Systematic Review on Opioid Treatments for Chronic Pain: Surveillance Report 2

Literature Update Period: October 2021 through November 2021

Background and Purpose

This is the second surveillance report for the 2020 report *Opioid Treatments for Chronic Pain*[1] (https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research), covering the period October 2021 through November 2021. The 2020 report addressed benefits and harms of opioids in patients with chronic pain, opioid dosing strategies, and risk assessment and risk mitigation strategies. Given the clinical and public health importance of this topic, it is important to identify new evidence that could impact practice or policy. The purpose of this update is to identify new evidence published after September 2021 and to determine how the new evidence impacts findings of the 2020 report and Surveillance Report 1, which added evidence from August 2019 through September 2021 and was published on the Agency for Healthcare Research and Quality (AHRQ) website (https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research). A subsequent update is planned for April 2022 (based on evidence published through mid-March 2022).

Scope

The scope and eligibility criteria established at the time of the original report[1] were utilized for this surveillance report; no changes were made. The report focused on use of opioids in adults for chronic pain management and addressed the following areas:

- The effectiveness and comparative effectiveness (benefits and harms, in Key Questions 1 and 2, respectively) of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy.
- The comparative effectiveness and harms of various opioid dosing strategies (Key Question 3).
- The accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse; the effectiveness of risk prediction instruments; the effectiveness of various risk mitigation strategies; and comparative effectiveness of strategies for managing patients with opioid use disorder (Key Question 4).

The full protocol for the original report, including detailed inclusion criteria using the PICOTS (populations, interventions, comparators, outcomes, timing, settings) framework (https://www.ncbi.nlm.nih.gov/books/NBK556255/table/ch4.tab1) and full Key Questions (https://www.ncbi.nlm.nih.gov/books/n/cer229/ch3/#ch3.s2), are also available on the AHRQ website (https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol) and on the PROSPERO systematic reviews registry (CRD42019127423).

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Methods

Update searches were conducted to identify evidence published after September 2021 through November 2021. Search strategies from the original report were utilized.[1] In addition, to capture articles not yet indexed in Medline®, we supplemented the original search strategies with a previously developed[2] optimized (text-word only) search in pre-Medline to identify new studies not yet indexed with Medical Subject Headings (MeSH). As in the original report, searches on electronic databases were supplemented by review of reference lists of relevant articles. Search strategies are available in Appendix A.

As in the original review, one investigator screened citations identified through searches for eligibility for full-text review. (Key Questions and inclusion criteria are available in Appendix B.) In addition, to increase efficiency of abstract review, we utilized a machine learning classifier in conjunction with a second investigator to assist in conducting dual reviews. The machine learning classifier was previously shown to have 100 percent recall for identifying eligible studies in update searches for this review.[2] The machine learning classifier screened all citations; the second investigator performed dual review on all studies that the machine learning classifier did not classify as very low probability. Any citation identified as potentially eligible by either investigator underwent full-text review to determine final eligibility.

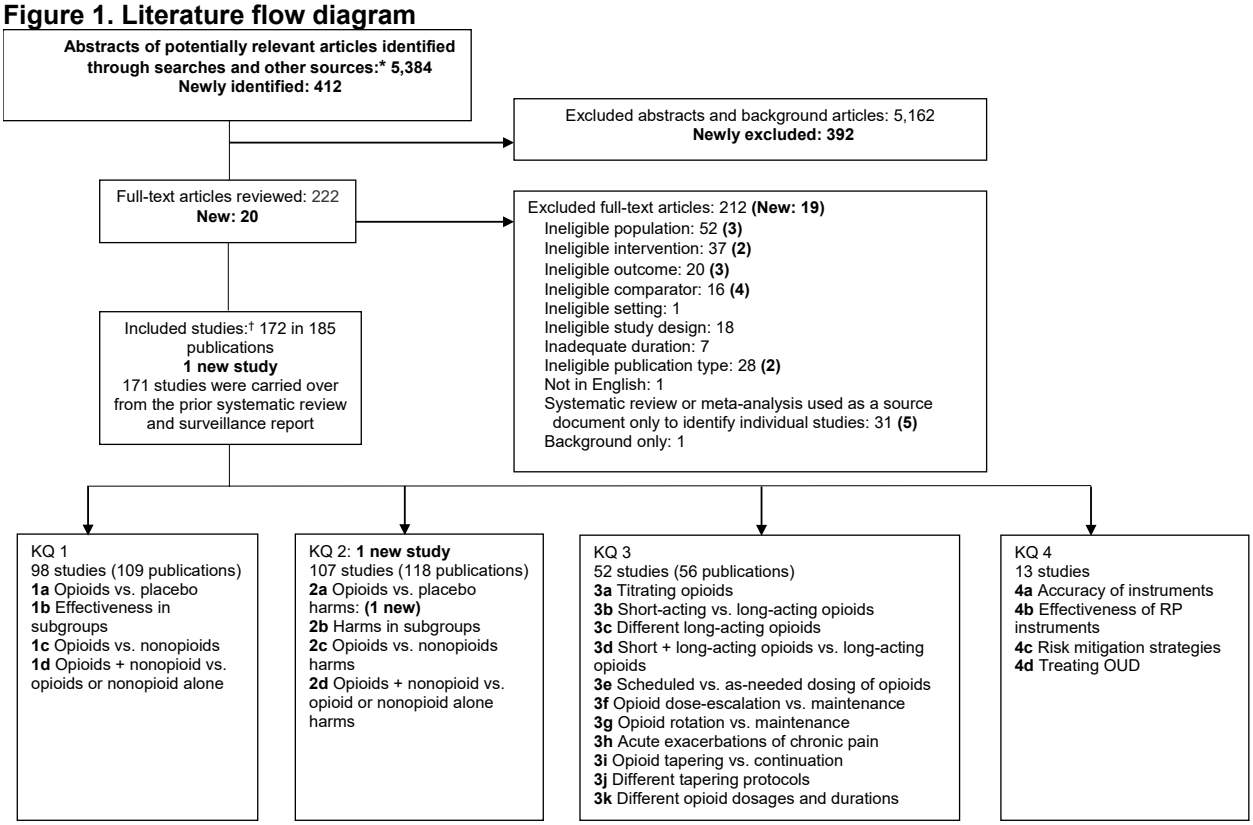
We utilized the same methods for data abstraction and quality assessment as for the original report. The decision to update meta-analyses from the original report was based on the number and sample sizes of new studies eligible for meta-analysis (meta-analysis performed if new evidence was large relative to the studies in the original meta-analysis); consistency in findings between the new studies and the original meta-analysis (meta-analysis performed if findings from new evidence appear inconsistent and new studies were appropriate for pooling based on similarity in populations, interventions, and comparisons, in order to determine whether new studies impact conclusions); or whether new evidence could impact the strength of evidence (meta-analysis performed if the strength of evidence based on the original meta-analysis was low or insufficient and new evidence could increase the strength of evidence due to increased precision, high quality, or other factors). The strength of evidence was based on the totality of evidence (evidence in the original report plus new evidence from all surveillance updates) and determined using the methods described in the original report. Changes in the strength of evidence assessments resulting from this current surveillance update are described separately from the findings reported in Surveillance Report 1.

A list of included studies identified for this update is provided in Appendix C. Evidence tables providing data from included studies are available in Appendix D, and quality assessments for each study are shown in Appendix E. A list of articles excluded at full-text review, along with reasons for exclusion, is available in Appendix F.

Results

The search for Surveillance Report 2 from October 2021 through November 2021 yielded 412 citations and identified 1 new eligible study on harms (Figure 1). It is an observational study of patients with rheumatoid arthritis that evaluated the risk of cardiovascular events among tramadol users versus non-users (Appendix D, Table D-2).[3] The study reported estimates adjusted for potential confounders but was rated fair quality, primarily due to unreported attrition and unclear blinding of data analysts to treatments (Appendix E, Table E-2). No new eligible RCTs were identified for Surveillance Report 2.

Figure 1. Literature flow diagram



Note: New studies are those added since the original systematic review and Surveillance Report 1.
* Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
† Some studies were included for multiple KQs.
Abbreviation: KQ = Key Question; OUD = opioid use disorder; RP = risk prediction.

