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

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 report¹ 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).
Methods

Update searches were conducted to identify evidence published after September 2021 through November 2021. Search strategies from the original report were utilized. In addition, to capture articles not yet indexed in Medline®, we supplemented the original search strategies with a previously developed 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. 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). 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.
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

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Conclusions From 2020 Report</th>
<th>Findings From Surveillance</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ 1a. Opioids vs. placebo, short-term pain</td>
<td>Opioids associated with small improvement in short-term pain</td>
<td>1 small (n=40) new RCT found tapentadol associated with moderate improvement in short-term pain</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ 1a. Opioids vs. placebo, short-term function</td>
<td>Opioids associated with small improvement in short-term function</td>
<td>1 small (n=40) new RCT found no difference between tapentadol versus placebo in function</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ 1a. Opioids vs. no opioid, long-term pain and function</td>
<td>Opioids associated with decreased likelihood of improvement in pain and no difference in function at 1 year; no differences in function at 2 years; no differences on either outcome at 2 years</td>
<td>1 cohort study (n=4,172) found persistent opioid use associated with increased pain and worse function</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ 2a. Opioids vs. placebo, short-term harms</td>
<td>Opioids associated with increased risk of nausea, vomiting, constipation, dizziness, somnolence, pruritus</td>
<td>1 small (n=40) new RCT found tapentadol associated with increased risk of short-term harms vs. placebo</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ 2a. Opioids vs. no opioids, long-term harms (all-cause mortality and cardiovascular events)</td>
<td>Opioids associated with increased risk of all-cause mortality and cardiovascular events (myocardial infarction or cardiovascular mortality)</td>
<td>1 retrospective cohort study (n=1,320) of patients with rheumatoid arthritis found tramadol associated with increased risk of all-cause mortality and cardiovascular events vs. no tramadol</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>New evidence for Surveillance Report 2</td>
<td></td>
<td>1 retrospective cohort study (n=2,311) found long-acting opioids associated with increased risk of overdose vs. short-acting opioids</td>
<td></td>
</tr>
<tr>
<td>KQ 2b. Harms by dose or duration</td>
<td>Opioids associated with increased risk of overdose, and 1 observational study found higher dose of opioids associated with increased risk of mortality</td>
<td>1 case-control study (2,311 cases) found higher dose of opioids associated with increased risk of mortality and overdose</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ 2b. Mixed mechanism vs. opioid agonist and mortality, falls/fracture, hospitalization for adverse event, or cardiovascular adverse events</td>
<td>No studies</td>
<td>1 retrospective cohort study (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</td>
<td>SOE insufficient, based on new evidence</td>
</tr>
<tr>
<td>KQ 3b. Long- vs. short-acting opioids</td>
<td>Long-acting opioids associated with increased risk of overdose vs. short-acting opioids</td>
<td>1 case-control study (2,311 cases) found long-acting opioids associated with increased risk of mortality and overdose vs. short-acting opioids</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>Key Question</td>
<td>Conclusions From 2020 Report</td>
<td>Findings From Surveillance</td>
<td>Assessment</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>KQ 3f. Dose escalation vs. dose maintenance</td>
<td>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</td>
<td>1 cohort study(^9) (n=53,187) found no difference between dose escalation vs. dose maintenance</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ 3i. Dose tapering vs. no tapering and risk of serious harms</td>
<td>Insufficient evidence on association between tapering and risk of overdose death, based on 1 cohort study • SOE: Insufficient</td>
<td>2 cohort studies(^8,10) (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</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ 3j. Dose tapering strategies</td>
<td>Slower tapering associated with decreased risk of opioid-related emergency department visit or hospitalization • SOE: Low, based on 1 cohort study</td>
<td>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</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ 4c. Risk mitigation strategies (integrated psychosocial group treatment model)</td>
<td>No study in the original report evaluated this risk mitigation strategy</td>
<td>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</td>
<td>SOE insufficient, based on new evidence</td>
</tr>
<tr>
<td>KQ 4c. Treatment of opioid use disorder (buprenorphine/naloxone vs. methadone)</td>
<td>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</td>
<td>1 small (n=19) poor quality RCT(^12) reported no differences between buprenorphine/naloxone vs. methadone, but data were poorly reported</td>
<td>No change in conclusions</td>
</tr>
</tbody>
</table>

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 quality13,14 (one case-control study15 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.
References


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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: research associate and librarian Tracy Dana, M.L.S., research associate Christina Bougatsos, M.P.H., and student research assistant Daniel Oron, B.S., all from Oregon Health & Science University; and Task Order Officer Suchitra Iyer, Ph.D., at the Agency for Healthcare Research and Quality.

