Systematic Review on Opioid Treatments for Chronic Pain: Surveillance Report 1

Literature Update Period: August 2019 through September 2021

Background and Purpose

This is the first update for the 2020 report *Opioid Treatments for Chronic Pain*[1] (https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research), covering the period August 2019 through September 2021. This report addressed benefits and harms of opioids in patients with chronic pain, 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 since the 2020 report and to determine how the new evidence impacts findings of the 2020 report. Subsequent updates are planned for January 2022 (based on evidence published from October to December 2021) and April 2022 (based on evidence published from January to 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 with chronic pain 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 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 Agency for Healthcare Research and Quality 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 from August 2019 through September 2021. Search strategies from the original report were utilized.[1] In addition, to capture

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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 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.

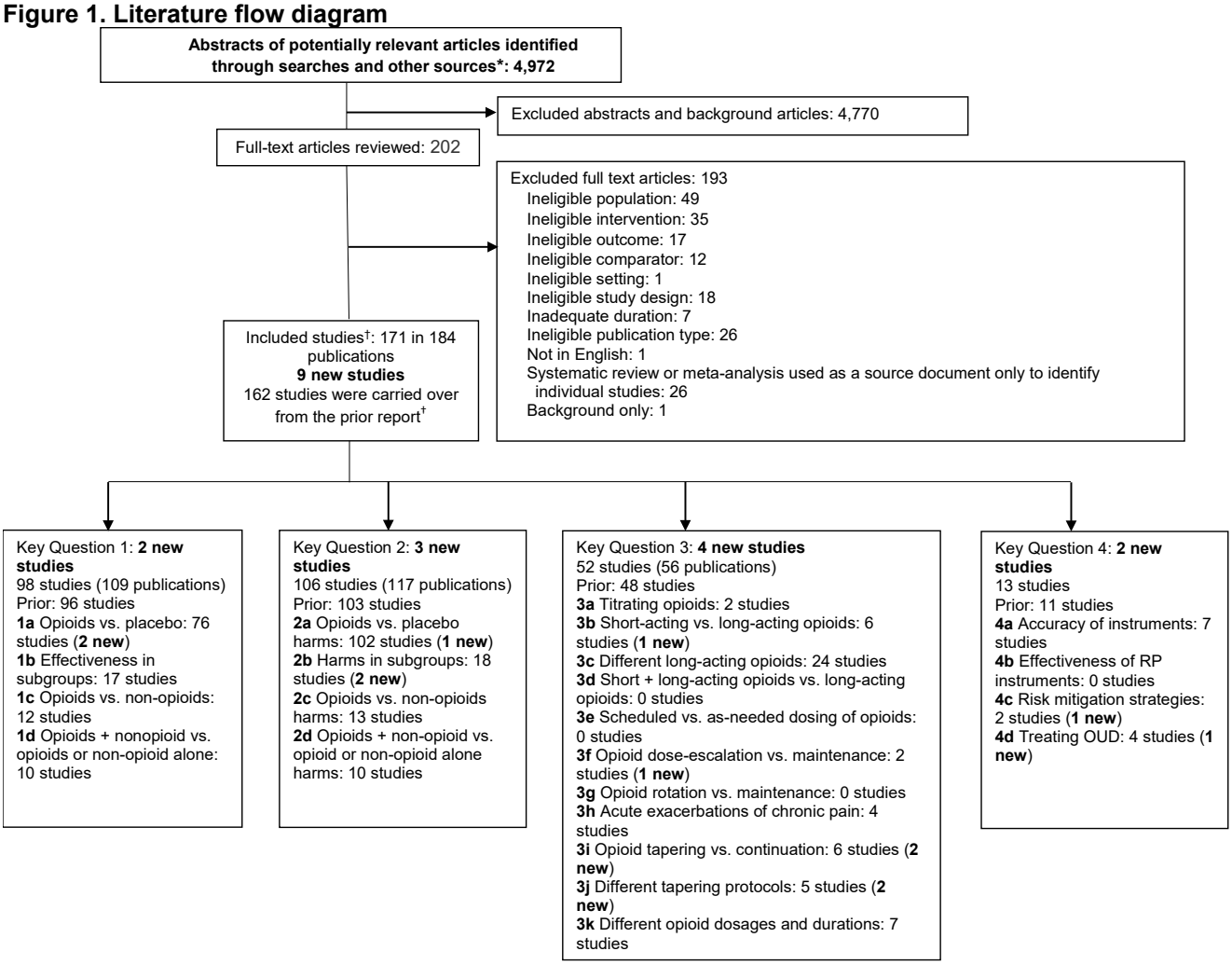
We utilized the same methods for data abstraction and quality assessment as for the original report. The decision to update meta-analyses from the original report was based on the number and sample sizes of new studies eligible for meta-analysis (meta-analysis performed if new evidence was large relative 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); 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) and determined using the methods described in the original report. We highlighted any changes in the strength of evidence assessments.