Summary of Findings

- One new observational study was identified for Surveillance Report 2. It was consistent with the original report in finding an opioid (tramadol) associated with increased risk of all-cause mortality and cardiovascular events versus no opioid.

Table 1 provides the conclusions from the 2020 report and the new findings from studies identified in this and the prior surveillance update report; new findings from Surveillance Report 2 are indicated in the table by bolded and italicized text. Table 1 focuses on Key Questions (KQs) with new evidence since the original report; the full strength of evidence table is available in the full report (https://www.ncbi.nlm.nih.gov/books/NBK556241/bin/appi-et1.docx). New evidence identified for Surveillance Report 1 did not change any of the overall assessments that were included in the original report regarding opioids versus placebo and short-term (KQ 1a) or long-term (KQ 2a) pain or function; harms by dose or duration (KQ 2b); long- versus short-acting opioids (KQ 3b); dose escalation versus dose maintenance (KQ 3f); dose tapering versus no tapering (KQ 3i); different dose tapering strategies (KQ 3j); or buprenorphine/naloxone versus methadone for treatment of opioid use disorder (KQ 4c). For comparisons between mixed-mechanism medications and opioid agonists assessing risk of falls/fracture, hospitalization for adverse events, or cardiovascular adverse events (KQ 2b), there were no

studies in the original report. Although Surveillance Report 1 included one new cohort study on this issue, the strength of evidence was insufficient to draw conclusions.

Table 1. Summary of conclusions and assessments informed by new evidence from surveillance reports

Key Question	Conclusions From 2020 Report	Findings From Surveillance	Assessment
KQ 1a. Opioids vs. placebo, short-term pain	Opioids associated with small improvement in short-term pain • SOE: High, based on 44 to 71 RCTs	1 small (n=40) new RCT[4] found tapentadol associated with moderate improvement in short-term pain	No change in conclusions
KQ 1a. Opioids vs. placebo, short-term function	Opioids associated with small improvement in short-term function • SOE: High, based on 44 RCTs	1 small (n=40) new RCT[4] found no difference between tapentadol versus placebo in function	No change in conclusions
KQ 1a. Opioids vs. no opioid, long-term pain and function	Opioids associated with decreased likelihood of improvement in pain and no difference in function at 1 year; no differences on either outcome at 2 years • SOE: Low, based on 1 cohort study	1 cohort study[5] (n=4,172) found persistent opioid use associated with increased pain and worse function	No change in conclusions
KQ 2a. Opioids vs. placebo, short-term harms	Opioids associated with increased risk of nausea, vomiting, constipation, dizziness, somnolence, pruritus • SOE: High, based on 30 to 60 RCTs	1 small (n=40) new RCT[4] found tapentadol associated with increased risk of short-term harms vs. placebo	No change in conclusions
KQ 2a. Opioids vs. no opioids, long-term harms (all-cause mortality and cardiovascular events) ***New evidence for Surveillance Report 2***	***Opioids associated with increased risk of all-cause mortality and cardiovascular events (myocardial infarction or cardiovascular mortality)*** • ***SOE: low, based on 1 (all-cause mortality) or 3 (cardiovascular events) observational studies***	***1 retrospective cohort study[3] (n=1,320) of patients with rheumatoid arthritis found tramadol associated with increased risk of all-cause mortality and cardiovascular events vs. no tramadol***	***No change in conclusions***
KQ 2b. Harms by dose or duration	Opioids associated with increased risk of overdose, and 1 observational study found higher dose of opioids associated with increased risk of mortality • SOE: Low, based on 4 observational studies	1 case-control study[6] (2,311 cases) found higher dose of opioids associated with increased risk of mortality and overdose	No change in conclusions
KQ 2b. Mixed mechanism vs. opioid agonist and mortality, falls/fracture, hospitalization for adverse event, or cardiovascular adverse events	No studies	1 retrospective cohort study[7] (n=77,697) found tramadol associated with decreased risk of cardiovascular adverse events versus opioid agonists; there was no difference in risk of mortality, falls/fracture, or safety event hospitalizations	SOE insufficient, based on new evidence
KQ 3b. Long- vs. short-acting opioids	Long-acting opioids associated with increased risk of overdose vs. short-acting opioids • SOE: Low, based on 1 cohort study	1 case-control study[6] (2,311 cases) found long-acting opioids associated with increased risk of mortality and overdose vs. short-acting opioids	No change in conclusions

Key Question	Conclusions From 2020 Report	Findings From Surveillance	Assessment
KQ 3f. Dose escalation vs. dose maintenance	No differences between dose escalation vs. maintenance of current doses in pain, function, or risk of discontinuation due to opioid misuse • SOE: Low, based on 1 RCT	1 cohort study[8] (n=53,187) found no difference between dose escalation vs. dose maintenance	No change in conclusions
KQ 3i. Dose tapering vs. no tapering and risk of serious harms	Insufficient evidence on association between tapering and risk of overdose death, based on 1 cohort study • SOE: Insufficient	2 cohort studies[9,10] (n=113,618 and 14,596) found opioid dose reduction or discontinuation associated with increased risk of mental health crisis events (1 study[9]) or fatal or nonfatal suicide attempt (1 study[10]); evidence on the association between tapering or discontinuation and risk of overdose was inconsistent. Studies could not evaluate the indication or circumstances for dose reduction, or discontinuation methods used to support dose reductions or discontinuation, with potential for confounding	No change in conclusions
KQ 3j. Dose tapering strategies	Slower tapering associated with decreased risk of opioid-related emergency department visit or hospitalization • SOE: Low, based on 1 cohort study	1 cohort study[9] (n=113,618) found larger dose reductions associated with increased risk of harms, and 1 cohort study (n=14,596)[10] found no difference between abrupt discontinuation vs. dose reduction and discontinuation in risk of harms	No change in conclusions
KQ 4c. Risk mitigation strategies (integrated psychosocial group treatment model)	No study in the original report evaluated this risk mitigation strategy	1 small (n=27) RCT[11] of patients at high risk for opioid misuse found no differences between the integrated psychosocial group treatment model vs. usual care in risk of opioid misuse events, pain, or function, but estimates were imprecise	SOE insufficient, based on new evidence
KQ 4c. Treatment of opioid use disorder (buprenorphine/naloxone vs. methadone)	No difference between buprenorphine/naloxone vs. methadone in likelihood of study retention, pain, function, or likelihood of a positive urine drug test • SOE: Low, based on 1 RCT	1 small (n=19) poor quality RCT[12] reported no differences between buprenorphine/naloxone vs. methadone, but data were poorly reported	No change in conclusions

Abbreviations: KQ = Key Question; RCT = randomized controlled trial; SOE = strength of evidence

Evidence Details

Key Question 1: Benefits

No new studies were identified for Surveillance Report 2.

Key Question 2: Harms

Key Question 2a (Opioids Vs. Placebo): Long-Term Followup; Harms (Mortality and Cardiovascular Events)

The original report included one retrospective cohort study of patients with chronic noncancer pain (n=22,912) that found opioids associated with increased risk of all-cause mortality versus no opioids.[13] The original report also included three observational studies (2 cohort studies [N=449,036][13,14] and 1 case-control study [11,693 cases][15]) that found opioids associated with increased risk of cardiovascular events (myocardial infarction in 2 studies and cardiovascular mortality in 1 study) versus no opioid therapy in patients with chronic noncancer pain due to various causes. The strength of evidence was rated low because data were observational, with potential for residual confounding, and two of the studies were rated fair quality[13,14] (one case-control study[15] was rated good-quality). One new fair-quality retrospective cohort study identified for Surveillance Report 2 of patients with rheumatoid arthritis (n=1,320) evaluated risk of major cardiovascular events (ischemic heart disease, congestive heart failure, acute ischemic stroke, and intracranial hemorrhage) associated with tramadol use versus no tramadol.[3] It was conducted in Taiwan using a national health insurance database. Consistent with the original report, the new study found tramadol associated with increased risk of cardiovascular events (adjusted hazard ratio [HR] 1.72, 95% confidence interval [CI] 1.08 to 2.72) and mortality (adjusted HR 3.94, 95% CI 1.86 to 8.31) versus no tramadol.

Key Question 3: Dosing Strategies

No new studies were identified for Surveillance Report 2.

