Systematic Review on Opioid Treatments for Chronic Pain: Surveillance Report 3

Literature Update Period: December 2021 to March 16 2022

Background and Purpose

This is the third and final surveillance report for the 2020 report *Opioid Treatments for Chronic Pain*[1] (https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research), covering the period December 2021 to March 16, 2022. 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 November 2021 and to determine how the new evidence impacts findings of the 2020 report and Surveillance Reports 1 and 2, which added evidence from August 2019 through November 2021 and were published on the Agency for Healthcare Research and Quality (AHRQ) website (https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research). This is the final surveillance update planned for this topic.

Scope

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

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

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

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Methods

Update searches were conducted to identify evidence published after November 2021 through March 16, 2022. Search strategies from the original report were utilized.[1] In addition, to capture articles not yet indexed in Medline®, we supplemented the original search strategies with a previously developed[2] optimized (text-word only) search in pre-Medline to identify new studies not yet indexed with Medical Subject Headings (MeSH). As in the original report, searches on electronic databases were supplemented by review of reference lists of relevant articles. Search strategies are available in Appendix A.

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

We utilized the same methods for data abstraction and quality assessment as for the original report. Studies with at least 1 month of followup were included, and results were stratified according to short-term (1 to <6 months), intermediate term (6 to <12 months), and long-term (≥12 months) followup. We also classified the magnitude of effects for pain and function using the same approach as the original report. A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale or visual analog scale (VAS) and for function as a standardized mean difference (SMD) of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent. A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent. Large/substantial effects were defined as greater than moderate.

As in prior surveillance reports, 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). In addition, because this is the final surveillance update, meta-analyses for comparisons involving opioid versus placebo were updated with new evidence from all three surveillance reports even if they did not meet the updating criteria. We also planned to update meta-analyses for the primary outcomes of pain and function for other comparisons; however, no new studies suitable for pooling were identified for non-placebo comparisons. 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

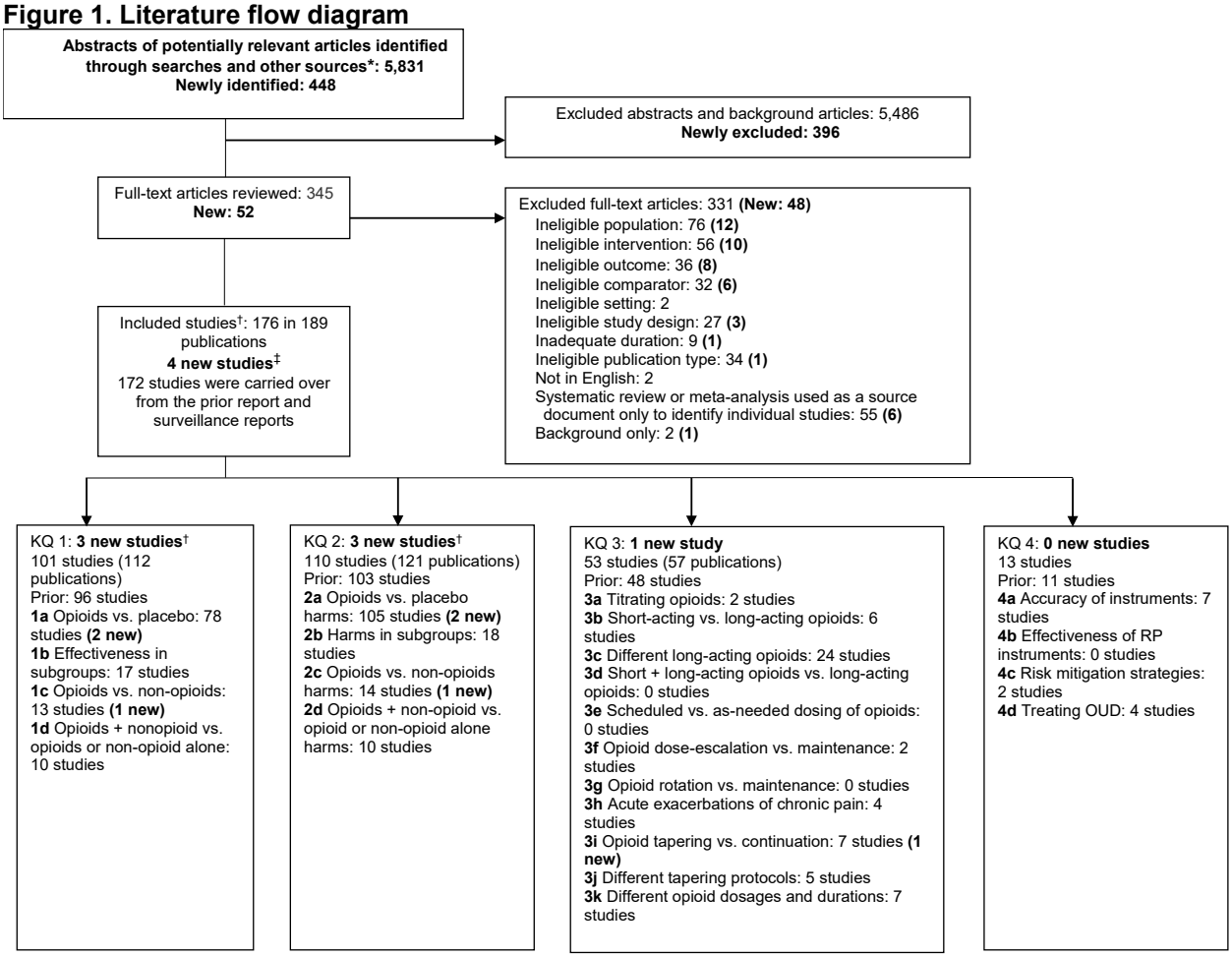
using the methods described in the original report. Changes in the strength of evidence assessments resulting from this current surveillance update are described separately from the findings reported in Surveillance Reports 1 and 2. In addition, a table detailing updated strength of evidence assessments with new evidence from all three surveillance reports is provided.

A comprehensive list of included studies identified for all three surveillance report periods is provided in Appendix C. Evidence tables providing data from these included studies are available in Appendix D, and quality assessments for each of these studies are shown in Appendix E. Updated meta-analyses are included in Appendix F, and updated strength of evidence tables for outcomes with new evidence are available in Appendix G. A list of articles excluded at full-text review, along with reasons for exclusion, is available in Appendix H.

Results

The search for Surveillance Report 3 from December 2021 through March 16, 2022, yielded 448 citations; of these, 3 new studies[3-5] met inclusion criteria (2 randomized controlled trials [RCTs] and 1 observational study); in addition, one older placebo-controlled trial[6] of opioids in patients with osteoarthritis that met inclusion criteria was identified from reference list review (Figure 1). One of the new trials[5] was placebo controlled and evaluated opioids for chronic low back pain, and the other new trial[4] compared transcutaneous electrical nerve stimulation (TENS) versus opioids for chronic knee osteoarthritis pain (Appendix D, Table D-1). The observational study compared involuntary opioid reduction, voluntary opioid reduction, and no opioid reduction in patients with chronic pain[3] (Appendix D, Table D-2).

Figure 1. Literature flow diagram



Note: New studies are those added since the original systematic review, Surveillance Report 1, and Surveillance Report 2.
* Other sources include prior reports and reference lists of relevant articles and systematic reviews.
† Some studies were included for multiple KQs.
‡ One study identified from reference list.
Abbreviations: KQ = Key Question; OUD = opioid use disorder; RP = risk prediction.

Summary of Findings

- Two new placebo-controlled trials of opioids for chronic pain were identified for Surveillance Report 3. In these trials, opioids and placebo were associated with similar effects on pain and function at short-term followup (2 trials) and intermediate-term followup (1 trial). Opioids were associated with increased risk of various adverse events, including withdrawal due to adverse events, nausea, vomiting, constipation, dizziness, and somnolence. Meta-analyses updated with these two trials and one placebo-controlled trial identified in an earlier surveillance report provided estimates very similar to the original report, with opioids associated with a small improvement in short- and intermediate-term pain and function versus placebo, and increased risk of adverse events.
- One new trial found TENS associated with decreased pain, improved function, and fewer adverse events than opioids in patients with knee osteoarthritis but was rated poor quality; the original report and prior surveillance reports did not evaluate this comparison.

- One new observational study of involuntary or voluntary opioid tapering versus no tapering in patients with chronic pain found no differences in pain or function but was rated poor quality; the original report and prior surveillance reports did not evaluate this comparison.

Table 1 provides the conclusions from the 2020 report and the new findings from studies identified in this and the prior surveillance update reports. 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) and a table showing strength of evidence ratings updated for areas with new evidence is shown in Appendix G.

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

Key Question	Conclusions From 2020 Report	Findings From Surveillance	Assessment
KQ 1a. Opioids vs. placebo, short-term[a] pain	***Opioids associated with small improvement in short-term pain*** • ***SOE: High, based on 71 RCTs (mean difference in pain intensity −0.79 point on a 0 to 10 scale, 95% CI −0.93 to −0.67, I^2=71%) and 44 trials (for pain response, RR 1.35, 95% CI 1.24 to 1.48, I^2=81%; ARD 15%, 95% CI 11 to 19%)***	***3 additional RCTs (2 identified for Surveillance Report 3 [n=1,011 and 293][5,6] and 1 from Surveillance Report 1 [n=40])[7] found opioids associated with no to moderate improvement in short-term pain; updated meta-analyses reported estimates very similar to the 2020 report for pain intensity (74 RCTs, mean difference −0.78, 95% CI −0.91 to −0.65, I^2=73%) and for likelihood of pain response (47 RCTs, RR 1.33, 95% CI 1.22 to 1.46, I^2=83%; ARD 14%, 95% CI 11 to 18%)***	***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 (SMD −0.22, 95% CI −0.28 to −0.16, I^2=53%)***	***3 additional RCTs (2 identified for Surveillance Report 3 [n=1,011 and 292][5,6] and 1 from Surveillance Report 1 [n=40])[7] found opioids and placebo associated with similar effects on short-term function; an updated meta-analysis with 2 trials (1 trial did not report poolable data) reported an estimate very similar to the 2020 report (46 RCTs, SMD −0.21, 95% CI −0.27 to −0.15, I^2=55%)***	***No change in conclusions***
KQ 1a. Opioids vs. no opioid, long-term pain and function	Opioids associated with decreased likelihood of improvement in pain and no difference in function at 1 year; no differences on either outcome at 2 years • SOE: Low, based on 1 cohort study	1 cohort study[8] (n=4,172) from Surveillance Report 1 found persistent opioid use associated with increased pain and worse function	No change in conclusions
KQ 1c. Opioids vs. nonopioids (TENS), short-term pain and function	***No evidence***	***1 RCT (n=110)[4] identified for Surveillance Report 3 found TENS associated with a small improvement in pain and moderate improvement in function versus opioids***	***SOE: low, based on new evidence***

