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

(<u>https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research</u>). This is the final surveillance update planned for this topic.

Scope

The scope and eligibility criteria established at the time of the original report¹ were utilized for this surveillance report; no changes were made. The report focused on use of opioids in adults for chronic pain management and addressed the following areas:

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

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



Methods

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

As in the original review, one investigator screened citations identified through searches for eligibility for full-text review. (Key Questions and inclusion criteria are available in Appendix B.) In addition, 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. 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 betweengroup 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.

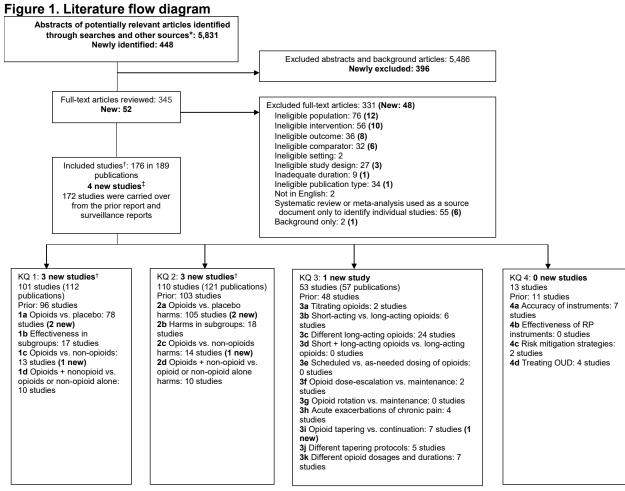
As in prior surveillance reports, the decision to update meta-analyses from the original report was based on the number and sample sizes of new studies eligible for meta-analysis (metaanalysis performed if new evidence was large relative to the studies in the original metaanalysis); consistency in findings between the new studies and the original meta-analysis (metaanalysis 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 <u>Appendix C</u>. Evidence tables providing data from these included studies are available in <u>Appendix D</u>, and quality assessments for each of these studies are shown in <u>Appendix E</u>. Updated meta-analyses are included in <u>Appendix F</u>, and updated strength of evidence tables for outcomes with new evidence are available in <u>Appendix G</u>. A list of articles excluded at full-text review, along with reasons for exclusion, is available in <u>Appendix H</u>.

Results

The search for Surveillance Report 3 from December 2021 through March 16, 2022, yielded 448 citations; of these, 3 new studies³⁻⁵ met inclusion criteria (2 randomized controlled trials [RCTs] and 1 observational study); in addition, one older placebo-controlled trial⁶ of opioids in patients with osteoarthritis that met inclusion criteria was identified from reference list review (Figure 1). One of the new trials⁵ was placebo controlled and evaluated opioids for chronic low back pain, and the other new trial⁴ 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 pain³ (Appendix D, Table D-2).



Note: New studies are those added since the original systematic review, Surveillance Report 1, and Surveillance Report 2.

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.

^{*} 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.

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, I²=71%) and 44 trials (for pain response, RR 1.35, 95% CI 1.24 to 1.48, I²=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, I²=73%) and for likelihood of pain response (47 RCTs, RR 1.33, 95% CI 1.22 to 1.46, I²=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.	Opioids associated with	3 additional RCTs (2 identified	No change in
placebo, short-term	increased risk of withdrawal	for Surveillance Report 3	conclusions
harms	due to adverse events, nausea,	[n=1,011 and 299] ^{5,6} and 1 from	
	vomiting, constipation,	Surveillance Report 1 [n=40])7	
	dizziness, somnolence,	found opioids associated with	
	pruritus	increased risk of short-term	
	SOE: High, based on 30 to	harms versus placebo. In	
	60 RCTs	updated meta-analyses:	
		Withdrawal due to adverse	
		events (64 RCTs): RR 2.27	
		(95% Cl 1.89 to 2.74),	
		l 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),	
		l²=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%	
KO 0 - Onici I	Onicide consists to the	to 9%)	NIl
KQ 2a. Opioids vs. no	Opioids associated with	1 retrospective cohort study ⁹	No change in
opioids, long-term harms	increased risk of all-cause	(n=1,320) from Surveillance	conclusions
(all-cause mortality and	mortality and cardiovascular	Report 2 of patients with	
cardiovascular events)	events (myocardial infarction or	rheumatoid arthritis found	
	cardiovascular mortality)	tramadol associated with	
	SOE: low, based on 1 (all-	increased risk of all-cause	
	cause mortality) or 3	mortality and cardiovascular	
	(cardiovascular events)	events vs. no tramadol	
KO 2h Harma by doos	observational studies Opioids associated with	1 case control study ¹⁰ (2 211	No change in
KQ 2b. Harms by dose		1 case-control study ¹⁰ (2,311	No change in conclusions
or duration	increased risk of overdose, and 1	cases) from Surveillance Report 1	CONCIUSIONS
	observational study found higher	found higher dose of opioids	
	dose of opioids associated with	associated with increased risk of	
	increased risk of mortality	mortality and overdose	
	SOE: Low, based on 4 sharmational studies		
	observational studies		

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. shortacting 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

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, I²=71%), likelihood of a pain response (44 trials, relative risk [RR] 1.35, 95% CI 1.24 to 1.48, I²=81%), and improvement in function (44 trials, standardized mean difference [SMD] –0.22, 95% CI –0.28 to –0.16, I²=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 trial⁵ (n=1,011) and the other was an older trial⁶ (n=293) identified by reference list review (Appendix D, Table D-1). The new trial evaluated the mixed agent tranadol 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.

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

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 $\geq 30\%$ 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 $\geq 30\%$ 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 trial⁷ (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, I²=73%; <u>Appendix F</u>, Figure F-1), likelihood of pain response (47 RCTs, RR 1.33, 95% CI 1.22 to 1.46, I²=83%; absolute risk difference [ARD] 14%, 95% CI 11 to 18%; <u>Appendix F</u>, Figure F-2), and function (46 RCTs, SMD –0.21, 95% CI –0.27 to –0.15, I²=55%; <u>Appendix F</u>, 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 osteoarthritis⁴ (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 $\geq 30\%$ 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 $\geq 20\%$ 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 trial⁷ 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, I²=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, I²=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, I²=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, I²=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, I²=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, I²=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, I²=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, I²=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, I²=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 <u>Appendix D</u>, 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) trial¹⁷ 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 therapy³ (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, dosedependent 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.

References

- 1. 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.
- 2. Chou R, Dana T, Shetty KD. AHRQ
 Methods for Effective Health Care. Testing
 a Machine Learning Tool for Facilitating
 Living Systematic Reviews of Chronic Pain
 Treatments. Rockville (MD): Agency for
 Healthcare Research and Quality (US);
 2020.
- 3. 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.
- 4. 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: https://dx.doi.org/10.1177/1759720X211066233. PMID: 35069809.
- 5. 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 Sep 1;161(9):2068-78. doi:10.1097/j.pain.00000000000001928. PMID: 32453139.
- 6. 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.
- 7. 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/PR9.00000000000000877. PMID: 33364540.

- 8. Shah D, Zhao X, Wei W, et al. A longitudinal study of the association of opioid use with change in pain interference and functional limitations in a nationally representative cohort of adults with osteoarthritis in the United States. Adv Ther. 2020 Feb;37(2):819-32. doi:10.1007/s12325-019-01200-4. PMID: 31875300.
- 9. 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 Oct 28;zwab176. doi:10.1093/eurjpc/zwab176. PMID: 34718505.
- 10. 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 Feb;37(2):367-74. doi:10.1007/s11606-021-06792-8. PMID: 34258726.
- 11. 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.
- 12. Hayes CJ, Krebs EE, Hudson T, et al. Impact of opioid dose escalation on pain intensity: a retrospective cohort study. Pain. 2020 May;161(5):979-88. doi:10.1097/j.pain.0000000000001784. PMID: 31917775.
- 13. 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.
- 14. Hallvik SE, El Ibrahimi S, Johnston K, et al. Patient outcomes following opioid dose reduction among patients with chronic opioid therapy. Pain. 2022 Jan 1;163(1):83-90. doi: 10.1097/j.pain.0000000000002298. PMID: 33863865.

- 15. 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 Sep 8;22(9):2007-2018. doi:10.1093/pm/pnaa461. PMID: 33576415.
- 16. 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.

17. Sullivan MD, Turner JA, DiLodovico C, et al. Prescription opioid taper support for outpatients with chronic pain: a randomized controlled trial. J Pain. 2017 Mar;18(3):308-18. doi: 10.1016/j.jpain.2016.11.003. PMID: 27908840.

Authors

Roger Chou, M.D., FACP Shelley Selph, M.D., M.P.H. Jesse Wagner, M.A. Azrah Y. Ahmed, B.A. Rebecca Jungbauer, D.Ph., M.P.H, M.A. Kim Mauer, M.D. Kanaka D. Shetty, M.D., M.S. Yun Yu, M.S. Rongwei Fu, Ph.D.

Acknowledgments

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

Disclaimers

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

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

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

This report is made available to the public under the terms of a licensing agreement between the author and the Agency for Healthcare Research and Quality. Most AHRQ documents are publicly available to use for noncommercial purposes (research, clinical or patient education, quality improvement projects) in the United States, and do not need specific permission to be reprinted and used unless they contain material that is copyrighted by others. Specific written permission is needed for commercial use (reprinting for sale, incorporation into software, incorporation into for-profit training courses) or for use outside of the U.S. If organizational policies require permission to adapt or use these materials, AHRQ will provide such permission in writing.

AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

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

Suggested citation: Chou R, Selph S, Wagner J, Ahmed AY, Jungbauer R, Mauer K, Shetty KD, Yu Y, Fu R. Systematic Review on Opioid Treatments for Chronic Pain: Surveillance Report 3. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 22-EHC032. Rockville, MD: Agency for Healthcare Research and Quality; June 2022. DOI: https://doi.org/10.23970/AHRQEPCSURVEILLANCE3OPIOIDCHRONIC. Posted final reports are located on the Effective Health Care Program search-page.

Afterword

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

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

This 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.

Robert Otto Valdez, Ph.D., M.H.S.A.

Director

Agency for Healthcare Research and Quality

Craig A. Umscheid, M.D., M.S. Director

Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.

Director

Center for Evidence and Practice Improvement Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D. Task Order Officer

Evidence-based Practice Center Program Center for Evidence and Practice Improvement Agency for Healthcare Research and Quality

Appendix Contents

Appendix A. Literature Search Strategies	A-1
Optimized Search for Machine Learning	A-9
Appendix B. Key Questions and Inclusion and Exclusion Criteria	B-1
Key Questions	B-1
Inclusion and Exclusion Criteria	B-4
Appendix C. Included Studies List	C-1
Appendix D. Evidence Tables	D-1
Appendix E. Quality Assessment	E-1
Appendix F. Meta-analysis Results	F-1
Appendix G. Strength of Evidence Tables	G-1
Appendix H. Excluded Studies List	H-1

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) adj 1 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 coprescribing 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.
- 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/PR9.00000000000000877. 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

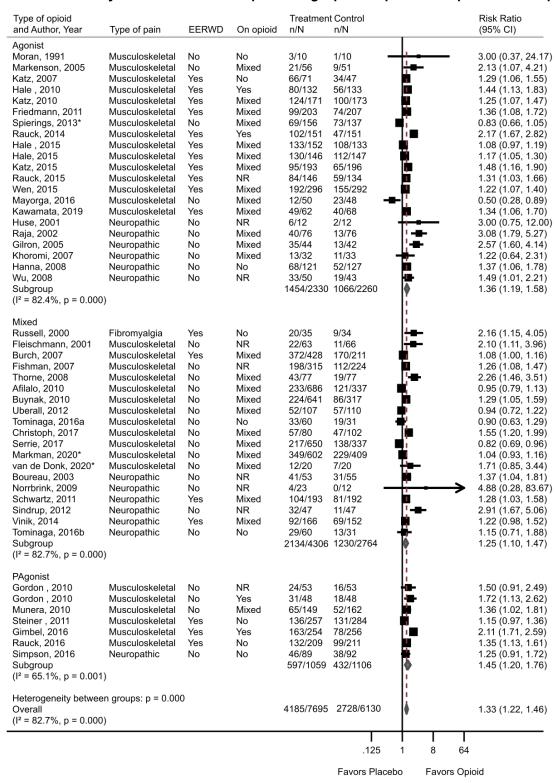
Figure F-1. Meta-analysis of improvement in mean pain measures for opioids versus placebo