Key Question 4: Risk Assessment Instruments and Risk Mitigation Strategies

No new studies were identified for Surveillance Report 2.

Conclusions

One new study of opioids for chronic pain identified for Surveillance Report 2 was consistent with the findings of the original report with regard to increased risk of all-cause mortality and cardiovascular events with opioids versus no opioids. However, the strength of evidence for these outcomes remained low due to methodological limitations (observational studies with some methodological shortcomings). Surveillance Report 2 builds on Surveillance Report 1, which identified new studies on short-term benefits and harms, long-term benefits, risk mitigation strategies, dose-dependent risks of opioids, and management of opioid use disorder, all reporting results consistent with the original report. No new studies on harms of opioid discontinuations or dose reductions were identified for Surveillance Report 2. The next surveillance report is scheduled for April 2022.

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Disclaimers

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Afterword

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

This and future quarterly progress reports will provide up-to-date information about the evidence base to inform health plans, providers, purchasers, government programs, and the healthcare system as a whole on the state of the science. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov. They will be considered in the next version of the report.

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Appendix Contents

Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R), All 2020 to November 30, 2021

Key Questions 1-3

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. 9 or 10 or 11
13. 8 and 12
14. limit 13 to english language
15. 14 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
16. limit 15 to yr="2014 -Current"
17. limit 16 to (comparative study or controlled clinical trial or randomized controlled trial)
18. exp cohort studies/
19. cohort$.tw.
20. controlled clinical trial.pt.
21. epidemiologic methods/
22. limit 21 to yr=1966-1989
23. exp case-control studies/
24. (case$ and control$).tw.
25. or/18-20,22-24
26. randomized controlled trial.pt.
27. (random* or placebo* or control* or trial or blind*).ti,ab.
28. (animals not humans).sh.
29. (comment or editorial or meta-analysis or practice-guideline or review or letter).pt.
30. (26 or 27) not (28 or 29)
31. 16 and (25 or 30)
32. 17 or 31
33. limit 16 to (meta analysis or systematic reviews)
34. review.pt.
35. (medline or medlars or embase or pubmed or cochrane).tw,sh.
36. (scisearch or psychinfo or psycinfo).tw,sh.
37. (psychlit or psyclit).tw,sh.

38. cinahl.tw,sh.
39. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
40. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
41. (pooling or pooled or mantel haenszel).tw,sh.
42. (peto or dersimonian or der simonian or fixed effect).tw,sh.
43. or/35-42
44. 34 and 43
45. meta-analysis.pt.
46. meta-analysis.sh.
47. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
48. (systematic$ adj5 review$).tw,sh.
49. (systematic$ adj5 overview$).tw,sh.
50. (quantitativ$ adj5 review$).tw,sh.
51. (quantitativ$ adj5 overview$).tw,sh.
52. (quantitativ$ adj5 synthesis$).tw,sh.
53. (methodologic$ adj5 review$).tw,sh.
54. (methodologic$ adj5 overview$).tw,sh.
55. (integrative research review$ or research integration).tw.
56. or/45-55
57. 44 or 56
58. 16 and 57
59. 33 or 58
60. 32 or 59

Key Questions 4a and 4b
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15

17. Decision Support Techniques/
18. "Predictive Value of Tests"/
19. Prognosis/
20. Risk Assessment/
21. Risk Factors/
22. Proportional Hazards Models/
23. "Reproducibility of Results"/
24. "Sensitivity and Specificity"/
25. (sensitivity or specificity or accuracy).ti,ab,kf.
26. (risk and (predict$ or assess$)).ti,ab,kf.
27. or/17-26
28. 16 and 27
29. limit 28 to yr="2020 -Current"
30. limit 29 to english language

Key Question 4c
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. Contracts/
23. Patient Education as Topic/
24. Drug Overdose/
25. or/17-24
26. risk$.ti,ab,kf.

27. ("risk evaluation and mitigation" or "rems").ti,ab,kf.
28. Risk Reduction Behavior/ or Risk/
29. or/26-28
30. 16 and 25 and 29
31. limit 30 to yr="2020 -Current"
32. Naloxone/
33. naloxone.ti,ab,kf.
34. 16 and 29 and (32 or 33)
35. 31 or 34

Key Question 4d
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. (abus$ or misus$ or diversion$ or divert$).ti,ab,kf.
23. (opioid$ adj7 (contract$ or agree$)).ti,ab,kf.
24. Contracts/
25. Patient Education as Topic/
26. Drug Overdose/
27. or/17-26
28. Substance Abuse Detection/
29. Opiate Substitution Treatment/
30. Risk Management/
31. or/28-30

32. 16 and 27 and 31
33. Treatment Outcome/
34. (treatment and (outcome or strateg$ or plan$)).ti,ab,kf.
35. 32 and (33 or 34)
36. limit 35 to yr="2020 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials, 2020 to November 30, 2021

Key Questions 1-3

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. 9 or 10 or 11
13. 8 and 12
14. limit 13 to english language
15. 14 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
16. limit 15 to yr="2020 -Current"

Key Questions 4a and 4b

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.

11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Decision Support Techniques/
18. "Predictive Value of Tests"/
19. Prognosis/
20. Risk Assessment/
21. Risk Factors/
22. Proportional Hazards Models/
23. "Reproducibility of Results"/
24. "Sensitivity and Specificity"/
25. (sensitivity or specificity or accuracy).ti,ab,kf.
26. (risk and (predict$ or assess$)).ti,ab,kf.
27. or/17-26
28. 16 and 27
29. limit 28 to yr="2020 -Current"
30. limit 29 to english language

Key Question 4c
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/

20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. Contracts/
23. Patient Education as Topic/
24. Drug Overdose/
25. or/17-24
26. risk$.ti,ab,kf.
27. ("risk evaluation and mitigation" or "rems").ti,ab,kf.
28. Risk Reduction Behavior/ or Risk/
29. or/26-28
30. 16 and 25 and 29
31. limit 30 to yr="2020 -Current"
32. Naloxone/
33. naloxone.ti,ab,kf.
34. 16 and 29 and (32 or 33)
35. 31 or 34

Key Question 4d
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. (abus$ or misus$ or diversion$ or divert$).ti,ab,kf.
23. (opioid$ adj7 (contract$ or agree$)).ti,ab,kf.
24. Contracts/

25. Patient Education as Topic/
26. Drug Overdose/
27. or/17-26
28. Substance Abuse Detection/
29. Opiate Substitution Treatment/
30. Risk Management/
31. or/28-30
32. 16 and 27 and 31
33. Treatment Outcome/
34. (treatment and (outcome or strateg$ or plan$)).ti,ab,kf.
35. 32 and (33 or 34)
36. limit 35 to yr="2020 -Current"

Database: EBM Reviews - Cochrane Database of Systematic Reviews, 2020 to September 30, 2021

All Key Questions

1.chronic.ti,ab,kw.
2. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
3. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
4. opioid*.ti,ab,kw.
5. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw.
6. (or/1-3) and (4 or 5)
7. 5 not postoperative.ti.
8. limit 7 to full systematic reviews

Database: PsycINFO, 2020 to November 30, 2021

All Key Questions

1. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
2. exp pain/
3. chronic.ti,ab,id.
4. 2 and 3
5. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab.
6. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
7. 1 or 4 or 5 or 6
8. exp Opiates/
9. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,id,hw.
10. opioid*.ti,ab,id.
11. or/8-10
12. 7 and 11

13. 12 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
14. limit 13 to english language
15. limit 14 to yr="2020 -Current"
16. exp animals/
17. 15 not 16

Database: Elsevier Embase® Online, 2020 to November 30, 2021
All Key Questions
('chronic pain'/exp OR 'chronic pain' OR 'arthralgia'/exp OR arthralgia OR 'back pain'/exp OR 'back pain' OR 'backache'/exp OR backache OR 'cancer pain'/exp OR 'cancer pain' OR 'headache'/exp OR headache OR 'musculoskeletal pain'/exp OR 'musculoskeletal pain' OR 'neck pain'/exp OR 'neck pain' OR 'neuralgia'/exp OR neuralgia OR 'fibromyalgia'/exp OR fibromyalgia OR 'myalgia'/exp OR myalgia) AND ('opiate'/exp OR 'opiate' OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR methadone OR morphine OR naloxone OR oxycodone OR oxymorphone OR tapentadol) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [2014-2019]/py AND 'human'/de AND ('clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative effectiveness'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross-sectional study'/de OR 'double blind procedure'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de) NOT (postoperative OR intravenous OR intramuscular OR injection* OR intrathecal OR epidural OR block OR preoperative OR perioperative OR acute) AND [english]/lim

