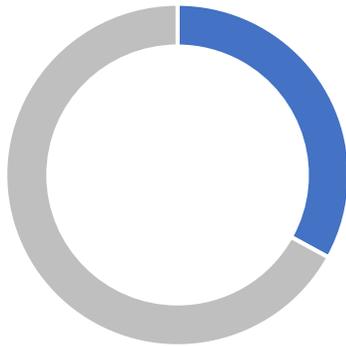
Results of 15 Prioritized Studies



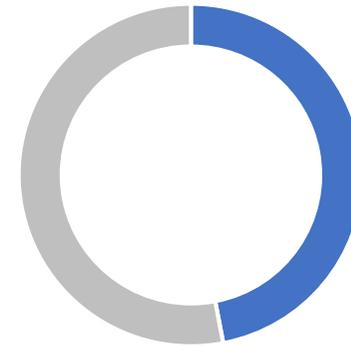
33% in VHA Setting



60% Voluntary Tapers



33% Back Pain Most Common



47% Fast Taper Speed

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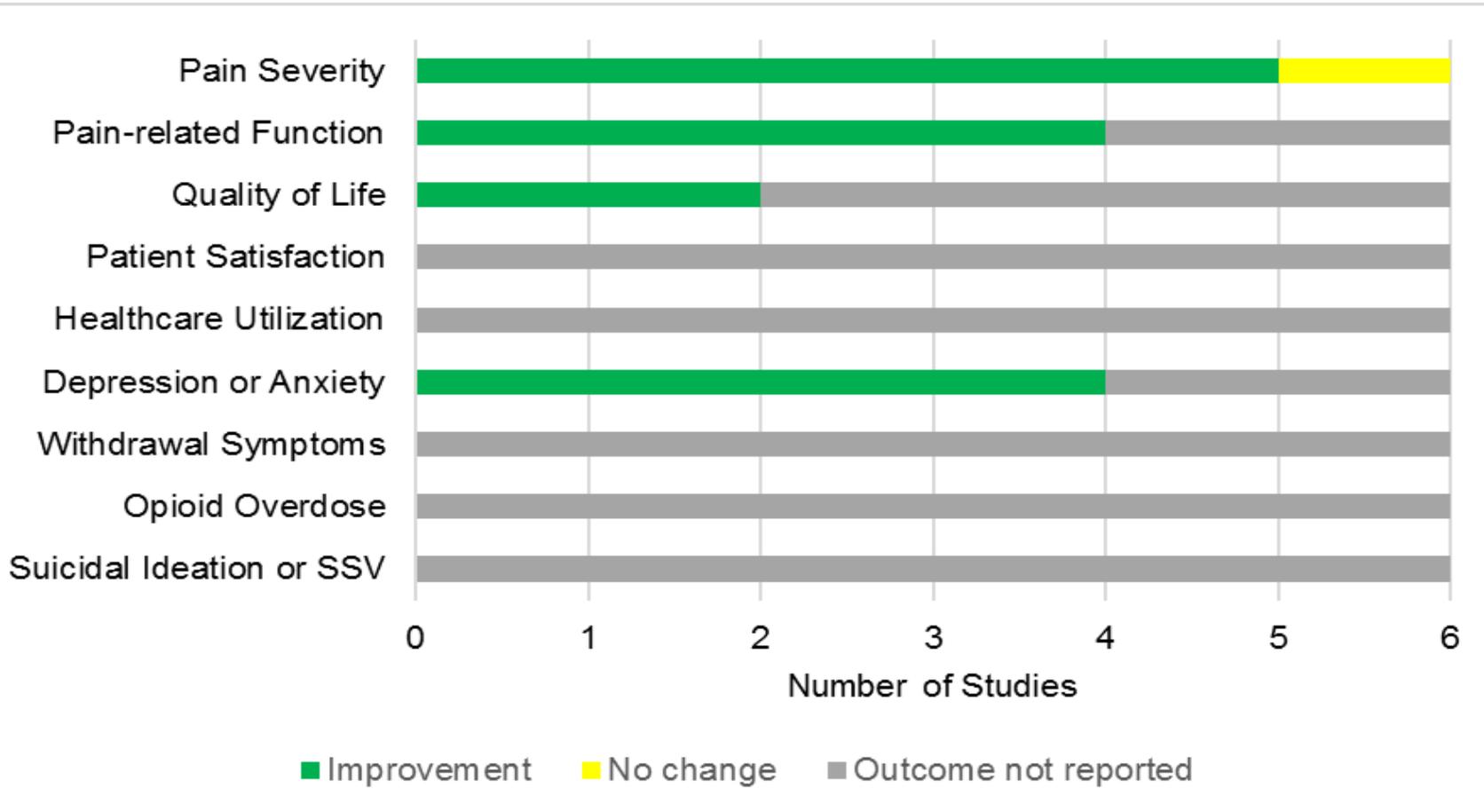
KQ1: Summary of Results

