

ESP

Evidence Synthesis Program

Evidence Brief: Managing Acute Pain in Patients with Opioid Use Disorder on Medication-Assisted Treatment

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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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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.

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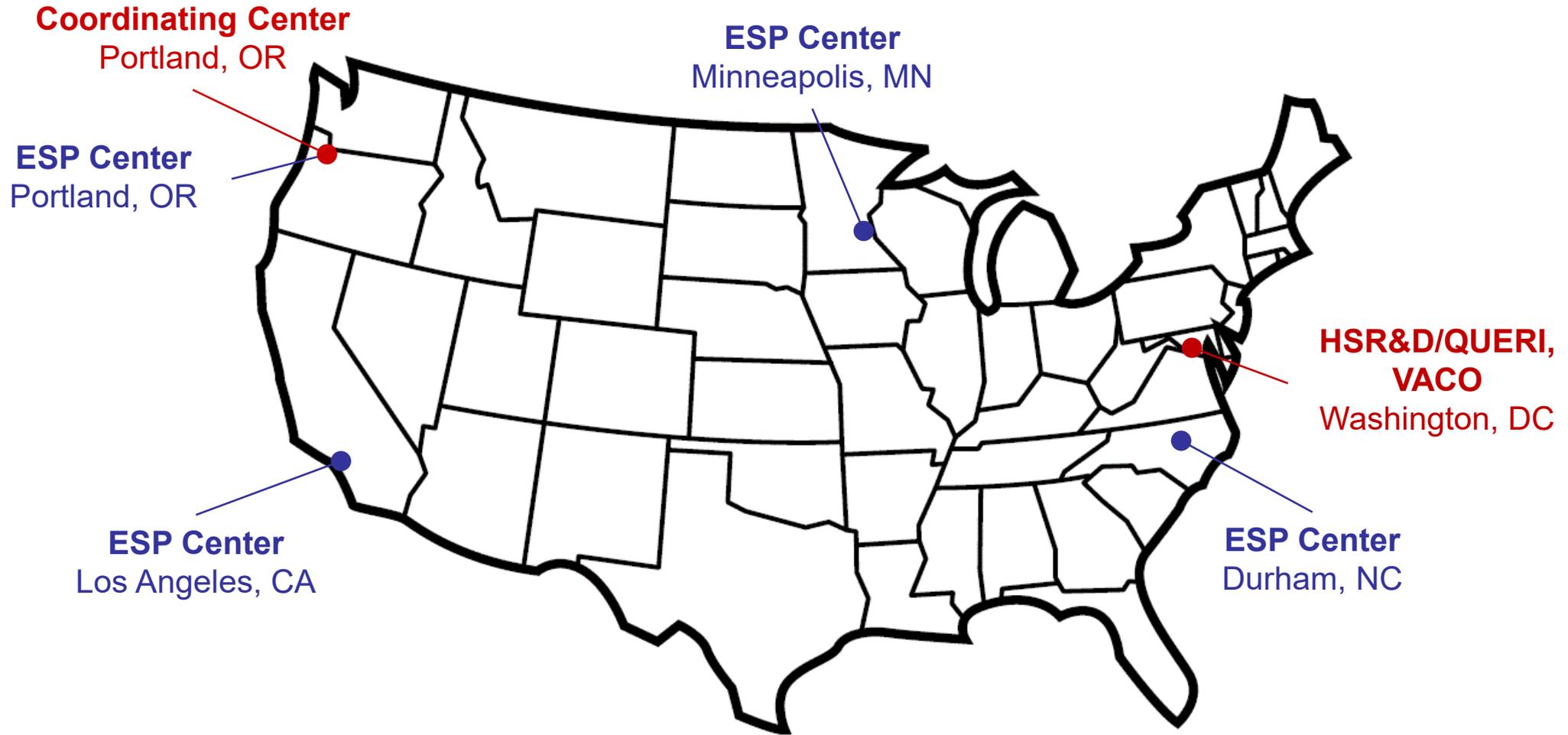
The screenshot shows the website's header with the VA logo and search bar. The main navigation menu includes Health, Benefits, Burials & Memorials, About VA, Resources, News Room, Locations, and Contact Us. The breadcrumb trail reads: VA » Health Care » HSR&D » Publications » Esp » Evidence Synthesis Program. The page title is "Health Services Research & Development". A left sidebar lists various program areas like "About Us", "Research Impacts", and "Funding". The main content area features the "Evidence Synthesis Program" title, a description of the program's mission, and a list of its goals. A right sidebar contains buttons for "View Published Reports", "Nominate an ESP Topic", and "ESP Reports in Progress", along with an RSS feed subscription link.

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

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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).