Optimized Search for Machine Learning

Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations, Ovid MEDLINE(R) Epub Ahead of Print, 2020 to November 30, 2021
1 ((chronic or pain) and (back or spine or spinal or cervical or radicular or neck or knee or hip)).ti,ab,kw.
2 (chronic adj2 pain).ti,ab,kw.
3 ("ankylosing spondylitis" or "neuropathic pain" or neuropathy or polyneuropathy or neuralgia or fibromyalgia or "sickle cell" or headache* or migraine or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis" or sciatica).ti,ab,kw.
4 or/1-3
5 opioid*.ti,ab,kw.
6 (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol or tramadol).ti,ab,kw.
7 5 or 6
8 4 and 7
9 8 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
10 (random* or control* or placebo or sham or trial).ti,ab,kw.
11 9 and 10

12 ((chronic or pain) and (back or spine or spinal or cervical or radicular or neck or knee or hip)).ti,ab,kw.
13 (chronic adj2 pain).ti,ab,kw.
14 ("ankylosing spondylitis" or "neuropathic pain" or neuropathy or polyneuropathy or neuralgia or fibromyalgia or "sickle cell" or headache* or migraine or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis" or sciatica).ti,ab,kw.
15 or/12-14
16 opioid*.ti,ab,kw.
17 (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol or tramadol).ti,ab,kw.
18 16 or 17
19 15 and 18
20 19 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
21 (sensitivity or specificity or accuracy).ti,ab,kf.
22 (risk and (predict$ or assess$)).ti,ab,kf.
23 20 and (21 or 22)
24 limit 23 to yr="2019 -Current"
25 ((chronic or pain) and (back or spine or spinal or cervical or radicular or neck or knee or hip)).ti,ab,kw.
26 (chronic adj2 pain).ti,ab,kw.
27 ("ankylosing spondylitis" or "neuropathic pain" or neuropathy or polyneuropathy or neuralgia or fibromyalgia or "sickle cell" or headache* or migraine or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis" or sciatica).ti,ab,kw.
28 or/25-27
29 opioid*.ti,ab,kw.
30 (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol or tramadol).ti,ab,kw.
31 29 or 30
32 28 and 31
33 32 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
34 (abuse or addict* or misuse or diversion).ti,ab,kw.
35 (management or education or screen$ or test$ or detect$).ti,ab,kw.
36 risk$.ti,ab,kw.
37 ("risk evaluation and mitigation" or "rems").ti,ab,kw.
38 naloxone.ti,ab,kw.
39 or/34-38
40 33 and 39
41 11 or 23 or 40

Appendix B. Key Questions and Inclusion and Exclusion Criteria

Key Questions

Key Question 1. Effectiveness and Comparative Effectiveness:

a. In patients with chronic pain, what is the effectiveness of opioids versus placebo or no opioid for outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?
b. How does effectiveness vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity); (2) patient demographics (e.g., age, race, ethnicity, gender, socioeconomic status); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities, and high risk for opioid use disorder); (4) the mechanism of action of opioids used (e.g., pure opioid agonists, partial opioid agonists such as buprenorphine, or drugs with mixed opioid and nonopioid mechanisms of action such as tramadol or tapentadol)?
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacologic or nonpharmacologic, including cannabis) on outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

Key Question 2. Harms and Adverse Events:

a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents,

endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?
b. How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity); (2) patient demographics; (3) patient comorbidities (including past or current opioid use disorder or at high risk for opioid use disorder); (4) the dose of opioids used and duration of therapy; (5) the mechanism of action of opioids used (e.g., pure opioid agonists, partial opioid agonists such as buprenorphine, or drugs with opioid and nonopioid mechanisms of action such as tramadol and tapentadol); (6) use of sedative hypnotics; (7) use of gabapentinoids; (8) use of cannabis?
c. In patients with chronic pain, what are the comparative risks of opioids versus nonopioid therapies on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms (e.g., depression)?
d. In patients with chronic pain, what are the comparative risks of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms (e.g., depression)?

Key Question 3. Dosing Strategies:

a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?
b. In patients with chronic pain, what is the comparative effectiveness of short-acting versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?
c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; and overdose?

d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?
e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?
f. In patients with chronic pain, what is the comparative effectiveness of opioid dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?
g. In patients with chronic pain, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life, and doses of opioids used?
h. In patients with chronic pain, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?
i. In patients with chronic pain, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and opiate withdrawal symptoms?
j. In patients with chronic pain, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, opiate withdrawal symptoms, and likelihood of opioid cessation?
k. In patients with chronic pain, what is the comparative effectiveness of different opioid dosages and durations of therapy for outcomes related to pain, function, and quality of life?

Key Question 4. Risk Assessment and Risk Mitigation Strategies:

a. In patients with chronic pain being considered for opioid therapy, what is the accuracy of instruments and tests (including metabolic and/or genetic testing) for predicting risk of opioid use disorder, abuse, or misuse, and overdose?
b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments and tests (including metabolic and/or genetic testing) on outcomes related to opioid use disorder, abuse, or misuse, and overdose?
c. In patients with chronic pain who are prescribed opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use

of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of co-prescribing of sedative hypnotics, and (11) co-prescribing of naloxone on outcomes related to opioid use disorder, abuse, or misuse, and overdose?
d. In patients with chronic pain, what is the comparative effectiveness of treatment strategies for managing patients with opioid use disorder related to prescription opioids on outcomes related to pain, function, quality of life, opioid use disorder, abuse, misuse, and overdose?

Inclusion and Exclusion Criteria

Table B-1. Inclusion and exclusion criteria

PICOTS	Include	Exclude
Populations and Conditions	All KQs: Adults (age ≥18 years) with chronic pain (pain lasting >3 months). KQs 1b, 2b: Subgroups based on specific type or cause of pain, patient demographics, patient comorbidities	• Pain at the end of life • Acute pain • Pain due to active malignancy • Pain due to sickle cell crisis • Episodic migraine
Interventions	KQs 1a-c, 2a-c: Long- or short-acting opioids (including partial agonists and dual mechanism agents) KQs 1d and 2d: Opioid + nonopioid (pharmacologic or nonpharmacologic) KQ 3: Opioid dosing strategy (initiation and titration strategy [3a], short-acting opioid [3b], long-acting opioid [3c], short plus long-acting opioid [3d], scheduled, continuous dosing [3e], opioid dose escalation [3f], opioid rotation [3g], treatments for acute exacerbations of chronic pain [3h], decreasing opioid doses or tapering off opioids [3i], tapering protocols and strategies [3j]) KQs 4a-b: Instruments, genetic metabolic tests for predicting risk of opioid use disorder, abuse, misuse, and overdose KQ 4c: Risk mitigation strategies (opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, use of abuse-deterrent formulations, consultation with mental health providers when mental health conditions are present, avoidance of benzodiazepine co-prescribing, co-prescribing of naloxone)	• Intravenous or intramuscular administration of opioids • Surgical or interventional procedures