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 update search yielded 4,972 citations, and identified 9 new eligible studies (3 randomized controlled trials [RCTs] and 6 observational studies) (Figure 1). One RCT[3] compared tapentadol versus placebo for low back pain, one RCT[4] evaluated a psychosocial group treatment model in patients prescribed opioids for pain at increased risk of opioid misuse, and one RCT[5] compared buprenorphine/naloxone versus methadone in patients with opioid use disorder due to prescription opioids (Appendix D, Table D-1). The observational studies evaluated long-term outcomes of opioid therapy,[6,7] long-acting versus short-acting formulations,[8] dose escalation versus dose maintenance,[9] and outcomes associated with opioid discontinuation or tapering (Appendix D, Table D-2).[10,11] The RCT of buprenorphine/naloxone versus methadone was rated poor quality due to open label design, very high attrition, and some crossover, with incomplete reporting of outcomes. The other RCTs were rated fair quality (Appendix E, Table E-1). All of the observational studies reported adjusted estimates and were rated fair quality, primarily due to unreported attrition or missing data; in addition, it was unclear if outcomes assessors were blinded to treatments (Appendix E, Tables E-2 and E-3).

Figure 1. Literature flow diagram



Abbreviations: OUD = opioid use disorder; RP = risk prediction.
*Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
†Some studies were included for multiple Key Questions.

Summary of Findings

- Three new RCTs and six observational studies were identified for this update.
- One small new RCT did not change prior conclusions regarding small benefits of opioids versus placebo on short-term pain and function, and increased risk of short-term harms.
- One small new RCT of an interactive psychosocial group model for patients was insufficient to determine effects on pain or other outcomes due to imprecision.
- One small new RCT of buprenorphine/naloxone versus methadone for treatment of opioid use disorder associated with prescription opioids had serious methodological limitations and did not change prior conclusions that these medications are associated with similar outcomes.
- One new case-control study was consistent with the original report in finding higher doses of opioids associated with increased risk of overdose and mortality.
- Two new cohort studies found opioid discontinuation or dose reductions associated with increased risk of mental health crisis events, fatal or nonfatal suicide attempt, or overdose

versus continuation of current doses, although there was some inconsistency in results, indications for and circumstances for opioid discontinuation or dose reductions were unknown, and findings are susceptible to confounding by indication. Evidence on the association between the velocity or size of dose reductions was also somewhat mixed.

- New observational studies on long-term outcomes (opioid use not associated with improved pain or function vs. non-use), long- versus short-acting opioids (long-acting opioids associated with increased risk of overdose and mortality), and dose escalation versus maintenance (no difference between dose escalation vs. maintenance) were consistent with the findings of the original report and did not change conclusions.

Table 1 provides the conclusions from the 2020 report and the new findings from studies identified in this update report. Table 1 focuses on Key Questions with new evidence; the full strength of evidence (SOE) table is available in the full report (https://www.ncbi.nlm.nih.gov/books/NBK556241/bin/appi-et1.docx). New evidence did not change any of the overall assessments that were included in the prior report. One new cohort study was included in this update for KQ 2b; the prior report did not find any studies meeting criteria for this question. Despite new evidence, the SOE for this question is insufficient to draw conclusions.