Key Question	Conclusions From 2020 Report	Findings From Surveillance	Assessment
KQ 2a. Opioids vs. placebo, short-term harms	***Opioids associated with increased risk of withdrawal due to adverse events, nausea, vomiting, constipation, dizziness, somnolence, pruritus*** • ***SOE: High, based on 30 to 60 RCTs***	***3 additional RCTs (2 identified for Surveillance Report 3 [n=1,011 and 299][5,6] and 1 from Surveillance Report 1 [n=40])[7] found opioids associated with increased risk of short-term harms versus placebo. In updated meta-analyses:*** • ***Withdrawal due to adverse events (64 RCTs): RR 2.27 (95% CI 1.89 to 2.74), I^2=71%; ARD 9% (95% CI 7 to 12%)*** • ***Constipation (61 RCTs): RR 3.45 (95% CI 3.03 to 4.01), I^2=22%; ARD 14% (95% CI 11 to 17%)*** • ***Nausea (63 RCTs): RR 2.51 (95% CI 2.21 to 2.86), I^2=51%; ARD 14% (95% CI 11 to 16%)*** • ***Vomiting (51 RCTs): RR 3.61 (95% CI 3.01 to 4.38), I^2=15%; ARD 7% (95% CI 6 to 9%)*** • ***Dizziness (56 RCTs): RR 2.69 (95% CI 2.40 to 3.01), I^2=0%; ARD 8% (95% CI 6 to 10%)*** • ***Somnolence (56 RCTs): RR 2.93 (95% CI 2.41 to 3.61), I^2=48%; ARD 9% (95% CI 7 to 11%)*** • ***Pruritus (31 RCTs): RR 3.58 (95% CI 2.53 to 5.24), I^2=49%; ARD 7% (95% CI 4% to 9%)***	***No change in conclusions***
KQ 2a. Opioids vs. no opioids, long-term harms (all-cause mortality and cardiovascular events)	Opioids associated with increased risk of all-cause mortality and cardiovascular events (myocardial infarction or cardiovascular mortality) • SOE: low, based on 1 (all-cause mortality) or 3 (cardiovascular events) observational studies	1 retrospective cohort study[9] (n=1,320) from Surveillance Report 2 of patients with rheumatoid arthritis found tramadol associated with increased risk of all-cause mortality and cardiovascular events vs. no tramadol	No change in conclusions
KQ 2b. Harms by dose or duration	Opioids associated with increased risk of overdose, and 1 observational study found higher dose of opioids associated with increased risk of mortality • SOE: Low, based on 4 observational studies	1 case-control study[10] (2,311 cases) from Surveillance Report 1 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 Surveillance	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[11] (n=77,697) from Surveillance Report 1 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 evidence from prior surveillance report
KQ 2c. Opioids vs. nonopioids (TENS), short-term harms	***No studies***	***1 RCT (n=110)[4] identified for Surveillance Report 3 found TENS associated with decreased risk of any adverse event, nausea, constipation, and dizziness versus opioids***	***SOE: low, 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[10] (2,311 cases) from Surveillance Report 1 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[12] (n=53,187) from Surveillance Report 1 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[13,14] (n=113,618 and 14,596) from Surveillance Report 1 found opioid dose reduction or discontinuation associated with increased risk of mental health crisis events (1 study[9]) or fatal or nonfatal suicide attempt (1 study[10]); evidence on the association between tapering or discontinuation and risk of overdose was inconsistent. Studies could not evaluate the indication or circumstances for dose reduction, or discontinuation methods used to support dose reductions or discontinuation, with potential for confounding	No change in conclusions
KQ 3i. Dose tapering vs. no tapering and long-term pain and function	***No evidence***	***1 cohort study (n=290)[3] identified for Surveillance Report 3 found no differences between involuntary or voluntary opioid tapering vs. no tapering in pain intensity or function, but was rated poor quality***	***SOE: insufficient, based on new evidence***

Key Question	Conclusions From 2020 Report	Findings From Surveillance	Assessment
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[13] (n=113,618) from Surveillance Report 1 found larger dose reductions associated with increased risk of harms, and 1 cohort study (n=14,596)[14] from prior Surveillance Report 1 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[15] from Surveillance Report 1 examining 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 evidence from prior surveillance report
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[16] from Surveillance Report 1 reported no differences between buprenorphine/naloxone vs. methadone, but data were poorly reported	No change in conclusions

Abbreviations: ARD = absolute risk difference: CI = confidence interval; KQ = Key Question; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference; SOE = strength of evidence; TENS = transcutaneous electrical nerve stimulation

[a] Duration of followup is defined as: short-term = 1 to <6 months; intermediate term = 6 to <12 months; long-term (≥12 months).

Evidence Details

Key Question 1: Benefits

Key Question 1a (Opioids Vs. Placebo): Short-Term Followup; Pain and Function

The 2020 report found opioids associated with a small improvement in pain intensity (71 trials, mean difference −0.79 on a 0 to 10 scale, 95% confidence interval [CI] −0.93 to −0.67, I^2=71%), likelihood of a pain response (44 trials, relative risk [RR] 1.35, 95% CI 1.24 to 1.48, I^2=81%), and improvement in function (44 trials, standardized mean difference [SMD] −0.22, 95% CI −0.28 to −0.16, I^2=53%) versus placebo at short-term (1 to <6 month) followup. Two additional placebo-controlled trials were identified for Surveillance Report 3.[5,6] One was a new trial[5] (n=1,011) and the other was an older trial[6] (n=293) identified by reference list review (Appendix D, Table D-1). The new trial evaluated the mixed agent tramadol in patients with chronic low back pain (duration of followup, 16 weeks) and the other trial evaluated oxycodone (an opioid agonist) in patients with hip or knee osteoarthritis (duration of followup, 8 weeks). Both trials also included a tanezumab intervention arm, for which we did not extract data because tanezumab (a nerve growth factor inhibitor) is not approved by the Food and Drug Administration and has been withdrawn from further development. Both trials had high attrition and were rated fair quality.

In the larger trial, tramadol was associated with similar effects versus placebo in pain intensity at 6 months (mean difference −0.12 point on a 0 to 10 scale, 95% CI −0.46 to 0.21), likelihood of pain response at 3 months (defined as ≥30% improvement in pain, RR 1.02, 95% CI 0.90 to 1.17), and improvement in function at 6 months (mean difference −0.26 point on the 0 to 24 RDQ, 95% CI −1.09 to 0.57). The smaller trial also reported little difference between oxycodone versus placebo in pain intensity (mean difference −0.11, 95% CI −0.17 to −0.05), likelihood of ≥30% improvement in pain (RR 0.88, 95% CI 0.67 to 1.16), and function (change from baseline on the Western Ontario and McMaster Universities Arthritis Index [WOMAC] Physical Function, 0 to 10 scale, −1.71 vs. −1.67).

In meta-analyses that were updated with the two trials identified for Surveillance Report 3 and one other small trial[7] (n=40) identified in an earlier surveillance report, estimates were very similar to the 2020 report for pain intensity (74 RCTs, mean difference −0.78, 95% CI −0.91 to −0.65, I^2=73%; Appendix F, Figure F-1), likelihood of pain response (47 RCTs, RR 1.33, 95% CI 1.22 to 1.46, I^2=83%; absolute risk difference [ARD] 14%, 95% CI 11 to 18%; Appendix F, Figure F-2), and function (46 RCTs, SMD −0.21, 95% CI −0.27 to −0.15, I^2=55%; Appendix F, Figure F-3).

Key Question 1c (Opioids Vs. Nonopioid [TENS]): Short-Term Followup; Pain, Function, and Quality of Life

No study in the 2020 report evaluated this comparison. One new trial (n=110) compared TENS versus opioids (tramadol, dihydrocodeine, and/or codeine-acetaminophen; tramadol-acetaminophen; and opium-acetaminophen; dose not specified) in patients with knee osteoarthritis[4] (Appendix D, Table D-1). TENS was delivered as high-frequency (100 Hz) and low-frequency (2 Hz) stimulation with intensity and duration controlled by the patient. The trial was open label and rated fair quality (Appendix E, Table E-1).

At 3 months, TENS was associated with decreased pain intensity (mean difference −0.92 on 0 to 10 scale, 95% CI −1.71 to −0.12), greater likelihood of ≥30% improvement in pain (52.7% vs. 34.5%, RR 1.53, 95% CI 0.98 to 2.37), better function (mean difference −6.2 on 0 to 68 WOMAC Physical Function scale), greater likelihood of ≥20% improvement in function (52.7% vs. 35.2%, RR 1.50, 95% CI 0.97 to 2.33), and better quality of life (mean 7.0 vs. 7.7 on the 5 to 12 EuroQol-5D Global Score, p=0.006).

Key Question 2: Harms

Key Question 2a (Opioids Vs. Placebo): Short-Term Followup; Harms

The two additional placebo-controlled trials identified for Surveillance Report 3 were consistent with the 2020 report in finding opioids associated with increased risk of withdrawal due to adverse events, constipation, nausea, vomiting, dizziness, pruritus, and somnolence.[5,6] Estimates for serious adverse events were imprecise (1.7% vs. 1.0%, RR 1.69, 95% CI 0.53 to 5.34, and 2.5% vs. 1.4%, RR 1.76, 95% CI 0.33 to 9.50). As in the 2020 report, meta-analyses updated with the two additional trials identified for Surveillance Report 3 and one trial[7] identified in an earlier surveillance report found opioids associated with increased risk of withdrawal due to adverse events (64 RCTs, RR 2.27, 95% CI 1.89 to 2.74, I^2=71%; ARD 9%, 95% CI 7 to 12%; Appendix F, Figure F-4), constipation (61 RCTs, RR 3.45, 95% CI 3.03 to 4.01, I^2=22%; ARD 14%, 95% CI 11 to 17%; Appendix F, Figure F-5), nausea (63 RCTs, RR 2.51, 95% CI 2.21 to 2.86, I^2=51%; ARD 14%, 95% CI 11 to 16%; Appendix F, Figure F-6),

vomiting (51 RCTs, RR 3.61, 95% CI 3.01 to 4.38, I^2=15%; ARD 7%, 95% CI 6 to 9%; Appendix F, Figure F-7), dizziness (56 RCTs, RR 2.69, 95% CI 2.40 to 3.01, I^2=0%; ARD 8%, 95% CI 6 to 10%; Appendix F, Figure F-8), somnolence (56 RCTs, RR 2.93, 95% CI 2.41 to 3.61, I^2=48%; ARD 9%, 95% CI 7 to 11%; Appendix F, Figure F-9), and pruritus (31 RCTs, RR 3.58, 95% CI 2.53 to 5.24, I^2=49%; ARD 7%, 95% CI 4% to 9%; Appendix F, Figure F-10), with very similar pooled estimates. As in the 2020 report, opioids were associated with a non–statistically significant increased risk of serious adverse events versus placebo (40 RCTs, RR 1.25, 95% CI 0.91 to 1.74, I^2=35%; Appendix F, Figure F-11) and similar risk of headache versus placebo (51 RCTs, RR 1.07, 95% CI 0.97 to 1.19, I^2=0%; Appendix F, Figure F-12).

Key Question 2c (Opioids Vs. Nonopioid [TENS]): Short-Term Followup; Pain, Function, and Quality of Life

One new trial (n=110) found TENS associated with decreased likelihood of experiencing at least one adverse event potentially related to study medications compared with opioids (12.7% vs. 29.1%, RR 0.44, 95% CI 0.20 to 0.98;[4] Appendix D, Table D-1). There were no serious adverse events with either TENS or opioids. Among patients randomized to opioids, 13 percent experienced constipation, 13 percent nausea, 5.5 percent dizziness, and 7.3 percent drowsiness; no cases of these adverse events were reported in patients randomized to TENS.

Key Question 3: Dosing Strategies

Key Question 3i (Opioid Tapering Vs. No Tapering): Long-Term Followup; Pain, Function, and Quality of Life

The 2020 report included no studies on the association between opioid tapering versus no tapering on long-term pain, function, and quality of life, although one small (n=34) trial[17] in the 2020 report found a taper support intervention associated with no difference versus usual care in pain intensity and greater improvement in function at intermediate-term followup. One cohort study (n=290) identified for Surveillance Report 3 compared involuntary or voluntary opioid dose reduction versus no opioid dose reduction in patients in the Veterans Health Administration with chronic pain on long-term opioid therapy[3] (Appendix D, Table D-2). Involuntary opioid reduction was defined as occurring without the patients' consent or against their wishes, based on self-report. At 18 months, changes from baseline in pain intensity (−0.12 for involuntary opioid reduction vs. −0.50 for voluntary opioid reduction vs. −0.41 for no opioid reduction, p=0.20), interference with enjoyment of life (0.03 vs. −0.41 vs. −0.31, p=0.43), and interference with general activity (−0.06 vs. −0.41 vs. 0.03, p=0.41) measured using the 0 to 10 Pain, Enjoyment, General activity (PEG) scale were similar between groups, with no statistically significant between-group differences. There were also no differences in quality of life measured using the 0 to 10 Veterans RAND 12-item Health Survey (3.9 vs. 3.6 vs. 3.9). The study was rated poor quality due to substantial missing data and failure to adjust for potential confounders, although similarity between groups in baseline characteristics was noted (Appendix E, Table E-2).

Key Question 4: Risk Assessment Instruments and Risk Mitigation Strategies

No new studies were identified for Surveillance Report 3.