PICOTS	Include	Exclude
Comparators	KQs 1a, 1b and 2a, 2b: Placebo or no opioid therapy KQs 1c and 2c: Nonopioid therapies (pharmacologic or nonpharmarmacologic [noninvasive]) KQs 1d and 2d: Nonopioid therapy or opioid alone KQ 3: Alternative opioid dosing strategy (alternative initiation and titration strategy [3a], long-acting opioid [3b], alternative long-acting opioid [3c], long-acting opioid alone [3d], as-needed dosing [3e], dose maintenance or use of dose thresholds [3f], maintenance of current opioid therapy [3g], other treatment for acute exacerbation of chronic pain [3h], continuation of opioids [3i], other tapering protocols or strategies [3j], other dose of same opioid [3k]) KQ 4a: Reference standard for opioid use disorder, abuse, misuse, or overdose KQ 4b: Usual care KQ 4c: Other treatment strategies	• Nonpharmacologic treatment (comparison with nonopioids included in review of nonpharmacologic treatments) • Opioid treatment
Outcomes	Pain, function, and quality of life Mood, sleep Doses of opioids used (KQs 1c and 1d) Harms: Discontinuation due to adverse events, serious adverse events, overdose, substance misuse, substance use disorder related outcomes, other harms (gastrointestinal, somnolence, pruritus, dizziness, headache, fracture, motor vehicle accidents, cardiovascular events, endocrinological effects) KQ 4a: Measures of diagnostic accuracy	• Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)
Timing	Short- (1 to <6 months), intermediate- (6 to <12 months), and long-term (≥12 months) treatment duration	• Studies or outcomes reported with <1 month duration of treatment
Setting	Outpatient settings (e.g., primary care, pain clinics, emergency rooms, urgent care clinics)	• Inpatient settings (for tapering treatment initiation in inpatient settings and continued as outpatient permitted)
Study Design	All KQs: Randomized controlled trials KQs 1 and 2: Cohort and case-control studies for long-term (≥12 months) outcomes KQs 3 and 4: Cohort studies KQ 4a: Studies reporting diagnostic accuracy English language publications	• Uncontrolled observational studies, case series, and case reports • Non-English language publications

Abbreviations: KQ=Key Question; PICOTS=Population, Interventions, Comparators, Outcomes, Timing, Setting

Appendix C. Included Studies List

1. Agnoli A, Xing G, Tancredi DJ, et al. Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids. JAMA. 2021 08 03;326(5):411-9. doi:10.1001/jama.2021.11013. PMID: 34342618.
2. Gau S-Y, Huang J-Y, Wei JC-C. Tramadol use increases mortality and risk of major adverse cardiovascular events in rheumatoid arthritis patients: evidence from a population-based cohort study. Eur J Prev Cardiol. 2021. doi:10.1093/eurjpc/zwab176. PMID: 34718505
3. Hallvik SE, El Ibrahimi S, Johnston K, et al. Patient outcomes following opioid dose reduction among patients with chronic opioid therapy. Pain. 2021 Apr 7. doi: 10.1097/j.pain.0000000000002298. PMID: 33863865.
4. Hayes CJ, Krebs EE, Hudson T, et al. Impact of opioid dose escalation on pain intensity: a retrospective cohort study. Pain. 2020 05;161(5):979-88. doi:10.1097/j.pain.0000000000001784. PMID: 31917775.
5. Hruschak V, Rosen D, Tierney M, et al. Integrated Psychosocial Group Treatment: A Randomized Pilot Trial of a Harm Reduction and Preventive Approach for Patients with Chronic Pain at Risk of Opioid Misuse. Pain Med. 2021 Feb 12;12:12. doi:10.1093/pm/pnaa461. PMID: 33576415.
6. Musich S, Wang SS, Schaeffer JA, et al. Safety Events Associated with Tramadol Use Among Older Adults with Osteoarthritis. Popul Health Manag. 2021 02;24(1):122-32. doi:10.1089/pop.2019.0220. PMID: 32119805.
7. Neumann AM, Blondell RD, Hoopsick RA, et al. Randomized clinical trial comparing buprenorphine/naloxone and methadone for the treatment of patients with failed back surgery syndrome and opioid addiction. J Addict Dis. 2020 Jan-Mar;38(1):33-41. doi:10.1080/10550887.2019.1690929. PMID: 31774028.
8. Salkar M, Ramachandran S, Bentley JP, et al. Do Formulation and Dose of Long-Term Opioid Therapy Contribute to Risk of Adverse Events among Older Adults? J Gen Intern Med. 2021 Jul 13;13:13. doi:10.1007/s11606-021-06792-8. PMID: 34258726.
9. Shah D, Zhao X, Wei W, et al. A Longitudinal Study of the Association of Opioid Use with Change in Pain Interference and Functional Limitations in a Nationally Representative Cohort of Adults with Osteoarthritis in the United States. Adv Ther. 2020 02;37(2):819-32. doi:10.1007/s12325-019-01200-4. PMID: 31875300.
10. van de Donk T, van Cosburgh J, van Dasselaar T, et al. Tapentadol treatment results in long-term pain relief in patients with chronic low back pain and associates with reduced segmental sensitization. Pain Rep. 2020 Nov-Dec;5(6):e877. doi:10.1097/PR9.0000000000000877. PMID: 33364540.

Appendix D. Evidence Tables

Shown in associated Excel files for Surveillance Report 2 at https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research.

Appendix E. Quality Assessment

Shown in associated Excel files for Surveillance Report 2 at https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research.

Appendix F. Excluded Studies List

1. Abdel Shaheed C, Maher CG, McLachlan AJ. Efficacy and Safety of Low-dose Codeine-containing Combination Analgesics for Pain: Systematic Review and Meta-Analysis. Clin J Pain. 2019 10;35(10):836-43. doi:10.1097/AJP.0000000000000746. PMID: 31318725. **Exclusion reason:** Inadequate duration

2. Adejumo AC, Akanbi O, Alayo Q, et al. Predictors, rates, and trends of opioid use disorder among patients hospitalized with chronic pancreatitis. Ann Gastroenterol. 2021;34(2):262-72. doi:10.20524/aog.2021.0579. PMID: 33654369. **Exclusion reason:** Ineligible intervention

3. Akazawa M, Igarashi A, Ebata N, et al. A Cost-Effectiveness Analysis Of Pregabalin For The Treatment Of Patients With Chronic Cervical Pain With A Neuropathic Component In Japan. J Pain Res. 2019;12:2785-97. doi:10.2147/JPR.S203712. PMID: 31576163. **Exclusion reason:** Ineligible comparator

4. Alderson SL, Farragher TM, Willis TA, et al. The effects of an evidence- and theory-informed feedback intervention on opioid prescribing for non-cancer pain in primary care: A controlled interrupted time series analysis. PLoS Med. 2021 Oct;18(10):e1003796. doi:10.1371/journal.pmed.1003796. PMID: 34606504. **Exclusion reason:** Ineligible outcome

5. Alenezi A, Yahyouche A, Paudyal V. Interventions to optimize prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review. Eur J Clin Pharmacol. 2021 Apr;77(4):467-90. doi:10.1007/s00228-020-03026-4. PMID: 33123784. **Exclusion reason:** Systematic review used as source document

6. Alhaj-Suliman SO, Milavetz G, Salem AK. Model-based Meta-analysis to Compare Primary Efficacy-endpoint, Efficacy-time Course, Safety, and Tolerability of Opioids Used in the Management of Osteoarthritic Pain in Humans. Curr Drug Metab. 2020;21(5):390-9. doi:10.2174/1389200221666200514130441. PMID: 32407270. **Exclusion reason:** Ineligible publication type

7. Anderson AB, Grazal CF, Balazs GC, et al. Can Predictive Modeling Tools Identify Patients at High Risk of Prolonged Opioid Use After ACL Reconstruction? Clin Orthop Relat Res. 2020 07;478(7):0-1618. doi:10.1097/CORR.0000000000001251. PMID: 32282466. **Exclusion reason:** Ineligible population

8. Anele UA, Wood HM, Angermeier KW. Management of Urosymphyseal Fistula and Pelvic Osteomyelitis: A Comprehensive Institutional Experience and Improvements in Pain Control. Eur Urol Focus. 2021doi:10.1016/j.euf.2021.08.008. PMID: 34479839. **Exclusion reason:** Ineligible intervention

9. Arienti C. Are there effective interventions for reducing the use of prescribed opioids in adults with chronic non-cancer pain? - A Cochrane Review summary with commentary. J Rehabil Med. 2019 Oct 03;51(9):719-20. doi:10.2340/16501977-2608. PMID: 31580469. **Exclusion reason:** Ineligible publication type

10. Bagaphou TC, Cerotto V, Gori F. Efficacy of tapentadol prolonged release for pre- and post-operative low back pain: a prospective observational study. Eur Rev Med Pharmacol Sci. 2019 Nov;23(4 Suppl):14-20. doi:10.26355/eurrev_201911_19377. PMID: 31755078. **Exclusion reason:** Ineligible intervention