Type of opioid and Author, Year	Type of pain	EERWD	On opioid	N, Mean (SD), Opioid	N, Mean (SD), Comparison		Mean Difference (95% CI)
Agonist Moran, 1991	Musculoskolotol	No	No	7 4 96 (4 24)	9 7 23 (4 60)	<u>-</u>	_2 27 (_2 02 0 74)
Moran, 1991 Caldwell, 1999	Musculoskeletal Musculoskeletal	No Yes	NO NR	7, 4.96 (1.34) 34, 1.47 (2.53)	8, 7.23 (1.69) 36, 3.33 (2.60)		-2.27 (-3.83, -0.71) -1.87 (-3.07, -0.66)
Peloso, 2000	Musculoskeletal	No	Mixed	31, 2.91 (2.03)	35, 4.43 (2.37)		-1.52 (-2.59, -0.45)
Caldwell, 2002	Musculoskeletal	No	Mixed	222, 5.08 (3.11)	73, 5.93 (2.73)	- +-	-0.85 (-1.64, -0.05)
Markenson, 2005	Musculoskeletal	No	Mixed	55, -1.70 (2.22)	51, -0.60 (2.86)	=; -	-1.10 (-2.07, -0.13)
Matsumoto, 2005	Musculoskeletal	No	Mixed	365, -2.04 (2.21)	124, -1.24 (2.23)	-+ -	-0.80 (-1.25, -0.34)
Langford, 2006	Musculoskeletal	No	Yes	202, -2.36 (2.56)	197, -1.79 (2.67)	_ **	-0.57 (-1.08, -0.06)
Webster, 2006	Musculoskeletal	No	Mixed	205, 4.00 (2.53)	101, 5.20 (3.06)	_ -= †	-1.20 (-1.85, -0.55)
Hale, 2007	Musculoskeletal	Yes	Yes	70, 0.87 (2.51)	72, 3.16 (2.46)	— — ;	-2.29 (-3.11, -1.47)
Katz, 2007 Hale, 2010	Musculoskeletal Musculoskeletal	Yes Yes	No Yes	105, 1.09 (2.45) 133, 3.10 (1.90)	100, 2.60 (2.79) 133, 3.80 (1.75)		-1.69 (-2.36, -1.02) -0.70 (-1.14, -0.26)
Katz, 2010	Musculoskeletal	Yes	Mixed	170, -0.20 (1.90)	173, 0.30 (2.10)	<u> </u>	-0.70 (-1.14, -0.20)
Friedmann, 2011	Musculoskeletal	Yes	Mixed	203, -0.70 (2.05)	207, -0.30 (2.48)	Lee	-0.40 (-0.84, 0.04)
Vojtassak, 2011	Musculoskeletal	No	Mixed	138, -2.40 (2.10)	149, -2.60 (2.30)	1	0.20 (-0.31, 0.71)
Chu, 2012	Musculoskeletal	No	Mixed	48, -2.11 (1.59)	55, -1.25 (1.92)		-0.86 (-1.55, -0.17)
Cloutier, 2013	Musculoskeletal	No	Mixed	54, 4.86 (2.31)	54, 5.59 (2.54)		-0.73 (-1.65, 0.19)
Rauck, 2013	Musculoskeletal	No	Mixed	649, -2.20 (2.60)	331, -1.90 (2.90)	! -= 	-0.30 (-0.66, 0.06)
Spierings, 2013*	Musculoskeletal	No	Mixed	156, -2.17 (3.00)	137, -2.28 (3.04)	! 	0.11 (-0.58, 0.80)
Rauck, 2014	Musculoskeletal	Yes	Yes	151, 0.48 (1.56)	151, 0.96 (1.55)	<u>'=</u> -	-0.48 (-0.83, -0.13)
Hale, 2015	Musculoskeletal	Yes	Mixed	146, -0.60 (3.24)	147, -0.03 (2.63)		-0.57 (-1.25, 0.11)
Hale, 2015	Musculoskeletal	Yes	Mixed	191, -0.03 (1.70)	179, 0.55 (1.90)	📆	-0.58 (-0.91, -0.25)
Katz, 2015 Rauck, 2015	Musculoskeletal	Yes	Mixed NR	193, 0.29 (2.10) 146, 0.60 (2.00)	196, 1.85 (3.10) 134, 1.23 (2.10)	 -	-1.56 (-2.06, -1.06) -0.62 (-1.10, -0.14)
Trenkwalder, 2015	Musculoskeletal Musculoskeletal	Yes No	No	88, 5.00 (2.36)	106, 5.60 (2.34)	_=_	-0.62 (-1.10, -0.14)
Wen, 2015	Musculoskeletal	Yes	Mixed	NR	NR	<u></u>	-0.53 (-0.88, -0.18)
Arai, 2015a	Musculoskeletal	Yes	No	73, -0.02 (1.82)	77, 0.69 (2.08)	_ <u></u>	-0.73 (-1.34, -0.12)
Lin, 2016	Musculoskeletal	No	No	11, -1.52 (2.40)	10, -1.46 (1.39)	<u> </u>	-0.75 (-1.34, -0.12)
Mayorga, 2016	Musculoskeletal	No	Mixed	50, -1.45 (2.55)	48, -2.93 (2.56)	: 1 -	1.48 (0.47, 2.49)
Kawamata, 2019	Musculoskeletal	Yes	Mixed	62, 0.10 (1.57)	68, 0.50 (1.65)	÷∎∔	-0.40 (-0.96, 0.16)
Watson, 1998	Neuropathic	No	NR	38, 3.50 (2.50)	38, 5.40 (2.50)	 ¦⁻l	-1.90 (-3.02, -0.78)
Huse, 2001	Neuropathic	No	NR	12, 3.26 (1.59)	12, 3.99 (1.23)		-0.73 (-1.87, 0.41)
Raja, 2002	Neuropathic	No	Mixed	44, 4.40 (2.40)	44, 6.00 (2.00)		-1.60 (-2.52, -0.68)
Gimbel, 2003	Neuropathic	No	Mixed	82, -2.60 (2.54)	77, -1.50 (2.54)	;	-1.10 (-1.89, -0.31)
Watson, 2003	Neuropathic	No	NR	36, 2.18 (2.07)	36, 4.86 (2.66)	 ;	-2.68 (-3.78, -1.58)
Gilron, 2005	Neuropathic	No	Mixed	44, 3.30 (2.65)	44, 3.90 (2.65)		-0.60 (-1.71, 0.51)
Khoromi, 2007	Neuropathic	No	Mixed	28, 3.40 (2.80)	28, 3.70 (2.70)		-0.30 (-1.74, 1.14)
Hanna, 2008	Neuropathic	No	No	138, -2.10 (2.61)	145, -1.50 (2.38)		-0.55 (-0.95, -0.15)
Wu, 2008	Neuropathic	No	NR	50, -2.80 (2.00) 84, -0.03 (2.13)	43, -1.40 (2.70) 79, 0.96 (2.04)		-1.40 (-2.36, -0.44)
Arai, 2015b Subgroup (I ² = 74.1%,	Neuropathic p = 0.000)	Yes	No	84, -0.03 (2.13)	79, 0.90 (2.04)	<u>▼</u>	-0.87 (-1.50, -0.24) -0.80 (-1.02, -0.60)
Mixed						i	
Russell, 2000	Fibromyalgia	Yes	No	35, 5.90 (2.89)	34, 7.20 (2.33)	 -	-1.30 (-2.54, -0.06)
Schnitzer, 2000	Musculoskeletal	Yes	NR	127, 3.50 (2.79)	127, 5.10 (2.98)	 '	-1.60 (-2.31, -0.89)
Fleischmann, 2001	Musculoskeletal	No	NR	63, 5.25 (2.65)	66, 6.20 (2.82)		-0.95 (-1.90, -0.00)
Babul, 2004	Musculoskeletal	No	Mixed	124, -3.04 (2.57)	122, -1.77 (2.42)	- 	-1.27 (-1.89, -0.65)
Gana, 2006	Musculoskeletal	No	Mixed	806, -2.90 (2.98)	205, -2.02 (2.86)	- <u></u>	-0.88 (-1.33, -0.43)
Burch, 2007	Musculoskeletal	Yes	Mixed	393, -3.03 (2.12)	196, -2.29 (1.97)	* ! "_	-0.70 (-1.02, -0.38)
Fishman, 2007	Musculoskeletal Musculoskeletal	No No	NR Mixed	315, -0.87 (0.91) 77, 3.74 (2.39)	224, -0.65 (0.96)		-0.22 (-0.42, -0.03) -0.77 (-1.53, -0.01)
Thorne, 2008 Vorsanger, 2008	Musculoskeletal	Yes	Mixed	256, 3.23 (2.52)	77, 4.51 (2.43) 126, 4.03 (2.52)	===	-0.77 (-1.33, -0.01)
Afilalo, 2010	Musculoskeletal	No	Mixed	NR	NR	-	-0.51 (-0.82, -0.20)
Buynak, 2010	Musculoskeletal	No	Mixed	646, -2.90 (2.59)	319, -2.10 (2.33)	- -	-0.86 (-1.18, -0.53)
Delemos, 2011	Musculoskeletal	No	Mixed	599, -1.94 (4.36)	200, -1.90 (2.52)	~ 	-0.04 (-0.68, 0.59)
Uberall, 2012	Musculoskeletal	No	Mixed	107, -2.10 (2.00)	110, -2.00 (1.80)	i- -	-0.10 (-0.61, 0.41)
Tominaga, 2016a	Musculoskeletal	No	No	60, -3.05 (1.99)	31, -2.90 (2.22)		-0.15 (-1.05, 0.75)
Christoph, 2017	Musculoskeletal	No	Mixed	123, -3.05 (2.60)	125, -2.16 (2.30)	— 	-0.89 (-1.50, -0.28)
Serrie, 2017	Musculoskeletal	No	Mixed	NR	NR	i 🛨	-0.04 (-0.34, 0.27)
Markman, 2020*	Musculoskeletal	No	Mixed	602, -2.75 (2.45)	409, -2.40 (2.02)	i #	-0.12 (-0.45, 0.21)
van de Donk, 2020*	Musculoskeletal	No	Mixed	20, -1.95 (0.94)	20, -0.71 (0.80)	-■ i	-1.24 (-1.78, -0.70)
Harati, 1998	Neuropathic	No	No	65, 1.40 (0.81)	66, 2.20 (0.81)	_ 🔻 📗	-0.80 (-1.08, -0.52)
Sindrup, 1999	Neuropathic	No	NR	28, 4.00 (2.50)	28, 6.00 (1.75)		-2.00 (-3.13, -0.87)
Boureau, 2003	Neuropathic Neuropathic	No No	NR NR	63, 2.53 (2.30)	62, 3.36 (2.54) 12, 5.50 (2.59)		-0.90 (-1.69, -0.11)
Norrbrink, 2009 Schwartz, 2011	Neuropathic Neuropathic	No Yes	Mixed	23, 3.00 (1.48) NR	12, 5.50 (2.59) NR		-2.50 (-3.84, -1.16) -1.31 (-1.70, -0.92)
Sindrup, 2012	Neuropathic	No	NR	56, -2.40 (2.10)	55, -0.70 (1.80)		-1.70 (-2.29, -1.11)
Niesters, 2014	Neuropathic Neuropathic	No	Mixed	12, 4.30 (3.10)	12, 5.80 (2.40)		-1.70 (-2.29, -1.11)
Vinik, 2014	Neuropathic	Yes	Mixed	166, 0.28 (2.04)	152, 1.30 (2.43)		-1.02 (-1.51, -0.53)
Tominaga, 2016b	Neuropathic	No	No	60, -2.60 (2.23)	31, -2.60 (2.65)		0.00 (-1.03, 1.03)
Subgroup (I ² = 78.1%,				, ()	,, <u></u> (2.00)	φĪ	-0.80 (-1.02, -0.59)
PAgonist						i	
Breivik, 2010	Musculoskeletal	No	No	95, 3.75 (1.80)	99, 4.15 (1.75)	*= -	-0.43 (-0.88, 0.02)
Gordon, 2010	Musculoskeletal	No	NR	79, 3.92 (2.05)	79, 4.39 (2.13)		-0.47 (-1.12, 0.18)
Gordon, 2010	Musculoskeletal	No	Yes	75, 4.46 (2.14)	75, 5.24 (2.40)		-0.78 (-1.51, -0.05)
Munera, 2010	Musculoskeletal	No	Mixed	149, -1.84 (2.70)	162, -1.40 (2.70)	*■ †	-0.44 (-1.04, 0.16)
Steiner, 2011	Musculoskeletal	Yes	No	257, 3.81 (2.73)	283, 4.39 (2.52)	_==-	-0.58 (-1.02, -0.14)
Gimbel, 2016	Musculoskeletal	Yes	Yes	254, 0.88 (1.79)	256, 1.92 (1.87)	₹.	-0.98 (-1.32, -0.64)
Rauck, 2016	Musculoskeletal	Yes	No	209, 3.76 (1.94)	211, 4.39 (2.00)	==	-0.67 (-1.07, -0.27)
Simpson, 2016 Subgroup (II ² = 8.6%,	Neuropathic p = 0.334)	No	No	NR	NR		-1.20 (-1.83, -0.57) -0.71 (-0.90, -0.49)
Heterogeneity betwee	n groups: p = 0.515					i l	
Overall (I ² = 72.9%, p						<u> </u>	-0.78 (-0.91, -0.65)
						-2 0 2	
						Ferrer Oniold Ferr	
						Favors Opioid Favors Pla	acedo

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.

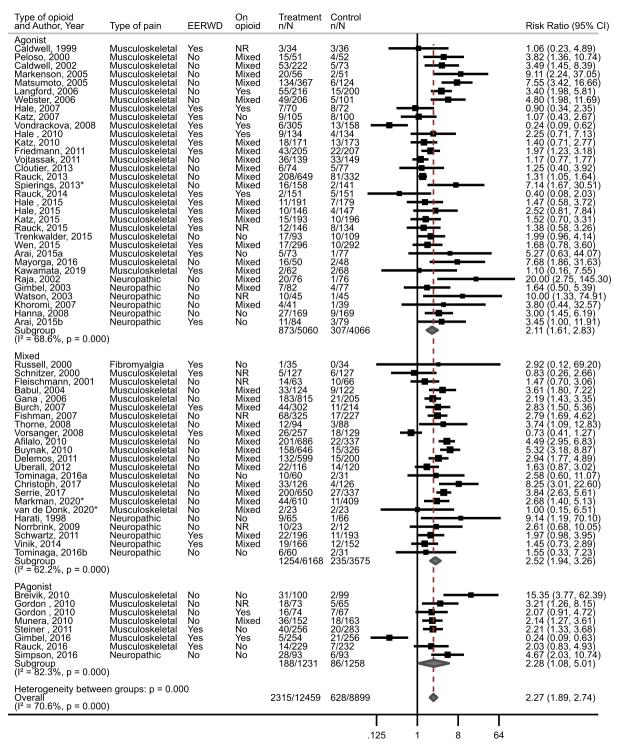
Figure F-3. Meta-analysis of improvement in mean function measures for opioids versus placebo