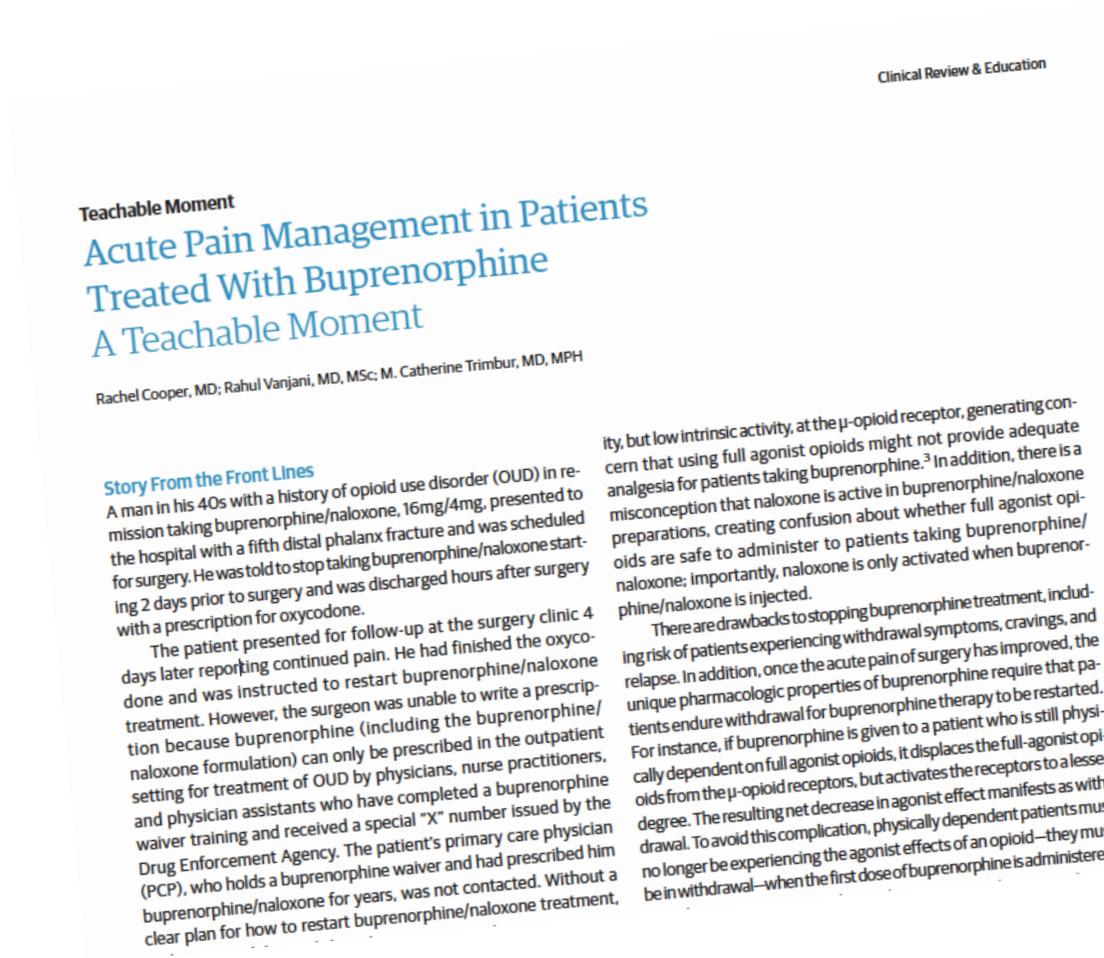
- **Background:** In September 2019, VA HSR&D will hold a State of the Art Conference (SOTA) on *Effective Management of Pain and Addiction: Strategies to Improve Opioid Safety*
- **Goals:**
 - Assess current VA burden and clinical practice
 - Review state of the evidence and relevance to VA population
 - 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



July 2019 *JAMA Internal Medicine* article discusses challenges managing acute pain in an OUD patient being treated with buprenorphine.

Cooper R, Vanjani R, Trimbur MC. Acute Pain Management in Patients Treated With Buprenorphine: A Teachable Moment. *JAMA Intern Med*. Published online July 29, 2019. doi:10.1001/jamainternmed.2019.3103

- **Opioid Use Disorder (OUD)** is “the misuse of prescribed opioid medications, use of diverted opioid medications, or use of illicitly obtained heroin.”
- **Medications for OUD (ie, Medication-Assisted Treatment)** include opioid agonists and opioid antagonists (e.g., methadone, buprenorphine/naloxone, and naltrexone)
- **Acute pain** is: “sudden-onset, time-limited pain that can vary in intensity, modulating factors, and impact on functionality and quality of life.”

Strain E. Opioid use disorder: Epidemiology, pharmacology, clinical manifestations, course, screening, assessment, and diagnosis. UpToDate. Last updated Aug 15 2019.

Saxon AJ, Strain E, Peavy KM. Approach to treating opioid use disorder. UpToDate. Last updated May 16 2019.

Kent ML, Tighe PJ, Belfer I, et al. The ACTION-APS-AAPM Pain Taxonomy (AAAPT) Multidimensional Approach to Classifying Acute Pain Conditions. *Pain Med.* 2017;18(5):947-958.

Challenges in managing acute pain in OUD patients taking medication include:

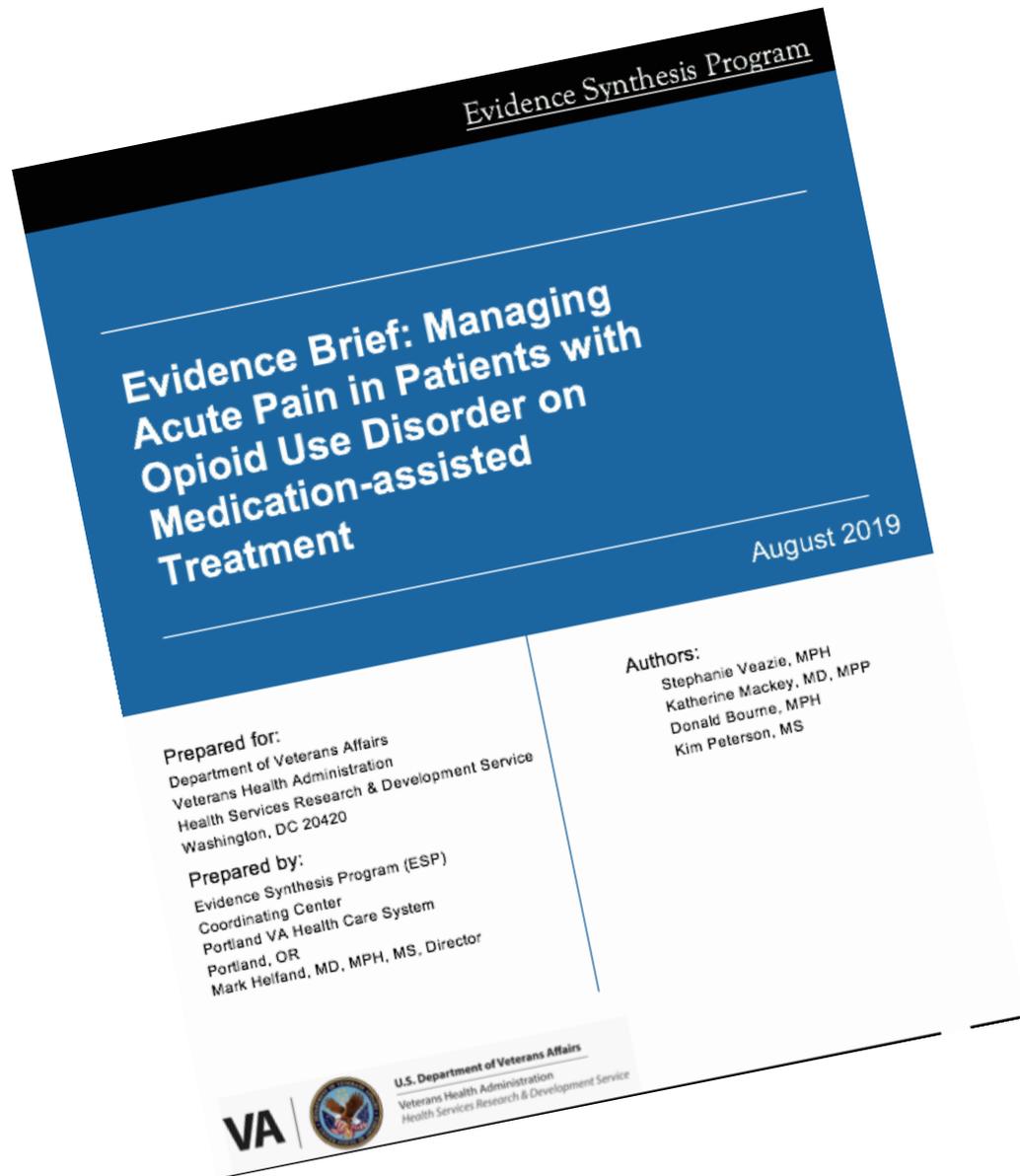
- Higher sensitivity to pain
- Need for higher doses of opioids
- Clinicians tend to undertreat pain
- Different clinical considerations for each OUD medication



Medication	Opioid receptor activity	Considerations for pain management
Methadone	Full activation (“full opioid agonist”)	<ul style="list-style-type: none"> • Unpredictable effects with dose changes • Multiple drug-drug interactions • Risk of respiratory depression and overdose • Risk of heart arrhythmia • Risk of withdrawal when discontinued
Buprenorphine/ naloxone	Partial activation (“partial opioid agonist”)	<ul style="list-style-type: none"> • May reduce the effectiveness of other opioids used at the same time for acute pain • Risk of withdrawal when discontinued
Naltrexone	Blocks the effects of opioids (“opioid antagonist”)	<ul style="list-style-type: none"> • Blocks the effects of opioids used to treat acute pain • Blocking activity may be overcome with higher opioid doses, but may increase the risk of overdose • Extended-release injectable form can last up to 30 days

Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. *Harvard review of psychiatry*. 2015;23(2):63-75.
 Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med*. 2006;144(2):127-134.
 Vickers AP, Jolly A. Naltrexone and problems in pain management. *BMJ (Clinical research ed)*. 2006;332(7534):132-133.

- **Methadone**
 - Continue/increase usual dose, potentially by dividing doses, w/wo opioids/non-opioid pain treatments
- **Buprenorphine/naloxone**
 - Continue/increase usual dose, potentially by dividing doses, w/wo other opioids/non-opioid pain treatments
 - **OR** discontinue & use other opioids instead
- **Naltrexone**
 - Use non-opioid pain treatments
 - **OR** treat with higher doses of opioids



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

Key Question 1: What are the benefits and harms of strategies to manage acute pain in adults with OUD on MAT?

Key Question 2: Do these benefits and harms vary by patient characteristics, such as MAT medication or type of acute pain (emergency condition vs planned surgery)?

Population: Adults (excluding pregnant women) with OUD taking medication (methadone, buprenorphine [with or without naloxone], or naltrexone) with acute pain

Intervention: Any pain management approach (e.g., OUD medication discontinuation or dose change, use of other opioid, or non-opioid therapies)