11. Bagg MK, O'Hagan E, Zahara P, et al. Systematic reviews that include only published data may overestimate the effectiveness of analgesic medicines for low back pain: a systematic review and meta-analysis. J Clin Epidemiol. 2020 08;124:149-59. doi:10.1016/j.jclinepi.2019.12.006. PMID: 31816418. **Exclusion reason:** Ineligible study design

12. Bahji A, Cheng B, Gray S, et al. Reduction in mortality risk with opioid agonist therapy: a systematic review and meta-analysis. Acta Psychiatr Scand. 2019 10;140(4):313-39. doi:10.1111/acps.13088. PMID: 31419306. **Exclusion reason:** Ineligible outcome

13. Baker JF, Stokes A, Pedro S, et al. Obesity and the Risk of Incident Chronic Opioid Use in Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2020 May 31;31:31. doi:10.1002/acr.24341. PMID: 32475039. **Exclusion reason:** Ineligible outcome

14. Barrett D, Brintz CE, Zaski AM, et al. Dialectical Pain Management: Feasibility of a Hybrid Third-Wave Cognitive Behavioral Therapy Approach for Adults Receiving Opioids for Chronic Pain. Pain Med. 2021 05 21;22(5):1080-94. doi:10.1093/pm/pnaa361. PMID: 33175158. **Exclusion reason:** Ineligible study design

15. Barry AR, Chris CE. Treatment of chronic noncancer pain in patients on opioid therapy in primary care: A retrospective cohort study. Canadian Pharmacists Journal 2020 Jan-Feb;153(1):52-8. doi:10.1177/1715163519887766. PMID: 32002103. **Exclusion reason:** Ineligible comparator

16. Becker SJ, Scott K, Helseth SA, et al. Effectiveness of medication for opioid use disorders in transition-age youth: A systematic review. J Subst Abuse Treat. 2021 May 29;132:108494. doi:10.1016/j.jsat.2021.108494. PMID: 34098208. **Exclusion reason:** Systematic review used as source document

17. Belcher AM, Cole TO, Greenblatt AD, et al. Open-label dose-extending placebos for opioid use disorder: a protocol for a randomised controlled clinical trial with methadone treatment. BMJ Open. 2019 06 21;9(6):e026604. doi:10.1136/bmjopen-2018-026604. PMID: 31230007. **Exclusion reason:** Ineligible publication type

18. Beliveau A, Castilloux AM, Tanenbaum C, et al. Incidence of chronic opioid use in seniors. Pharmacoepidemiol Drug Saf. 2019;28:329. doi: 10.1002/pds.4864. PMID: 31429168. **Exclusion reason:** Ineligible publication type

19. Beliveau A, Castilloux AM, Tannenbaum C, et al. Predictors of long-term use of prescription opioids in the community-dwelling population of adults without a cancer diagnosis: a retrospective cohort study. CMAJ Open. 2021 Jan-Mar;9(1):E96-E106. doi:10.9778/cmajo.20200076. PMID: 33563639. **Exclusion reason:** Ineligible outcome

20. Bendiks S, Cheng DM, Blokhina E, et al. Pilot study of tolerability and safety of opioid receptor antagonists as novel therapies for chronic pain among persons living with HIV with past year heavy drinking: a randomized controlled trial. AIDS Care. 2021 Mar 07:1-10. doi:10.1080/09540121.2021.1896663. PMID: 33682527. **Exclusion reason:** Ineligible intervention

21. Besic N, Goricar K, Vidic Z, et al. Association of OPRM1, MIR23B,and MIR107 genetic variability with acute and chronic pain after postoperative tramadol treatment in breast cancer. J Clin Oncol. 2021;39(15 SUPPL)doi: 10.1200/JCO.2021.39.15_suppl.e24052. **Exclusion reason:** Ineligible publication type

22. Besic N, Smrekar J, Strazisar B. Chronic adverse effects after an axillary lymphadenectomy in breast cancer patients after administering weaker and stronger postoperative analgesia: results of a prospective double-blind randomized study. Breast Cancer Res Treat. 2020 Aug;182(3):655-63. doi:10.1007/s10549-020-05713-3. PMID: 32557338. **Exclusion reason:** Ineligible population

23. Bialas P, Maier C, Klose P, et al. Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: Systematic review and meta-analysis of open-label extension trials with a study duration >=26 weeks. Eur J Pain. 2020 02;24(2):265-78. doi:10.1002/ejp.1496. PMID: 31661587. **Exclusion reason:** Ineligible study design

24. Binswanger IA, Glanz JM, Faul M, et al. The Association between Opioid Discontinuation and Heroin Use: A Nested Case-Control Study. Drug Alcohol Depend. 2020 12 01;217:108248. doi:10.1016/j.drugalcdep.2020.108248. PMID: 32927194. **Exclusion reason:** Ineligible outcome

25. Blitz MJ, Rochelson B, Prasannan L, et al. Scheduled versus as-needed postpartum analgesia and oxycodone utilization. J Matern Fetal Neonatal Med. 2020 Mar 20:1-9. doi:10.1080/14767058.2020.1742318. PMID: 32193961. **Exclusion reason:** Ineligible population

26. Bobrova OP, Zyryanov SK, Shnayder NA, et al. Predicting opioid therapy safety in pancreatic cancer patients. Russian Open Medical Journal. 2020;9(4)doi: 10.15275/rusomj.2020.0417. **Exclusion reason:** Ineligible population

27. Bodden J, Joseph GB, Schiro S, et al. Opioid users show worse baseline knee osteoarthritis and faster progression of degenerative changes: a retrospective case-control study based on data from the Osteoarthritis Initiative (OAI). Arthritis Res Ther. 2021 05 22;23(1):146. doi:10.1186/s13075-021-02524-9. PMID: 34022942. **Exclusion reason:** Ineligible outcome

28. Borsari B, Li Y, Tighe J, et al. A pilot trial of collaborative care with motivational interviewing to reduce opioid risk and improve chronic pain management. Addiction. 2021 Sep;116(9):2387-97. doi:10.1111/add.15401. PMID: 33405304. **Exclusion reason:** Ineligible population

29. Boulter JH, Curry BP, Szuflita NS, et al. Protocolization of Post-Transforaminal Lumbar Interbody Fusion Pain Control with Elimination of Benzodiazepines and Long-Acting Opioids. Neurosurgery. 2020 05 01;86(5):717-23. doi:10.1093/neuros/nyz232. PMID: 31274165. **Exclusion reason:** Ineligible population

30. Boya C, Bansal D, Kanakagiri S, et al. Efficacy and Safety of Opioid Analgesics for the Management of Chronic Low Back Pain: An Evidence from Bayesian Network Meta-Analysis. Pain Physician. 2021 01;24(1):73-82. PMID: 33400430. **Exclusion reason:** Systematic review used as source document

31. Bruehl S, Burns JW, Koltyn K, et al. Are endogenous opioid mechanisms involved in the effects of aerobic exercise training on chronic low back pain? A randomized controlled trial. Pain. 2020 12;161(12):2887-97. doi:10.1097/j.pain.0000000000001969. PMID: 32569082. **Exclusion reason:** Ineligible intervention

32. Bruehl S, Burns JW, Koltyn K, et al. Does aerobic exercise training alter responses to opioid analgesics in individuals with chronic low back pain? A randomized controlled trial. Pain. 2021 08 01;162(8):2204-13. doi:10.1097/j.pain.0000000000002165. PMID: 33394881. **Exclusion reason:** Ineligible intervention

33. Bushey MA, Slaven J, Outcalt SD, et al. Design and methods of the Care Management for the Effective Use of Opioids (CAMEO) trial. Contemporary clinical trials. 2021 Jul;106:106456. doi:10.1016/j.cct.2021.106456. PMID: 34048943. **Exclusion reason:** Ineligible publication type

34. Camilleri M, Hale M, Morlion B, et al. Naldemedine improves patient-reported outcomes of opioid-induced constipation in patients with chronic non-cancer pain in the compose phase 3 studies. J Pain Res. 2021;14:2179-89. doi: 10.2147/JPR.S282738. PMID: 34295186. **Exclusion reason:** Ineligible outcome