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

Key Question	Conclusions From 2020 Report	Findings From Update	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 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 found no difference between tapentadol versus placebo in function	No change in conclusions
KQ 1a. Opioids vs. placebo, long-term outcomes	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 (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 found tapentadol associated with increased risk of short-term harms vs. placebo	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 (2,311 cases) found higher dose of opioids associated with increased risk of mortality and overdose	No change in conclusions

Key Question	Conclusions From 2020 Report	Findings From Update	Assessment
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 (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 (2,311 cases) found long-acting opioids associated with increased risk of mortality and overdose vs. short-acting opioids	No change in conclusions
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 (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 (n=113,618 and 14,596) found opioid dose reduction or discontinuation associated with increased risk of mental health crisis events (1 study) or fatal or nonfatal suicide attempt (1 study); 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 (n=113,618) found larger dose reductions associated with increased risk of harms and 1 cohort study (n=14,596) 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 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

Key Question	Conclusions From 2020 Report	Findings From Update	Assessment
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 reported no differences between buprenorphine/naloxone vs. methadone, but data were poorly reported	No change in conclusions

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

Evidence Details

Key Question 1: Benefits

Key Question 1a (Opioids Vs. Placebo)

Short-Term Followup

One new, small (n=40), fair-quality RCT of tapentadol prolonged release (mean dose 94 mg) versus placebo in patients with nonspecific chronic low back pain reported outcomes at short-term followup generally consistent with the original report.[3] Tapentadol was associated with decreased pain intensity versus placebo (mean difference −1.24 on a 0 to 10 scale, 95% confidence interval [CI] −1.37 to −1.11) and increased likelihood of experiencing a pain response (>30% reduction in pain intensity, 60% vs. 35%, relative risk [RR] 1.71, 95% CI 0.85 to 3.44 and >50% reduction, 30% vs. 5%, RR 6.00, 95% CI 0.79 to 45.42). There was no difference on the Roland Morris Disability Questionnaire (data not provided).

Long-Term Followup

One new fair-quality cohort study of patients with osteoarthritis (n=4,172) that reported outcomes through 2 years of follow-up found persistent opioid use associated with increased likelihood of extreme/severe pain interference versus no use; persistent opioid use was also associated with increased likelihood of functional limitations.[7] However, results are potentially susceptible to residual confounding related to the indication for using persistent opioids.

Key Question 2: Harms

Key Question 2a (Opioids Vs. Placebo)

Short-Term Followup

The small RCT of tapentadol (described above) reports results for short-term harms consistent with the original report.[3] Tapentadol was associated with increased risk of any adverse event and harms commonly associated with opioids such as dizziness, nausea, and pruritus. Serious adverse events were not reported.

Key Question 2b (Harms According to Dose or Duration of Opioids)

The original report included one observational study that found higher opioid dose associated with increased risk of all-cause mortality and three observational studies that found higher opioid dose associated with increased risk of overdose. Evidence from one new fair-quality case-control study of Medicare patients (2,311 cases with matched controls) was generally consistent with these findings.[8] Among patients prescribed opioids, it reported higher opioid doses associated

with increased risk of mortality (vs. <20 morphine mg equivalents [MME], 20 to 50 MME associated with adjusted odds ratio [OR] 1.61, 95% CI 1.24 to 2.10 and ≥50 MME associated with adjusted OR 1.99, 95% CI 1.28 to 3.10). For overdose, 20–50 MME was associated with increased risk versus less than 20 MME (adjusted OR 2.39, 95% CI 0.89 to 6.46). The estimate for 50 MME or more did not indicate increased risk but was very imprecise (adjusted OR 1.01, 95% CI 0.30 to 3.46).