Moulin, 1996 Musc Peloso, 2000 Musc Caldwell, 2002 Musc Markenson, 2005 Musc Matsumoto, 2005 Musc Langford, 2006 Musc Katz, 2010 Musc Chu, 2012 Musc Cloutier, 2013 Musc Rauck, 2013 Musc Spierings, 2013* Musc Katz, 2015 Musc Katz, 2016 Musc Kawamata, 2019	culoskeletal	No N	No Mixed Mixed Mixed Mixed Mixed Yes Yes Mixed Mixed Mixed Mixed Mixed Mixed Mixed Mixed	BPIIC(0-10)	7, 2.30 (0.60) NR 31, 456.20 (316.20) 222, -197.11 (612.82) 56, -1.90 (2.24) 365, -277.60 (549.83) 202, -1.10 (1.40) 133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06) 54, 34.30 (15.60)	8, 2.30 (0.60) NR 35, 687.50 (415.50) 73, -96.70 (367.39) 51, -0.60 (2.14) 124, -175.00 (557.00) 197, -0.70 (1.40) 133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35) 55, -0.51 (4.14)	0.00 (-1.01, 1.0 -0.07 (-0.48, 0.3 -0.61 (-1.11, -0. -0.18 (-0.44, 0.0 -0.59 (-0.98, -0. -0.19 (-0.39, 0.0 -0.29 (-0.48, -0. -0.54 (-0.78, -0. -0.21 (-0.43, -0. -0.00 (-0.23, 0.2 -0.41 (-0.80, -0.
Moulin, 1996 Musc Peloso, 2000 Musc Caldwell, 2002 Musc Markenson, 2005 Musc Matsumoto, 2005 Musc Langford, 2006 Musc Lale, 2010 Musc Catz, 2010 Musc Colutier, 2013 Musc Cloutier, 2013 Musc Spierings, 2013* Musc Spierings, 2013* Musc Katz, 2015 Musc Katz, 2016 Musc Kawamata, 2019 Musc Kawamata, 2019 Musc Kawamata, 2019 Musc	culoskeletal	No N	Mixed Mixed Mixed Mixed Mixed Mixed Yes Yes Mixed Mixed Mixed Mixed Mixed Mixed Mixed Mixed	PDI (0-70) WOMAC (0-1700) WOMAC (0-1700) BPIIC (0-10) WOMAC (0-1700) WOMAC (0-10) RMDS (0-24) WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI (0-70)	NR 31, 456.20 (316.20) 222, -197.11 (612.82) 56, -1.90 (2.24) 365, -277.60 (549.83) 202, -1.10 (1.40) 133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	NR 35, 687.50 (415.50) 73, -96.70 (367.39) 51, -0.60 (2.14) 124, -175.00 (557.00) 197, -0.70 (1.40) 133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35)	-0.07 (-0.48, 0.3 -0.61 (-1.11, -0. -0.18 (-0.44, 0.0 -0.59 (-0.98, -0. -0.19 (-0.39, 0.0 -0.29 (-0.48, -0. -0.54 (-0.78, -0. -0.21 (-0.43, -0.
Peloso, 2000 Musc Caldwell, 2002 Musc Alarkenson, 2005 Musc Alatsumoto, 2005 Musc Alatsumoto, 2006 Musc Alate, 2010 Musc Catz, 2010 Musc Chu, 2012 Musc Chu, 2012 Musc Chut, 2013 Musc Spierings, 2013 Musc Spierings, 2013 Musc Alatek, 2015 Musc Catz, 2016 Musc Catz, 2016 Musc Catz, 2016 Musc Catz, 2016 Musc Catz, 2017 Musc Catz, 2017 Musc Catz, 2018 Musc Catz, 2018 Musc Catz, 2019 Musc Catz, 2019 Musc	culoskeletal	No No No No Yes No No No No No No Yes	Mixed Mixed Mixed Yes Yes Mixed Mixed Mixed Mixed Mixed Mixed	WOMAC (0-1700) WOMAC (0-1700) BPIIC(0-10) WOMAC (0-1700) WOMAC (0-100) RMDS (0-24) WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI(0-70)	31, 456.20 (316.20) 222, -197.11 (612.82) 56, -1.90 (2.24) 365, -277.60 (549.83) 202, -1.10 (1.40) 133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	35, 687.50 (415.50) 73, -96.70 (367.39) 51, -0.60 (2.14) 124, -175.00 (557.00) 133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35)	-0.61 (-1.11, -00.18 (-0.44, 0.0 -0.59 (-0.98, -00.19 (-0.98, -00.29 (-0.48, -00.54 (-0.78, -00.21 (-0.43, -0.
Additional (1997) Additional (1	culoskeletal	No No No Yes Yes No No No No No Yes	Mixed Mixed Mixed Yes Yes Mixed Mixed Mixed Mixed Mixed	WOMAC (0-1700) BPIIC(0-10) WOMAC (0-1700) WOMAC (0-10) WOMAC (0-10) WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI(0-70)	222, -197.11 (612.82) 56, -1.90 (2.24) 365, -277.60 (549.83) 202, -1.10 (1.40) 133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	73, -96.70 (367.39) 51, -0.60 (2.14) 124, -175.00 (557.00) 197, -0.70 (1.40) 133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35)	-0.18 (-0.44, 0.0 -0.59 (-0.98, -0. -0.19 (-0.39, 0.0 -0.29 (-0.48, -0. -0.54 (-0.78, -0. -0.21 (-0.43, -0.
tarkenson, 2005 Musc tatsumoto, 2005 Musc angford, 2006 Musc tale, 2010 Musc tale, 2010 Musc tolitassak, 2011 Musc tolitassak, 2011 Musc cloutier, 2013 Musc tauck, 2013 Musc tauck, 2013 Musc tauck, 2015 Musc tale, 2015 Musc talet, 2016 Musc talet, 2019 Musc	culoskeletal	No No No Yes Yes No No No No No Yes	Mixed Mixed Yes Yes Mixed Mixed Mixed Mixed Mixed	BPIIC(0-10) WOMAC (0-1700) WOMAC (0-10) RMDS (0-24) WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI(0-70)	56, -1.90 (2.24) 365, -277.60 (549.83) 202, -1.10 (1.40) 133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	51, -0.60 (2.14) 124, -175.00 (557.00) 197, -0.70 (1.40) 133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35)	-0.59 (-0.98, -0. -0.19 (-0.39, 0.0 -0.29 (-0.48, -0. -0.54 (-0.78, -0. -0.21 (-0.43, -0. -0.00 (-0.23, 0.2
Adstaumoto, 2005 Musc angford, 2006 Musc angford, 2006 Musc angford, 2010 Musc (atz, 2010 Musc (o)tats, 2011 Musc Cloutier, 2013 Musc atauck, 2013 Musc (atz, 2015 Musc atauck, 2016 Musc atauck, 2016 Musc atauck, 2019 Musc atauck	culoskeletal	No No Yes Yes No No No No No Yes	Mixed Yes Yes Mixed Mixed Mixed Mixed Mixed	WOMAC (0-1700) WOMAC (0-10) RMDS (0-24) WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI(0-70)	365, -277.60 (549.83) 202, -1.10 (1.40) 133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	124, -175.00 (557.00) 197, -0.70 (1.40) 133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35)	-0.19 (-0.39, 0.0 -0.29 (-0.48, -0. -0.54 (-0.78, -0. -0.21 (-0.43, -0. -0.00 (-0.23, 0.2
angford, 2006 Musc lale, 2010 Musc catz, 2010 Musc cojtassak, 2011 Musc chu, 2012 Musc cloutier, 2013 Musc lauck, 2013 Musc lale, 2015 Musc catz, 2015 Musc ca	culoskeletal	No Yes Yes No No No No No No	Yes Yes Mixed Mixed Mixed Mixed Mixed	WOMAC (0-10) RMDS (0-24) WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI(0-70)	202, -1.10 (1.40) 133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	197, -0.70 (1.40) 133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35)	-0.29 (-0.48, -0. -0.54 (-0.78, -0. -0.21 (-0.43, -0. -0.00 (-0.23, 0.2
lale, 2010 Musc latz, 2010 Musc lojtassak, 2011 Musc loutier, 2012 Musc loutier, 2013 Musc lauck, 2013 Musc lale, 2015 Musc latz, 2016 Musc lawamata, 2019 Musc lawamata, 2019 Musc	culoskeletal	Yes Yes No No No No No No Yes	Yes Mixed Mixed Mixed Mixed Mixed	RMDS (0-24) WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI(0-70)	133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35)	-0.54 (-0.78, -0. -0.21 (-0.43, -0. -0.00 (-0.23, 0.2
lale, 2010 Musc latz, 2010 Musc lojtassak, 2011 Musc loutier, 2012 Musc loutier, 2013 Musc lauck, 2013 Musc lale, 2015 Musc latz, 2016 Musc lawamata, 2019 Musc lawamata, 2019 Musc	culoskeletal	Yes Yes No No No No No No Yes	Yes Mixed Mixed Mixed Mixed Mixed	RMDS (0-24) WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI(0-70)	133, 8.20 (4.70) 171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	133, 11.00 (5.65) 173, 6.20 (17.80) 149, -11.90 (14.35)	-0.54 (-0.78, -0. -0.21 (-0.43, -0. -0.00 (-0.23, 0.2
atz, 2010 Musc ojtassak, 2011 Musc chu, 2012 Musc cloutier, 2013 Musc clauck, 2013 Musc atauck, 2013 Musc atz, 2015 Musc atz, 2016 Musc awamata, 2019 Musc	culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal	Yes No No No No No No Yes	Mixed Mixed Mixed Mixed	WOMAC (0-100) WOMAC (0-100) RMDS (0-24) PDI(0-70)	171, 2.30 (18.40) 138, -11.93 (13.17) 48, -2.02 (3.06)	173, 6.20 (17.80) 149, -11.90 (14.35)	-0.21 (-0.43, -0. -0.00 (-0.23, 0.2
ojtassak, 2011 Musc chu, 2012 Musc cloutier, 2013 Musc clauck, 2013 Musc cipierings, 2013 Musc clate, 2015 Musc clatz, 2015 Musc clauck, 2015 Musc clauck, 2015 Musc clauck, 2015 Musc clauck, 2015 Musc clauck, 2015 Musc clauck, 2015 Musc	culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal	No No No No No Yes	Mixed Mixed Mixed Mixed	WOMAC (0-100) RMDS (0-24) PDI(0-70)	138, -11.93 (13.17) 48, -2.02 (3.06)	149, -11.90 (14.35)	-0.00 (-0.23, 0.2
hu, 2012 Musc cloutier, 2013 Musc clauck, 2013 Musc pierings, 2013* Musc lale, 2015 Musc clauck, 2015 Musc clauck, 2015 Musc clauck, 2016 Musc dayorga, 2016 Musc cawamata, 2019 Musc	culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal	No No No No Yes	Mixed Mixed Mixed	RMDS (0-24) PDI(0-70)	48, -2.02 (3.06)	· · · · · · · · · · · · · · · · · · ·	Τ
Cloutier, 2013 Musc tauck, 2013 Musc piperings, 2013* Musc tale, 2015 Musc tatz, 2015 Musc tauck, 2015 Musc tauck, 2016 Musc tayorga, 2016 Musc tawamata, 2019 Musc	culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal	No No No Yes	Mixed Mixed	PDI(0-70)		00, 0.01 (4.14)	
tauck, 2013 Musc spierings, 2013* Musc lale, 2015 Musc satz, 2015 Musc tauck, 2015 Musc flayorga, 2016 Musc sawamata, 2019 Musc	culoskeletal culoskeletal culoskeletal culoskeletal culoskeletal	No No Yes	Mixed			54, 37.50 (15.20)	-0.21 (-0.58, 0.1
pierings, 2013* Musc lale, 2015 Musc latz, 2015 Musc lauck, 2015 Musc layorga, 2016 Musc lawamata, 2019 Musc	culoskeletal culoskeletal culoskeletal culoskeletal	No Yes		VVOIVIAC (U-UU)	649, -1.60 (2.00)	331, -1.30 (2.00)	-0.15 (-0.28, -0.
Alale, 2015 Musc (atz, 2015 Musc Rauck, 2015 Musc Mayorga, 2016 Musc (awamata, 2019 Musc	culoskeletal culoskeletal culoskeletal	Yes	iviixea	, ,		T	
atz, 2015 Musc tauck, 2015 Musc flayorga, 2016 Musc fawamata, 2019 Musc	culoskeletal culoskeletal		A discount	WOMAC (0-10)	156, -1.71 (2.75)	136, -1.67 (2.80)	-0.01 (-0.24, 0.2
lauck, 2015 Musc layorga, 2016 Musc lawamata, 2019 Musc	culoskeletal	Yes	Mixed	RMDS (0-24)	191, -1.29 (5.00)	179, -1.57 (4.80)	0.06 (-0.14, 0.2
layorga, 2016 Musc awamata, 2019 Musc			Mixed	RMDS (0-24)	193, 0.40 (4.83)	196, 0.70 (5.32)	-0.06 (-0.26, 0.1
awamata, 2019 Musc		Yes	NR	RMDS (0-24)	NR	NR F	0.04 (-0.20, 0.2
	culoskeletal	No	Mixed	WOMAC (0-100)	50, -1.34 (2.69)	48, -2.99 (2.70)	0.61 (0.20, 1.01
/atson, 1998 Neuro	culoskeletal	Yes	Mixed	RDQ (0-24)	62, 0.10 (3.94)	68, 1.20 (3.30)	-0.30 (-0.65, 0.0
	ropathic	No	NR	CS (0-3)	38, 0.30 (0.80)	38, 0.70 (1.00)	-0.44 (-0.89, 0.0
aja, 2002 Neuro	ropathic	No	Mixed	MPII(0-6)	44, 2.30 (1.50)	44, 2.50 (1.50)	-0.13 (-0.55, 0.2
imbel, 2003 Neur	ropathic	No	Mixed	BPIPFS(0-10)	82, -2.40 (2.54)	77, -1.90 (2.54)	-0.20 (-0.51, 0.1
atson, 2003 Neuro	ropathic	No	NR	PDI (0-70)	36, 16.80 (15.60)	36, 25.20 (16.70)	-0.51 (-0.98, -0.
ilron, 2005 Neur	ropathic	No	Mixed	BPIGA(0-10)	44, 3.10 (2.65)	44, 4.50 (2.65)	-0.52 (-0.95, -0.
horomi, 2007 Neur	ropathic	No	Mixed	OSI	28, 25.70 (16.50)	28, 30.50 (15.90)	-0.29 (-0.82, 0.2
ubgroup ($I^2 = 56.1\%$, p = 0	0.000)					•	-0.19 (-0.29, -0.
lixed						i	
	omyalgia	Yes	No	FIQ (0-100)	35, 44.60 (17.96)	34, 47.20 (15.72)	-0.15 (-0.62, 0.3
	culoskeletal	Yes	NR	RDQ(0-24)	127, 8.80 (6.20)	127, 10.20 (6.20)	-0.23 (-0.47, 0.0
	culoskeletal	No	NR	WOMAC (0-10)	63, 4.19 (2.06)	66, 4.92 (2.29)	-0.33 (-0.68, 0.0
	culoskeletal	No	Mixed	WOMAC (0-1700)	124, -407.00 (431.13)	122, -208.50 (488.11)	-0.43 (-0.68, -0.
	culoskeletal	No	Mixed	, ,		205, -234.30 (402.30)	-0.25 (-0.41, -0.
	culoskeletal		Mixed	PDI(0-70)	77, 22.80 (14.50)	77, 27.20 (14.80)	-0.30 (-0.62, 0.0
		No		, ,			, ,
-	culoskeletal	Yes	Mixed	RMDI (0-24)	256, 8.40 (5.70)	126, 9.80 (5.90)	-0.24 (-0.46, -0.
	culoskeletal	No	Mixed	WOMAC (0-10)	NR	NR -	-0.44 (-0.70, -0.
	culoskeletal	No	Mixed	BPI (0-10)	NR	NR -	-0.23 (-0.36, -0.
	culoskeletal	No	Mixed	WOMAC (0-1700)	599, -300.70 (709.76)	200, -290.10 (411.54)	-0.02 (-0.18, 0.1
hristoph, 2017 Musc	culoskeletal	No	Mixed	ODI (0 to 100)	77, -16.20 (15.60)	98, -12.80 (16.20)	-0.21 (-0.51, 0.0
errie, 2017 Musc	culoskeletal	No	Mixed	WOMAC (0-4)	298, -1.00 (0.75)	218, -0.90 (0.74)	-0.11 (-0.28, 0.0
larkman, 2020* Musc	culoskeletal	No	Mixed	RDQ (0-24)	602, -5.10 (4.91)	409, -4.90 (4.04)	-0.04 (-0.16, 0.0
orrbrink, 2009 Neuro	ropathic	No	NR	MPI (0-6)	23, 2.45 (1.48)	12, 3.64 (2.73)	-0.58 (-1.30, 0.1
inik, 2014 Neur	ropathic	Yes	Mixed	BPII (0-10)	147, -3.00 (2.07)	137, -2.60 (2.38)	-0.18 (-0.41, 0.0
ubgroup ($I^2 = 34.9\%$, p = (0.089)					•	-0.20 (-0.29, -0.
Agonist						;	
	culoskeletal	No	No	WOMAC (0-68)	94, 27.50 (12.40)	96, 28.60 (11.70)	-0.28 (-0.57, 0.0
•	culoskeletal	No	NR	QBDS(0-100)	53, 2.30 (0.90)	53, 2.40 (1.00)	-0.10 (-0.49, 0.2
	culoskeletal	Yes	No	BPII (0-10)	167, 2.00 (1.15)	196, 2.90 (1.49)	-0.67 (-0.88, -0.
	culoskeletal	Yes	Yes	RMDS (0-24)	254, 0.50 (5.03)	256, 1.60 (5.63)	-0.24 (-0.41, -0.
	culoskeletal	Yes	No	RMDS (0-24)	193, 11.00 (6.08)	189, 11.90 (6.34)	-0.15 (-0.35, 0.0
			No	BPIGA (0 to 10)	89, -1.85 (2.96)	92, -1.89 (2.79)	0.01 (-0.28, 0.3
impson, 2016 Neuroubgroup ($I^2 = 69.1\%$, p = 0	ropathic 0.002)	No	INO	DF1GA (0 t0 10)	03, -1.03 (2.90)	92, -1.09 (2.79)	-0.25 (-0.46, -0.
latana analiku babusa						1	
Heterogeneity between gro Overall ($I^2 = 54.7\%$, p = 0.0							-0.21 (-0.27, -0.