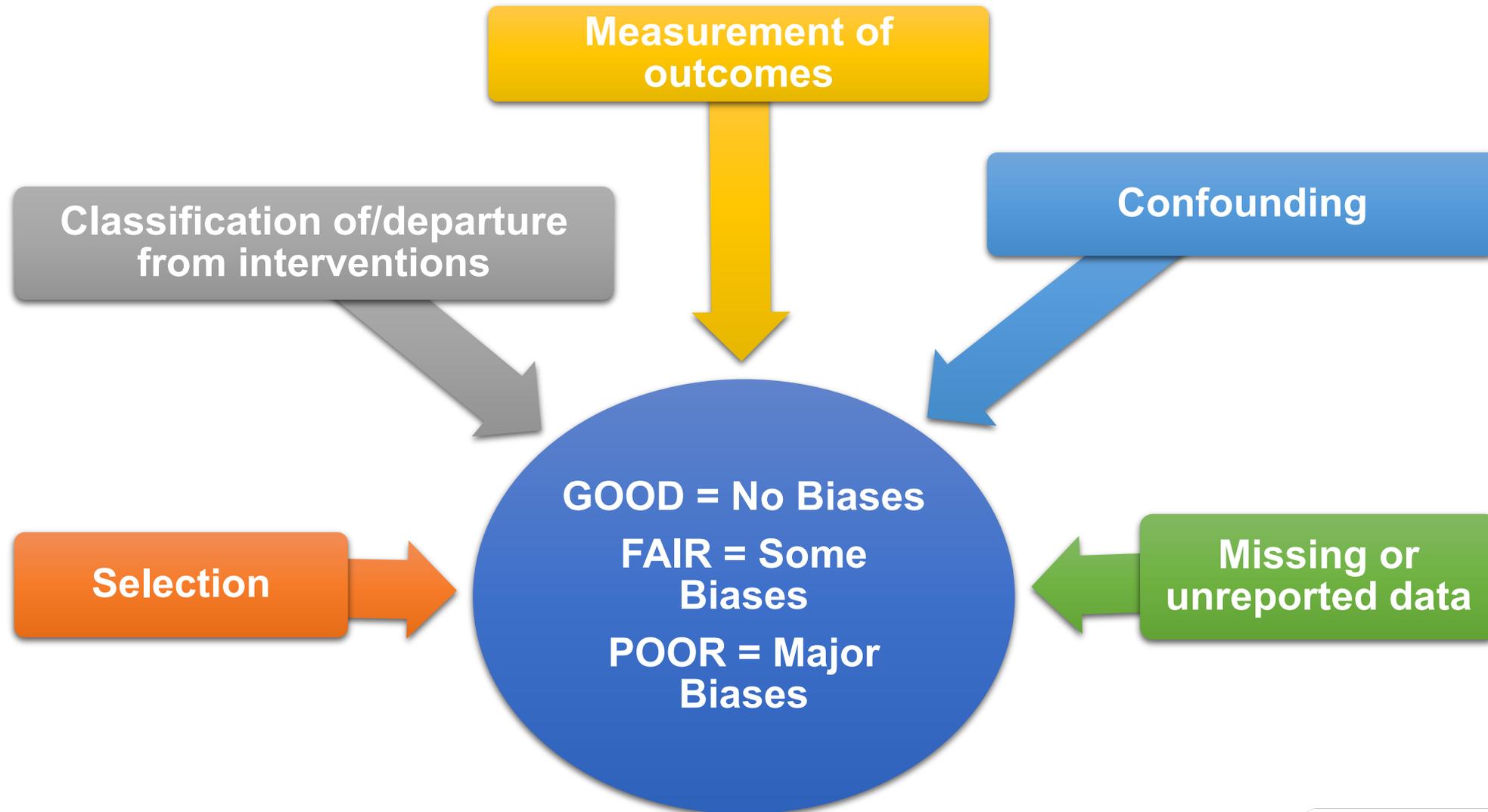
Comparator: Any

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

Timing, Setting, Study Design: Any

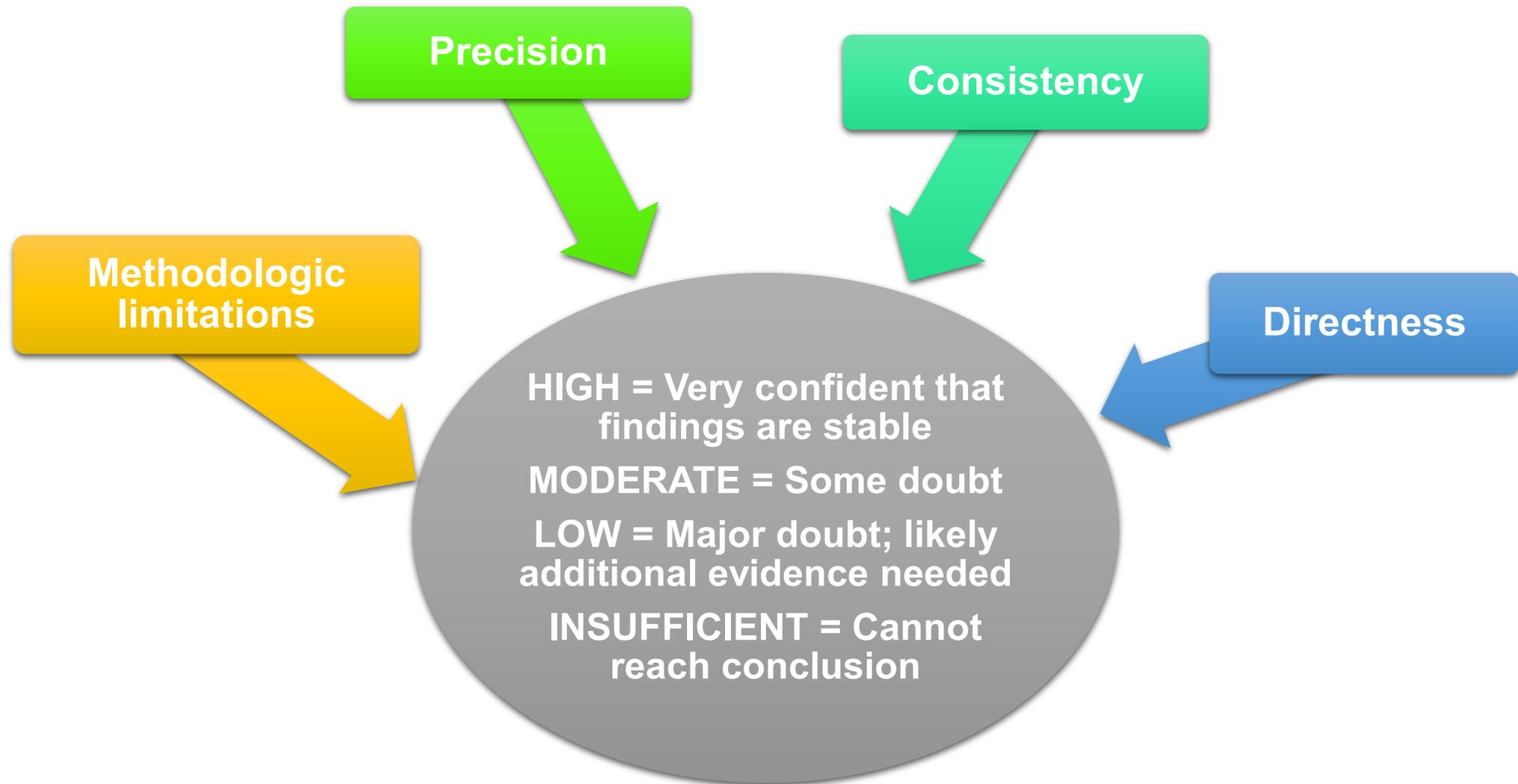
- **Search:** MEDLINE, PsycINFO, Cochrane databases and other sources (inception through April 2019) and consulted with experts
- **Study selection:** Based on eligibility criteria
- **Data abstraction:** Study characteristics (PICO) and results
- **Critical appraisal:** Use of standardized tools
- **Quality 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