| Author, Year | Patient Outcomes | | | | | | Adverse Events | | |
|---|------------------|-----------------------|-----------------|----------------------|------------------------|-----------------------|---------------------|------------------------|--------------------------|
| | Pain Severity | Pain-related Function | Quality of Life | Patient Satisfaction | Healthcare Utilization | Depression or Anxiety | Withdrawal Symptoms | SUD or Opioid Overdose | Suicidal Ideation or SSV |
| <i>High Intensity Interventions</i> | | | | | | | | | |
| Darchuk, 2010 ⁴³ | ✓ | ✓ | | | | ✓ | | | |
| Hooten, 2007b ⁴⁵ | ✓ | ✓ | ✓ | | | ✓ | | | |
| Hooten, 2009 ⁴⁸ | ✓ | | | | | | | | |
| Huffman, 2017 ⁵² | ✓ | ✓ | | | | ✓ | | | |
| McPherson, 2018⁷⁴ | = | | | | | | | | |
| Townsend, 2008 ⁶² | ✓ | ✓ | ✓ | | | ✓ | | | |
| <i>Moderate/Low/Unknown Intensity Interventions</i> | | | | | | | | | |
| Darnall, 2018 ⁷¹ | = | = | | | | | | | |
| Demidenko, 2017⁷² | | | | | | | | | ✗ |
| Harden, 2015 | ✓ | | | | | | | | |
| Hundley, 2018⁷³ | | | | | = | | | ✗ | ✗ |
| Kurita, 2018 ⁶⁶ | = | | ✓ | | | = | ✗ | | |
| Mark, 2019 ⁷⁵ | | | | | ✗ | | | ✗ | |
| Murphy, 2013 | ✓ | ✓ | ✓ | ✓ | | | | | |
| Sullivan, 2017 ³⁴ | ✓ | ✓ | | | | | | | |
| Von Korff, 2019 ⁷⁰ | | | | | | | | ✗ | |
| Overall Evidence Quality | Low | Low | Very low | Very low | Very Low | Very Low | | | |

*New since Frank 2017; Bold = VHA study; Abbreviations: SUD = substance use disorder, SSV=suicidal self-directed violence
Blank cells no data reported; No studies reported on opioid-related side effect outcomes

✓ Symptoms improved; = No change in symptoms; ✗ Unclear effect on symptoms/no comparator