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=standard deviation 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



Favors Opioid Favors 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

pe of opioid				Treatment	Control	
nd Author, Year	Type of pain	EERWD	On opioid	n/N	n/N	Risk Ratio (95% 0
gonist						
Moulin, 1996	Musculoskeletal	No	Mixed	19/46	2/46	9.50 (2.35, 38.47
Caldwell, 2002	Musculoskeletal	No	Mixed	87/222	3/73	9.54 (3.11, 29.23
Markenson, 2005	Musculoskeletal Musculoskeletal	No	Mixed	27/56	5/51	4.92 (2.05, 11.80 3.20 (1.92, 5.34)
latsumoto, 2005 angford, 2006	Musculoskeletal	No No	Mixed Yes	132/365 22/216	14/124 3/200	6.79 (2.06, 22.34)
Vebster, 2006	Musculoskeletal	No	Mixed	146/206	28/101	2.56 (1.84, 3.54)
lale, 2007	Musculoskeletal	Yes	Yes	4/70	1/72	4.11 (0.47, 35.91
latz, 2007	Musculoskeletal	Yes	No	7/105	1/100	6.67 (0.84, 53.22
ondrackova, 2008	Musculoskeletal	Yes	Yes	31/305	8/158	2.01 (0.95, 4.26)
lale , 2010	Musculoskeletal	Yes	Yes	10/134	5/134	2.00 (0.70, 5.70)
atz, 2010	Musculoskeletal	Yes	Mixed	12/171	7/173	1.73 (0.70, 4.30)
riedmann, 2011	Musculoskeletal	Yes	Mixed	35/205	9/207	3.93 (1.94, 7.96)
loutier, 2013	Musculoskeletal	No	Mixed	6/74	2/77	3.12 (0.65, 14.98
auck, 2013	Musculoskeletal	No	Mixed	286/649	39/332	3.75 (2.76, 5.10)
pierings, 2013*	Musculoskeletal	No	Mixed	24/158	2/141	10.71 (2.58, 44.5
auck, 2014	Musculoskeletal	Yes	Yes	12/151	0/151	25.00 (1.49, 418.
ale , 2015	Musculoskeletal	Yes	Mixed	27/191	8/179	3.16 (1.48, 6.78)
ale, 2015	Musculoskeletal	Yes	Mixed	19/146	7/147	2.73 (1.18, 6.30)
atz, 2015	Musculoskeletal	Yes	Mixed	10/193	1/196	10.16 (1.31, 78.5
auck, 2015	Musculoskeletal	Yes	NR	5/146	3/134	1.53 (0.37, 6.28)
enkwalder, 2015	Musculoskeletal	No	No	16/92	6/109	3.16 (1.29, 7.74)
/en, 2015	Musculoskeletal	Yes	Mixed	10/296	7/292	1.41 (0.54, 3.65)
ai, 2015a	Musculoskeletal	Yes	No	6/73	3/77	2.11 (0.55, 8.12)
ayorga, 2016	Musculoskeletal	No	Mixed	16/50	0/48	31.71 (1.96, 514
nja, 2002	Neuropathic	No	Mixed	23/76	8/76	2.88 (1.37, 6.02)
mbel, 2003	Neuropathic	No	Mixed	35/82	11/77	2.99 (1.64, 5.45)
atson, 2003	Neuropathic	No No	NR Mixed	13/45	4/45 2/43	3.25 (1.15, 9.21)
ron, 2005	Neuropathic	No	Mixed	17/44		8.31 (2.04, 33.8° 9.00 (2.30, 35.20
oromi, 2007	Neuropathic	No	Mixed	18/28	2/28	
inna, 2008	Neuropathic	No	No NR	45/168	10/167 2/43	4.47 (2.33, 8.58)
и, 2008 ai, 2015b	Neuropathic	No Yes	No	17/50 12/84	10/79	7.31 (1.79, 29.86 1.13 (0.52, 2.46)
bgroup	Neuropathic	165	NO	1149/4897	213/3880	3.26 (2.79, 3.97)
= 9.1%, p = 0.058)				1143/4037	213/3000	3.20 (2.19, 3.91)
xed					l i	
eischmann, 2001	Musculoskeletal	No	NR	8/63	0/66	17.80 (1.05, 302
bul, 2004	Musculoskeletal	No	Mixed	32/124	7/122	4.50 (2.06, 9.80)
ana , 2006	Musculoskeletal	No	Mixed	164/806	12/205	3.48 (1.97, 6.12)
irch, 2007	Musculoskeletal	Yes	Mixed	61/432	9/214	3.36 (1.70, 6.63)
shman, 2007	Musculoskeletal	No	NR	39/315	3/227	9.37 (2.93, 29.94
orne, 2008	Musculoskeletal	No	Mixed	22/94	5/88	4.12 (1.63, 10.4)
rsanger, 2008	Musculoskeletal	Yes	Mixed	26/257	1/129	13.05 (1.79, 95.
ilalo, 2010	Musculoskeletal	No	Mixed	191/686	22/337	4.26 (2.80, 6.50)
ynak, 2010	Musculoskeletal	No	Mixed	132/646 98/599	16/319 5/200	4.07 (2.47, 6.72)
elemos, 2011	Musculoskeletal Musculoskeletal	No No	Mixed Mixed		3/120	6.54 (2.70, 15.8
erall, 2012		No	No	5/116 13/60	2/31	1.72 (0.42, 7.05)
minaga, 2016a ristoph, 2017	Musculoskeletal Musculoskeletal	No	Mixed	22/126	5/126	3.36 (0.81, 13.9 4.40 (1.72, 11.2
rrie, 2017	Musculoskeletal	No	Mixed	173/650	31/337	2.89 (2.02, 4.14
arkman, 2020*	Musculoskeletal	No	Mixed	45/602	6/409	5.10 (2.19, 11.8
n de Donk, 2020*	Musculoskeletal	No	Mixed	4/20	0/20	9 .00 (0.52, 156.
rati, 1998	Neuropathic	No	No	14/65	2/66	7.11 (1.68, 30.0
orrbrink, 2009	Neuropathic	No	NR	8/23	4/12	1.04 (0.39, 2.77)
hwartz, 2011	Neuropathic	Yes	Mixed	12/196	2/193	5.91 (1.34, 26.0
ndrup, 2012	Neuropathic	No	NR	14/56	1/55	13.75 (1.87, 101
nik, 2014	Neuropathic	Yes	Mixed	9/166	0/152	17.41 (1.02, 296
minaga, 2016b	Neuropathic	No	No	16/60	0/31	17.31 (1.07, 279
bgroup = 1.4%, p = 0.297)	•			1108/6162	136/3459	3.88 (3.26, 4.93
gonist	Musculoskeletal	No	No	24/100	5/99	4 75 /1 90 11 O
eivik, 2010 ordon , 2010	Musculoskeletal	No No	NO NR	20/73	14/65	4.75 (1.89, 11.9 1.27 (0.70, 2.31
ordon , 2010	Musculoskeletal	No	Yes	12/73	4/68	2.79 (0.95, 8.25
inera, 2010	Musculoskeletal	No	Mixed	15/152	3/163	5.36 (1.58, 18.1
einer , 2011	Musculoskeletal	Yes	No	9/256	3/283	3.32 (0.91, 12.1
mbel, 2016	Musculoskeletal	Yes	Yes	7/254	2/256	3.53 (0.74, 16.8)
nuck, 2016	Musculoskeletal	Yes	No	9/229	6/232	1.52 (0.55, 4.20)
bgroup	Musculoskeletal	103	140	96/1137	37/1166	2.53 (1.56, 4.55
= 32.5%, p = 0.137)				33, 1101		2.00 (1.00, 4.00)
terogeneity between	groups: p = 0.018			005041045	000/0505	0.45 (0.00 : 5:
				2353/12196	386/8505	3.45 (3.03, 4.01)
verall = 21.8%, p = 0.016)						

^{*} Newly included since the original 2020 systematic review.

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

d Author, Year	Type of pain	EERWD	opioid	n/N	n/N		Risk Ratio (95% 0
gonist						1	
oulin, 1996	Musculoskeletal	No	Mixed	18/46	3/46	 <u>-</u> -	6.00 (1.90, 18.99
eloso, 2000	Musculoskeletal	No	Mixed	25/51	6/52	1 1 -	4.25 (1.90, 9.48)
aldwell, 2002	Musculoskeletal	No	Mixed	58/222	7/73		2.72 (1.30, 5.70)
arkenson, 2005	Musculoskeletal	No	Mixed	23/56	7/51	 _ _	2.99 (1.40, 6.37)
atsumoto, 2005	Musculoskeletal	No	Mixed	199/365	13/124	1	5.20 (3.08, 8.77)
angford, 2006	Musculoskeletal	No	Yes	94/216	37/200	1	2.35 (1.69, 3.27)
/ebster, 2006	Musculoskeletal	No	Mixed	124/206	21/101	T	2.90 (1.95, 4.30)
ale, 2007	Musculoskeletal	Yes	Yes	2/70	1/72		2.06 (0.19, 22.18
atz, 2007	Musculoskeletal	Yes	No	12/105	9/100	T	1.27 (0.56, 2.88)
ondrackova, 2008	Musculoskeletal	Yes	Yes	22/305	11/158	T 1	1.04 (0.52, 2.08)
ale , 2010 atz, 2010	Musculoskeletal	Yes	Yes	12/134 20/171	10/134 13/173	E	1.20 (0.54, 2.68) 1.56 (0.80, 3.03)
riedmann, 2011	Musculoskeletal Musculoskeletal	Yes Yes	Mixed Mixed	41/205	20/207		2.07 (1.26, 3.41)
loutier, 2013	Musculoskeletal	No	Mixed	9/74	9/77		1.04 (0.44, 2.48)
auck, 2013	Musculoskeletal	No	Mixed	216/649	32/332	T	3.45 (2.44, 4.88)
pierings, 2013*	Musculoskeletal	No	Mixed	25/158	0/141	<u>-</u>	4 5.55 (2.80, 741)
auck, 2014		Yes	Yes	11/151			2.20 (0.78, 6.18)
	Musculoskeletal Musculoskeletal	Yes		20/191	5/151 14/179	<u> </u>	
ale , 2015			Mixed			T.	1.34 (0.70, 2.57)
le, 2015	Musculoskeletal	Yes	Mixed	19/146	9/147	Tage	2.13 (0.99, 4.54)
tz, 2015	Musculoskeletal	Yes	Mixed	21/193	9/196	 	2.37 (1.11, 5.04)
uck, 2015	Musculoskeletal	Yes	NR	21/146	5/134	<u></u>	3.85 (1.50, 9.93)
enkwalder, 2015	Musculoskeletal	No	No	18/92	13/109		1.64 (0.85, 3.17)
en, 2015	Musculoskeletal	Yes	Mixed	24/296	16/292		1.48 (0.80, 2.73)
ai, 2015a	Musculoskeletal	Yes	No	5/73	6/77		0.88 (0.28, 2.76)
yorga, 2016	Musculoskeletal	No	Mixed	14/50	4/48		3.36 (1.19, 9.49)
a, 2002	Neuropathic	No	Mixed	30/76	5/76	<u> </u>	6.00 (2.46, 14.6
nbel, 2003	Neuropathic	No	Mixed	30/82	6/77		4.70 (2.07, 10.6
tson, 2003	Neuropathic	No	NR	16/45	8/45	—	2.00 (0.95, 4.20
ron, 2005	Neuropathic	No	Mixed	2/44	0/43	T .	4.89 (0.24, 98.9
oromi, 2007	Neuropathic	No	Mixed	2/28	0/28		5.00 (0.25, 99.6
nna, 2008	Neuropathic	No	No	43/168	18/167	T	2.37 (1.43, 3.94)
, 2008	Neuropathic	No	NR	4/50	2/43		1.72 (0.33, 8.94)
ni, 2015b	Neuropathic	Yes	No	13/84	10/79	7	1.22 (0.57, 2.63)
bgroup = 46.0%, p = 0.001)				1193/4948	329/3932	T T	2.31 (1.92, 2.78)
xed							
chnitzer, 2000	Musculoskeletal	Yes	NR	11/127	3/127		3.67 (1.05, 12.83
ischmann, 2001	Musculoskeletal	No	NR	11/63	2/66		5.76 (1.33, 24.9)
bul, 2004	Musculoskeletal	No	Mixed	30/124	10/122	175	2.95 (1.51, 5.77)
na , 2006	Musculoskeletal	No	Mixed	178/806	15/205	1.2	3.02 (1.82, 5.00
rch, 2007	Musculoskeletal	Yes	Mixed	66/432	12/214 13/227	17	2.72 (1.51, 4.93
hman, 2007	Musculoskeletal	No	NR	62/325			3.33 (1.88, 5.91
orne, 2008	Musculoskeletal	No	Mixed	40/94	22/88	5	1.70 (1.11, 2.62)
rsanger, 2008	Musculoskeletal	Yes	Mixed	35/257	9/129	7_	1.95 (0.97, 3.94
alo, 2010	Musculoskeletal	No	Mixed	199/686	23/337		4.25 (2.82, 6.41
ynak, 2010	Musculoskeletal	No	Mixed	177/646	29/319	T	3.01 (2.08, 4.36
emos, 2011	Musculoskeletal	No	Mixed	124/599	17/200	₹_	2.44 (1.51, 3.94
erall, 2012	Musculoskeletal	No	Mixed	22/116	3/120	_ 	7.59 (2.33, 24.6
ninaga, 2016a	Musculoskeletal	No	No	20/60	5/31	7	2.07 (0.86, 4.98
ristoph, 2017	Musculoskeletal	No	Mixed	33/126	8/126	T_	4.13 (1.98, 8.58
rie, 2017	Musculoskeletal	No	Mixed	189/650	21/337	I	4.67 (3.03, 7.18
rkman, 2020*	Musculoskeletal	No	Mixed	68/602	7/409	<u>-</u>	6.60 (3.06, 14.2
de Donk, 2020*	Musculoskeletal	No	Mixed	9/20	4/20		2.25 (0.83, 6.13
rati, 1998	Neuropathic	No	No	15/65	1/66		15.23 (2.07, 111
rrbrink, 2009	Neuropathic	No	NR Mixed	9/23	3/12	7=-	1.57 (0.52, 4.72
nwartz, 2011	Neuropathic	Yes	Mixed	27/196	12/193		2.22 (1.16, 4.25
drup, 2012	Neuropathic	No	NR	14/56	4/55		3.44 (1.21, 9.79
ik, 2014	Neuropathic	Yes	Mixed	35/166	15/152		2.14 (1.22, 3.75
ninaga, 2016b	Neuropathic	No	No	19/60	0/31		20.46 (1.28, 327
ogroup = 28.0%, p = 0.048)				1393/6299	238/3586	l Y	3.04 (2.56, 3.63
gonist							
eivik, 2010	Musculoskeletal	No	No	24/100	5/99		4.75 (1.89, 11.9
rdon , 2010	Musculoskeletal	No	NR	28/73	11/65	- -	2.27 (1.23, 4.18
rdon , 2010	Musculoskeletal	No	Yes	39/73	12/68	 - -	3.03 (1.74, 5.28
nera, 2010	Musculoskeletal	No	Mixed	41/152	13/163	 	3.38 (1.89, 6.06
iner , 2011	Musculoskeletal	Yes	No	32/256	31/283	+ .	1.14 (0.72, 1.82
nbel, 2016	Musculoskeletal	Yes	Yes	19/254	19/256	+	1.01 (0.55, 1.86
uck, 2016	Musculoskeletal	Yes	No	23/229	17/232	₩ .	1.37 (0.75, 2.50
ogroup = 65.7%, p = 0.002)				206/1137	108/1166	*	1.99 (1.29, 3.19
,							
terogeneity between erall	groups: p = 0.000			2792/12384	675/8684	I i	2.51 (2.21, 2.86)
= 50.7%, p = 0.000)				2102/12004	510/0007	*	2.01 (2.21, 2.00)