Key Question 2b (Harms According to Mechanism of Action of Opioids Used)

One new fair-quality retrospective cohort study (n=77,697) of patients with Medicare supplement insurance found tramadol (a mixed mechanism agent) associated with similar risk of all-cause mortality, falls/hip fractures, and safety event hospitalizations compared with opioid agonists.[6] Tramadol was associated with slightly decreased risk of cardiovascular disease hospitalizations when compared with opioid agonists, but higher risk of hospitalization when compared with no opioids (for tramadol vs. no opioid, adjusted hazard ratio [HR] 1.41, 95% CI 1.32 to 1.51 and HR 1.66, 95% CI 1.55 to 1.77 for tramadol vs. opioid agonists). The original report did not include any studies comparing mixed mechanism agents versus opioids directly on these outcomes.

Key Question 3: Dosing Strategies

Key Question 3b (Long- Vs. Short-Acting Opioids)

Consistent with a cohort study included in the original report,[12] one new fair-quality case-control study of veterans (2,311 cases with matched controls) found long-acting opioids associated with increased risk of overdose (adjusted OR 13.00, 95% CI 1.30 to 130.16) and all-cause mortality (adjusted OR 1.61, 95% CI 0.89 to 2.89).

Key Question 3f (Dose Escalation Vs. Maintenance)

One new fair-quality cohort study (n=53,187) compared outcomes associated with dose escalation (≥20% increase in daily opioid dose) versus dose maintenance in veterans with chronic pain on long-term opioid therapy.[9] In a propensity-matched analysis, there were no differences in pain intensity between dose escalation versus dose maintenance at 90 or 180 days. Findings are consistent with a randomized trial[13] included in the original report, but due to the observational design are potentially susceptible to residual confounding related to the indication for dose escalation.

Key Question 3i (Opioid Tapering Vs. No Tapering)

In the original report, evidence on serious harms associated with opioid tapering versus no tapering was limited to one poor-quality cohort study.[14] Two new fair-quality cohort studies evaluated serious harms associated with opioid dose tapering or discontinuation.[10,11] One large (n=113,618) cohort study of commercially insured and Medicare Advantage patients on stable higher doses (mean ≥50 MME) found periods with opioid tapering (defined as ≥15% reduction in mean daily dose) associated with increased risk of overdose events versus periods without tapering (9.3 vs. 5.5 events per 100 person-years, adjusted incidence rate ratio [IRR] 1.68, 95% CI 1.53 to 1.85).[10] Tapering was also associated with increased likelihood of mental health crisis events (7.6 vs. 3.3 per 100 person-years, adjusted IRR 2.28, 95% CI 1.96 to 2.65). A study of Oregon Medicaid recipients (n=14,596) prescribed long-term opioid therapy evaluated various

patterns of opioid discontinuation or tapering (abrupt discontinuation, dose reduction and discontinuation, or dose reduction without discontinuation) versus stable or increased doses of opioids.[11] Although abrupt discontinuation and dose reduction and discontinuation were both associated with increased risk of fatal or nonfatal suicide attempt when compared with stable or increased doses (adjusted HR 3.63, 95% CI 1.42 to 9.25 and 4.47, 95% CI 1.68 to 11.88, respectively), dose reduction without discontinuation was not associated with increased suicide risk (adjusted HR 1.29, 95% CI 0.48 to 3.45). In contrast to the study of Medicare Advantage patients, the study of Oregon Medicaid recipients found that all of the opioid discontinuation and tapering strategies were associated with decreased risk of overdose (with adjusted HRs ranging from 0.36 to 0.62). An important limitation of the studies is that the indications and circumstances for opioid dose reductions or discontinuation were not known but represent important potential sources of confounding. In addition, the studies were not able to describe or assess methods used to support tapering.

Key Question 3j (Opioid Tapering Strategies)

In the original report, one observational study found more rapid opioid discontinuation among Medicaid recipients associated with increased risk of emergency department visit or hospitalization with a diagnosis of opioid poisoning or substance use disorder.[15] Two new cohort studies of tapering addressing Key Question 3i also evaluated different opioid tapering strategies and were included for this Key Question. One of the new studies found larger dose reductions associated with increased risk of harms.[10] For every 10 percent increase in the maximum monthly dose reduction velocity, the adjusted IRR for overdose was 1.09 (95% CI 3.2 to 5.3) and for mental health events was 1.18 (95% CI 1.14 to 1.21). The other new cohort study was somewhat inconsistent with the original report; it found abrupt discontinuation associated with similar increased risk of suicide (fatal or nonfatal) but similar decreased risk of overdose events when compared with dose reduction and discontinuation.[11]