High Intensity Interventions



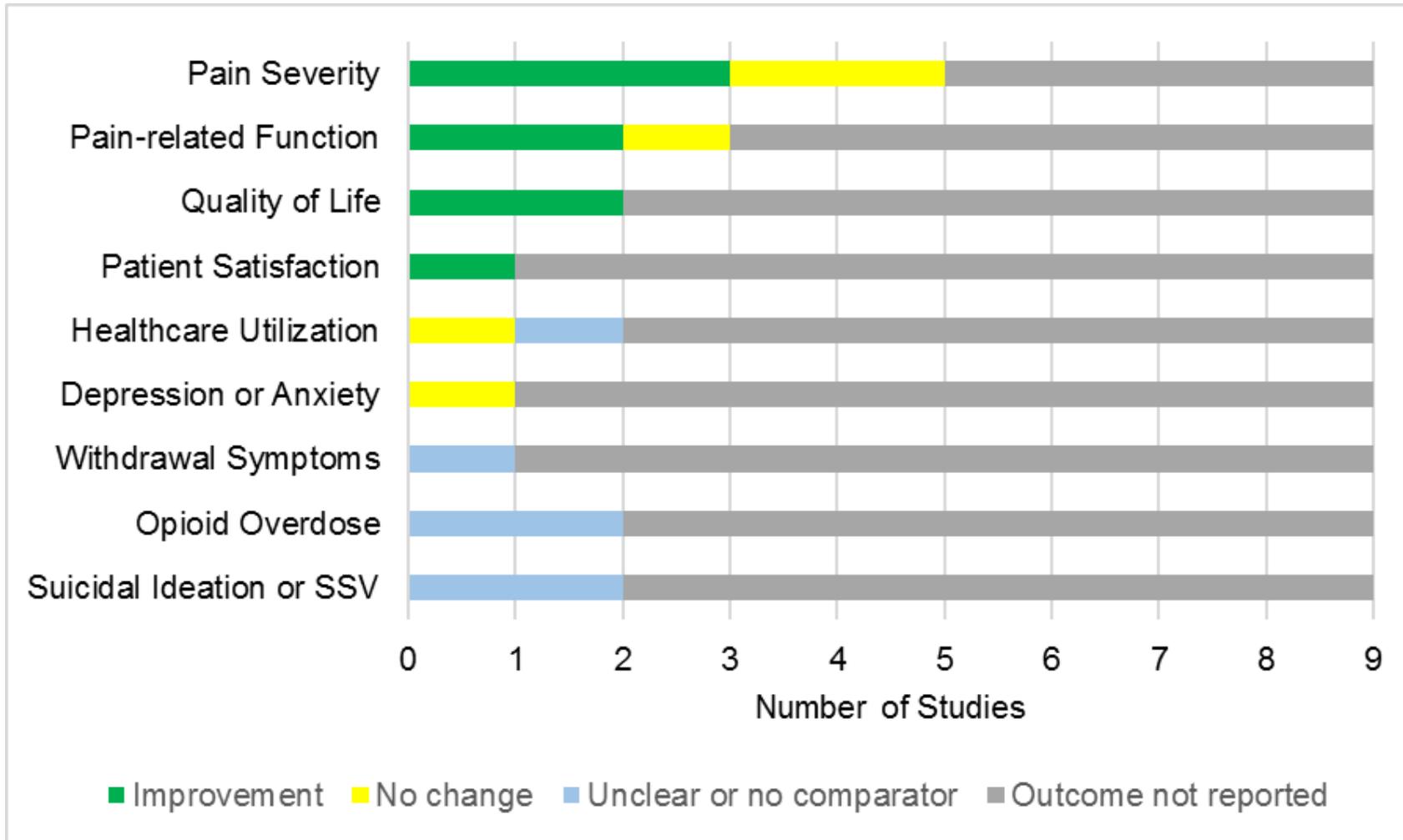
Example of High Intensity Intervention

Description of Cleveland Clinic outpatient Interdisciplinary Chronic Pain Rehabilitation Program:

“Participation from 7:30 AM to 5:00 PM Monday to Friday, and includes daily medical management, individual psychotherapy (2-3 per week), group psychotherapy (7 hours per week), and cognitive behavioral group interventions and psychoeducation, physical and occupational therapy, substance use education, weaning from habituating medications, and optional monthly aftercare.”