Conclusions

Two placebo-controlled trials identified for Surveillance Report 3 were consistent with the findings of the original report with regard to an association between opioids and small improvements in short-term pain and function and increased risk of harms. Updated meta-analyses based on placebo-controlled trials provided estimates very similar to the original report. One new trial provided low strength of evidence that TENS may be associated with improved short-term pain and function and decreased adverse events versus placebo; no studies evaluating this comparison were in the original report. One observational study identified for Surveillance Report 3 found no differences between involuntary or voluntary tapering versus no tapering in pain or function, but was rated poor quality and provided insufficient evidence to inform new conclusions on the effects of tapering on these outcomes, which had no prior studies. Surveillance Report 3 builds on Surveillance Reports 1 and 2, which identified new studies on short-term benefits and harms, long-term benefits and harms, risk mitigation strategies, dose-dependent risks of opioids, and management of opioid use disorder; for all of these areas, findings with the addition of studies identified in this surveillance report were consistent with the original report.

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Disclaimers

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

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

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Afterword

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

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

This quarterly surveillance report provides 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.

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Appendix Contents

Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R), All 2020 to March 16, 2022

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 March 16, 2022

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 March 16, 2022

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 March 16, 2022

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 March 16, 2022
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 March 16, 2022
1 ((chronic or pain) and (back or spine or spinal or cervical or radicular or neck or knee or hip)).ti,ab,kw.
2 (chronic adj2 pain).ti,ab,kw.
3 ("ankylosing spondylitis" or "neuropathic pain" or neuropathy or polyneuropathy or neuralgia or fibromyalgia or "sickle cell" or headache* or migraine or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis" or sciatica).ti,ab,kw.
4 or/1-3
5 opioid*.ti,ab,kw.
6 (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol or tramadol).ti,ab,kw.
7 5 or 6
8 4 and 7
9 8 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
10 (random* or control* or placebo or sham or trial).ti,ab,kw.
11 9 and 10

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

Appendix B. Key Questions and Inclusion and Exclusion Criteria

Key Questions

Key Question 1. Effectiveness and Comparative Effectiveness:

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

Key Question 2. Harms and Adverse Events:

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

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

Key Question 3. Dosing Strategies:

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

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

Key Question 4. Risk Assessment and Risk Mitigation Strategies:

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

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

Inclusion and Exclusion Criteria

Table B-1. Inclusion and exclusion criteria

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

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

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

Appendix C. Included Studies List

1. Agnoli A, Xing G, Tancredi DJ, et al. Association of dose tapering with overdose or mental health crisis among patients prescribed long-term opioids. JAMA. 2021 08 03;326(5):411-9. doi:10.1001/jama.2021.11013. PMID: 34342618.

2.* Frank JW, Carey E, Nolan C, et al. Association between opioid dose reduction against patients' wishes and change in pain severity. J Gen Intern Med. 2020 12;35(Suppl 3):910-7. doi:10.1007/s11606-020-06294-z. PMID: 33145690.

3. Gau S-Y, Huang J-Y, Wei JC-C. Tramadol use increases mortality and risk of major adverse cardiovascular events in rheumatoid arthritis patients: evidence from a population-based cohort study. Eur J Prev Cardiol. 2021. doi:10.1093/eurjpc/zwab176.

4. Hallvik SE, El Ibrahimi S, Johnston K, et al. Patient outcomes following opioid dose reduction among patients with chronic opioid therapy. Pain. 2021 Apr 7. doi:10.1097/j.pain.0000000000002298. PMID: 33863865.

5. Hayes CJ, Krebs EE, Hudson T, et al. Impact of opioid dose escalation on pain intensity: a retrospective cohort study. Pain. 2020 05;161(5):979-88. doi:10.1097/j.pain.0000000000001784. PMID: 31917775.

6. Hruschak V, Rosen D, Tierney M, et al. Integrated psychosocial group treatment: a randomized pilot trial of a harm reduction and preventive approach for patients with chronic pain at risk of opioid misuse. Pain Med. 2021 Feb 12;12:12. doi:10.1093/pm/pnaa461. PMID: 33576415.

7.* Maheu E, Soriot-Thomas S, Noel E, et al. Wearable transcutaneous electrical nerve stimulation (actiTENS R) is effective and safe for the treatment of knee osteoarthritis pain: a randomized controlled trial versus weak opioids. Ther Adv Musculoskelet Dis. 2022;14:1759720X211066233. doi:10.1177/1759720X211066233. PMID: 35069809.

8.* Markman JD, Bolash RB, McAlindon TE, et al. Tanezumab for chronic low back pain: a randomized, double-blind, placebo- and active-controlled, phase 3 study of efficacy and safety. Pain. 2020 09 01;161(9):2068-78. doi:10.1097/j.pain.0000000000001928. PMID: 32453139.

9. Musich S, Wang SS, Schaeffer JA, et al. Safety events associated with tramadol use among older adults with osteoarthritis. Popul Health Manag. 2021 02;24(1):122-32. doi:10.1089/pop.2019.0220. PMID: 32119805.

10. Neumann AM, Blondell RD, Hoopsick RA, et al. Randomized clinical trial comparing buprenorphine/naloxone and methadone for the treatment of patients with failed back surgery syndrome and opioid addiction. J Addict Dis. 2020 Jan-Mar;38(1):33-41. doi:10.1080/10550887.2019.1690929. PMID: 31774028.

11. Salkar M, Ramachandran S, Bentley JP, et al. Do formulation and dose of long-term opioid therapy contribute to risk of adverse events among older adults? J Gen Intern Med. 2021 Jul 13;13:13. doi:10.1007/s11606-021-06792-8. PMID: 34258726.

12. Shah D, Zhao X, Wei W, et al. A Longitudinal study of the association of opioid use with change in pain interference and functional limitations in a nationally representative cohort of adults with osteoarthritis in the United States. Adv Ther. 2020 02;37(2):819-32. doi:10.1007/s12325-019-01200-4. PMID: 31875300.

13.* Spierings ELH, Fidelholtz J, Wolfram G, et al. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. Pain. 2013 Sep;154(9):1603-12. doi: 10.1016/j.pain.2013.04.035. PMID: 23707270.

14. van de Donk T, van Cosburgh J, van Dasselaar T, et al. Tapentadol treatment results in long-term pain relief in patients with chronic low back pain and associates with reduced segmental sensitization. Pain Rep. 2020 Nov-Dec;5(6):e877. doi:10.1097/PR9.0000000000000877. PMID: 33364540.

*Studies identified since the last surveillance report

Appendix D. Evidence Tables

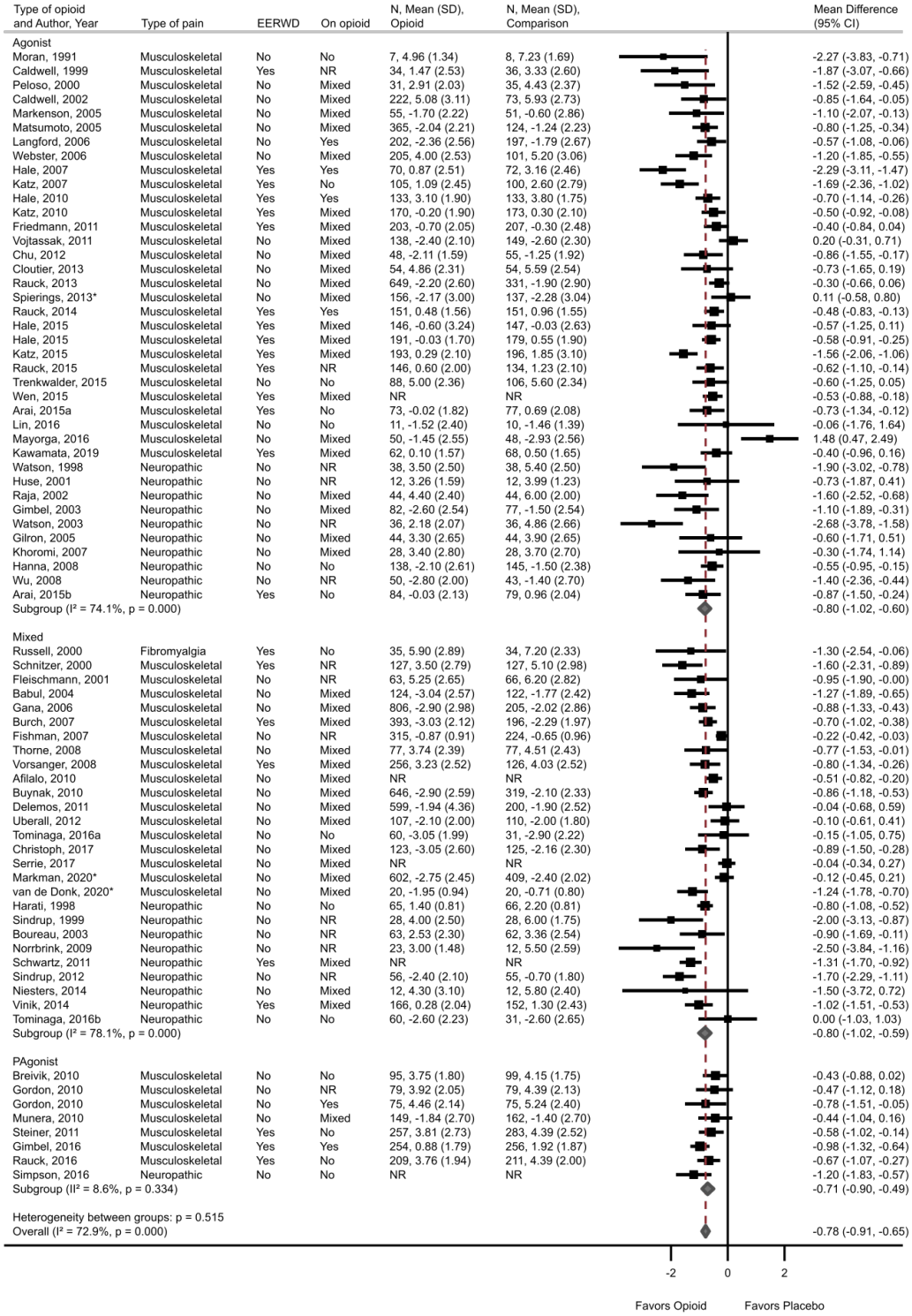
Shown in associated Excel files for Surveillance Report 3 at https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research.

Appendix E. Quality Assessment

Shown in associated Excel files for Surveillance Report 3 at https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research.

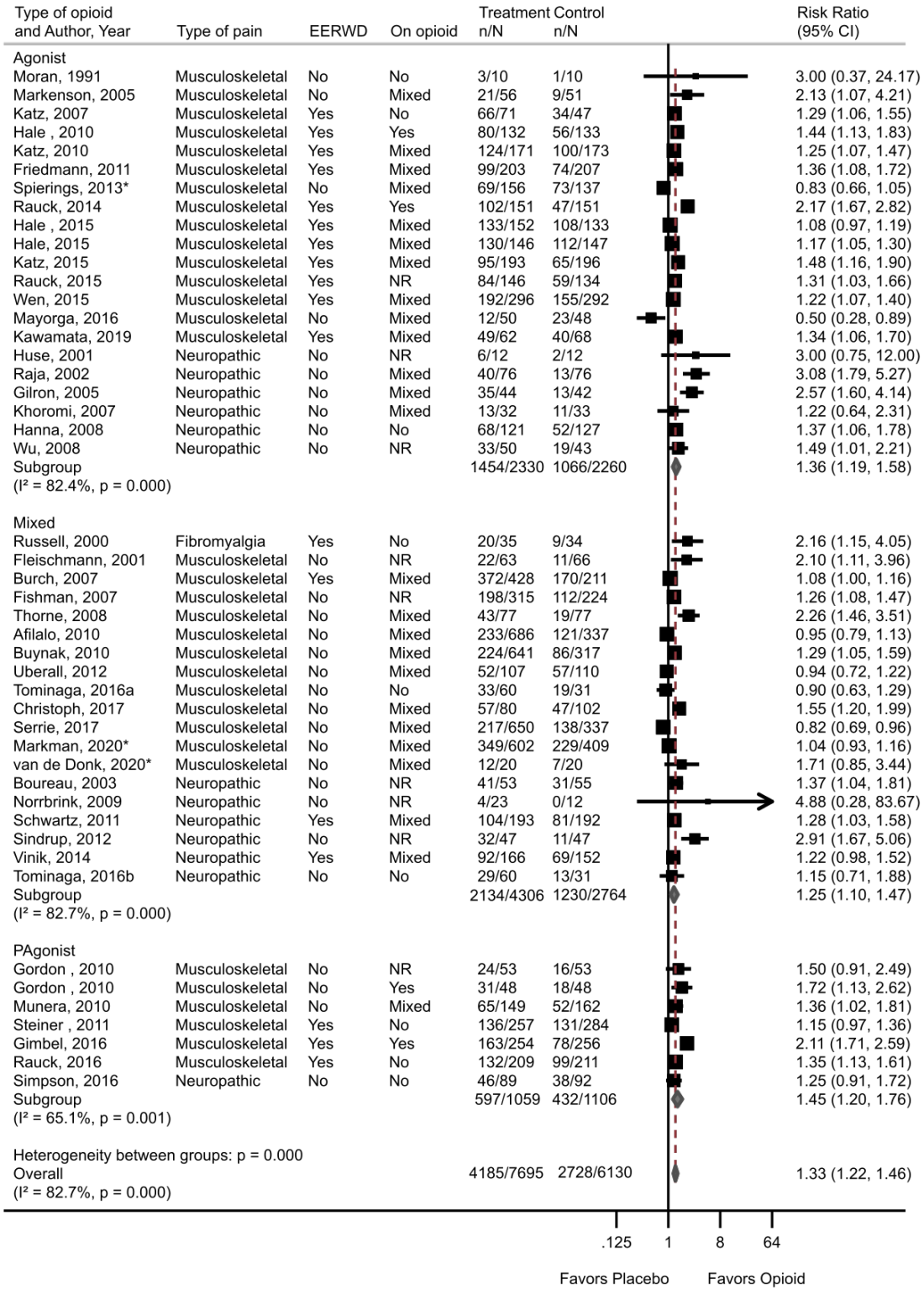
Appendix F. Meta-Analysis Results

Figure F-1. Meta-analysis of improvement in mean pain measures for opioids versus placebo