35. Cammarota S, Conti V, Corbi G, et al. Predictors of opioid prescribing for non-malignant low back pain in an italian primary care setting. J Clin Med. 2021;10(16)doi: 10.3390/jcm10163699. PMID: 34441993. **Exclusion reason:** Ineligible outcome

36. Canseco JA, Chang M, Karamian BA, et al. Predictors of Prolonged Opioid Use After Lumbar Fusion and the Effects of Opioid Use on Patient-Reported Outcome Measures. Global Spine J. 2021:21925682211041968. doi:10.1177/21925682211041968. PMID: 34441993. **Exclusion reason:** Ineligible study design

37. Capelle JM, Reddy PJ, Nguyen AT, et al. A Prospective Assessment of Opioid Utilization Post-Operatively in Orthopaedic Sports Medicine Surgeries. Arch. 2021 Sep;9(5):503-11. doi:10.22038/abjs.2020.49306.2455. PMID: 34692932. **Exclusion reason:** Ineligible population

38. Cha Y, Jang SY, Yoo JI, et al. Effect of Opioids on All-cause Mortality and Opioid Addiction in Total Hip Arthroplasty: a Korea Nationwide Cohort Study. J Korean Med Sci. 2021 Apr 05;36(13):e87. doi:10.3346/jkms.2021.36.e87. PMID: 33821594. **Exclusion reason:** Ineligible outcome

39. Chalmers BP, Mayman DJ, Jerabek SA, et al. Reduction of Opioids Prescribed Upon Discharge After Total Knee Arthroplasty Significantly Reduces Consumption: A Prospective Study Comparing Two States. J Arthroplasty. 2021 01;36(1):160-3. doi:10.1016/j.arth.2020.07.032. PMID: 32778420. **Exclusion reason:** Ineligible population

40. Cheesman Q, DeFrance M, Stenson J, et al. The effect of preoperative education on opioid consumption in patients undergoing arthroscopic rotator cuff repair: a prospective, randomized clinical trial-2-year follow-up. J Shoulder Elbow Surg. 2020 Sep;29(9):1743-50. doi:10.1016/j.jse.2020.04.036. PMID: 32815803. **Exclusion reason:** Ineligible intervention

41. Chen C, Lo-Ciganic W-H, Winterstein AG, et al. Concurrent Use of Prescription Opioids and Gabapentinoids in Older Adults. American journal of preventive medicine. 2021doi:10.1016/j.amepre.2021.08.024. **Exclusion reason:** Ineligible outcome

42. Cooper TE, Hambleton IR, Ballas SK, et al. Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults. Cochrane Database Syst Rev. 2019(11)doi: https://doi.org/10.1002/14651858.CD012187.pub2. PMID: 31742673. **Exclusion reason:** Systematic review used as source document

43. Cooperman NA, Hanley AW, Kline A, et al. A pilot randomized clinical trial of mindfulness-oriented recovery enhancement as an adjunct to methadone treatment for people with opioid use disorder and chronic pain: Impact on illicit drug use, health, and well-being. J Subst Abuse Treat. 2021 Aug;127:108468. doi:10.1016/j.jsat.2021.108468. PMID: 34134880. **Exclusion reason:** Ineligible population

44. Corcoran KL, Bastian LA, Gunderson CG, et al. Association Between Chiropractic Use and Opioid Receipt Among Patients with Spinal Pain: A Systematic Review and Meta-analysis. Pain Med. 2020 02 01;21(2):e139-e45. doi:10.1093/pm/pnz219. PMID: 31560777. **Exclusion reason:** Ineligible intervention

45. Cozowicz C, Bekeris J, Poeran J, et al. Multimodal Pain Management and Postoperative Outcomes in Lumbar Spine Fusion Surgery: A Population-based Cohort Study. Spine. 2020 May 01;45(9):580-9. doi:10.1097/BRS.0000000000003320. PMID: 31770340. **Exclusion reason:** Ineligible outcome

46. Cumenal M, Selvy M, Kerckhove N, et al. The Safety of Medications used to Treat Peripheral Neuropathic Pain, Part 2 (Opioids, Cannabinoids and Other Drugs): review of Double-Blind, Placebo-Controlled, Randomized Clinical Trials. Expert Opin Drug Saf. 2021 Jan;20(1):51-68. doi:10.1080/14740338.2021.1842871. PMID: 33103931. **Exclusion reason:** Systematic review used as source document

47. Curry ZA, Dang MC, Sima AP, et al. Combination therapy with methadone and duloxetine for cancer-related pain: a retrospective study. Ann Palliat Med. 2021 Mar;10(3):2505-11. doi:10.21037/apm-20-1455. PMID: 33474965. **Exclusion reason:** Ineligible population

48. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ. 2021 10 12;375:n2321. doi:10.1136/bmj.n2321. PMID: 34642179. **Exclusion reason:** Systematic review used as source document

49. da Rocha AP, Mizzaci CC, Nunes Pinto ACP, et al. Tramadol for management of fibromyalgia pain and symptoms: Systematic review. Int J Clin Pract. 2020 Mar;74(3):e13455. doi:10.1111/ijcp.13455. PMID: 31799728. **Exclusion reason:** Systematic review used as source document

50. Dai J, Teng L, Zhao L, et al. The combined analgesic effect of pregabalin and morphine in the treatment of pancreatic cancer pain, a retrospective study. Cancer Med. 2021 03;10(5):1738-44. doi:10.1002/cam4.3779. PMID: 33594813. **Exclusion reason:** Ineligible population

51. Darnall BD, Mackey SC, Lorig K, et al. Comparative Effectiveness of Cognitive Behavioral Therapy for Chronic Pain and Chronic Pain Self-Management within the Context of Voluntary Patient-Centered Prescription Opioid Tapering: The

EMPOWER Study Protocol. Pain Med. 2020 08 01;21(8):1523-31. doi:10.1093/pm/pnz285. PMID: 31876947. **Exclusion reason:** Ineligible publication type

52. DeBar L, Mayhew M, Benes L, et al. A Primary Care-Based Cognitive Behavioral Therapy Intervention for Long-Term Opioid Users With Chronic Pain : A Randomized Pragmatic Trial. Ann Intern Med. 2021doi:10.7326/M21-1436. **Exclusion reason:** Ineligible comparator

53. Derry S, Wiffen PJ, Moore AR, et al. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. Cochrane Database Syst Rev. 2017;7(7)doi: https://doi.org/10.1002/14651858.CD012638. PMID: 28700091. **Exclusion reason:** Ineligible population

54. Dhokia M, Elander J, Clements K, et al. A randomized-controlled pilot trial of an online compassionate mind training intervention to help people with chronic pain avoid analgesic misuse. Psychology of Addictive Behaviors. 2020 Nov;34(7):726-33. doi:10.1037/adb0000579. PMID: 32271055. **Exclusion reason:** Ineligible intervention

55. Diasso PDK, Sjogren P, Hojsted J, et al. Patient reported outcomes and neuropsychological testing in patients with chronic non-cancer pain in long-term opioid therapy: a pilot study. Scand J Pain. 2019 07 26;19(3):533-43. doi:10.1515/sjpain-2019-0007. PMID: 31031263. **Exclusion reason:** Ineligible study design

56. Dong X, Deng J, Rashidian S, et al. Identifying risk of opioid use disorder for patients taking opioid medications with deep learning. Journal of the American Medical Informatics Association : JAMIA. 2021;28(8):1683-93. doi:10.1093/jamia/ocab043. **Exclusion reason:** Ineligible intervention

57. Drks. Experiencing the Risks of Overutilizing Opioids Among Patients With Non-Tumor Chronic Pain in Ambulant Care. Experiencing the Risks of Overutilizing Opioids Among Patients With Non-Tumor Chronic Pain in Ambulant Care - ERONA. 2020. **Exclusion reason:** Ineligible publication type

58. Duarte FCN, Ferraro L, Ferreira A, et al. A Randomized Controlled Trial Evaluating the Analgesic Effect of the Combination of Methadone With Morphine for Cancer Related Pain. Clin J Pain. 2021 09 01;37(9):664-8. doi:10.1097/AJP.0000000000000959. PMID: 34265791. **Exclusion reason:** Ineligible population