Favors Opioid Favors 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

Figure F-7. Meta	a-analysis of	risk of v		g for opic	oids vers	us placebo	
and Author, Year	Type of pain	EERWD	On opioid	Treatment n/N	n/N		Risk Ratio (95% CI)
Agonist						_	
Moulin, 1996	Musculoskeletal	No	Mixed	18/46	1/46	 	18.00 (2.51, 129.30)
Caldwell, 2002	Musculoskeletal	No	Mixed	22/222	1/73	1_	7.23 (0.99, 52.74)
Markenson, 2005	Musculoskeletal	No No	Mixed	7/56	1/51		6.38 (0.81, 50.05)
Matsumoto, 2005 Langford, 2006	Musculoskeletal Musculoskeletal	No	Mixed Yes	81/365 61/216	2/124 5/200	<u></u>	13.76 (3.43, 55.13) 11.30 (4.63, 27.54)
Webster, 2006	Musculoskeletal	No	Mixed	47/206	9/101		2.56 (1.31, 5.01)
Hale, 2007	Musculoskeletal	Yes	Yes	0/70	1/72	 -	0.34 (0.01, 8.27)
Katz, 2007	Musculoskeletal	Yes	No	8/105	1/100		7.62 (0.97, 59.82)
Vondrackova, 2008	Musculoskeletal	Yes	Yes	15/305	5/158	- =-;	1.55 (0.58, 4.20)
Hale , 2010	Musculoskeletal	Yes	Yes	8/134	6/134	→= →	1.33 (0.48, 3.74)
Katz, 2010	Musculoskeletal	Yes	Mixed	12/171	4/173	—=	3.04 (1.00, 9.22)
Friedmann, 2011	Musculoskeletal	Yes	Mixed	29/205	6/207	_ -=-	4.88 (2.07, 11.51)
Cloutier, 2013	Musculoskeletal	No	Mixed	4/74	3/77	- - <u></u>	1.39 (0.32, 5.99)
Rauck, 2013	Musculoskeletal	No	Mixed Mixed	67/649 15/158	7/332 1/141	<u>-=-</u>	4.90 (2.27, 10.55)
Spierings, 2013* Rauck, 2014	Musculoskeletal Musculoskeletal	No Yes	Yes	7/151	1/151		13.39 (1.79, 100.05) 7.00 (0.87, 56.21)
Hale , 2015	Musculoskeletal	Yes	Mixed	8/191	6/179		1.25 (0.44, 3.53)
Hale, 2015	Musculoskeletal	Yes	Mixed	9/146	5/147	- [= -	1.81 (0.62, 5.28)
Rauck, 2015	Musculoskeletal	Yes	NR	9/146	4/134		2.07 (0.65, 6.55)
Trenkwalder, 2015	Musculoskeletal	No	No	7/92	3/109	 - -	2.76 (0.74, 10.39)
Wen, 2015	Musculoskeletal	Yes	Mixed	18/296	9/292	 = •	1.97 (0.90, 4.32)
Arai, 2015a	Musculoskeletal	Yes	No	3/73	1/77		3.16 (0.34, 29.74)
Mayorga, 2016	Musculoskeletal	No	Mixed	8/50	3/48	 	2.56 (0.72, 9.08)
Gimbel, 2003	Neuropathic	No	Mixed	17/82	2/77	_ 	7.98 (1.91, 33.41)
Watson, 2003	Neuropathic	No	NR	5/45	2/45	1 = :-	2.50 (0.51, 12.22)
Hanna, 2008	Neuropathic	No	No	16/168	7/167	_==:	2.27 (0.96, 5.38)
Arai, 2015b Subgroup	Neuropathic	Yes	No	5/84 506/4506	1/79 97/3494	T	4.70 (0.56, 39.37) 3.25 (2.43, 4.44)
(l ² = 30.8%, p = 0.029))			300/4300	9113494	Ť	3.23 (2.43, 4.44)
,	,					1 !	
Mixed	Museuleeleeletel	NI-	Missaul	0/404	0/400	<u> </u>	40.70 (4.40, 047.70)
Babul, 2004	Musculoskeletal Musculoskeletal	No No	Mixed	9/124 59/806	0/122 6/205		18.70 (1.10, 317.73) 2.50 (1.10, 5.71)
Gana, 2006 Fishman, 2007	Musculoskeletal	No	Mixed NR	26/325	1/227		18.16 (2.48, 132.86)
Thorne, 2008	Musculoskeletal	No	Mixed	6/94	2/88		2.81 (0.58, 13.55)
Afilalo, 2010	Musculoskeletal	No	Mixed	79/686	11/337		3.53 (1.90, 6.54)
Buynak, 2010	Musculoskeletal	No	Mixed	92/646	5/319	Tab	9.09 (3.73, 22.13)
Delemos, 2011	Musculoskeletal	No	Mixed	43/599	5/200	≡	2.87 (1.15, 7.15)
Uberall, 2012	Musculoskeletal	No	Mixed	13/116	1/120		13.45 (1.79, 101.16)
Tominaga, 2016a	Musculoskeletal	No	No	12/60	1/31	 ;	6.20 (0.84, 45.51)
Christoph, 2017	Musculoskeletal	No	Mixed	15/126	5/126		3.00 (1.12, 8.01)
Serrie, 2017	Musculoskeletal	No	Mixed	119/650	13/337	 	4.75 (2.72, 8.29)
van de Donk, 2020* Harati, 1998	Musculoskeletal Neuropathic	No No	Mixed No	1/20 3/65	0/20 0/66		3.00 (0.13, 69.52) 7.11 (0.37, 134.91)
Schwartz, 2011	Neuropathic	Yes	Mixed	13/196	2/193		6.40 (1.46, 27.99)
Sindrup, 2012	Neuropathic	No	NR	6/56	0/55	1	12.77 (0.74, 221.40)
Vinik, 2014	Neuropathic	Yes	Mixed	21/166	7/152	_ 	2.75 (1.20, 6.28)
Tominaga, 2016b	Neuropathic	No	No	11/60	1/31	 	5.68 (0.77, 42.02)
Subgroup				528/4795	60/2629	b	4.18 (3.22, 5.63)
$(I^2 = 0.0\%, p = 0.631)$						l î	, , ,
PAgonist						l i	
Breivik, 2010	Musculoskeletal	No	No	16/100	2/99	<u> </u>	7.92 (1.87, 33.54)
Gordon , 2010	Musculoskeletal	No	NR	11/73	3/65	<u> </u>	3.26 (0.95, 11.19)
Gordon , 2010	Musculoskeletal	No	Yes	16/73	3/68		4.97 (1.51, 16.30)
Munera, 2010	Musculoskeletal	No	Mixed	16/152	4/163	- -	4.29 (1.47, 12.54)
Steiner, 2011	Musculoskeletal	Yes	No	11/256	5/283	 -= ;-	2.43 (0.86, 6.91)
Gimbel, 2016	Musculoskeletal	Yes	Yes	14/254	6/256	 -≡ i-	2.35 (0.92, 6.02)
Rauck, 2016	Musculoskeletal	Yes	No	9/229	1/232	- i	9.12 (1.16, 71.39)
Subgroup				93/1137	24/1166	•	3.65 (2.34, 5.86)
$(I^2 = 0.0\%, p = 0.711)$!	
Heterogeneity between	en aroups: p = 0.31	0				1 :	
Overall	9			1127/1043	8 181/7289	♦	3.61 (3.01, 4.38)
$(I^2 = 14.6\%, p = 0.138)$	3)					l '	, , ,
						- 	
						.125 1 8 64	
						.120 1 0 04	

Favors Opioid Favors 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

and Author, Year	Type of pain	EERWD	On opioid	n/N	n/N		Risk Ratio (95% CI
Agonist				.=			
Moulin, 1996	Musculoskeletal	No	Mixed	17/46	1/46		17.00 (2.36, 122.5)
Peloso, 2000	Musculoskeletal	No	Mixed	17/51	4/52	_ 	4.33 (1.57, 12.00)
Caldwell, 2002 Markenson, 2005	Musculoskeletal Musculoskeletal	No	Mixed Mixed	23/222 18/56	1/73 3/51		7.56 (1.04, 55.03)
Matsumoto, 2005	Musculoskeletal	No No	Mixed	104/365	5/124	T	5.46 (1.71, 17.46) 7.07 (2.95, 16.93)
angford, 2006	Musculoskeletal	No	Yes	26/216	10/200		2.41 (1.19, 4.86)
Vebster, 2006	Musculoskeletal	No	Mixed	76/206	13/101		2.87 (1.67, 4.91)
(atz, 2007	Musculoskeletal	Yes	No	5/105	3/100	——	1.59 (0.39, 6.47)
ondrackova, 2008	Musculoskeletal	Yes	Yes	11/305	6/158		0.95 (0.36, 2.52)
atz, 2010	Musculoskeletal	Yes	Mixed	3/171	3/173	 _	1.01 (0.21, 4.94)
riedmann, 2011	Musculoskeletal	Yes	Mixed	17/205	9/207	├ ═┼	1.91 (0.87, 4.18)
Cloutier, 2013	Musculoskeletal	No	Mixed	3/74	2/77		1.56 (0.27, 9.08)
Rauck, 2013	Musculoskeletal	No	Mixed	82/649	20/332		2.10 (1.31, 3.36)
pierings, 2013*	Musculoskeletal	No	Mixed	10/158	2/141		4.46 (0.99, 20.02)
Rauck, 2014	Musculoskeletal	Yes	Yes	3/151	1/151		3.00 (0.32, 28.52)
lale, 2015	Musculoskeletal	Yes	Mixed	2/191	4/179 —	 !	0.47 (0.09, 2.53)
lale, 2015	Musculoskeletal	Yes	Mixed	3/146	1/147		3.02 (0.32, 28.70)
Rauck, 2015	Musculoskeletal	Yes	NR	6/146	1/134	Li	5.51 (0.67, 45.15)
renkwalder, 2015	Musculoskeletal	No	No	12/92	12/109	1	1.18 (0.56, 2.51)
Ven, 2015	Musculoskeletal	Yes	Mixed	9/296	5/292		1.78 (0.60, 5.24)
rai, 2015a Mayorga, 2016	Musculoskeletal Musculoskeletal	Yes	No Mixed	1/73 7/50	2/77 —— 1/48		0.53 (0.05, 5.69)
rayorga, 2016 Raja, 2002	Neuropathic	No No	Mixed	10/76	5/76		6.72 (0.86, 52.59) 2.00 (0.72, 5.58)
Gimbel, 2003	Neuropathic	No	Mixed	26/82	8/77		3.05 (1.47, 6.33)
Vatson, 2003	Neuropathic	No	NR	7/45	3/45		2.33 (0.64, 8.46)
(horomi, 2007	Neuropathic	No	Mixed	4/28	1/28		4.00 (0.48, 33.58)
lanna, 2008	Neuropathic	No	No	25/168	6/167	 -	4.14 (1.74, 9.84)
Vu, 2008	Neuropathic	No	NR	2/50	2/43		0.86 (0.13, 5.85)
Arai, 2015b	Neuropathic	Yes	No	6/84	3/79		1.88 (0.49, 7.27)
ubgroup				535/4507	137/3487	•	2.45 (1.95, 3.11)
² = 12.1%, p = 0.140)							
lixed	Musculoskeletal	No	NR	6/63	2/66	<u> </u>	2 14 (0 66 15 00)
leischmann, 2001 abul, 2004	Musculoskeletal	No	Mixed	41/124	15/122	T-6-	3.14 (0.66, 15.00) 2.69 (1.57, 4.60)
Sana , 2006	Musculoskeletal	No	Mixed	169/806	13/205	175	3.31 (1.92, 5.69)
urch, 2007	Musculoskeletal	Yes	Mixed	42/432	8/214		2.60 (1.24, 5.44)
ishman, 2007	Musculoskeletal	No	NR	46/325	11/227		2.92 (1.55, 5.52)
horne, 2008	Musculoskeletal	No	Mixed	5/94	3/88		1.56 (0.38, 6.34)
orsanger, 2008	Musculoskeletal	Yes	Mixed	31/257	12/129	- 	1.30 (0.69, 2.44)
filalo, 2010	Musculoskeletal	No	Mixed	126/686	16/337	 	3.87 (2.34, 6.40)
Buynak, 2010	Musculoskeletal	No	Mixed	94/646	18/319	- 1	2.58 (1.59, 4.19)
Delemos, 2011	Musculoskeletal	No	Mixed	123/599	15/200	-II -	2.74 (1.64, 4.57)
Jberall, 2012	Musculoskeletal	No	Mixed	15/116	4/120	- 	3.88 (1.33, 11.34)
Christoph, 2017	Musculoskeletal	No	Mixed	36/126	11/126	- -	3.27 (1.75, 6.14)
Serrie, 2017	Musculoskeletal	No	Mixed	159/650	29/337	 -	2.84 (1.96, 4.13)
Markman, 2020*	Musculoskeletal	No	Mixed	31/602	5/409	T	4.21 (1.65, 10.74)
an de Donk, 2020*	Musculoskeletal	No	Mixed	9/20	3/20		3.00 (0.95, 9.48)
larati, 1998 Iorrbrink, 2009	Neuropathic Neuropathic	No No	No NR	3/65 12/23	0/66 3/12		7.11 (0.37, 134.91)2.09 (0.73, 5.99)
Schwartz, 2011	Neuropathic	Yes	Mixed	15/196	3/193	T	4.92 (1.45, 16.74)
Sindrup, 2012	Neuropathic	No	NR	9/56	4/55		2.21 (0.72, 6.76)
'inik, 2014	Neuropathic	Yes	Mixed	12/166	3/152		3.66 (1.05, 12.73)
Subgroup	, , , , , , , , , , , , , , , , , , ,			984/6052	178/3397	♦	2.84 (2.43, 3.31)
l ² = 0.0%, p = 0.895)							
Agonist Breivik, 2010	Musculoskeletal	No	No	25/100	9/99	<u>_</u>	2.75 (1.35, 5.59)
Gordon , 2010	Musculoskeletal	No No	NO NR	25/100 16/73	5/65		2.75 (1.35, 5.59)
Gordon , 2010 Gordon , 2010	Musculoskeletal	No	Yes	24/73	3/68	<u> </u>	7.45 (2.35, 23.63)
Munera, 2010	Musculoskeletal	No	Mixed	30/152	14/163		2.30 (1.27, 4.16)
teiner , 2011	Musculoskeletal	Yes	No	10/256	3/283		3.68 (1.03, 13.24)
Simbel, 2016	Musculoskeletal	Yes	Yes	2/254	2/256		1.01 (0.14, 7.10)
Rauck, 2016	Musculoskeletal	Yes	No	4/229	1/232		4.05 (0.46, 35.98)
Subgroup $I^2 = 0.0\%$, p = 0.595)				111/1137	37/1166	•	2.85 (1.99, 4.30)
leterogeneity between	aroune: n = 0.562						
neterogeneity between Overall	i groups. p = 0.563			1630/11696	352/8050	↓	2.69 (2.40, 3.01)
						*	(
Overall (I ² = 0.0%, p = 0.527)				1630/11696	352/8050	5 1 8 64	2.69 (2.40, 3.0