Huffman KL, Rush TE, Fan Y, et al. Sustained improvements in pain, mood, function and opioid use post interdisciplinary pain rehabilitation in patients weaned from high and low dose chronic opioid therapy. *Pain*. 2017;158(7):1380-1394.

Moderate, Low, or Unclear Intensity Interventions



Moderate Intensity Intervention:

- 2 RCTs embedded in multidisciplinary pain clinics, 1 with medication optimization prior to a scheduled taper and 1 with enhanced psychosocial supports

Low Intensity Intervention:

- 1 uncontrolled observational study of a self-help book paired with individual clinician guidance

Unclear:

- 6/15 studies did not describe a specific tapering intervention

- No studies reported the proportions of patients who experienced a clinically significant worsening in pain severity
- Common measures of pain severity:
 - Pain Numerical Rating Scale (NRS)
 - Multidimensional Pain Inventory (MPI)
 - Brief Pain Inventory (BPI)
- A limitation of assessments of mean change is that they do not tell us whether a change in score was clinically meaningful for patients

- Evidence is unclear; studies have not directly examined this outcome
- Best evidence: 2019 study by Mark et al of Medicaid claims data in Vermont
 - Between 2013-17 opioids were discontinued in 494/694 patients on ≥ 120 mg MEDD
 - Prior to discontinuation, 60% of patients had a diagnosis of substance use disorder and after almost half (49%) of patients had an ED visit or hospitalization due to opioid poisoning or substance use disorder
- Study does not describe LTOT discontinuation reasons or exclude reverse causation

- Evidence is unclear; few studies have examined this outcome
- Best evidence: 2019 large retrospective cohort study by Von Korff et al examining opioid overdose rates following different phases of an opioid risk reduction initiative in Washington
 - Overdose rates decreased by 17% per year within the intervention group (patients in Washington's Group Health practice) after a dose reduction effort (relative annual change 0.83; 95% CI 0.70 to 0.99)
 - Reduction was not significantly different when compared to the control group (patients followed at Group Health's contracted community clinics)
- Provides inconsistent support that reducing opioid doses leads to lower overdose rates
- Does not capture the potential for reverse causation

- Evidence is unclear; few studies have examined this outcome
- Best evidence: 2017 retrospective study by Demidenko et al
 - 509 VA patients *with substance use disorders* and matched controls underwent clinician-initiated tapers due mostly (75%) to aberrant behaviors
 - 47 (9.2%) had new-onset suicidal ideation and 12 patients (2.4%) had suicidal self-directed violence in the year following opioid discontinuation
 - Baseline PTSD (OR = 2.56, 95% CI 1.23 to 5.32) and psychotic disorders (OR = 3.19, 95% CI 1.14 to 8.89) were associated with suicidal ideation and suicidal self-direction violence
- Important limitations: data obtained by chart review only; patients who died in the year after opioid discontinuation were excluded from analysis; excluded patients who had no VHA contact in the year following discontinuation

Key Question 1: Among patients prescribed long-term opioid therapy for chronic pain, what are the benefits and harms of opioid dose reduction or discontinuation?