Disclaimers

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00006). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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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AHRQ appreciates appropriate acknowledgment and citation of its work. Suggested language for acknowledgment: This work is the second update report of a living systematic evidence report, Opioid Treatments for Chronic Pain, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

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 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$).tw,sh.
41. (pooling or pooled or mantel haenszel).tw,sh.
42. (peto or dersimonian or der simonian or fixed effect).tw,sh.
43. or/35-42
44. 34 and 43
45. meta-analysis.pt.
46. meta-analysis.sh.
47. (meta-analy$ 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

<table>
<thead>
<tr>
<th>PICOTS</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Populations and Conditions</td>
<td>All KQs: Adults (age ≥18 years) with chronic pain (pain lasting &gt;3 months). KQs 1b, 2b: Subgroups based on specific type or cause of pain, patient demographics, patient comorbidities</td>
<td>• Pain at the end of life • Acute pain • Pain due to active malignancy • Pain due to sickle cell crisis • Episodic migraine</td>
</tr>
<tr>
<td>Interventions</td>
<td>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)</td>
<td>• Intravenous or intramuscular administration of opioids • Surgical or interventional procedures</td>
</tr>
<tr>
<td>PICOTS</td>
<td>Include</td>
<td>Exclude</td>
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<tr>
<td>Comparators</td>
<td>KQs 1a, 1b and 2a, 2b: Placebo or no opioid therapy</td>
<td>• Nonpharmacologic treatment (comparison with nonopioids included in review of nonpharmacologic treatments)</td>
</tr>
<tr>
<td></td>
<td>KQs 1c and 2c: Nonopioid therapies (pharmacologic or nonpharmacologic)</td>
<td>• Opioid treatment</td>
</tr>
<tr>
<td></td>
<td>KQs 1d and 2d: Nonopioid therapy or opioid alone</td>
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<td></td>
<td>KQ 3: Alternative opioid dosing strategy (alternative initiation and titration strategy)</td>
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<td></td>
<td>KQs 1a, 1b and 2a, 2b: Placebo or no opioid therapy</td>
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<td></td>
<td>KQs 1c and 2c: Nonopioid therapies (pharmacologic or nonpharmacologic)</td>
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<td>KQs 1d and 2d: Nonopioid therapy or opioid alone</td>
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<td>KQ 3: Alternative opioid dosing strategy (alternative initiation and titration strategy)</td>
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<td>KQs 1a, 1b and 2a, 2b: Placebo or no opioid therapy</td>
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<td>KQs 1c and 2c: Nonopioid therapies (pharmacologic or nonpharmacologic)</td>
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<td>KQs 1d and 2d: Nonopioid therapy or opioid alone</td>
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<td>KQ 3: Alternative opioid dosing strategy (alternative initiation and titration strategy)</td>
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<td>KQ 4a: Reference standard for opioid use disorder, abuse, misuse, or overdose</td>
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<td></td>
<td>KQ 4c: Other treatment strategies</td>
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<td></td>
<td>KQs 1c and 1d: Doses of opioids used</td>
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<td></td>
<td>KQs 1e and 1f: Dose maintenance or use of dose thresholds</td>
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<td></td>
<td>KQs 1g and 1h: Treatment for acute exacerbation of chronic pain</td>
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<td>KQs 1j: Other tapering protocols or strategies</td>
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<td>KQs 1k: Other dose of same opioid</td>
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<tr>
<td></td>
<td>KQs 2a, 2b, 2c, 2d: Nonopioid therapies (pharmacologic or nonpharmacologic)</td>
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<td></td>
<td>KQs 2e and 2f: Dose maintenance or use of dose thresholds</td>
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<td></td>
<td>KQs 2g and 2h: Treatment for acute exacerbation of chronic pain</td>
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<tr>
<td></td>
<td>KQs 2i and 2j: Other tapering protocols or strategies</td>
<td></td>
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<tr>
<td></td>
<td>KQs 2k: Other dose of same opioid</td>
<td></td>
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<tr>
<td>Outcomes</td>
<td>Pain, function, and quality of life</td>
<td>• Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)</td>
</tr>
<tr>
<td></td>
<td>Mood, sleep</td>
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<td></td>
<td>Doses of opioids used (KQs 1c and 1d)</td>
<td></td>
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<td></td>
<td>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)</td>
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<tr>
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<td>KQ 4a: Measures of diagnostic accuracy</td>
<td></td>
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<tr>
<td>Timing</td>
<td>Short- (1 to &lt;6 months), intermediate- (6 to &lt;12 months) treatment duration</td>
<td>• Studies or outcomes reported with &lt;1 month duration of treatment</td>
</tr>
<tr>
<td>Setting</td>
<td>Outpatient settings (e.g., primary care, pain clinics, emergency rooms, urgent care clinics)</td>
<td>• Inpatient settings (for tapering treatment initiation in inpatient settings and continued as outpatient permitted)</td>
</tr>
<tr>
<td>Study Design</td>
<td>All KQs: Randomized controlled trials</td>
<td>• Uncontrolled observational studies, case series, and case reports</td>
</tr>
<tr>
<td></td>
<td>KQs 1 and 2: Cohort and case-control studies for long-term (≥12 months) outcomes</td>
<td>• Non-English language publications</td>
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<tr>
<td></td>
<td>KQs 3 and 4: Cohort studies</td>
<td></td>
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<td>KQ 4a: Studies reporting diagnostic accuracy</td>
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<td>English language publications</td>
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**Abbreviations:** KQ=Key Question, PICOTS=Population, Interventions, Comparators, Outcomes, Timing, Setting
Appendix C. Included Studies List


Appendix D. Evidence Tables

Shown in associated Excel files for Surveillance Report 2 at
Appendix E. Quality Assessment

Shown in associated Excel files for Surveillance Report 2 at
Appendix F. Excluded Studies List


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


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


142. Nicholas MK, Asghari A, Sharpe L, et al. Reducing the use of opioids by patients with


PMID: 32131996. Exclusion reason: Ineligible population


181. Soin A, Soin Y, Dann T, et al. Low-Dose Naltrexone Use for Patients with Chronic Regional Pain Syndrome: A Systematic