Favors Opioid Favors 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

Type of opioid		IISK UI S				sus placebo	Dist. Datis (050/ Ol)
and Author, Year	Type of pain	EERWD	opioid	n/N	n/N		Risk Ratio (95% CI)
Agonist Peloso, 2000	Musculoskeletal	No	Mixed	20/51	5/52		4.08 (1.66, 10.04)
Caldwell, 2002	Musculoskeletal	No	Mixed	30/222	0/73		20.24 (1.25, 326.95)
Markenson, 2005	Musculoskeletal	No	Mixed	18/56	5/51		3.28 (1.31, 8.19)
Matsumoto, 2005 Langford, 2006	Musculoskeletal Musculoskeletal	No No	Mixed Yes	108/365 48/216	6/124 7/200		6.12 (2.76, 13.56) 6.35 (2.94, 13.70)
Webster, 2006	Musculoskeletal	No	Mixed	171/206	50/101	I	1.68 (1.36, 2.06)
Hale, 2007	Musculoskeletal	Yes	Yes	2/70	0/72		- 5.14 (0.25, 105.21)
Katz, 2007	Musculoskeletal	Yes	No	2/105	0/100		4 .76 (0.23, 98.03)
Vondrackova, 2008	Musculoskeletal	Yes	Yes	12/305	4/158		1.55 (0.51, 4.74)
Hale, 2010 Katz, 2010	Musculoskeletal Musculoskeletal	Yes Yes	Yes Mixed	1/134 2/171	0/134 5/173		3.00 (0.12, 72.99) 0.40 (0.08, 2.06)
Friedmann, 2011	Musculoskeletal	Yes	Mixed	23/205	4/207		5.81 (2.04, 16.49)
Cloutier, 2013	Musculoskeletal	No	Mixed	4/74	0/77		9.36 (0.51, 170.88)
Rauck, 2013	Musculoskeletal	No	Mixed	102/649	16/332	- @-	3.26 (1.96, 5.43)
Spierings, 2013*	Musculoskeletal	No Yes	Mixed	7/158 1/151	0/141 0/151 —		13.40 (0.77, 232.46)
Rauck, 2014 Hale, 2015	Musculoskeletal Musculoskeletal	Yes	Yes Mixed	6/191	2/179		3.00 (0.12, 73.06) 2.81 (0.57, 13.75)
Hale, 2015	Musculoskeletal	Yes	Mixed	3/146	1/147		3.02 (0.32, 28.70)
Rauck, 2015	Musculoskeletal	Yes	NR	1/146	1/134		0.92 (0.06, 14.53)
Trenkwalder, 2015	Musculoskeletal	No	No	12/92	15/109	- 	0.95 (0.47, 1.92)
Wen, 2015 Arai, 2015a	Musculoskeletal Musculoskeletal	Yes Yes	Mixed No	3/296 3/73	2/292 0/77		1.48 (0.25, 8.79) 7.38 (0.39, 140.42)
Mayorga, 2016	Musculoskeletal	No	Mixed	11/50	2/48		5.28 (1.23, 22.59)
Raja, 2002	Neuropathic	No	Mixed	23/76	11/76		2.09 (1.10, 3.98)
Gimbel, 2003	Neuropathic	No	Mixed	33/82	1/77	i ———	30.99 (4.34, 221.09)
Watson, 2003	Neuropathic	No	NR	9/45	11/45		0.82 (0.38, 1.78)
Gilron, 2005	Neuropathic	No No	Mixed	7/44	6/43 1/28		1.14 (0.42, 3.12) 7.00 (0.92, 53.23)
Khoromi, 2007 Hanna, 2008	Neuropathic Neuropathic	No No	Mixed No	7/28 37/168	9/167		4.09 (2.04, 8.20)
Wu, 2008	Neuropathic	No	NR	9/50	3/43	┼ ┪ <u>¯</u>	2.58 (0.75, 8.93)
Arai, 2015b	Neuropathic	Yes	No	12/84	5/79	 	2.26 (0.83, 6.12)
Subgroup				727/4709	172/3690	•	2.76 (2.05, 3.84)
$(l^2 = 56.6\%, p = 0.000)$	')					1	
Mixed							
Babul, 2004	Musculoskeletal	No	Mixed	10/124	2/122	i =	4.92 (1.10, 21.99)
Gana , 2006 Burch, 2007	Musculoskeletal Musculoskeletal	No Yes	Mixed Mixed	97/806 29/432	5/205 8/214	1	4.93 (2.04, 11.96) 1.80 (0.84, 3.86)
Fishman, 2007	Musculoskeletal	No	NR	39/325	2/227		13.62 (3.32, 55.83)
Thorne, 2008	Musculoskeletal	No	Mixed	35/94	19/88	- ■-!	1.72 (1.07, 2.78)
Afilalo, 2010	Musculoskeletal	No	Mixed	104/686	14/337	 -	3.65 (2.12, 6.28)
Buynak, 2010	Musculoskeletal	No	Mixed	95/646	8/319	 	5.86 (2.89, 11.91)
Delemos, 2011 Uberall, 2012	Musculoskeletal Musculoskeletal	No No	Mixed Mixed	51/599 7/116	2/200 3/120		8.51 (2.09, 34.66) 2.41 (0.64, 9.11)
Tominaga, 2016a	Musculoskeletal	No	No	22/60	3/31		3.79 (1.23, 11.68)
Christoph, 2017	Musculoskeletal	No	Mixed	18/126	6/126		3.00 (1.23, 7.31)
Serrie, 2017	Musculoskeletal	No	Mixed	82/650	13/337		3.27 (1.85, 5.78)
van de Donk, 2020*	Musculoskeletal	No	Mixed	6/20	5/20		1.20 (0.44, 3.30)
Harati, 1998 Norrbrink, 2009	Neuropathic Neuropathic	No No	No NR	8/65 17/23	4/66 2/12		2.03 (0.64, 6.42) 4.43 (1.22, 16.08)
Vinik, 2014	Neuropathic	Yes	Mixed	12/166	1/152		10.99 (1.45, 83.50)
Tominaga, 2016b	Neuropathic	No	No	17/60	3/31	 -	2.93 (0.93, 9.23)
Subgroup				649/4998	100/2607	•	3.24 (2.47, 4.43)
$(I^2 = 31.1\%, p = 0.041)$)					1 ;	
PAgonist						i	
Breivik, 2010	Musculoskeletal	No	No	4/100	0/99		8.91 (0.49, 163.35)
Gordon , 2010	Musculoskeletal	No	NR	22/73	4/65		4.90 (1.78, 13.47)
Gordon , 2010 Munera, 2010	Musculoskeletal Musculoskeletal	No No	Yes Mixed	16/73 23/152	5/68 8/163		2.98 (1.15, 7.69) 3.08 (1.42, 6.68)
Steiner, 2011	Musculoskeletal	Yes	No	4/256	6/283		0.74 (0.21, 2.58)
Rauck, 2016	Musculoskeletal	Yes	No	2/229	1/232		2.03 (0.19, 22.19)
Subgroup				71/883	24/910		2.80 (1.47, 4.95)
$(l^2 = 0.0\%, p = 0.278)$							
Heterogeneity between	en groups: p = 0.01	12		4.49/.000	000/700-	l i	0.00 (6.11.5.51)
Overall	1)			1447/10590	296/7207	•	2.93 (2.41, 3.61)
(l ² = 48.4%, p = 0.000	'/						
					<u> </u>		
					.125	1 8 64	ł

Favors Opioid Favors 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

ERWD On opioi	d n/N	n/N	Risk Ratio (95% CI)
o Mixed	13/222	0/73	8.96 (0.54, 148.88)
o Mixed	12/56	0/51	22.81 (1.38, 375.65)
o Mixed	63/365	3/124	7.13 (2.28, 22.31)
o Mixed	105/206	5/101 i=	10.30 (4.34, 24.45)
es Yes	1/70	0/72	3.08 (0.13, 74.46)
s No	3/105	1/100	2.86 (0.30, 27.01)
es Mixed	1/171	1/173	1 .01 (0.06, 16.04)
es Mixed	7/205	6/207	1.18 (0.40, 3.45)
o Mixed	66/649	8/332	4.22 (2.05, 8.69)
Mixed	10/158	1/141	8.92 (1.16, 68.84)
s Mixed	2/191	2/179	0.94 (0.13, 6.58)
es Mixed	3/146	1/147	3.02 (0.32, 28.70)
s NR	2/146	0/134	4.59 (0.22, 94.79)
o Mixed	20/82	6/77	,
NR	4/45	1/45	4.00 (0.47, 34.41)
o Mixed	3/44	0/43	6.84 (0.36, 128.68)
es No	5/84	0/79	10.35 (0.58, 184.23)
	320/2945		4.15 (2.58, 6.61)
			(====, ====,
		1.1	
o NR	6/63	0/66	13.61 (0.78, 236.68)
o Mixed	9/124	2/122	4.43 (0.98, 20.07)
o Mixed	65/806	3/205	- 5.51 (1.75, 17.36)
o NR		0/227	38.47 (2.36, 627.38)
o Mixed	3/94	3/88	0.94 (0.19, 4.52)
o Mixed	67/686	4/337	8.23 (3.03, 22.38)
o Mixed	78/646	6/319	6 .42 (2.83, 14.57)
o Mixed	47/599	1/200	15.69 (2.18, 113.00)
o Mixed	40/650	6/337	3.46 (1.48, 8.07)
o No	4/65	0/66	9.14 (0.50, 166.36)
o NR	7/56	4/55	1.72 (0.53, 5.54)
	353/4114	29/2022	4.77 (3.01, 7.95)
o NR	22/73	18/65	1.09 (0.64, 1.84)
Yes		14/68	1.13 (0.61, 2.11)
Mixed		4/163	2.14 (0.66, 6.98)
MINEU		36/296	1.18 (0.80, 1.91)
	411230	30/230	1.10 (0.00, 1.91)
	720/7357	100/4396	3.58 (2.53, 5.24)
		- 	
		016 125 1	8 64
			.016 .125 1

Favors Opioid Favors 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 ype of opioid Treatment Control and Author, Year Type of pain **EERWD** (95% CI) opioid Agonist Moulin, 1996 Musculoskeletal No. Mixed 13/46 1/46 13.00 (1.77, 95.34) 6.39 (0.34, 120.71) Markenson, 2005 Musculoskeletal No Mixed 3/56 0/51 5.14 (0.25, 105.21) Hale, 2007 Musculoskeletal Yes Yes 2/70 0/72 Katz, 2007 Musculoskeletal Yes 2/105 3/100 0.63 (0.11, 3.72) No Vondrackova, 2008 Musculoskeletal Yes Yes 4/305 1/158 2.07 (0.23, 18.38) 6/134 1.50 (0.43, 5.20) Hale . 2010 Musculoskeletal Yes 4/134 Yes Katz, 2010 Musculoskeletal Yes Mixed 6/171 3/173 2.02 (0.51, 7.96) Friedmann, 2011 Musculoskeletal Yes Mixed 5/205 2/207 2.52 (0.50, 12.86) Vojtassak, 2011 7/149 0.61 (0.18, 2.05) Musculoskeletal No Mixed 4/139 Cloutier, 2013 Musculoskeletal No Mixed 2/74 2/77 1.04 (0.15, 7.20) 21/649 Rauck, 2013 Musculoskeletal No Mixed 5/332 2.15 (0.82, 5.65) Spierings, 2013* Musculoskeletal No Mixed 4/158 2/141 1.78 (0.33, 9.60) Hale , 2015 Musculoskeletal 3/191 3/179 0.94 (0.19, 4.58) Yes Mixed 1.01 (0.21, 4.91) Hale, 2015 Musculoskeletal Yes Mixed 3/146 3/147 Katz, 2015 Musculoskeletal Yes Mixed 2/193 2/196 1.02 (0.14, 7.14) Rauck, 2015 Musculoskeletal Yes 2.29 (0.45, 11.63) NR 5/146 2/134 Trenkwalder, 2015 Musculoskeletal No No 5/92 7/109 0.85 (0.28, 2.58) Wen, 2015 Musculoskeletal Mixed 2/296 5/292 0.39 (0.08, 2.02) Yes Arai, 2015a Musculoskeletal Yes No 2/73 0/77 5.27 (0.26, 107.96) Mayorga, 2016 Musculoskeletal No Mixed 1/50 1/48 0.96 (0.06, 14.92) Kawamata, 2019 Musculoskeletal Yes 0/68 Mixed 2/62 5.48 (0.27, 111.89) Watson, 2003 Neuropathic No NR 0/45 3/45 0.14 (0.01, 2.69) Arai, 2015b Neuropathic 8/84 4/79 1.88 (0.59, 6.00) Yes No Subgroup 105/3490 60/3014 1.43 (1.02, 2.01) $(l^2 = 0.0\%, p = 0.627)$ Mixed Fleischmann, 2001 NR 0/63 2/66 0.21 (0.01, 4.28) Musculoskeletal No 0.70 (0.10, 4.92) Fishman, 2007 Musculoskeletal No NR 2/325 2/227 Thorne, 2008 Musculoskeletal No Mixed 0/94 1/88 0.31 (0.01, 7.57) 14/686 Afilalo, 2010 Musculoskeletal No Mixed 6/337 1.15 (0.44, 2.96) Buynak, 2010 Musculoskeletal No 18/646 3/319 2.96 (0.88, 9.98) Mixed Musculoskeletal No 3/126 2/126 1.50 (0.25, 8.82) Christoph, 2017 Mixed Serrie, 2017 Musculoskeletal No Mixed 15/650 41/337 0.19 (0.11, 0.34) Markman, 2020* Musculoskeletal No Mixed 10/602 4/409 1.70 (0.54, 5.38) Schwartz, 2011 10/196 3/193 3.28 (0.92, 11.74) Neuropathic Yes Mixed Sindrup, 2012 0/64 3.00 (0.12, 72.29) Neuropathic No NR 1/64 Subgroup 73/3452 64/2166 1.02 (0.46, 2.28) $(I^2 = 62.3\%, p = 0.000)$ **PAgonist** Breivik, 2010 Musculoskeletal No 5/100 4/99 1.24 (0.34, 4.47) No Gordon, 2010 Musculoskeletal No. NR 0/73 1/65 0.30 (0.01, 7.17) Munera, 2010 Musculoskeletal No Mixed 0/152 2/163 0.21 (0.01, 4.43) Steiner, 2011 Musculoskeletal Yes No 3/256 2/283 1.66 (0.28, 9.84) Gimbel, 2016 Musculoskeletal Yes Yes 4/254 4/256 1.01 (0.25, 3.99) Rauck, 2016 3/229 3.04 (0.32, 29.00) Musculoskeletal Yes No 1/232 Simpson, 2016 Neuropathic No 7/93 4/93 1.75 (0.53, 5.78) No Subgroup 22/1157 18/1191 1.27 (0.68, 2.38) $(I^2 = 0.0\%, p = 0.785)$ Heterogeneity between groups: p = 0.007 200/8099 142/6371 Overall 1.25 (0.91, 1.74) $(I^2 = 35.3\%, p = 0.002)$