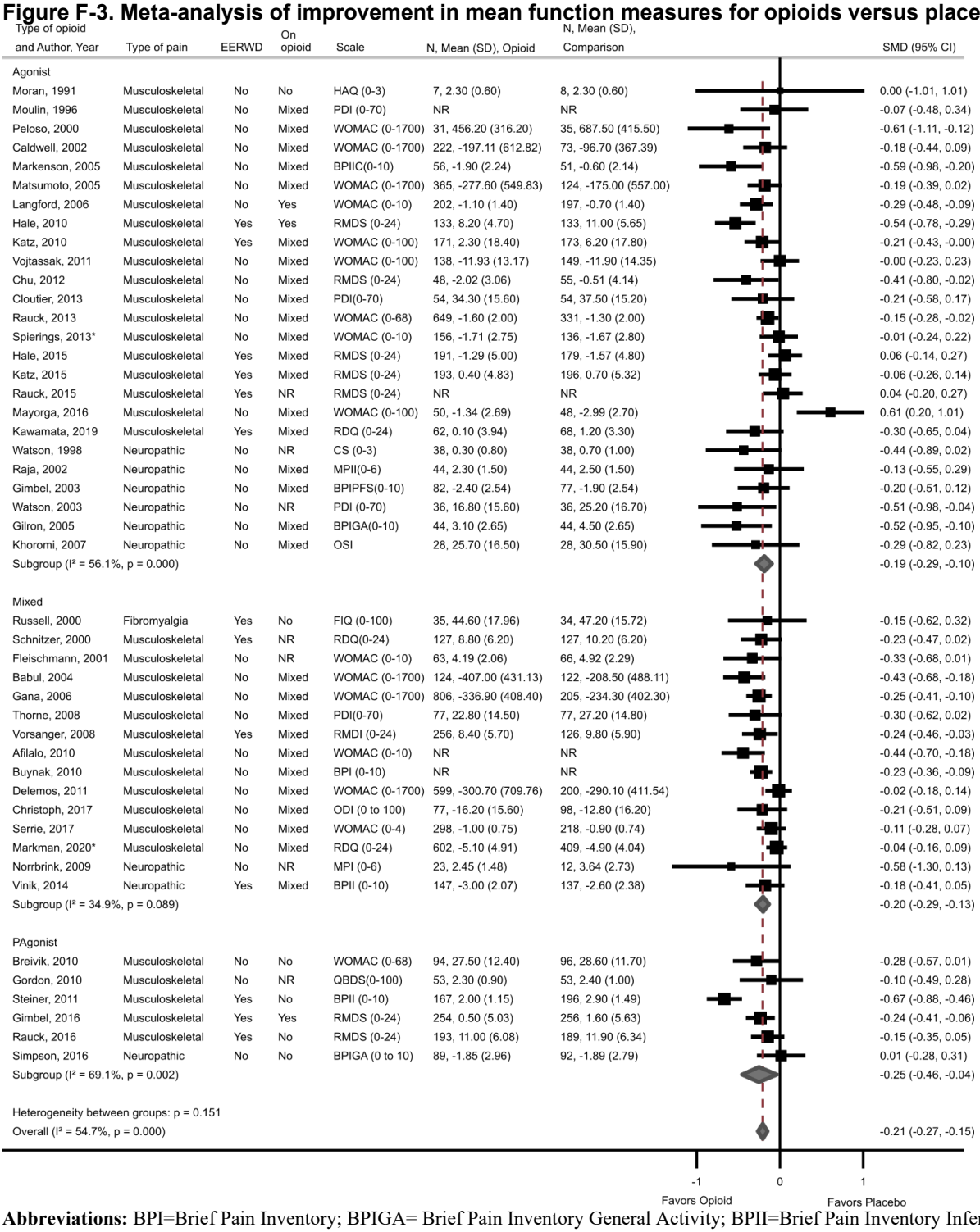
Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist; SD = standard deviation.
* Newly included since the original 2020 systematic review.

Figure F-2. Meta-analysis of likelihood of experiencing a pain response for opioids versus placebo



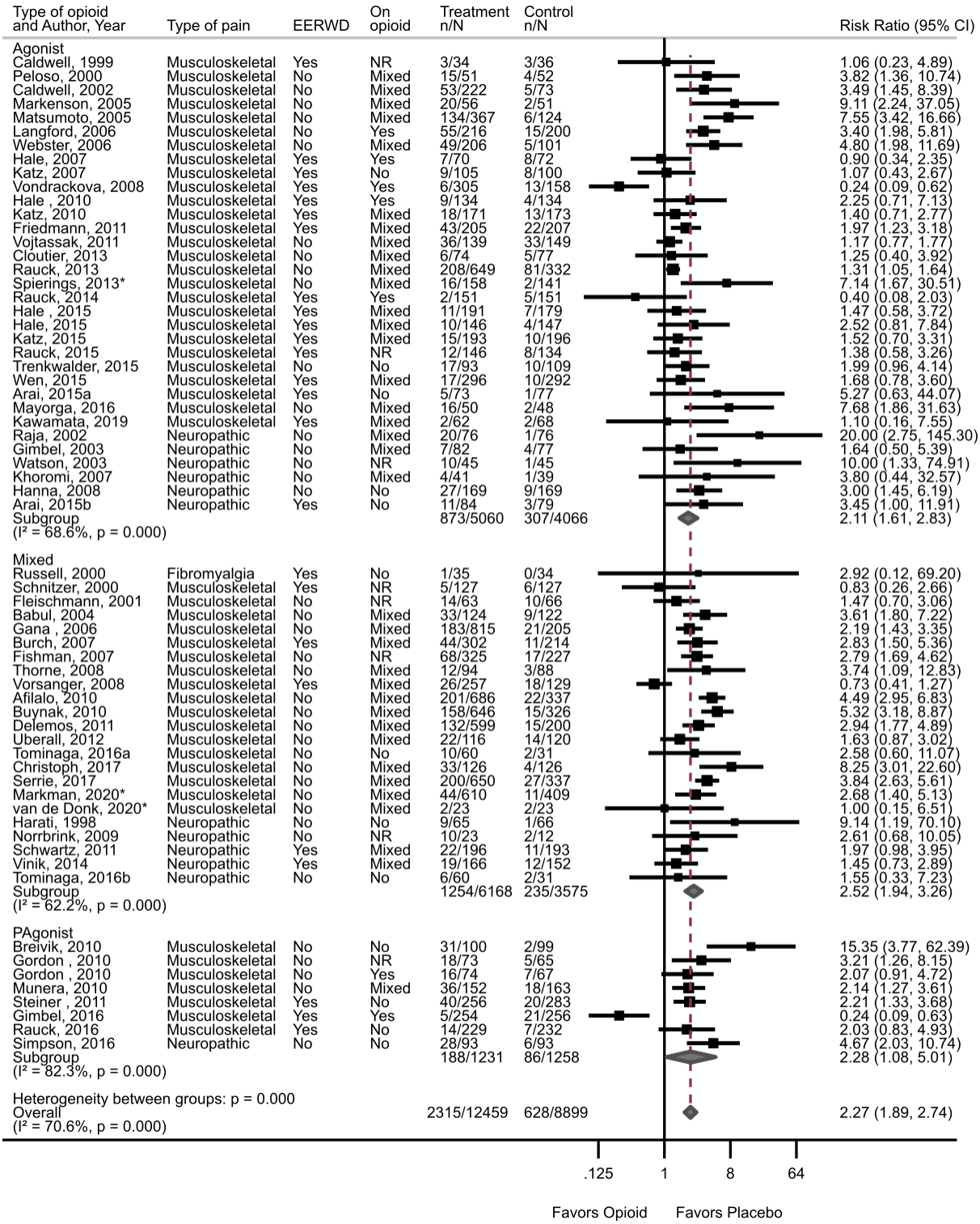
Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist.
* Newly included since the original 2020 systematic review.

Figure F-3. Meta-analysis of improvement in mean function measures for opioids versus placebo



Abbreviations: BPI=Brief Pain Inventory; BPIGA= Brief Pain Inventory General Activity; BPII=Brief Pain Inventory Inference; BPIIC=Brief Pain Inventory Inference Composite; BPIPFS= Brief Pain Inventory Physical Function Scale; CI=confidence interval; CS= Categorical scale; EERWD=enriched enrollment randomized withdrawal design; FIQ= Fibromyalgia Impact Questionnaire; HAQ= Health Activities Questionnaire; MPI= Multidimensional Pain Inventory; MPII= Multidimensional Pain Inventor Interference; N=overall sample; NR=not reported; ODI= Oswestry Disability Index; OSI=Oswestry Index; PAgonist=partial agonist; PDI= Pain Disability Index; QBDS= Quebec Back Disability Scale; RDQ=Roland-Morris Disability 45 Questionnaire; RMDI= Roland Morris Disability Index; RMDS= Roland Morris Disability Scale; SD=standard deviation; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.
* Newly included since the original 2020 systematic review.