Key Question 4: Risk Assessment Instruments and Risk Mitigation Strategies

Key Question 4c (Risk Mitigation Strategies)

One new, small (n=27), fair-quality RCT evaluated an interactive psychosocial group treatment model versus usual care for patients with chronic pain prescribed opioid therapy and at high risk of opioid misuse (based on a score >4 on the Opioid Risk Tool).[4] The treatment model used principles encompassing motivational interviewing, behavioral change, self-management, and empowerment, as well as psychological approaches and patient education. At 9 weeks, results for likelihood of misuse behaviors (adjusted OR 0.69, p=0.16) and pain interference severity (mean difference −9.20 on a 0 to 70 scale, 95% CI −20.25 to 1.85) favored the psychosocial group treatment model but were imprecise (not statistically significant). There was no difference in pain severity, and harms were not reported.

Key Question 4d (Treatment Strategies for Managing Patients With Opioid Use Disorder Related to Prescription Opioids)

One new, small (n=19) RCT evaluated buprenorphine/naloxone versus methadone for treatment of opioid use disorder related to prescription opioids in patients with post-surgical chronic low back pain.[5] The trial was rated poor quality; outcomes were not reported well, but

did not indicate differences in risk of drug use (cannabis, cocaine, benzodiazepines, or non-prescribed opioids), pain, functioning, or depression between the two groups. Harms were not reported by treatment group. One trial[16] in the original report found no difference between buprenorphine versus methadone in likelihood of study retention, pain, function, or likelihood of a positive urine drug test.

Conclusions

New evidence on opioids for chronic pain identified for this update was consistent with the findings of the original report with regard to benefits and harms and risk mitigation strategies. Although new observational studies found opioid discontinuations or dose reductions associated with serious harms, the evidence remains insufficient because the indications for and circumstances of dose reductions or discontinuations were unknown, with potential for confounding by indication if people who underwent dose reductions or discontinuations were at higher risk for serious harms; in addition, there was some inconsistency in findings. The next surveillance report is scheduled for January 2022.

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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.

Suggested citation: Chou R, Selph S, Wagner J, Ahmed AY, Jungbauer R, Mauer K, Shetty KD. Systematic Review on Opioid Treatments for Chronic Pain: Surveillance Report 1. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 22-EHC006. Rockville, MD: Agency for Healthcare Research and Quality; January 2022. DOI: https://doi.org/10.23970/AHRQEPCSURVEILLANCEOPIOIDCHRONIC. Posted final reports are located on the Effective Health Care Program search page.

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 September 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 September 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 September 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 September 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 September 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?

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: https://dx.doi.org/10.1001/jama.2021.11013. PMID: 34342618.
2. Hallvik SE, El Ibrahimi S, Johnston K, et al. Patient outcomes following opioid dose reduction among patients with chronic opioid therapy. Pain. 2021 Apr 7doi: 10.1097/j.pain.0000000000002298. PMID: 33863865.
3. 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: https://dx.doi.org/10.1097/j.pain.0000000000001784. PMID: 31917775.
4. 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: https://dx.doi.org/10.1093/pm/pnaa461. PMID: 33576415.
5. 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: https://dx.doi.org/10.1089/pop.2019.0220. PMID: 32119805.
6. 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: https://dx.doi.org/10.1080/10550887.2019.1690929. PMID: 31774028.
7. 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: https://dx.doi.org/10.1007/s11606-021-06792-8. PMID: 34258726.
8. 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: https://dx.doi.org/10.1007/s12325-019-01200-4. PMID: 31875300.
9. 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: https://dx.doi.org/10.1097/PR9.0000000000000877. PMID: 33364540.

Appendix D. Evidence Tables

Shown in associated Excel files for surveillance report 1 at https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research.