1 Favors Opioid Favors Placebo

64

8

.016 .125

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

Agonist Caldwell, 2002 Mus Markenson, 2005 Mus Matsumoto, 2005 Mus Langford, 2006 Mus Langford, 2007 Mus Langford, 2007 Mus Vondrackova, 2008 Mus Hale, 2010 Mus Friedmann, 2011 Mus Spierings, 2013* Mus Spierings, 2013* Mus Aguerings, 2015 Mus Hale, 2015 Mus Hale, 2015 Mus Hale, 2015 Mus Arai, 2015 Mus Mayorga, 2016 Mus Mayorga, 2016 Mus Mayorga, 2016 Mus Mayorga, 2016 Mus Gilbol, 2003 Neu Khoromi, 2007 Neu Khoromi, 2007 Neu Hanna, 2008 Neu Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Fleischmann, 2001 Mus Gana, 2006 Mus Fishman, 2007 Mus	pe of pain usculoskeletal	No No No No No No Yes Yes Yes Yes Yes Yes Yes Yes No	opioid Mixed Mixed Mixed Mixed Yes Yes No Yes Mixed Mixed Mixed Mixed Mixed Mixed Mixed Nixed Nixed No Mixed No	n/N 12/222 11/56 43/365 23/216 2/70 4/105 8/305 7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	n/N 4/73 10/51 14/124 23/200 0/72 2/100 11/158 10/134 6/173 11/207 38/332 7/141 2/151 8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	Risk Ratio (95% CI) 0.99 (0.33, 2.96) 1.00 (0.46, 2.16) 1.04 (0.59, 1.84) 0.93 (0.54, 1.60) 5.14 (0.25, 105.21) 1.90 (0.36, 0.17) 0.38 (0.15, 0.92) 0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02) 0.96 (0.80, 1.14)
Caldwell, 2002 Mus Markenson, 2005 Mus Matsumoto, 2005 Mus Langford, 2006 Mus Hale, 2007 Mus Hale, 2007 Mus Katz, 2007 Mus Katz, 2010 Mus Hale, 2010 Mus Katz, 2011 Mus Friedmann, 2011 Mus Friedmann, 2011 Mus Spierings, 2013* Mus Spierings, 2013* Mus Rauck, 2014 Mus Hale, 2015 Mus Hale, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Arai, 2015 Mus Mayorga, 2016 Mus Carinton, 2003 Net Miscal Schort, 2007 Net Hanna, 2008 Net Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Fleischmann, 2001 Mus Babul, 2004 Mus Gana, 2006 Mus Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus	usculoskeletal	No No No Yes Yes Yes Yes Yes No No Yes Yes Yes No	Mixed Mixed Yes Yes No Yes Yes Mixed Mixed Mixed Mixed Mixed Mixed No	11/56 43/365 23/216 23/216 23/216 2/70 4/105 8/305 7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	10/51 14/124 23/200 0/72 2/100 11/158 10/134 6/173 11/207 38/332 7/141 2/151 8/177 1/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.00 (0.46, 2.16) 1.04 (0.59, 1.84) 0.93 (0.54, 1.60) 5.14 (0.25, 105.21) 1.90 (0.36, 10.17) 0.38 (0.15, 0.92) 0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.36 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Markenson, 2005 Matsumoto, 2005 Langford, 2006 Mus Langford, 2006 Mus Hale, 2007 Mus Katz, 2007 Vondrackova, 2008 Hale, 2010 Mus Friedmann, 2011 Rauck, 2013 Spierings, 2013* Mus Rauck, 2014 Mus Hale, 2015 Mus Hale, 2015 Mus Hale, 2015 Mus Hale, 2015 Mus Gunder, 2015 Mus Gunder, 2015 Mus Mus Hale, 2016 Mus Hale, 2017 Mus Mus Hale, 2018 Mus Hale, 2018 Mus Hale, 2019 Mus Mus Hale, 2019 Mus	usculoskeletal	No No No Yes Yes Yes Yes Yes No No Yes Yes Yes No	Mixed Mixed Yes Yes No Yes Yes Mixed Mixed Mixed Mixed Mixed Mixed No	11/56 43/365 23/216 23/216 23/216 2/70 4/105 8/305 7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	10/51 14/124 23/200 0/72 2/100 11/158 10/134 6/173 11/207 38/332 7/141 2/151 8/177 1/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.00 (0.46, 2.16) 1.04 (0.59, 1.84) 0.93 (0.54, 1.60) 5.14 (0.25, 105.21) 1.90 (0.36, 10.17) 0.38 (0.15, 0.92) 0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.36 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Matsumoto, 2005 Langford, 2006 Mus Hale, 2007 Mus Katz, 2007 Mus Wondrackova, 2008 Hale , 2010 Mus Friedmann, 2011 Rauck, 2013 Spierings, 2013* Mus Rauck, 2014 Hale, 2015 Mus Hale, 2015 Mus Rauck, 2015 Mus Hale, 2015 Mus Gauck, 2015 Mus Mus Hale, 2015 Mus Hale, 2015 Mus Rauck, 2015 Mus Gilron, 2015 Mus Wen, 2015 Mus Hale, 2001 Mus Gilron, 2005 Neu Khoromi, 2007 Neu Khoromi, 2007 Neu Khoromi, 2007 Neu Subgroup (I² = 0.0%, p = 0.667) Mused Schnitzer, 2000 Mixed Schnitzer, 2000 Mus Gana , 2006 Mus Gana , 2006 Mus Fleischmann, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Vorsanger, 2008 Mus Delemos, 2011 Mus Mused Delemos, 2011 Mus Mused Mus	usculoskeletal	No No Yes Yes Yes Yes Yes Yes No No Yes Yes No	Mixed Yes Yes No Yes Yes Mixed Mixed Mixed Mixed Mixed Mixed Mixed No	43/365 23/216 2/70 4/105 8/305 7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	14/124 23/200 0/72 2/100 11/158 10/134 6/173 11/207 38/332 7/141 2/151 8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.04 (0.59, 1.84) 0.93 (0.54, 1.60) 5.14 (0.25, 105.21) 1.90 (0.36, 10.17) 0.38 (0.15, 0.92) 0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Langford, 2006 Hale, 2007 Mus Katz, 2007 Mus Vondrackova, 2008 Hale, 2010 Mus Katz, 2010 Mus Katz, 2010 Mus Rauck, 2013 Rauck, 2013 Mus Spierings, 2013* Mus Rauck, 2015 Mus Hale, 2015 Mus Hale, 2015 Mus Rauck, 2015 Mus Garbar, 2015 Mus Rauck, 2016 Mus Rauck, 2015 Mus Rayorga, 2016 Mus Gimbel, 2003 Net. Roinbel, 2004 Mus Schnitzer, 2000 Mus Schnitzer, 2000 Mus Fleischmann, 2001 Babul, 2004 Mus Fleischmann, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Affialo, 2010 Mus Delemos, 2011 Mus Mus Delemos, 2011 Mus	usculoskeletal	No Yes Yes Yes Yes Yes No No Yes Yes Yes No Yes Yes No Yos No	Yes Yes No Yes Yes Mixed Mixed Mixed Mixed Mixed NR No Mixed No Mixed Nr Mixed Nr Mixed Nr Mixed Nr	23/216 2/70 4/105 8/305 7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	23/200 0/72 2/100 11/158 10/134 6/173 11/207 38/332 7/141 2/151 8/179 8/147 7/134 9/109 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.93 (0.54, 1.60) 5.14 (0.25, 105.21) 1.90 (0.36, 10.17) 0.38 (0.15, 0.92) 0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Hale, 2007 Katz, 2007 Mus Katz, 2007 Mus Vondrackova, 2008 Mus Hale , 2010 Mus Friedmann, 2011 Rauck, 2013 Spierings, 2013* Mus Spierings, 2013* Mus Hale , 2015 Mus Hale , 2015 Mus Hale, 2015 Mus Hale, 2015 Mus Hale, 2015 Mus Girbel, 2015 Mus Arai, 2015 Mus Mayorga, 2016 Gimbel, 2003 Watson, 2003 Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mixed Mus Arai, 2006 Mus Mus Arai, 2010 Mus Babul, 2004 Mus Gana , 2006 Mus Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Delemos, 2011 Mus Mus Mus Delemos, 2011 Mus Mus Mus Mus Mus Mus Alialo, 2010 Mus	usculoskeletal	Yes Yes Yes Yes Yes Yes No No Yes Yes Yes Yes No	Yes No Yes Yes Mixed Mixed Mixed Mixed Mixed Mixed NR No Mixed No Mixed No Mixed Nr No Mixed No Mixed No Mixed Nr Mixed Nr Mixed Nr Mixed Nr No	2/70 4/105 8/305 7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	0/72 2/100 11/158 10/134 6/173 11/207 38/332 7/141 2/151 8/179 8/147 7/134 9/109 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	5.14 (0.25, 105.21) 1.90 (0.36, 10.17) 0.38 (0.15, 0.92) 0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Katz, 2007 Vondrackova, 2008 Hale , 2010 Mus Katz, 2010 Mus Friedmann, 2011 Rauck, 2013 Spierings, 2013* Mus Rauck, 2014 Hale , 2015 Hale , 2015 Mus Rauck, 2016 Gimbel, 2015 Mus Mayorga, 2016 Gimbel, 2003 Watson, 2003 Rea Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (I* = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mus Fleischmann, 2001 Babul, 2004 Mus Gana , 2006 Mus Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Delemos, 2011 Mus Buynak, 2010 Delemos, 2011 Mus	usculoskeletal	Yes Yes Yes Yes Yes No No Yes Yes Yes No No Yes Yos No	No Yes Yes Mixed Mixed Mixed Mixed Mixed Mixed NR No Mixed NO NO NO	4/105 8/305 7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	2/100 11/158 10/134 6/173 11/207 38/332 7/141 2/151 8/177 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.90 (0.36, 10.17) 0.38 (0.15, 0.92) 0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61)
Vondrackova, 2008 Hale , 2010 Hale , 2010 Katz, 2010 Katz, 2010 Rauck, 2013 Mus Spierings, 2013* Mus Rauck, 2014 Hale , 2015 Mus Hale , 2015 Mus Rauck, 2015 Trenkwalder, 2015 Mus Mayorga, 2016 Gimbel, 2003 Watson, 2003 Watson, 2003 Watson, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (I² = 0.0%, p = 0.667) Mus Mused Schnitzer, 2000 Mixed Mus Augus Mus Mus Mus Mus Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Delemos, 2011 Mus	usculoskeletal	Yes Yes Yes Yes No No Yes Yes Yes Yes No	Yes Yes Yes Mixed Mixed Mixed Mixed Mixed NR No Mixed No Mixed NIX Mixed NR No Mixed NR Mixed NR Mixed NR NO Mixed NR Mixed NR Mixed NO	8/305 7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	11/158 10/134 6/173 11/207 38/332 7/141 2/151 8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.38 (0.15, 0.92) 0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Hale , 2010 Mus Katz, 2010 Mus Katz, 2010 Mus Katz, 2010 Mus Rauck, 2013 Mus Spierings, 2013* Mus Rauck, 2014 Mus Hale , 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Grenkwalder, 2015 Mus Mayorga, 2016 Mus Mayorga, 2016 Mus Gilmoel, 2003 Net Gilmon, 2003 Net Moston, 2003 Net Moston, 2003 Net Moston, 2004 Net Moston, 2005 Net Khoromi, 2007 Net Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Schnitzer, 2001 Mus Schnitzer, 2001 Mus Schnitzer, 2008 Mus Afilalo, 2010 Mus	usculoskeletal	Yes Yes Yes No No Yes Yes Yes Yes No Yes Yes No No No No No No No	Yes Mixed Mixed Mixed Mixed Yes Mixed Mixed NR No Mixed No Mixed Mixed NR Mixed NO NO NO	7/134 12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	10/134 6/173 11/207 38/332 7/141 2/151 8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.70 (0.27, 1.78) 2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Katz, 2010 Kriedmann, 2011 Kriedmann, 2011 Kauck, 2013 Kauck, 2014 Kauck, 2015 Kauck, 2015 Kauck, 2015 Kauck, 2015 Kauck, 2015 Kushale, 2016 Kushale, 2016 Kushale, 2017 Kaushale, 2018 Kaushale, 2003 Katson, 2005 Koromi, 2007 Kanna, 2008 Kushale, 2007 Kushale, 2000 Kushale, 2008 Kushale, 2010 Kushale, 2011 Kushale, 2012 Kushale, 2011 Kushale, 2011 Kushale, 2012 Kushale, 2011 Kushale, 2012 Kushale, 2013 Kushale, 2013 Kushale, 2013 Kushale, 2013 Kushale, 2013 Kushale, 2013 Kushale, 2014 Kushale,	usculoskeletal	Yes Yes No No Yes Yes Yes Yes No	Mixed Mixed Mixed Mixed Yes Mixed NR No Mixed No Mixed Mixed No Mixed Nr No Mixed Nr No Mixed NR No Mixed NR Mixed NR	12/171 10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	6/173 11/207 38/332 7/141 2/151 8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	2.02 (0.78, 5.27) 0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Friedmann, 2011 Rauck, 2013 Mus Spierings, 2013* Mus Rauck, 2014 Hale, 2015 Hale, 2015 Rauck, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Mus Men, 2015 Mus Mayorga, 2016 Gimbel, 2003 Watson, 2003 Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (l² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mixed Mus Auguation Mus Babul, 2004 Mus Gana , 2006 Mixed Mus Alfialo, 2010 Mus Delemos, 2011 Mus Mus Delemos, 2011 Mus	usculoskeletal	Yes No No Yes Yes Yes Yes No	Mixed Mixed Mixed Yes Mixed NR NO Mixed No Mixed NR No Mixed No Mixed NR No Mixed NR No No Mixed NR NO NO Mixed NR NO NO Mixed NR NO NO NO NO NO NO NO NO NO	10/205 84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	11/207 38/332 7/141 2/151 8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.92 (0.40, 2.11) 1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Rauck, 2013 Spierings, 2013* Mus Spierings, 2013* Mus Rauck, 2014 Mus Hale , 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Wen, 2015 Mus Mayorga, 2016 Gimbel, 2003 Watson, 2003 Net Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (I* = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Fleischmann, 2001 Mus Gana , 2006 Mus Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Mus Mus Mus Mus Mus Mus M	usculoskeletal usculoskeletal	No No Yes Yes Yes Yes No Yes No	Mixed Mixed Yes Mixed Mixed NR No Mixed No Mixed No Mixed Nr Mixed NR Mixed NR Mixed NR Mixed NR Mixed NR Mixed NO	84/649 8/158 0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	38/332 7/141 2/151 8/177 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.13 (0.79, 1.62) 1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Spierings, 2013* Mus Rauck, 2014 Mus Hale , 2015 Mus Hale, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Arai, 2015a Mus Arai, 2015a Mus Mayorga, 2016 Gimbel, 2003 Net Gimbel, 2003 Net Gilron, 2005 Net Khoromi, 2007 Net Khoromi, 2007 Net Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Fleischmann, 2001 Babu, 2004 Babu, 2004 Babu, 2006 Fishman, 2007 Thorne, 2008 Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Belemos, 2011 Mus Belemos, 2011 Mus Mused Mus	usculoskeletal	No Yes Yes Yes No Yes Yes No No No No No	Mixed Yes Mixed Mixed NR No Mixed Mixed Mixed NR Mixed NR Mixed No	8/158 0/151 11/191 10/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	7/141 2/151 8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.02 (0.38, 2.74) 0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Rauck, 2014 Hale, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Rauck, 2015 Mus Trenkwalder, 2015 Mus Mayorga, 2016 Mis Mised Schnitzer, 2000 Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mus Mus Mus Mus Mus Mus Mus	usculoskeletal	Yes Yes Yes No Yes Yes No No No No No No No No	Yes Mixed Mixed NR No Mixed No Mixed Mixed Mixed Mixed Mixed No	0/151 11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	2/151 8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.20 (0.01, 4.13) 1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Hale , 2015 Mus Hale , 2015 Mus Rauck , 2015 Mus Rauck , 2015 Mus Wen , 2015 Mus Wen , 2015 Mus Arai , 2015a Mus Mayorga , 2016 Mus Mayorga , 2016 Mus Gimbel , 2003 Net Watson , 2003 Net Giffon , 2005 Net Khoromi , 2007 Net Hanna , 2008 Net Subgroup (I² = 0.0% , p = 0.667) Mixed Schnitzer , 2000 Mus Fleischmann , 2001 Babul , 2004 Mus Gana , 2006 Mus Grishman , 2007 Mus Thorne , 2008 Mus Vorsanger , 2008 Mus Afilalo , 2010 Mus Delemos , 2011 Mus Delemos , 2011 Mus Uberall , 2012 Mus	usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal europathic europathic europathic europathic europathic	Yes Yes Yes No Yes No No No No No No No No	Mixed Mixed NR No Mixed No Mixed Mixed NR Mixed No	11/191 10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	8/179 8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.29 (0.53, 3.13) 1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Hale, 2015 Rauck, 2015 Rauck, 2015 Mus Rauck, 2015 Mus Wen, 2015 Mus Arai, 2015 Mus Mayorga, 2016 Gimbel, 2003 Watson, 2003 Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mus Gana , 2006 Mus Gana , 2006 Mus Fishman, 2007 Mus Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus	usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal uropathic uropathic uropathic uropathic uropathic uropathic uropathic	Yes Yes No Yes No	Mixed NR No Mixed No Mixed Mixed NR Mixed Mixed No	10/146 2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	8/147 7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.26 (0.51, 3.10) 0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Rauck, 2015 Trenkwalder, 2015 Mus Wen, 2015 Mus Arai, 2015a Mus Mayorga, 2016 Gimbel, 2003 Watson, 2003 Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mus Babul, 2004 Mus Gana, 2006 Mus Fishman, 2007 Thorne, 2008 Mus Worsanger, 2008 Mus Worsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Mus Mus Mus Mus Mus Mus Mus Mus Mu	usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal usculoskeletal uropathic europathic europathic europathic europathic	Yes No Yes Yes No No No No No No Yes No	NR No Mixed No Mixed Mixed NR Mixed Mixed NR Mixed No	2/146 6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	7/134 9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.26 (0.06, 1.24) 0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Trenkwalder, 2015 Wen, 2015 Mus, 2015a Mus, Musyorga, 2016 Gimbel, 2003 Watson, 2003 Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (l² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Mixed Schnitzer, 2000 Muse Schnitzer, 2000 Muse Mu	usculoskeletal usculoskeletal usculoskeletal usculoskeletal urropathic urropathic urropathic urropathic urropathic urropathic	No Yes Yes No No No No No No	No Mixed No Mixed Mixed NR Mixed Mixed No	6/92 6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	9/109 5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.79 (0.29, 2.14) 1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Wen, 2015 Arai, 2015a Mus Mayorga, 2016 Gimbel, 2003 Watson, 2003 Neu Watson, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (l² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Gana, 2006 Mus Gana, 2006 Mus Gana, 2006 Mus Gana, 2006 Mus Gana, 2007 Thorne, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Mus Mus Mus Mus Mus Mus Mu	usculoskeletal usculoskeletal usculoskeletal uscupathic uropathic uropathic uropathic uropathic uropathic uropathic	Yes Yes No No No No No No Yes No	Mixed No Mixed Mixed NR Mixed Mixed No	6/296 0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	5/292 1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	1.18 (0.37, 3.84) 0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Arai, 2015a Mus Mayorga, 2016 Mus Gimbel, 2003 Net Watson, 2003 Net Watson, 2005 Net Khoromi, 2007 Net Hanna, 2008 Net (l² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Babul, 2004 Mus Gana , 2006 Mus Fishman, 2007 Mus Thorne, 2008 Mus Worsanger, 2008 Mus Babul, 2010 Mus Babul, 2011 Mus Delemos, 2011 Mus	usculoskeletal usculoskeletal europathic europathic europathic europathic europathic europathic	Yes No No No No No No No	No Mixed Mixed NR Mixed Mixed No	0/73 2/50 9/82 5/45 1/44 4/28 17/168 297/4168	1/77 5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.35 (0.01, 8.49) 0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Mayorga, 2016 Gimbel, 2003 Watson, 2003 Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (l² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Fleischmann, 2001 Bagana, 2006 Mus Gana, 2006 Mus Grishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Belynak, 2010 Mus Delemos, 2011 Mus Delemos, 2011 Mus	usculoskeletal europathic europathic europathic europathic europathic europathic	No No No No No No	Mixed Mixed NR Mixed Mixed No	2/50 9/82 5/45 1/44 4/28 17/168 297/4168	5/48 18/77 3/45 1/43 4/28 16/167 223/3262	0.38 (0.08, 1.89) 0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Gimbel, 2003 Neu Watson, 2003 Neu Gilron, 2005 Neu Khoromi, 2007 Neu Khoromi, 2007 Neu Hanna, 2008 Neu (l² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Fleischmann, 2001 Mus Babul, 2004 Mus Gana , 2006 Mus Fishman, 2007 Mus Fishman, 2007 Mus Forsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Delemos, 2011 Mus	europathic europathic europathic europathic europathic europathic	No No No No No Yes	Mixed NR Mixed Mixed No	9/82 5/45 1/44 4/28 17/168 297/4168	18/77 3/45 1/43 4/28 16/167 223/3262	0.47 (0.22, 0.98) 1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Watson, 2003 Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Fleischmann, 2001 Babul, 2004 Gana, 2006 Mus Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Affialo, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus	europathic europathic europathic europathic europathic usculoskeletal usculoskeletal usculoskeletal	No No No No Yes	NR Mixed Mixed No	5/45 1/44 4/28 17/168 297/4168	3/45 1/43 4/28 16/167 223/3262	1.67 (0.42, 6.56) 0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Gilron, 2005 Khoromi, 2007 Hanna, 2008 Subgroup (l² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Babul, 2004 Gana, 2006 Mus Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus	europathic europathic europathic usculoskeletal usculoskeletal usculoskeletal	No No No Yes	Mixed Mixed No	1/44 4/28 17/168 297/4168	1/43 4/28 16/167 223/3262	0.98 (0.06, 15.13) 1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Khoromi, 2007 Hanna, 2008 Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Fleischmann, 2001 Babul, 2004 Mus Gana , 2006 Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Delemos, 2011 Mus	europathic europathic usculoskeletal usculoskeletal usculoskeletal	No No Yes No	Mixed No NR	4/28 17/168 297/4168	4/28 16/167 223/3262	1.00 (0.28, 3.61) 1.06 (0.55, 2.02)
Hanna, 2008 Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Fleischmann, 2001 Babul, 2004 Mus Gana , 2006 Mishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus	europathic usculoskeletal usculoskeletal usculoskeletal	No Yes No	No NR	17/168 297/4168	16/167 —— - 223/3262	1.06 (0.55, 2.02)
Subgroup (I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Fleischmann, 2001 Babul, 2004 Mus Gana , 2006 Mus Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Affilalo, 2010 Mus Delemos, 2011 Mus Mus Mus Mus Mus Mus Mus Mus Mus Mu	usculoskeletal usculoskeletal usculoskeletal	Yes No	NR	297/4168	223/3262	
(I² = 0.0%, p = 0.667) Mixed Schnitzer, 2000 Mus Fleischmann, 2001 Mus Babul, 2004 Gana , 2006 Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Delemos, 2011 Mus	usculoskeletal usculoskeletal	No				0.96 (0.80, 1.14)
Mixed Schnitzer, 2000 Mus Fleischmann, 2001 Babul, 2004 Gana , 2006 Mus Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Delemos, 2011 Mus Mus Mus Mus Mus Mus Mus M	usculoskeletal usculoskeletal	No		6/127		
Schnitzer, 2000 Mus Fleischmann, 2001 Mus Babul, 2004 Mus Gana, 2006 Mus Fishman, 2007 Mus Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus	usculoskeletal usculoskeletal	No		6/127		
Schnitzer, 2000 Mus Fleischmann, 2001 Mus Babul, 2004 Mus Gana, 2006 Mus Fishman, 2007 Mus Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus	usculoskeletal usculoskeletal	No		6/127	r	
Fleischmann, 2001 Babul, 2004 Gana , 2006 Mus Fishman, 2007 Thorne, 2008 Worsanger, 2008 Mis Mus Mus Mus Mus Mus Mus Mus	usculoskeletal usculoskeletal		NR	0/12/	4/127	1.50 (0.43, 5.19)
Babul, 2004 Mus Gana , 2006 Mus Fishman, 2007 Mus Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus	usculoskeletal			5/63	0/66	11.52 (0.65, 204.06)
Fishman, 2007 Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Delemos, 2011 Mus Uberall, 2012 Mus Mus Mus Mus Mus Mus Mus Mus Mus Mu	isculoskolotal	110	Mixed	19/124	20/122	0.93 (0.53, 1.66)
Thorne, 2008 Mus Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus		No	Mixed	112/806	17/205	1.68 (1.03, 2.73)
Vorsanger, 2008 Mus Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus	usculoskeletal	No	NR	22/325	18/227 	0.85 (0.47, 1.55)
Afilalo, 2010 Mus Buynak, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus	usculoskeletal	No	Mixed	2/94	6/88	0.31 (0.06, 1.51)
Buynak, 2010 Mus Delemos, 2011 Mus Uberall, 2012 Mus	usculoskeletal	Yes	Mixed	34/257	14/129	1.22 (0.68, 2.19)
Delemos, 2011 Mus Uberall, 2012 Mus	usculoskeletal	No	Mixed	101/686	56/337	0.89 (0.66, 1.20)
Uberall, 2012 Mus	usculoskeletal	No	Mixed	118/646	44/319	1.32 (0.96, 1.82)
	usculoskeletal	No	Mixed	77/599	26/200	0.99 (0.65, 1.50)
Christoph, 2017 Mus	usculoskeletal	No	Mixed	4/116	2/120	2.07 (0.39, 11.08)
	usculoskeletal	No	Mixed	10/126	11/126	0.91 (0.40, 2.06)
Serrie, 2017 Mus	usculoskeletal	No	Mixed	60/650	31/337	1.00 (0.66, 1.52)
Markman, 2020* Mus	usculoskeletal	No	Mixed	38/602	16/409	1.61 (0.91, 2.85)
van de Donk, 2020* Mus	ısculoskeletal	No	Mixed	5/20	1/20	5.00 (0.64, 39.06)
Harati, 1998 Neu	europathic	No	No	11/65	3/66	3.72 (1.09, 12.73)
Schwartz, 2011 Neu	europathic	Yes	Mixed	10/196	10/193 	0.98 (0.42, 2.31)
Sindrup, 2012 Neu	europathic	No	NR	7/56	3/55	2.29 (0.62, 8.41)
Vinik, 2014 Neu	europathic	Yes	Mixed	4/166	8/152	0.46 (0.14, 1.49)
Subgroup				645/5724	290/3298	1.13 (0.97, 1.34)
$(I^2 = 7.5\%, p = 0.130)$					i	
PAgonist					1	
-	usculoskeletal	No	No	7/100	6/99	1.16 (0.40, 3.32)
	usculoskeletal	No	NR	8/73	6/65	1.19 (0.43, 3.24)
	usculoskeletal	No	Yes	9/73	3/68	2.79 (0.79, 9.89)
	usculoskeletal	No	Mixed	34/152	25/163	1.46 (0.91, 2.33)
	usculoskeletal	Yes	No	14/256	14/283	1.11 (0.54, 2.27)
	usculoskeletal	Yes	Yes	6/254	8/256	0.76 (0.27, 2.15)
	usculoskeletal	Yes	No	5/229	8/232	0.63 (0.21, 1.91)
Subgroup	asculoskeletai	163	140	83/1137	70/1166	1.23 (0.87, 1.67)
(I ² = 0.0%, p = 0.614)				03/113/	76/1166	1.25 (0.07, 1.07)
					l	
Heterogeneity between group				4005///005	500/7700	4.07.(0.07.4.40)
Overall	ıps: p = 0.251			1025/11029	583/7726	1.07 (0.97, 1.19)
$(l^2 = 0.0\%, p = 0.375)$	ıps: p = 0.251					
	ıps: p = 0.251					
	ıps: p = 0.251				- 	