Criteria for Assessing Quality & Reporting of Individual Studies

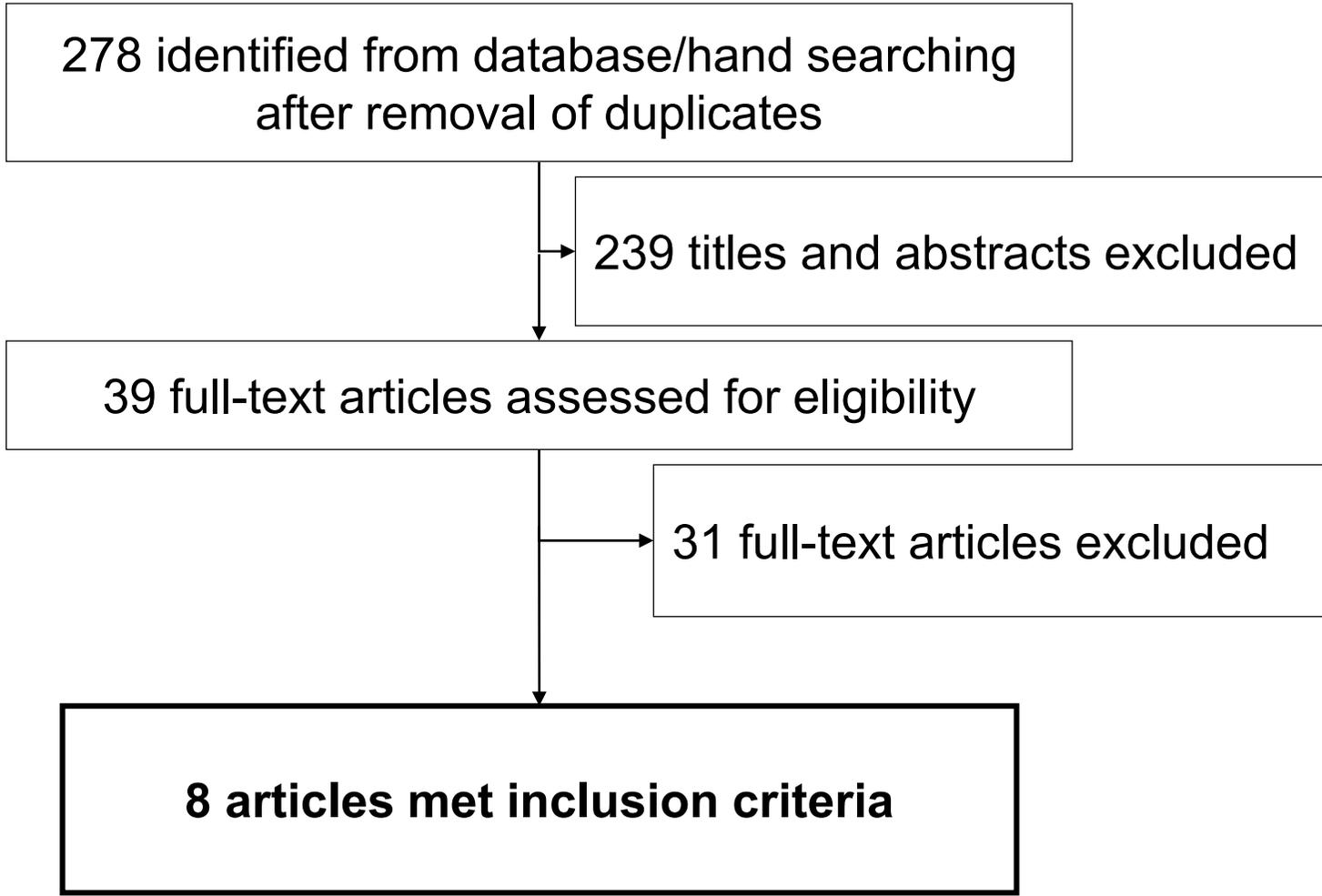


*Tool based on Cochrane's ROBINS-I Tool & CARE Checklist

Criteria for Assessing the Strength of a Body of Evidence

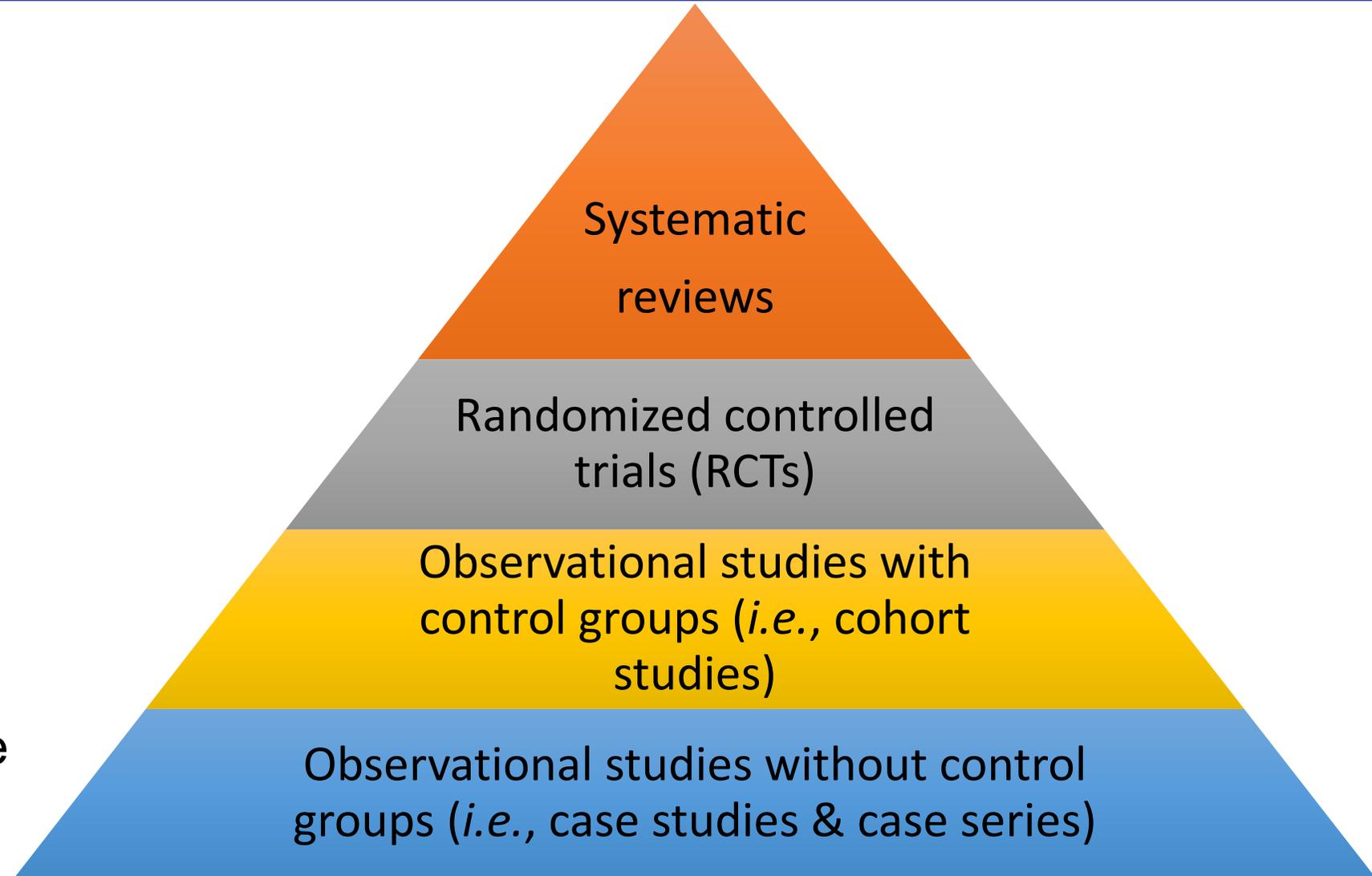


*Based on the AHRQ Methods Guide for Comparative Effectiveness Reviews



8 Included Studies

- No systematic reviews or RCTs
- No studies in Veterans or any patients taking naltrexone
- 3 observational studies with control groups & 5 without looking at methadone or buprenorphine



Studies with Control Groups (n=3)

Author, Year	Study Characteristics	Population	Comparison	Intervention	Outcomes
MacIntyre 2013	Retrospective cohort N=51 24 hours	Surgical pts	OUD pts taking methadone vs buprenorphine	<ul style="list-style-type: none"> 50%/76% of pts received OUD medication after surgery Similar, high doses of opioids in both groups Both groups used adjuvant analgesics 	<ul style="list-style-type: none"> Pain Functionality Adverse events Use of adjuvant analgesics
Hansen 2016	Retrospective cohort N=51 27 months	Surgical pts (knee & hip replacement)	OUD pts taking medication (methadone or buprenorphine/naloxone) vs non-OUD pts	<ul style="list-style-type: none"> Unclear if OUD medication was continued OUD medication group received 8x opioid dosage at discharge Similar use of adjuvant analgesics 	<ul style="list-style-type: none"> Pain Functionality Quality of life
Hines 2008	Retrospective cohort N=134 7 days	Pts with acute or surgical condition	OUD pts taking methadone vs. non-OUD pts	<ul style="list-style-type: none"> 12% of methadone pts had dose increased Similar opioid doses Similar use of adjuvant analgesics 	<ul style="list-style-type: none"> Pain reports Length of hospital stay Behavioral problems

MacIntyre PE, Russel RA, Usher KAN, Gaughwin M, Huxtable CA. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. *Anaesth Intensive Care*. 2013;41:222-230.

Hansen LE, Stone GL, Matson CA, et al. Total joint arthroplasty in patients taking methadone or buprenorphine/naloxone preoperatively for prior heroin addiction: A prospective matched cohort study. *J Arthroplasty*. 2016;31(8):1698-1701.