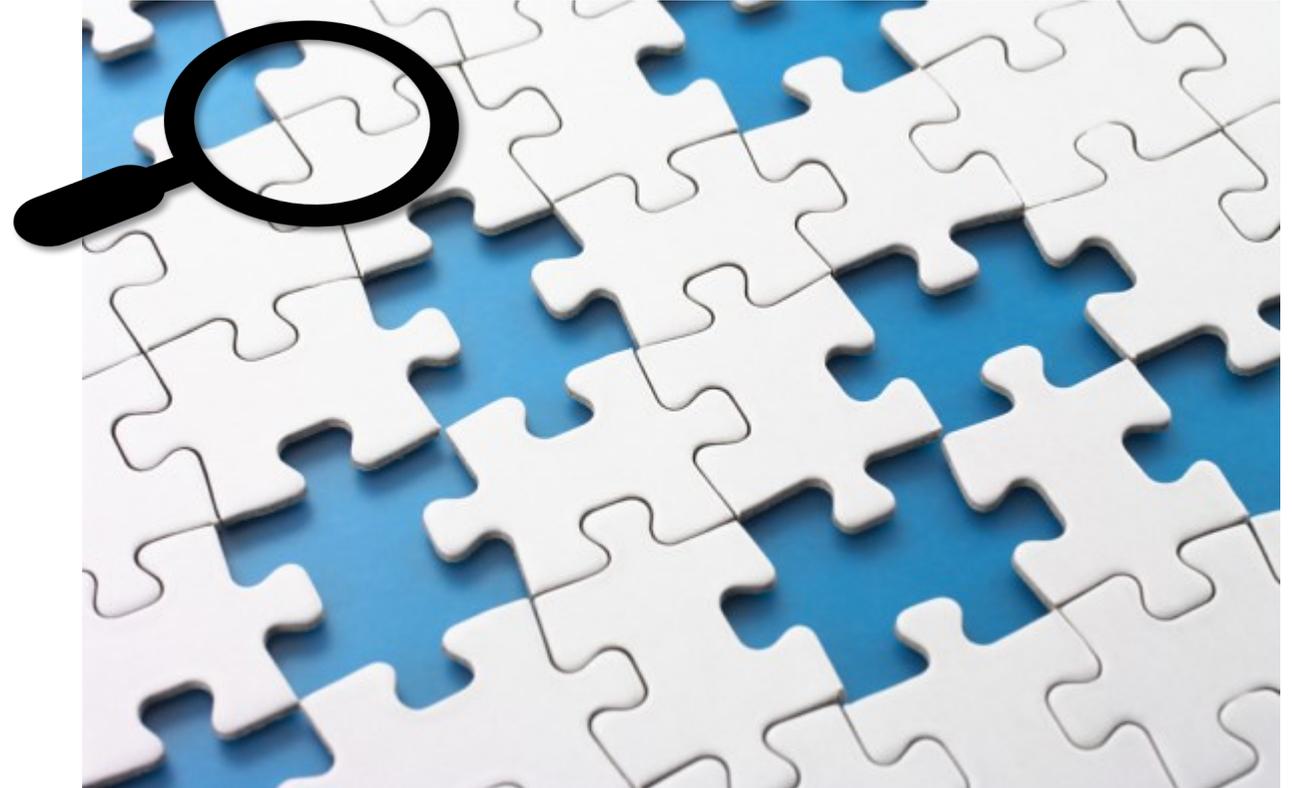
Key Question 2: Do the benefits and harms of opioid dose reduction or discontinuation vary by:

- Patient characteristics
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- LTOT regimen
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- Very limited evidence is available to address the question of whether benefits and harms of LTOT tapers vary by different patient characteristics or taper approaches
- Important evidence gap