59. Edler-Buggy S, Birtwistle J, ElMokhallalati Y, et al. Regular dosing compared with as-needed dosing of opioids for management of chronic cancer pain: systematic review and meta-analysis. Pain. 2020 04;161(4):703-12. doi:10.1097/j.pain.0000000000001755. PMID: 31770157. **Exclusion reason:** Ineligible population

60. Erosa SC, Haffey PR, Mehta N, et al. Tapentadol, Buprenorphine, and Levorphanol for the Treatment of Neuropathic Pain: a Systematic Review. Curr Pain Headache Rep. 2021 Feb 25;25(3):18. doi:10.1007/s11916-020-00934-z. PMID: 33630185. **Exclusion reason:** Systematic review used as source document

61. Falk J, Thomas B, Kirkwood J, et al. PEER systematic review of randomized controlled trials: Management of chronic neuropathic pain in primary care. Can Fam Physician. 2021 05;67(5):e130-e40. doi:10.46747/cfp.6705e130. PMID: 33980642. **Exclusion reason:** Systematic review used as source document

62. Feng B, Malloch YZ, Kravitz RL, et al. Assessing the effectiveness of a narrative-based patient education video for promoting opioid tapering. Patient Educ Couns. 2021;104(2):329-36. doi: https://doi.org/10.1016/j.pec.2020.08.019. PMID: 32900605. **Exclusion reason:** Ineligible outcome

63. Ferri CM, Natoli S, Sanz-Ayan P, et al. Quality of life and functional outcomes with tapentadol prolonged release in chronic musculoskeletal pain: post hoc analysis. Pain Manag. 2021 Mar;11(2):173-87. doi:10.2217/pmt-2020-0084. PMID: 33241725. **Exclusion reason:** Ineligible publication type

64. Ferris LM, Saloner B, Jackson K, et al. Performance of a Predictive Model versus Prescription-Based Thresholds in

Identifying Patients at Risk of Fatal Opioid Overdose. Substance Use & Misuse. 2021;56(3):396-403. doi:10.1080/10826084.2020.1868520. PMID: 33446000. **Exclusion reason:** Ineligible population

65. Fishman M, Wenzel K, Scodes J, et al. Young Adults Have Worse Outcomes Than Older Adults: Secondary Analysis of a Medication Trial for Opioid Use Disorder. J Adolesc Health. 2020 12;67(6):778-85. doi:10.1016/j.jadohealth.2020.07.038. PMID: 32873500. **Exclusion reason:** Ineligible population

66. Fishman MA, Antony AB, Hunter CW, et al. The Cost of Lost Productivity in an Opioid Utilizing Pain Sample. J Pain Res. 2021;14:2347-57. doi:10.2147/JPR.S309691. PMID: 34377015. **Exclusion reason:** Ineligible comparator

67. Flynn D, Doorenbos AZ, Steffen A, et al. Pain Management Telementoring, Long-term Opioid Prescribing, and Patient-Reported Outcomes. Pain Med. 2020 02 01;21(2):266-73. doi:10.1093/pm/pnz338. PMID: 31876948. **Exclusion reason:** Ineligible population

68. Frank JW, Carey E, Nolan C, et al. Association Between Opioid Dose Reduction Against Patients' Wishes and Change in Pain Severity. J Gen Intern Med. 2020 12;35(Suppl 3):910-7. doi:10.1007/s11606-020-06294-z. PMID: 33145690. **Exclusion reason:** Ineligible comparator

69. Freo U, Furnari M, Ambrosio F, et al. Efficacy and tolerability of tapentadol for the treatment of chronic low back pain in elderly patients. Aging Clin Exp Res. 2021 Apr;33(4):973-82. doi:10.1007/s40520-020-01586-0. PMID: 32418129. **Exclusion reason:** Ineligible comparator

70. Frers A, Shaffer J, Edinger J, et al. The relationship between sleep and opioids in chronic pain patients. Journal of Behavioral Medicine. 2021 06;44(3):412-20. doi:10.1007/s10865-021-00205-1. PMID: 33609232. **Exclusion reason:** Ineligible population

71. Freynhagen R, Elling C, Radic T, et al. Safety of tapentadol compared with other opioids in chronic pain treatment: network meta-analysis of randomized controlled and withdrawal trials. Curr Med Res Opin. 2021 01;37(1):89-100. doi:10.1080/03007995.2020.1832977. PMID: 33032466. **Exclusion reason:** Systematic review used as source document

72. Friedman BW, Irizarry E, Feliciano C, et al. A randomized controlled trial of oxycodone/acetaminophen versus acetaminophen alone for emergency department patients with musculoskeletal pain refractory to ibuprofen. Acad Emerg Med. 2021 Feb 12;12:12. doi:10.1111/acem.14231. PMID: 33576545. **Exclusion reason:** Ineligible population

73. Galindo SR, da Nobrega Marinho MH, Gatchel RJ, et al. Cross-cultural adaptation of the Pain Medication Questionnaire for use in Brazil. BMC Med Res Methodol. 2019 09 23;19(1):188. doi:10.1186/s12874-019-0821-x. PMID: 31547804. **Exclusion reason:** Ineligible intervention

74. Garland EL, Hanley AW, Nakamura Y, et al. Mindfulness-oriented recovery enhancement for opioid misuse and chronic pain in primary care: A full-scale randomized controlled trial. J Gen Intern Med. 2021;36(SUPPL 1):S122-S3. doi: 10.1007/s11606-021-06830-5. PMID: 34297318. **Exclusion reason:** Ineligible publication type

75. Garland EL, Hanley AW, Riquino MR, et al. Mindfulness-oriented recovery enhancement reduces opioid misuse risk via analgesic and positive psychological mechanisms: A randomized controlled trial. J Consult Clin Psychol. 2019 Oct;87(10):927-40. doi:10.1037/ccp0000390. PMID: 31556669. **Exclusion reason:** Ineligible comparator

76. Gersch WD, Delate T, Bergquist KM, et al. Clinical Effectiveness of an Outpatient Multidisciplinary Chronic Pain Management Telementoring Service. Clin J Pain. 2021 Jul 12;12:12. doi:10.1097/AJP.0000000000000967. PMID: 34265787. **Exclusion reason:** Ineligible intervention

77. Gimbel JS, Rauck RL, Bass A, et al. Effects of naltrexone exposure observed in two phase three studies with ALO-02, an extended-release oxycodone surrounding sequestered naltrexone. J Opioid Manag.

2019 Sep/Oct;15(5):417-27. doi:10.5055/jom.2019.0530. PMID: 31849032. **Exclusion reason:** Ineligible outcome

78. Girardot K, Hollister L, Zhu TH, et al. Effectiveness of Multimodal Pain Therapy on Reducing Opioid Use in Surgical Geriatric Hip Fracture Patients. J Trauma Nurs. 2020 Jul/Aug;27(4):207-15. doi:10.1097/JTN.0000000000000516. PMID: 32658061. **Exclusion reason:** Ineligible intervention

79. Green C, Eldabe SS, Taylor RS, et al. Resource Use and Cost of Subcutaneous Nerve Stimulation Versus Optimized Medical Management in Patients With Failed Back Surgery Syndrome: An Analysis of the SubQStim Study. Neuromodulation. 2021 Apr 27;27:27. doi:10.1111/ner.13405. PMID: 33905144. **Exclusion reason:** Ineligible intervention

80. Greiner RS, Boselli D, Patel JN, et al. Opioid Risk Screening in an Oncology Palliative Medicine Clinic. JCO Oncol Pract. 2020 11;16(11):e1332-e42. doi:10.1200/OP.20.00043. PMID: 32603251. **Exclusion reason:** Ineligible population

81. Groessl EJ, Liu L, Schmalzl L, et al. Secondary Outcomes from a Randomized Controlled Trial of Yoga for Veterans with Chronic Low-Back Pain. Int J Yoga Therap. 2020 Jan 01;30(1):69-76. doi:10.17761/2020-D-19-00036. PMID: 31509451. **Exclusion reason:** Ineligible intervention

82. Gudin J, Mavroudi S, Korfiati A, et al. Reducing Opioid Prescriptions by Identifying Responders on Topical Analgesic Treatment Using an Individualized Medicine and Predictive Analytics Approach. J Pain Res. 2020;13:1255-66. doi:10.2147/JPR.S246503. PMID: 32547186. **Exclusion reason:** Ineligible intervention

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