Hines S, Theodorou S, Williamson A, Fong D, Curry K. Management of acute pain in methadone maintenance therapy in-patients. *Drug Alcohol Rev*. 2008;27(5):519-523

- **Comparison:** Surgical pts with OUD taking methadone vs buprenorphine
- **Intervention:** 50%/76% of pts received OUD medication after surgery; similar, high doses of opioids in both groups; both used adjuvant analgesics
- **Results:**
 - Methadone and buprenorphine pts, and those that did and did not receive OUD medications the day after surgery, were similar in terms of pain, functionality, and adverse events (nausea, vomiting, sedation).
 - Those who didn't receive usual dose the day after surgery used more patient-controlled analgesia (PCA) for longer periods of time.
- **Major Limitations**
 - Differences between groups at baseline in terms of substance use (alcohol, cannabis and benzodiazepines) that were not controlled for.
 - Some patients had MAT discontinued and it is unclear why.

- **Comparison:** Knee & hip replacement pts with OUD pts taking OUD medication (methadone or buprenorphine/naloxone) vs non-OUD pts
- **Intervention:** Unclear if OUD medication was continued; OUD medication group received 8x opioid dosage at discharge; similar use of adjuvant analgesics
- **Results:**
 - Similar pain, functionality, and quality of life at 6 weeks and 1 year, except OUD medication group had worse knee range of motion at 1 year.
- **Major Limitations**
 - Unclear if OUD medication was continued for all, some, or no patients.
 - No information on which opioids were prescribed at discharge.
 - Pts on different OUD medications grouped together and no subgroup analysis.

- **Comparison:** Patients with surgical or acute condition with OUD taking methadone vs. non-OUD pts
- **Intervention:** 12% of methadone pts had dose increased; similar opioid doses; similar use of adjuvant analgesics
- **Results:**
 - Similar reports of pain
 - Pts taking methadone had longer hospital stays
 - Pts taking methadone were more likely to have behavioral problems, to discharge themselves against medical advice, and to transfer to another hospital
- **Major Limitations**
 - Pain assessments based on how often the word “pain” appears in a patient’s ward notes.
 - Unclear why some patients had methadone dose increased.

Cohort studies have **major** methodological limitations, including:

- Pain management strategies not adequately described (*i.e.*, timing, dosage)
- Inadequate methods used to assess pain severity outcomes
- Few studies reported other patient-important outcomes

Lessons learned:

- Continuing the use of buprenorphine and methadone for patients with OUD after surgery may reduce the need for additional opioids
- Patients with OUD on MAT are opioid-tolerant and need higher doses of opioid agonists for effective pain control compared to patients without OUD.
- Ineffective management of acute pain in OUD patients taking methadone can lead to disengagement in care.

Studies without Control Groups (n=5)

Author, Year	Study Characteristics	Population	Findings	Limitations
Kornfeld 2010	Case series N=5 2-9 days	Patients taking buprenorphine for chronic musculoskeletal pain before major surgery	Opioids, bupivacaine, and/or ketamine led to good pain control	<ul style="list-style-type: none"> Risk of selection & reporting bias Only a portion of patients in study had OUD and it is unclear which ones they were
Harrington 2010	Case study N=1 6 days	30-year-old man with multi-system injuries from a motorcycle accident taking buprenorphine	Full-agonist opiates could not be down-titrated without increasing pain. Buprenorphine was removed, pain stabilized, mental status improved, agitation was reduced	<ul style="list-style-type: none"> Risk of selection & reporting bias
Sartain 2002	Case study N=1 34 days	25-year-old man taking methadone then slow-release morphine prior to major trauma	Morphine, naproxen, MS contin, and ketamine not effective. Morphine and ketamine stopped and methadone was added, then pain was relieved	<ul style="list-style-type: none"> Risk of selection & reporting bias
McCormick 2013	Case study N=1 2 months	50-year-old man with acute thigh pain due to McArdle's Disease taking buprenorphine/naloxone	Higher than expected doses of hydrocodone needed for pain relief	<ul style="list-style-type: none"> Risk of selection & reporting bias Not clear if/when buprenorphine was discontinued
Tucker 1990	Case study N=1 7 days	52-year-old man taking methadone with abdominal pain who underwent surgery on his appendix	Morphine used, then switched to acetaminophen with codeine and methadone until discharge	<ul style="list-style-type: none"> Risk of selection & reporting bias Pain not reported

These studies have **critical** methodological limitations, including:

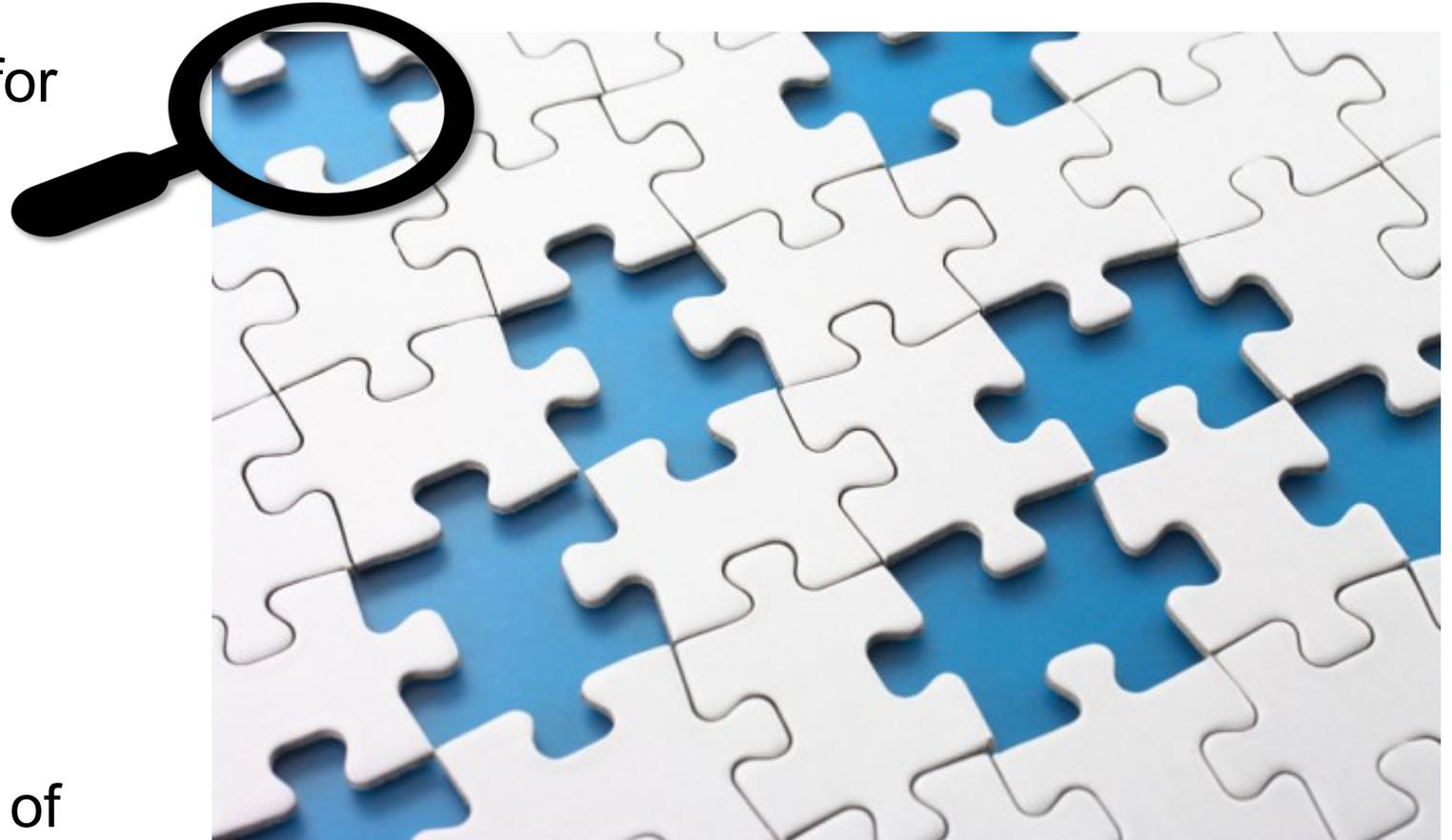
- No control groups
- Small number of patients (sometimes 1 patient)
- Rarely using measurement tools to assess outcomes
- High risk of both selection and reporting bias

Lessons learned:

- Management of acute pain in emergency conditions may involve some trial and error
- Methadone can be continued during periods of acute pain
- Higher doses of opioids may be needed for MAT patients

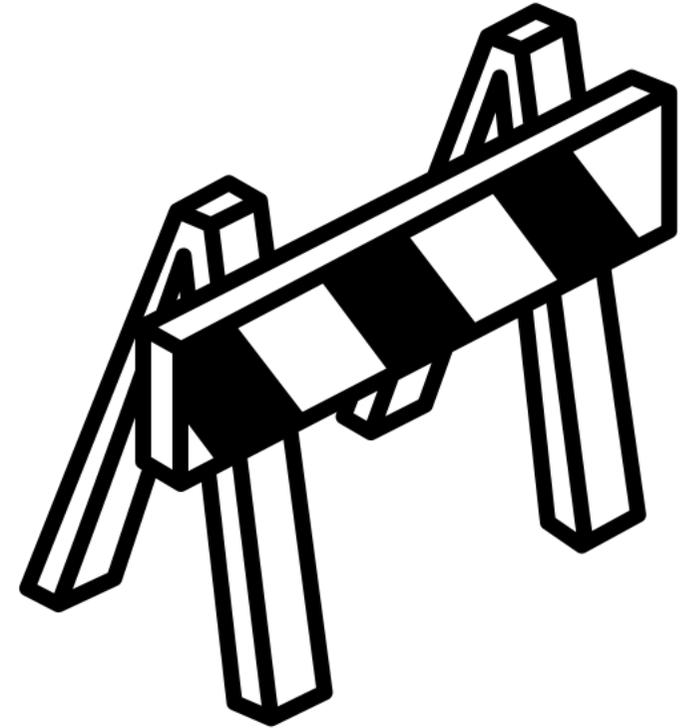
- There is **limited evidence** supporting any specific pain management strategy for OUD pts taking MAT, and our overall confidence in the findings is low.
- The evidence we did find **supports consensus-based guidelines** that:
 - Methadone can be maintained during acute pain episodes
 - Continuing buprenorphine is a reasonable approach for most patients with mild or moderate pain
- There are considerable **research gaps** that should be informed by future research

- Management of acute pain for patients taking naltrexone
- Adjuvant non-opioid pharmacological and non-pharmacologic acute pain management strategies for patients taking MAT
- Benefits and harms of adjusting the dose or timing of MAT



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- Only lower-tier evidence (cohort studies & case studies) available & that evidence had methodological limitations.
- Rapid reviews streamline systematic review methods which can result in missing eligible studies or study data.
 - However, our findings align with recent guidelines indicating we likely found most available literature.



- There is a **lack of rigorous evidence** on the management of acute pain in patients taking methadone, buprenorphine, or naltrexone.
- Although it has important limitations, the best available evidence suggests that **continuing methadone or buprenorphine during an acute pain episode is a clinically sound approach** for most patients taking these medications for OUD.
- **More research is needed** that evaluates patient outcomes following well-characterized acute pain management interventions including MAT dose and schedule adjustments and use of non-opioid pain management strategies.

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/>