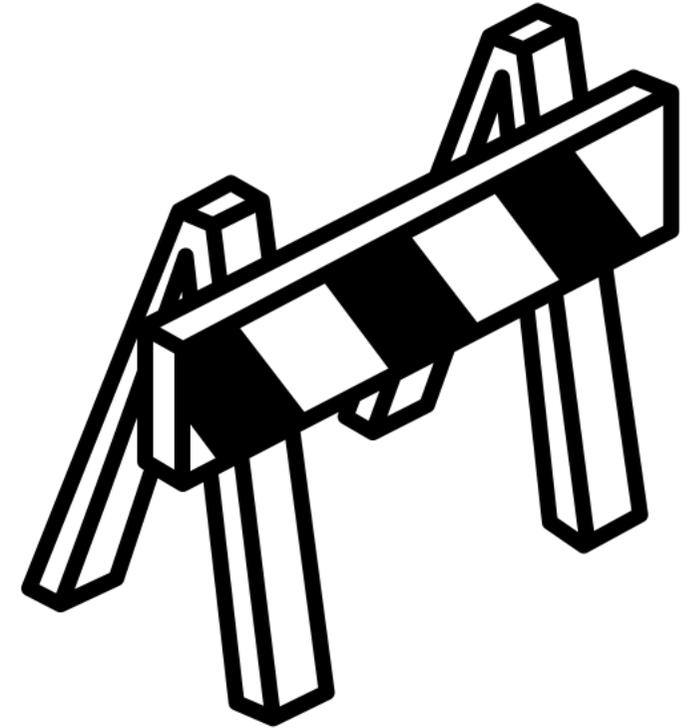
- Pain severity and function may improve with voluntary, intensive pain management interventions that incorporate opioid tapering and may not change with less intensive interventions
- Our confidence in these findings is low and additional evidence is needed before drawing stronger conclusions
- Findings for other outcomes are inconclusive
- We know the least about outcomes with clinician-initiated/involuntary tapers including outcomes for patients suspected of opioid misuse

- Rates of serious adverse events associated with LTOT tapers, including overdose and suicide
- Rates of newly diagnosed OUD during LTOT tapers
- Specific patient and intervention characteristics associated with improved pain and function following opioid tapers, including how outcomes differ between voluntary/patient-initiated tapers and mandated tapers and by opioid regimen

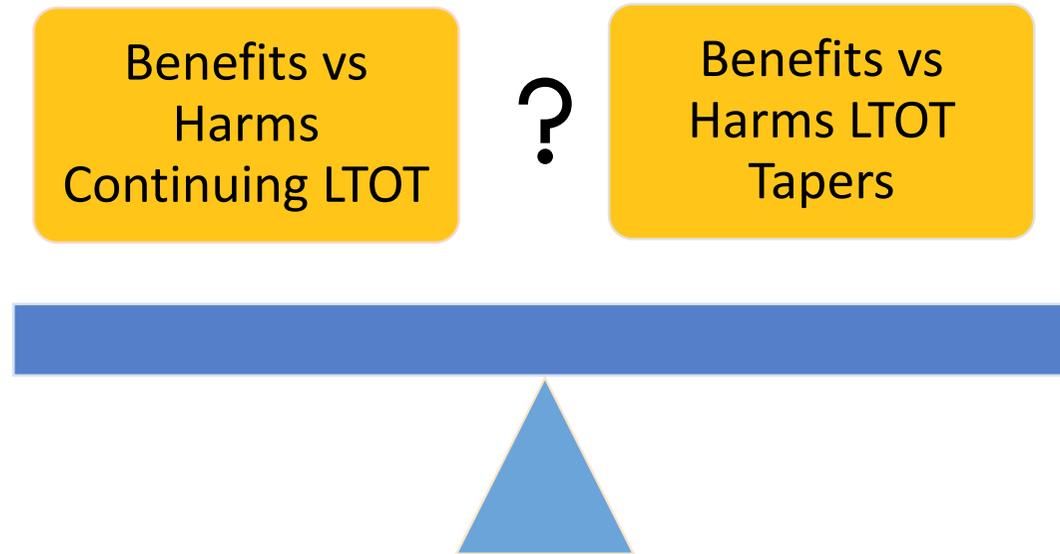


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- Inherent risk of bias in observational studies
- Lack of control groups
- Unclear fidelity to interventions
- Inadequate reporting or unclear handling of missing data
- Rapid reviews streamline systematic review methods which can result in missing eligible studies or study data



Barrier by Andy Ivandikov from the Noun Project



Evidence is inadequate to fully weigh the balance of the benefits and harms of LTOT for chronic pain against the benefits and harms of opioid tapering, primarily due to limited information on tapering harms.

If you have further questions, please feel free to contact:

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Full-length report and cyberseminar available on ESP website:

<http://www.hsrd.research.va.gov/publications/esp/>