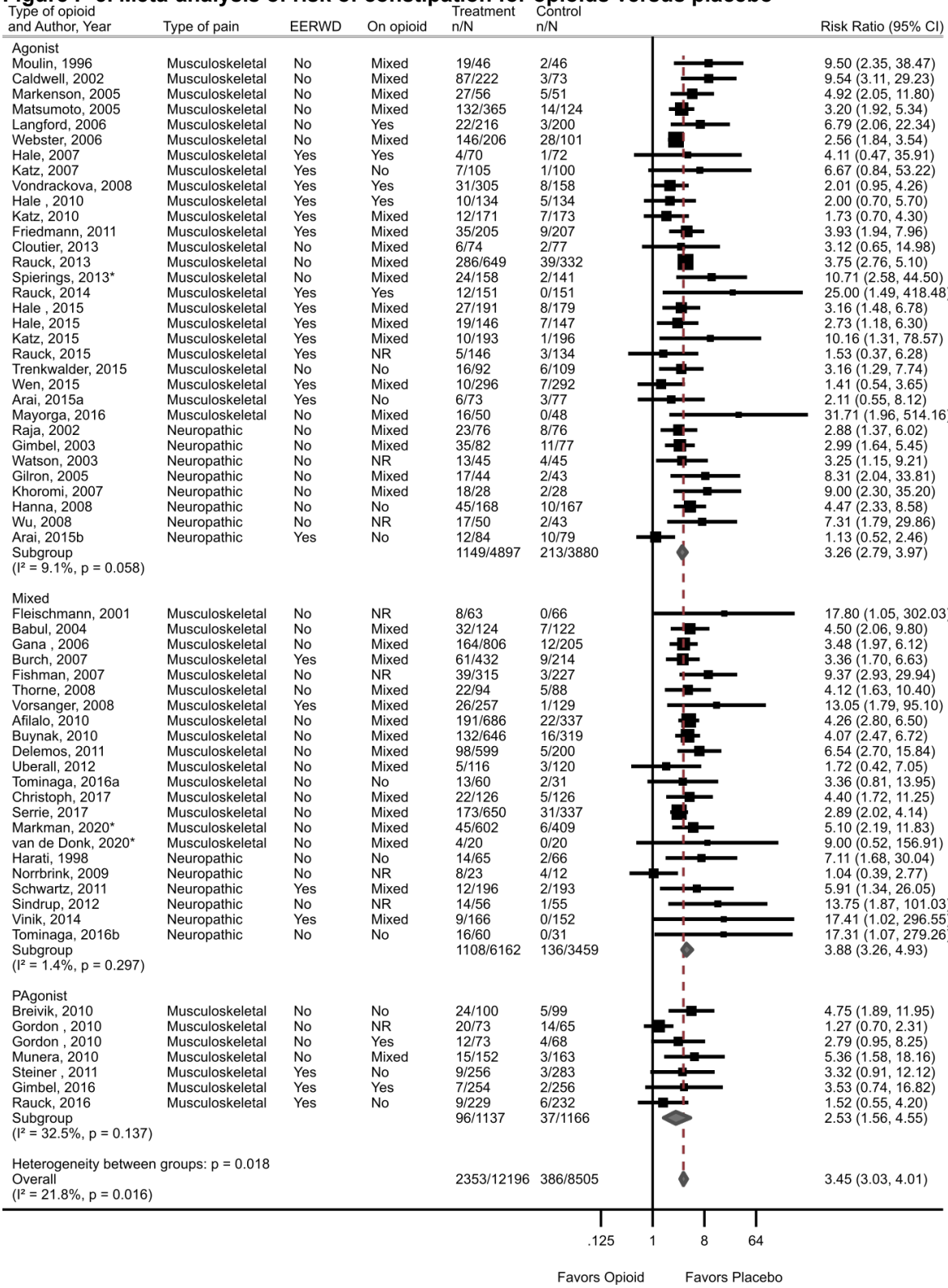
Figure F-4. Meta-analysis of risk of study withdrawal due to adverse events for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist.

* Newly included since the original 2020 systematic review.

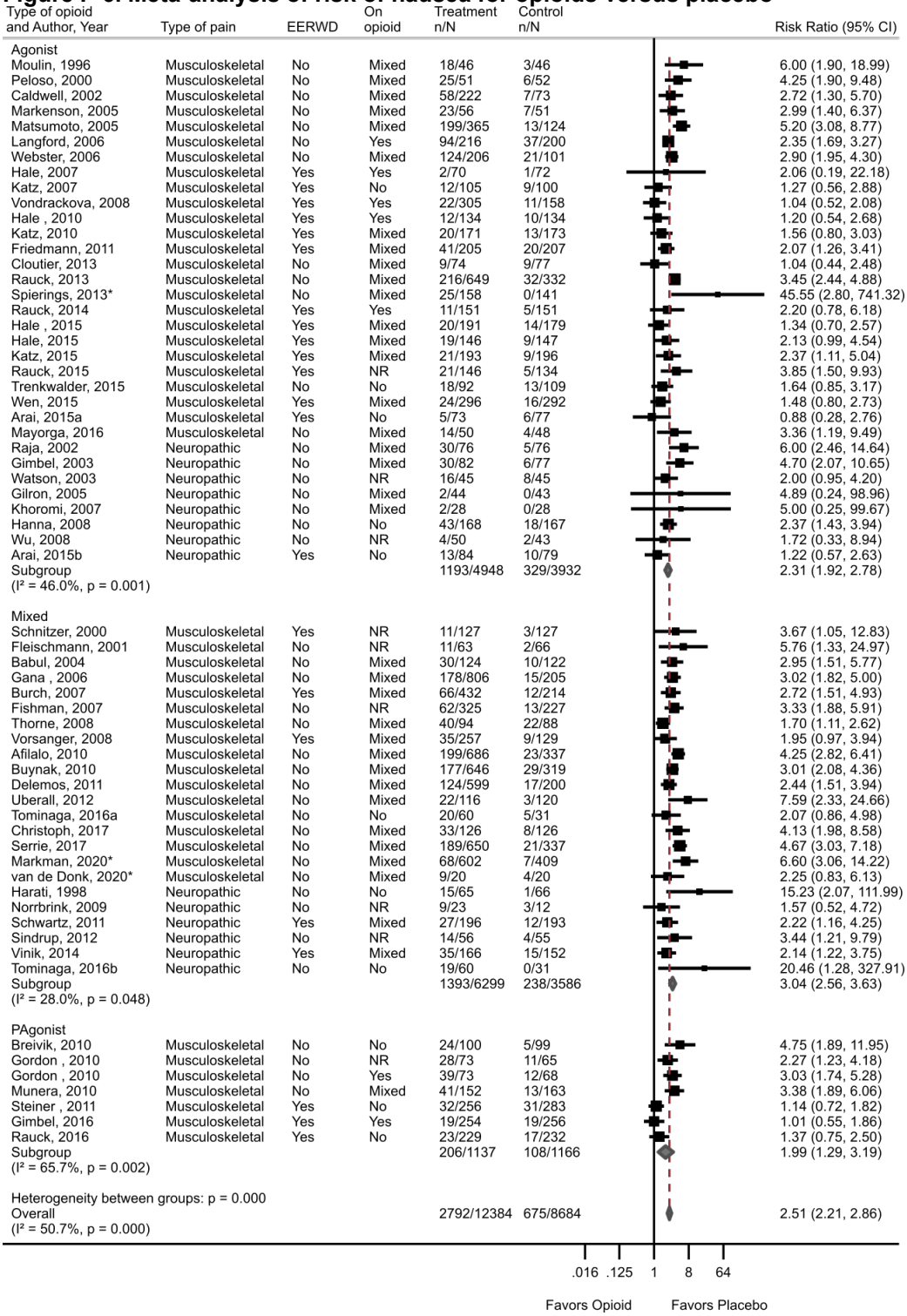
Figure F-5. Meta-analysis of risk of constipation for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist.

* Newly included since the original 2020 systematic review.

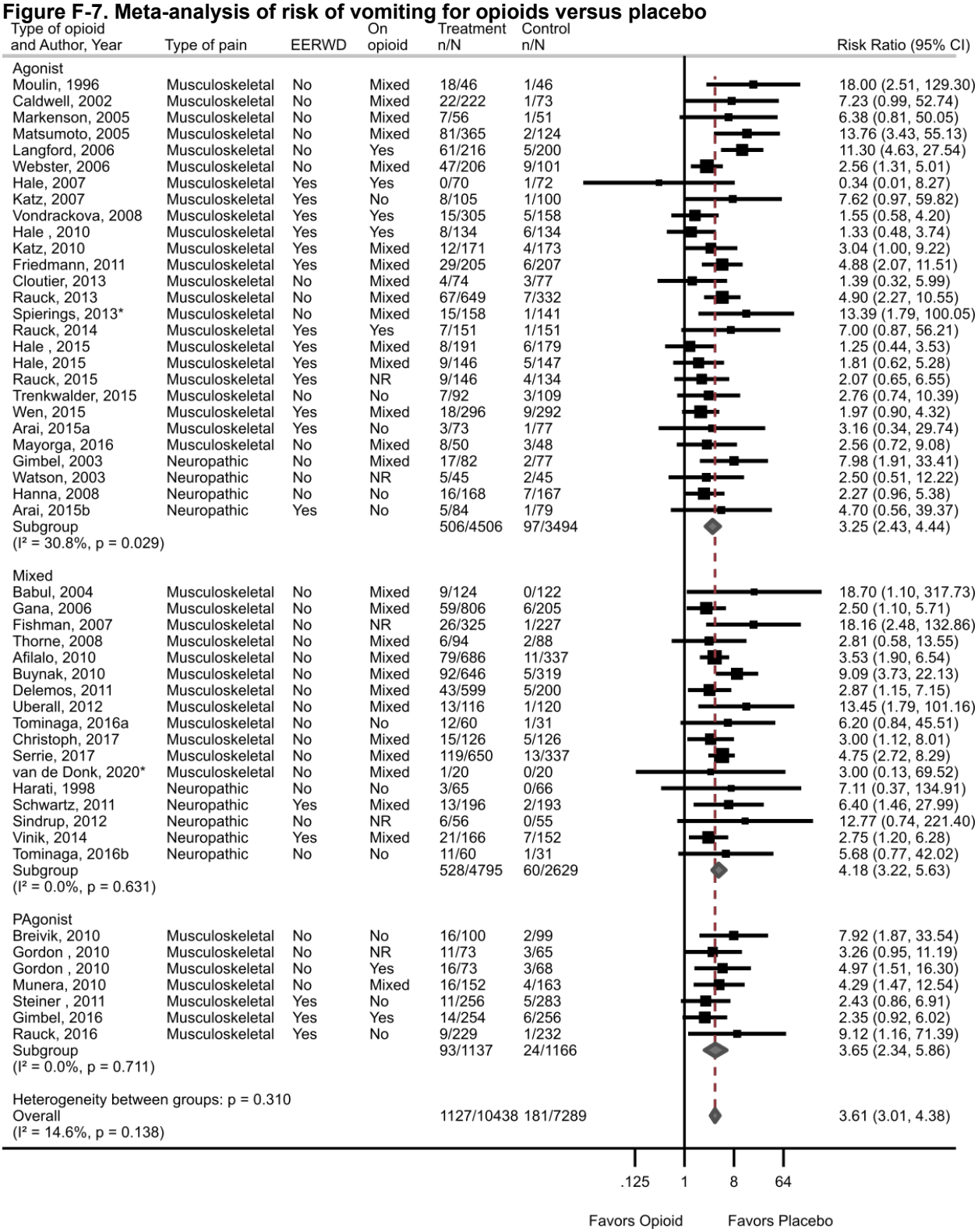
Figure F-6. Meta-analysis of risk of nausea for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist.

* Newly included since the original 2020 systematic review.

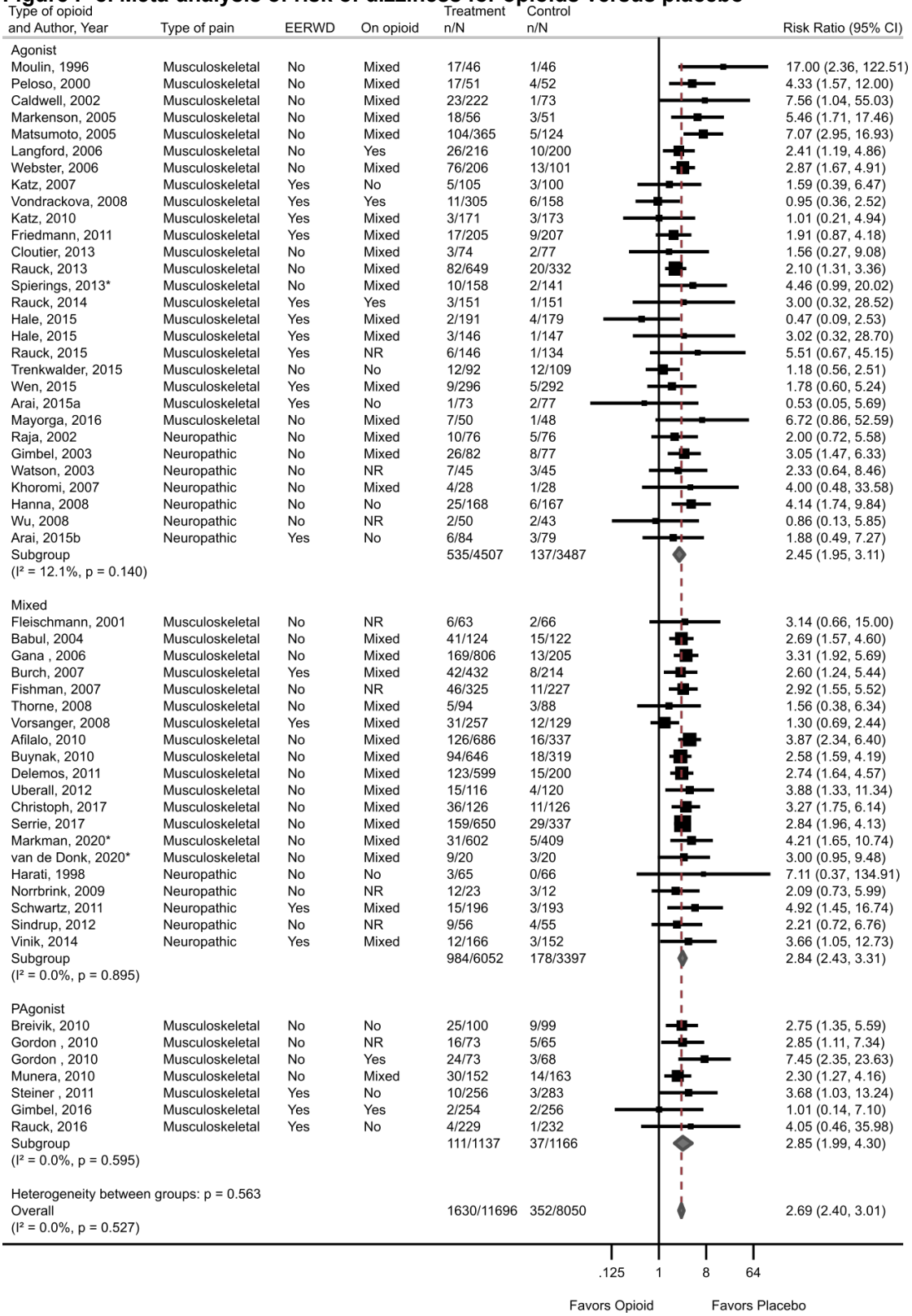
Figure F-7. Meta-analysis of risk of vomiting for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist.