Appendix E. Quality Assessment

Shown in associated Excel files for surveillance report 1 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: https://dx.doi.org/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: https://dx.doi.org/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: https://dx.doi.org/10.2147/JPR.S203712. PMID: 31576163. **Exclusion reason:** Ineligible comparison

4. 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: https://dx.doi.org/10.2174/1389200221666200514130441. PMID: 32407270. **Exclusion reason:** Ineligible publication type

5. 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. 2020 07;478(7):0-1618. doi: https://dx.doi.org/10.1097/CORR.0000000000001251. PMID: 32282466. **Exclusion reason:** Ineligible population

6. 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: https://dx.doi.org/10.1016/j.euf.2021.08.008. PMID: 34479839. **Exclusion reason:** Ineligible intervention

7. 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: https://dx.doi.org/10.2340/16501977-2608. PMID: 31580469. **Exclusion reason:** Ineligible publication type

8. 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: https://dx.doi.org/10.26355/eurrev_201911_19377. PMID: 31755078. **Exclusion reason:** Ineligible intervention

9. 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: https://dx.doi.org/10.1016/j.jclinepi.2019.12.006. PMID: 31816418. **Exclusion reason:** Ineligible study design

10. 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: https://dx.doi.org/10.1111/acps.13088. PMID: 31419306. **Exclusion reason:** Ineligible outcome

11. 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: https://dx.doi.org/10.1002/acr.24341. PMID: 32475039. **Exclusion reason:** Ineligible outcome

12. 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: https://dx.doi.org/10.1093/pm/pnaa361. PMID: 33175158. **Exclusion reason:** Ineligible study design

13. Barry AR, Chris CE. Treatment of chronic noncancer pain in patients on opioid therapy in primary care: A retrospective cohort study. Can Pharm J. 2020 Jan-Feb;153(1):52-8. doi: https://dx.doi.org/10.1177/1715163519887766. PMID: 32002103. **Exclusion reason:** Ineligible comparison

14. 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: https://dx.doi.org/10.1016/j.jsat.2021.108494. PMID: 34098208. **Exclusion reason:** Systematic review used as source document

15. 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: https://dx.doi.org/10.1136/bmjopen-2018-026604. PMID: 31230007. **Exclusion reason:** Ineligible publication type

16. 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

17. 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: https://dx.doi.org/10.9778/cmajo.20200076. PMID: 33563639. **Exclusion reason:** Ineligible outcome

18. 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: https://dx.doi.org/10.1080/09540121.2021.1896663. PMID: 33682527. **Exclusion reason:** Ineligible intervention

19. 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

20. 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: https://dx.doi.org/10.1007/s10549-020-05713-3. PMID: 32557338. **Exclusion reason:** Ineligible population

21. 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: https://dx.doi.org/10.1002/ejp.1496. PMID: 31661587. **Exclusion reason:** Ineligible study design

22. 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: https://dx.doi.org/10.1016/j.drugalcdep.2020.108248. PMID: 32927194. **Exclusion reason:** Ineligible outcome

23. 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: https://dx.doi.org/10.1080/14767058.2020.1742318. PMID: 32193961. **Exclusion reason:** Ineligible population

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

25. 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: https://dx.doi.org/10.1186/s13075-021-02524-9. PMID: 34022942. **Exclusion reason:** Ineligible outcome

26. 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: https://dx.doi.org/10.1111/add.15401. PMID: 33405304. **Exclusion reason:** Ineligible population

27. 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: https://dx.doi.org/10.1093/neuros/nyz232. PMID: 31274165. **Exclusion reason:** Ineligible population

28. 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

29. 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: https://dx.doi.org/10.1097/j.pain.0000000000001969. PMID: 32569082. **Exclusion reason:** Ineligible intervention

30. 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: https://dx.doi.org/10.1097/j.pain.0000000000002165. PMID: 33394881. **Exclusion reason:** Ineligible intervention

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

32. 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

33. 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 of Clin Med. 2021;10(16)doi: 10.3390/jcm10163699. PMID: 34441993. **Exclusion reason:** Ineligible outcome

34. 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: https://dx.doi.org/10.1177/21925682211041968. PMID: 34488470. **Exclusion reason:** Ineligible study design

35. 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: https://dx.doi.org/10.1016/j.arth.2020.07.032. PMID: 32778420. **Exclusion reason:** Ineligible population

36. 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: https://dx.doi.org/10.1016/j.jse.2020.04.036. PMID: 32815803. **Exclusion reason:** Ineligible intervention

37. Cooper TE, Hambleton IR, Ballas SK, et al. Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults. Cochrane Database Syst Rev. 2020(2) PMID: 31742673. **Exclusion reason:** Systematic review used as source document

38. 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: https://dx.doi.org/10.1016/j.jsat.2021.108468. PMID: 34134880. **Exclusion reason:** Ineligible population

39. 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: https://dx.doi.org/10.1093/pm/pnz219. PMID: 31560777. **Exclusion reason:** Ineligible intervention

40. 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: https://dx.doi.org/10.1097/BRS.0000000000003320. PMID: 31770340. **Exclusion reason:** Ineligible outcome

41. 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: https://dx.doi.org/10.1080/14740338.2021.1842871. PMID: 33103931. **Exclusion reason:** Systematic review used as source document

42. 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: https://dx.doi.org/10.21037/apm-20-1455. PMID: 33474965. **Exclusion reason:** Ineligible population

43. 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: https://dx.doi.org/10.1111/ijcp.13455. PMID: 31799728. **Exclusion reason:** Systematic review used as source document

44. 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: https://dx.doi.org/10.1002/cam4.3779. PMID: 33594813. **Exclusion reason:** Ineligible population

45. 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: https://dx.doi.org/10.1093/pm/pnz285. PMID: 31876947. **Exclusion reason:** Ineligible publication type

46. Derry S, Wiffen PJ, Moore AR, et al. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. Cochrane Database Syst Rev. 2020(2) PMID: 28700091. **Exclusion reason:** Ineligible population

47. 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. Psychol Addict Behav. 2020 Nov;34(7):726-33. doi: https://dx.doi.org/10.1037/adb0000579. PMID: 32271055. **Exclusion reason:** Ineligible intervention

48. 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: https://dx.doi.org/10.1515/sjpain-2019-0007. PMID: 31031263. **Exclusion reason:** Ineligible study design

49. 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: https://dx.doi.org/10.1097/AJP.0000000000000959. PMID: 34265791. **Exclusion reason:** Ineligible population

50. 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: https://dx.doi.org/10.1097/j.pain.0000000000001755. PMID: 31770157. **Exclusion reason:** Ineligible population

51. 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: https://dx.doi.org/10.1007/s11916-020-00934-z. PMID: 33630185. **Exclusion reason:** Systematic review used as source document

52. 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: https://dx.doi.org/10.46747/cfp.6705e130. PMID: 33980642. **Exclusion reason:** Systematic review used as source document

53. 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. PMID: 32900605. **Exclusion reason:** Ineligible outcome

54. 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: https://dx.doi.org/10.2217/pmt-2020-0084. PMID: 33241725. **Exclusion reason:** Ineligible publication type

55. 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. Subst Use Misuse. 2021;56(3):396-403. doi: https://dx.doi.org/10.1080/10826084.2020.1868520. PMID: 33446000. **Exclusion reason:** Ineligible population

56. 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: https://dx.doi.org/10.1016/j.jadohealth.2020.07.038. PMID: 32873500. **Exclusion reason:** Ineligible population

57. 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: https://dx.doi.org/10.2147/JPR.S309691. PMID: 34377015. **Exclusion reason:** Ineligible comparison

58. 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: https://dx.doi.org/10.1093/pm/pnz338. PMID: 31876948. **Exclusion reason:** Ineligible population

59. 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: https://dx.doi.org/10.1007/s11606-020-06294-z. PMID: 33145690. **Exclusion reason:** Ineligible comparison

60. 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: https://dx.doi.org/10.1007/s40520-020-01586-0. PMID: 32418129. **Exclusion reason:** Ineligible comparison

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