* Newly included since the original 2020 systematic review.

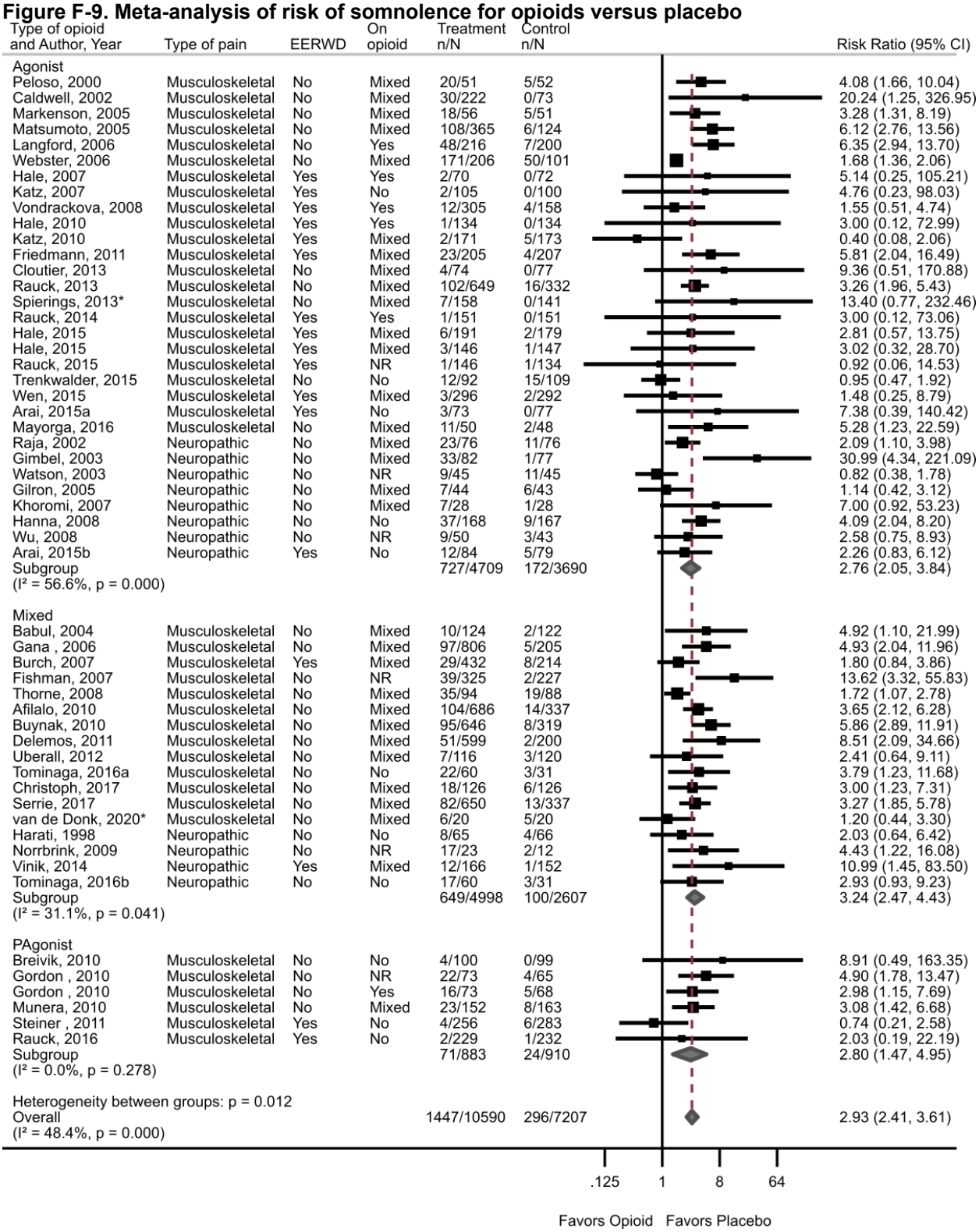
Figure F-8. Meta-analysis of risk of dizziness for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist.

* Newly included since the original 2020 systematic review.

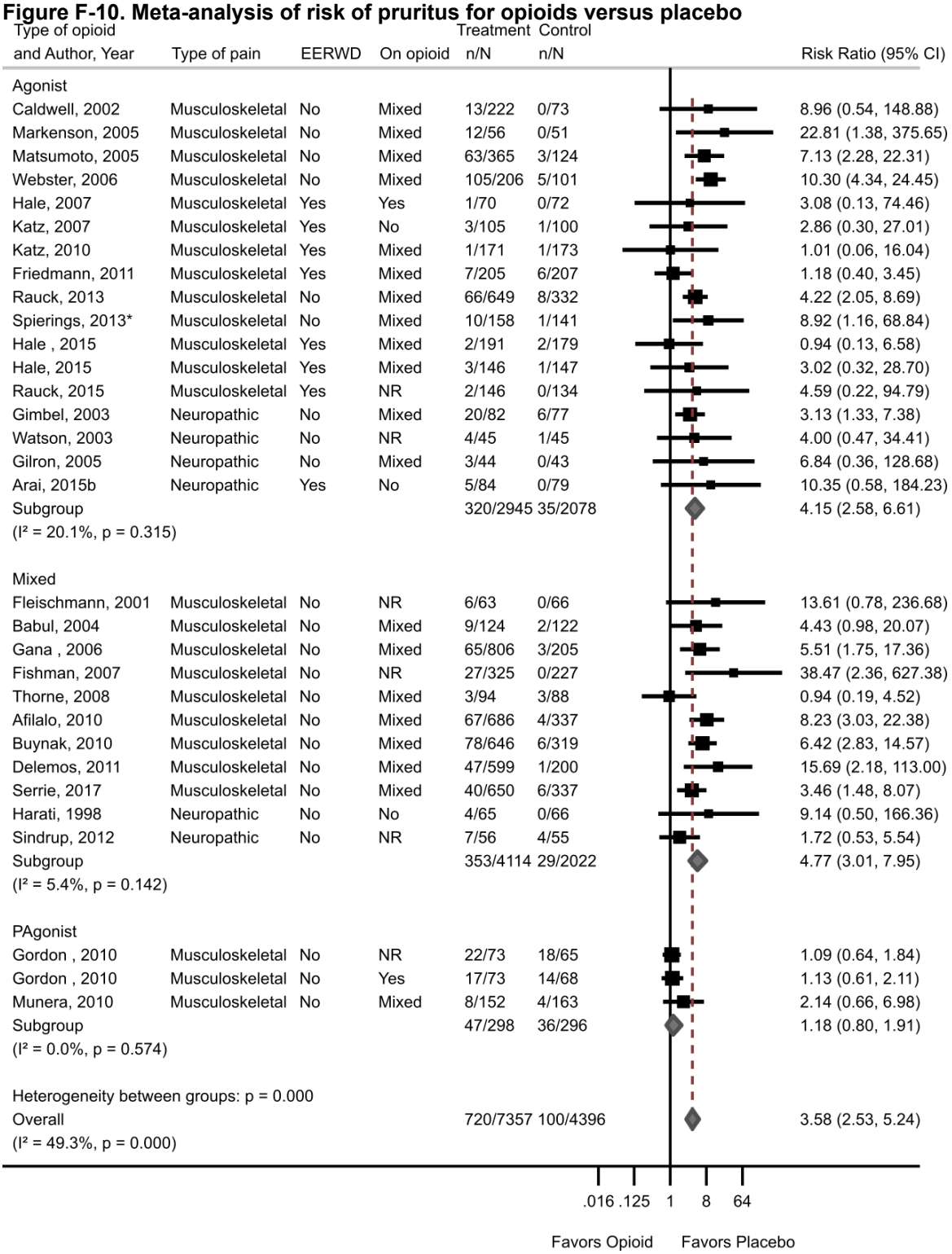
Figure F-9. Meta-analysis of risk of somnolence for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist.

* Newly included since the original 2020 systematic review.

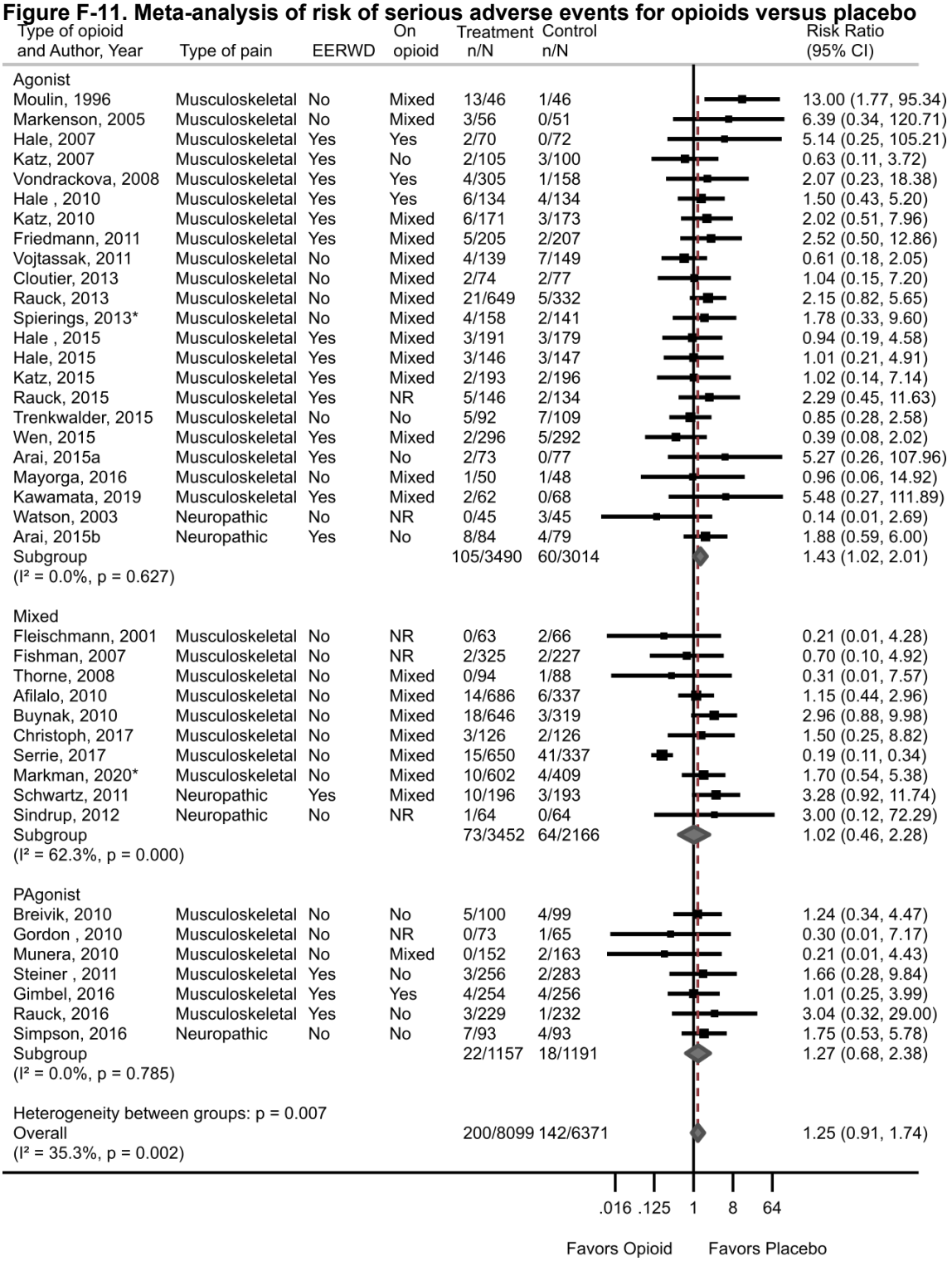
Figure F-10. Meta-analysis of risk of pruritus for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist

* Newly included study

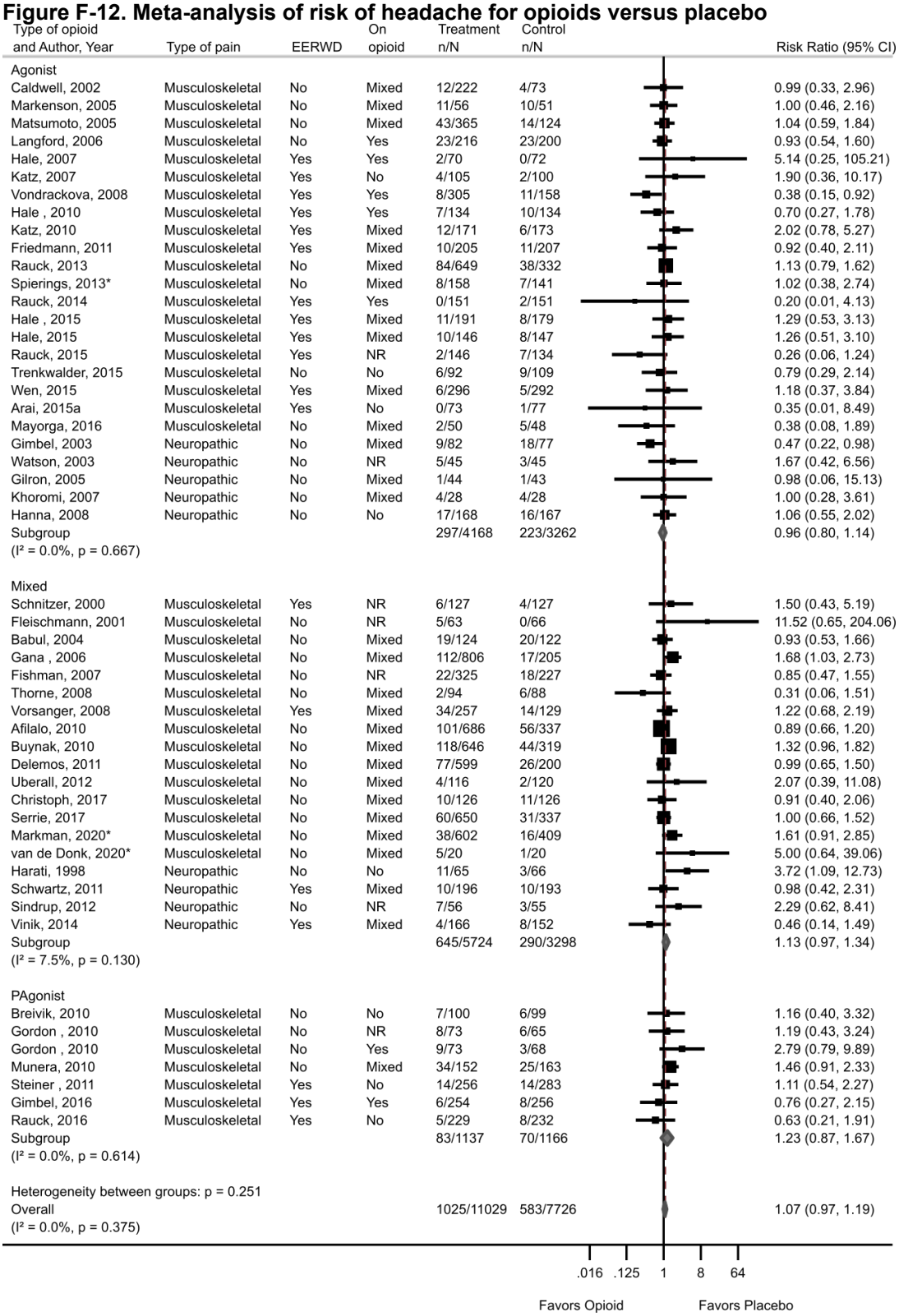
Figure F-11. Meta-analysis of risk of serious adverse events for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist

* Newly included study

Figure F-12. Meta-analysis of risk of headache for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; NR=not reported; PAgonist=partial agonist

* Newly included study

Appendix G. Strength of Evidence Table

Table G-1. Strength of evidence and key findings for new evidence*

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings† (95% CI)	SOE
Opioid vs. placebo or no opioid therapy	Pain (short-term)	74 (3 new) RCTs (continuous); 47 (3 new) RCTs (dichotomous)	20,960 (continuous); 13,825 (dichotomous)	Direct	Precise	Low	Consistent	MD −0.78 (−0.91 to −0.65); RR 1.33 (1.22 to 1.46)	High
	Function (short-term)	46 (2 new) RCTs	13,730	Direct	Precise	Low	Consistent	SMD −0.21 (−0.27 to −0.15)	High
	Pain and function (long-term)	2 (1 new) cohort studies	4,991	Direct	Precise	Moderate	Unknown	No differences at 2 years	Low
	Study withdrawal due to AEs	64 (3 new) RCTs	21,358	Direct	Precise	Low	Consistent	RR 2.27 (1.89 to 2.74)	High
	Serious AEs	40 (2 new) RCTs	14,470	Direct	Imprecise	Low	Consistent	RR 1.25 (0.91 to 1.74)	Moderate
	Nausea	63 (3 new) RCTs	21,068	Direct	Precise	Low	Consistent	RR 2.51 (2.21 to 2.86)	High
	Vomiting	51 (2 new) RCTs	17,736	Direct	Precise	Low	Consistent	RR 3.61 (3.01 to 4.38)	High
	Constipation	61 (3 new) RCTs	20,701	Direct	Precise	Low	Consistent	RR 3.41 (3.00 to 3.95)	High
	Dizziness	56 (3 new) RCTs	19,746	Direct	Precise	Low	Consistent	RR 2.69 (2.40 to 3.01)	High
	Headache	51 (3 new) RCTs	18,755	Direct	Precise	Low	Consistent	RR 1.07 (0.97 to 1.19)	High
	Somnolence	56 (3 new) RCTs	17,797	Direct	Precise	Low	Consistent	RR 2.93 (2.41 to 3.61)	High
	Pruritus	31 (1 new) RCTs	11,753	Direct	Precise	Low	Consistent	RR 3.58 (2.53 to 5.24)	High
	Cardiovascular events	4 (1 new) cohort studies	508,266	Direct	Precise	Moderate	Consistent	Opioids associated with increased risk	Low
Opioids vs. nonopioids (TENS)‡	Pain and function (short-term)	1 RCT	110	Direct	Precise	Moderate	Unknown	TENS associated with small improvement in pain and moderate improvement in function	Low

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings† (95% CI)	SOE
Opioids vs. nonopioids (TENS)‡ (continued)	Harms	1 RCT	110	Direct	Imprecise	Moderate	Unknown	TENS associated with reduced risk of short-term harms (any adverse event, nausea, constipation, and dizziness)	Low
Short-acting vs. long-acting opioids	Overdose	1 cohort study and 1 new case-control study	840,606 (cohort study) and 2,311 cases (case-control study)	Direct	Precise	Moderate	Unknown	Long-acting associated with increased risk	Low
Opioid dose escalation vs. dose maintenance	Pain, function	1 RCT and 1 cohort study	140 (RCT) and 53,187 (cohort study)	Direct	Imprecise	Moderate	Consistent	No differences	Low
Tapering off opioids vs. continuation of opioids	Pain, function (long-term)	1 new cohort study	290	Direct	Imprecise	High	Unknown	No differences	Insufficient
	Serious harms (overdose, suicide)	3 (2 new) cohort studies	128,786	Direct	Precise	High	Inconsistent	Findings inconsistent, with methodological shortcomings	Insufficient
Tapering protocols and strategies (slower vs. faster taper)	ED visit or hospitalization, overdose, mental health events, suicide event	3 (2 new) cohort studies	128,708	Direct	Precise	Moderate	Consistent	Slower taper associated with decreased harms	Low
Prescription opioid use disorder: Buprenorphine vs. methadone	Drug use, pain function	2 (1 new) RCTs	73	Indirect	Imprecise	Moderate	Consistent	No differences	Low

Abbreviations: AE = adverse events; CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SMD = standard mean difference; SOE = strength of evidence; TENS = transcutaneous electrical nerve stimulation.

* Reporting bias was undetected for all Key Questions/outcomes

† Mean differences for pain are reported on a 0 to 10 scale

‡ The original report did not evaluate this comparison.

Appendix H. Excluded Studies List

1. Abdel Shaheed C, Awal W, Zhang G, et al. Efficacy, safety, and dose-dependence of the analgesic effects of opioid therapy for people with osteoarthritis: systematic review and meta-analysis. Medical J Aust. 2022. doi: 10.5694/mja2.51392. **Exclusion reason:** Systematic review used as source document
2. Abdel Shaheed C, Maher CG, McLachlan AJ. Efficacy and Safety of Low-dose Codeine-containing Combination Analgesics for Pain: Systematic Review and Meta-Analysis. Clin J Pain. 2019 10;35(10):836-43. doi: 10.1097/AJP.0000000000000746. PMID: 31318725. **Exclusion reason:** Inadequate duration
3. Adams KK, Machnicz M, Sobieraj DM. Initiating buprenorphine to treat opioid use disorder without prerequisite withdrawal: a systematic review. Addict Sci Clin Pract. 2021 06 08;16(1):36. doi: 10.1186/s13722-021-00244-8. PMID: 34103087. **Exclusion reason:** Systematic review used as source document
4. Adejumo AC, Akanbi O, Alayo Q, et al. Predictors, rates, and trends of opioid use disorder among patients hospitalized with chronic pancreatitis. Ann Gastroenterol. 2021;34(2):262-72. doi: 10.20524/aog.2021.0579. PMID: 33654369. **Exclusion reason:** Ineligible intervention
5. Akazawa M, Igarashi A, Ebata N, et al. A Cost-Effectiveness Analysis Of Pregabalin For The Treatment Of Patients With Chronic Cervical Pain With A Neuropathic Component In Japan. J Pain Res. 2019;12:2785-97. doi: 10.2147/JPR.S203712. PMID: 31576163. **Exclusion reason:** Ineligible comparator
6. Akhurst J, Lovell M, Peacock A, et al. A Systematic Review and Meta-Analysis of Cognitive Performance among People with Chronic Use of Opioids for Chronic Non-Cancer Pain. Pain Med. 2021 04 20;22(4):979-93. doi: 10.1093/pm/pnab005. PMID: 33502504. **Exclusion reason:** Systematic review used as source document
7. Alderson SL, Farragher TM, Willis TA, et al. The effects of an evidence- and theory-informed feedback intervention on opioid prescribing for non-cancer pain in primary care: A controlled interrupted time series analysis. PLoS Med. 2021 Oct;18(10):e1003796. doi: 10.1371/journal.pmed.1003796. PMID: 34606504. **Exclusion reason:** Ineligible outcome
8. Alenezi A, Yahyouche A, Paudyal V. Interventions to optimize prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review. Eur J Clin Pharmacol. 2021 Apr;77(4):467-90. doi: 10.1007/s00228-020-03026-4. PMID: 33123784. **Exclusion reason:** Systematic review used as source document
9. Alhaj-Suliman SO, Milavetz G, Salem AK. Model-based Meta-analysis to Compare Primary Efficacy-endpoint, Efficacy-time Course, Safety, and Tolerability of Opioids Used in the Management of Osteoarthritic Pain in Humans. Curr Drug Metab. 2020;21(5):390-9. doi: 10.2174/1389200221666200514130441. PMID: 32407270. **Exclusion reason:** Ineligible publication type
10. Anastasiou C, Yazdany J. Review of publications evaluating opioid use in patients with inflammatory rheumatic disease. Curr Opin Rheumatol. 2022 03 01;34(2):95-102. doi: 10.1097/BOR.0000000000000868. PMID: 35044328. **Exclusion reason:** Systematic review used as source document
11. Anderson AB, Grazal CF, Balazs GC, et al. Can Predictive Modeling Tools Identify Patients at High Risk of Prolonged Opioid Use After ACL Reconstruction? Clin Orthop Relat Res. 2020 07;478(7):0-1618. doi: 10.1097/CORR.0000000000001251. PMID: 32282466. **Exclusion reason:** Ineligible population
12. Anele UA, Wood HM, Angermeier KW. Management of Urosymphyseal Fistula and Pelvic Osteomyelitis: A Comprehensive Institutional Experience and Improvements in Pain Control. Eur Urol Focus. 2021doi: 10.1016/j.euf.2021.08.008. PMID:

34479839. **Exclusion reason:** Ineligible intervention

13. Anger M, Valovska T, Beloeil H, et al. PROSPECT guideline for total hip arthroplasty: a systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 2021 08;76(8):1082-97. doi: 10.1111/anae.15498. PMID: 34015859. **Exclusion reason:** Systematic review used as source document

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

15. Azubike N, Moseley M, Powers JS. Opioid Management in Older Adults: Lessons Learned From a Geriatric Patient-Centered Medical Home. Fed Pract. 2021 Apr;38(4):168-73. doi: 10.12788/fp.0110. PMID: 34177221. **Exclusion reason:** Ineligible comparator

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

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

18. Bahji A, Carlone D, Altomare J. Acceptability and efficacy of naltrexone for criminal justice-involved individuals with opioid use disorder: a systematic review and meta-analysis. Addiction. 2020 08;115(8):1413-25. doi: 10.1111/add.14946. PMID: 31863669. **Exclusion reason:** Systematic review used as source document

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

20. Bahji A, Cheng B, Gray S, et al. Mortality Among People With Opioid Use Disorder: A Systematic Review and Meta-analysis. J Addict Med. 2020 Jul/Aug;14(4):e118-e32. doi: 10.1097/ADM.0000000000000606. PMID: 32011406. **Exclusion reason:** Systematic review used as source document

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

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

23. Barreveld AM, McCarthy RJ, Elkassabany N, et al. Opioid Stewardship Program and Postoperative Adverse Events: A Difference-in-differences Cohort Study. Anesthesiology. 2020 06;132(6):1558-68. doi: 10.1097/ALN.0000000000003238. PMID: 32167983. **Exclusion reason:** Ineligible setting

24. 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: 10.1177/1715163519887766. PMID: 32002103. **Exclusion reason:** Ineligible comparator

25. Barry Dt BMCCJFDAKRDMBAOLMLMLCGJ. An evaluation of the feasibility, acceptability, and preliminary efficacy of cognitive-behavioral therapy for opioid use disorder and chronic pain. Drug Alcohol Depend. 2019;194:460. **Exclusion reason:** Ineligible comparator

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

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

28. 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

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

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

31. Benedict G, Sabbagh A, Conermann T. Medical Cannabis Used as an Alternative Treatment for Chronic Pain Demonstrates Reduction in Chronic Opioid Use - A Prospective Study. Pain Physician. 2022 Jan;25(1):E113-E9. PMID: 35051158. **Exclusion reason:** Ineligible comparator

32. Benemei S, Lupi C, De Cesaris F, et al. Low-dose methadone for refractory chronic migraine accompanied by medication-overuse headache: a prospective cohort study. Neurological Sciences. 2021 Mar;42(3):987-94. doi: 10.1007/s10072-020-04602-3. PMID: 32691178. **Exclusion reason:** Ineligible comparator

33. 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

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

35. Beyer CA, Poltavskiy E, Walker LE, et al. Persistent Opioid Use After Combat Injury and Subsequent Long-term Risk of Abuse: A Retrospective Cohort Study. Ann Surg. 2021 12 01;274(6):e957-e65. doi: 10.1097/SLA.0000000000003658. PMID: 31714315. **Exclusion reason:** Ineligible population

36. Bhatia A, Kara J, Janmohamed T, et al. User Engagement and Clinical Impact of the Manage My Pain App in Patients With Chronic Pain: A Real-World, Multi-site Trial. JMIR Mhealth Uhealth. 2021 03 04;9(3):e26528. doi: 10.2196/26528. PMID: 33661130. **Exclusion reason:** Ineligible intervention

37. Bhatraju E, Liebschutz JM, Lodi S, et al. Post-traumatic stress disorder and risky opioid use among persons living with HIV and chronic pain. AIDS Care. 2021 Feb 04:1-8. doi: 10.1080/09540121.2021.1876838. PMID: 33535800. **Exclusion reason:** Ineligible outcome

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

10.1002/ejp.1496. PMID: 31661587. **Exclusion reason:** Ineligible study design

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

40. Black RA, McCaffrey SA, Butler SF. Development of a brief version of the current opioid misuse measure (comm): The comm-9. Postgrad Med. 2017;129(SUPPL 1):73-4. doi: 10.1080/00325481.2017.1367065. **Exclusion reason:** Ineligible publication type

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

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

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

44. Boland EG, Bennett MI, Allgar V, et al. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. BMJ Support. 2020 Mar;10(1):14-24. doi: 10.1136/bmjspcare-2019-002032. PMID: 31959586. **Exclusion reason:** Systematic review used as source document

45. Bonifonte A, Merchant R, Deppen K. Morphine Equivalent Total Dosage as Predictor of Adverse Outcomes in Opioid Prescribing. Pain Med. 2021 Dec 11;22(12):3062-71. doi: 10.1093/pm/pnab249. PMID: 34373930. **Exclusion reason:** Ineligible population

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

47. Boscarino JA, Withey CA, Dugan RJ, et al. Opioid Medication Use Among Chronic Non-Cancer Pain Patients Assessed with a Modified Drug Effects Questionnaire and the Association with Opioid Use Disorder. J Pain Res. 2020;13:2697-705. doi: 10.2147/JPR.S275397. PMID: 33122939. **Exclusion reason:** Ineligible intervention

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

49. 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

50. Boyett B, Wiest K, McLeod LD, et al. Assessment of craving in opioid use disorder: Psychometric evaluation and predictive validity of the opioid craving VAS. Drug Alcohol Depend. 2021 12 01;229(Pt B):109057. doi: 10.1016/j.drugalcdep.2021.109057. PMID: 34794061. **Exclusion reason:** Ineligible outcome

51. Breeden MA, Jacobs CK, Witthaus M, et al. Prescribing Patterns and Use of Risk-Reduction Tools After Implementing an Opioid-Prescribing Protocol. J Am Board Fam Med. 2020 Jan-Feb;33(1):27-33. doi: 10.3122/jabfm.2020.01.190247. PMID: 31907243. **Exclusion reason:** Ineligible study design

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

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

54. 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: 10.1016/j.cct.2021.106456. PMID: 34048943. **Exclusion reason:** Ineligible publication type

55. Bushey MA, Wu J, Outcalt SD, et al. Opioid use as a predictor of pain outcomes in Iraq and Afghanistan Veterans with chronic pain: Analysis of a randomized controlled trial. Pain Med. 2021 Aug 19;22(12):2964-70. doi: 10.1093/pm/pnab237. PMID: 34411252. **Exclusion reason:** Ineligible intervention

56. Cacicedo J, Ciria JP, Morillo V, et al. Pain response and quality of life assessment in patients with moderate/severe neuropathic pain due to bone metastasis undergoing treatment with palliative radiotherapy and tapentadol: A prospective multicentre pilot study. J Med Imaging Radiat Oncol. 2020 Dec;64(6):859-65. doi: 10.1111/1754-9485.13088. PMID: 32729219. **Exclusion reason:** Ineligible population

57. 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

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

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

60. Cao Z, Li Y, Wang W, et al. Is Lutikizumab, an Anti-Interleukin-1alpha/beta Dual Variable Domain Immunoglobulin, efficacious for Osteoarthritis? Results from a bayesian network meta-analysis. Biomed Res Int. 2020;2020:9013283. doi: 10.1155/2020/9013283. PMID: 33204726. **Exclusion reason:** Ineligible intervention

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

62. Cariveau D, Fay AE, Baker D, et al. Evaluation of a pharmacist-led naloxone coprescribing program in primary care. J Am Pharm Assoc (2003). 2019 Nov - Dec;59(6):867-71. doi: 10.1016/j.japh.2019.07.012. PMID: 31466899. **Exclusion reason:** Ineligible study design

63. Carrell DS, Albertson-Junkans L, Ramaprasan A, et al. Measuring problem prescription opioid use among patients receiving long-term opioid analgesic treatment: development and evaluation of an algorithm for use in EHR and claims data. J Drug Assess. 2020;9(1):97-105. doi: 10.1080/21556660.2020.1750419. PMID: 32489718. **Exclusion reason:** Ineligible population

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

33821594. **Exclusion reason:** Ineligible outcome

65. Challapalli V, Tremont-Lukats IW, McNicol ED, et al. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database Syst Rev. 2019 10 07;10(10):07. doi: 10.1002/14651858.CD003345.pub2. PMID: 31684682. **Exclusion reason:** Systematic review used as source document

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

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

68. Chen C, Lo-Ciganic W-H, Winterstein AG, et al. Concurrent Use of Prescription Opioids and Gabapentinoids in Older Adults. Am J Prev Med. 2021doi: 10.1016/j.amepre.2021.08.024. **Exclusion reason:** Ineligible outcome

69. Chou R, Hartung D, Turner J, et al. Opioid Treatments for Chronic Pain. Agency for Healthcare Research and Quality (US). 2020 Apr 2020;Report No.: 20-EHC011 PMID: 32338848. **Exclusion reason:** Systematic review used as source document

70. Chou R, Wagner J, Ahmed AY, et al. Agency for Healthcare Research and Quality (US). 2020 12;20(21):12. PMID: 33411426. **Exclusion reason:** Systematic review used as source document

71. Compton P, Halabicky OM, Aryal S, et al. Opioid Taper is Associated with Improved Experimental Pain Tolerance in Patients with Chronic Pain: An Observational Study. Pain Ther. 2022 Jan 12;12:12. doi: 10.1007/s40122-021-00348-8. PMID: 35020185. **Exclusion reason:** Ineligible comparator

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

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

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

75. Coyne CJ, Kettler E, Dong K, et al. Improving cancer pain management in the emergency department: An EMR-based solution. J Clin Oncol. 2021;39(15 SUPPL)doi: 10.1200/JCO.2021.39.15_suppl.12110. **Exclusion reason:** Ineligible population

76. Coyne KS, Barsdorf AI, Currie BM, et al. Construct validity and reproducibility of the Prescription Opioid Misuse And Abuse Questionnaire (POMAQ). Curr Med Res Opin. 2021 Mar;37(3):493-503. doi: 10.1080/03007995.2020.1865890. PMID: 33327799. **Exclusion reason:** Ineligible outcome

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

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

79. Cuomo A, Cascella M, Forte CA, et al. Careful Breakthrough Cancer Pain Treatment through Rapid-Onset Transmucosal Fentanyl Improves the Quality of Life in Cancer Patients: Results from the BEST Multicenter Study. J Clin Med. 2020 Apr 02;9(4):02. doi: 10.3390/jcm9041003. PMID: 32252426. **Exclusion reason:** Ineligible study design

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

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

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

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

84. Danielson EC, Harle CA, Silverman R, et al. Assessing Variation in State Opioid Tapering Laws: Comparing State Laws with the CDC Guideline. Pain Med. 2021 Dec 11;22(12):2941-9. doi: 10.1093/pm/pnab208. PMID: 34196723. **Exclusion reason:** Ineligible study design

85. Darnall BD, Mackey SC, Lorig K, et al. Comparative Effectiveness of Cognitive Behavioral Therapy for Chronic Pain and Chronic Pain Self-Management within the Context of Voluntary Patient-Centered Prescription Opioid Tapering: The EMPOWER Study Protocol. Pain Med. 2020 08 01;21(8):1523-31. doi: 10.1093/pm/pnz285. PMID: 31876947. **Exclusion reason:** Ineligible outcome

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