Favors Opioid Favors 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 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	20,960 (continuous);	Direct	Precise	Low	Consistent	MD -0.78 (-0.91 to -0.65); RR 1.33 (1.22 to 1.46)	
	Function (short- term)	RCTs ´	13,730	Direct	Precise	Low	Consistent	SMD -0.21 (-0.27 to -0.15)	High
(lor Stu due Ser Nar Vor Cor Diz Hea Sor Pru	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 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	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	cohort study	140 (RCT) and 53,187 (cohort study)	Direct	Imprecise	Moderate	Consistent	No differences	Low
Tapering off opioids vs.	Pain, function (long-term)	1 new cohort study	290	Direct	Imprecise	High	Unknown	No differences	Insufficient
continuation of opioids	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		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
- 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
- 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 NonCancer 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.000000000001251. 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.00000000000000606. 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.000000000003238. 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 cognitivebehavioral 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 medicationoveruse 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.000000000003658. 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.000000000001969. 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.000000000002165. 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 nonmalignant 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.CD01218 7.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
- 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
- 86. de Kleijn L, Pedersen J, Rijkels-Otters H, et al. Opioid reduction for patients with chronic pain in primary care: systematic review. British Journal of General Practice. 2022 Jan 12;12:12. doi: 10.3399/BJGP.2021.0537. PMID: 35023850. Exclusion reason: Systematic review used as source document
- 87. De Santis S, Simone MD, Mercadante S, et al. Oxycodone/acetaminophen: The tailoring combination treatment for specific clinical profile of opioid well-responsive cancer pain. Cancer Management and Research. 2021;13:1747-56. doi: 10.2147/CMAR.S290551. Exclusion reason: Ineligible population
- 88. De Sola H, Duenas M, Salazar A, et al.
 Prevalence of Therapeutic use of Opioids in
 Chronic non-Cancer Pain Patients and
 Associated Factors: A Systematic Review
 and Meta-Analysis. Frontiers in
 Pharmacology. 2020;11:564412. doi:
 10.3389/fphar.2020.564412. PMID:
 33364942. Exclusion reason: Systematic
 review used as source document
- 89. de Vries F, Bruin M, Lobatto DJ, et al.
 Opioids and Their Endocrine Effects: A
 Systematic Review and Meta-analysis. J
 Clin Endocrinol Metab. 2020 03
 01;105(3):01. doi: 10.1210/clinem/dgz022.
 PMID: 31511863. Exclusion reason:
 Systematic review used as source document
- 90. DeBar L, Mayhew M, Benes L, et al. A
 Primary Care-Based Cognitive Behavioral
 Therapy Intervention for Long-Term Opioid
 Users With Chronic Pain: A Randomized
 Pragmatic Trial. Ann Intern Med. 2021doi:
 10.7326/M21-1436. Exclusion reason:
 Ineligible intervention

- 91. Denawa Y, Kurtz W, Conerman T. The Social and Functional Implications of High versus Low Dose Opioids on Chronic Non-Cancer Pain. Postgrad Med. 2019;131(SUPPL 1):125. doi: 10.1080/00325481.2019.1655695.

 Exclusion reason: Ineligible publication type
- 92. Derry S, Wiffen PJ, Moore AR, et al. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. Cochrane Database Syst Rev. 2017;7(7)doi: https://doi.org/10.1002/14651858.CD01263 8. PMID: 28700091. Exclusion reason: Ineligible population
- 93. Deshpande KS, Roehmer C, Raum G, et al. Functional recovery program: An interdisciplinary approach to treating chronic pain. Journal of Pain Management. 2020;13(4):383-92. Exclusion reason: Ineligible comparator
- 94. Dhingra L, Schiller R, Teets R, et al. Pain Management in Primary Care: A Randomized Controlled Trial of a Computerized Decision Support Tool. Am J Med. 2021 12;134(12):1546-54. doi: 10.1016/j.amjmed.2021.07.014. PMID: 34411523. Exclusion reason: Ineligible intervention
- 95. Dhokia M, Elander J, Clements K, et al. A randomized-controlled pilot trial of an online compassionate mind training intervention to help people with chronic pain avoid analgesic misuse. Psychology of Addictive Behaviors. 2020 Nov;34(7):726-33. doi: 10.1037/adb0000579. PMID: 32271055. Exclusion reason: Ineligible intervention
- 96. Diasso PDK, Sjogren P, Hojsted J, et al. Patient reported outcomes and neuropsychological testing in patients with chronic non-cancer pain in long-term opioid therapy: a pilot study. Scand J Pain. 2019 07 26;19(3):533-43. doi: 10.1515/sjpain-2019-0007. PMID: 31031263. Exclusion reason: Ineligible study design
- 97. DiMeola KA, Haynes J, Barone M, et al. A Pilot Investigation of Nonpharmacological Pain Management Intervention Groups in Methadone Maintenance Treatment. J Addict Med. 2021 Jun 17;17:17. doi: 10.1097/ADM.00000000000000877. PMID:

- 34145187. **Exclusion reason:** Ineligible comparator
- 98. Dol M, Oremus M. Iatrogenic addiction or dependence as a result of prescription oxycodone use in persons with chronic noncancer pain: A systematic review. J Opioid Manag. 2021 Jan-Feb;17(1):79-96. doi: 10.5055/jom.2021.0616. PMID: 33735430. Exclusion reason: Systematic review used as source document
- 99. Donaldson K. Overview of development of a polygenetic risk source for OUD. Annals of Clinical and Laboratory Science. 2019;49(3):403. Exclusion reason: Ineligible publication type
- 100. Donaldson K, Cardamone D, Genovese M, et al. Clinical Performance of a Gene-Based Machine Learning Classifier in Assessing Risk of Developing OUD in Subjects Taking Oral Opioids: A Prospective Observational Study. Annals of clinical and laboratory science. 2021;51(4):451-60. Exclusion reason: Ineligible population
- 101. Dong X, Deng J, Hou W, et al. Predicting opioid overdose risk of patients with opioid prescriptions using electronic health records based on temporal deep learning. J Biomed Inform. 2021 04;116:103725. doi: 10.1016/j.jbi.2021.103725. PMID: 33711546. Exclusion reason: Ineligible intervention
- 102. Dong X, Deng J, Rashidian S, et al. Identifying risk of opioid use disorder for patients taking opioid medications with deep learning. Journal of the American Medical Informatics Association: JAMIA. 2021;28(8):1683-93. doi: 10.1093/jamia/ocab043. Exclusion reason: Ineligible intervention
- 103. Drks. Experiencing the Risks of
 Overutilizing Opioids Among Patients With
 Non-Tumor Chronic Pain in Ambulant Care.
 Experiencing the Risks of Overutilizing
 Opioids Among Patients With Non-Tumor
 Chronic Pain in Ambulant Care ERONA.
 2020. Exclusion reason: Ineligible
 publication type
- 104. Duarte FCN, Ferraro L, Ferreira A, et al. A
 Randomized Controlled Trial Evaluating the
 Analgesic Effect of the Combination of
 Methadone With Morphine for Cancer
 Related Pain. Clin J Pain. 2021 09

- 01;37(9):664-8. doi: 10.1097/AJP.00000000000000959. PMID: 34265791. **Exclusion reason:** Ineligible population
- 105. Edler-Buggy S, Birtwistle J, ElMokhallalati Y, et al. Regular dosing compared with asneeded dosing of opioids for management of chronic cancer pain: systematic review and meta-analysis. Pain. 2020 04;161(4):703-12. doi: 10.1097/j.pain.0000000000001755. PMID: 31770157. Exclusion reason: Ineligible population
- 106. Edwards KA, Vowles KE, McHugh R, et al. Changes in pain during buprenorphine maintenance treatment among patients with opioid use disorder and chronic pain. J Consult Clin Psychol. 2022 Jan:No Pagination Specified. doi: 10.1037/ccp0000692. PMID: 2022-18508-001. Exclusion reason: Ineligible intervention
- 107. Erosa SC, Haffey PR, Mehta N, et al. Tapentadol, Buprenorphine, and Levorphanol for the Treatment of Neuropathic Pain: a Systematic Review. Curr Pain Headache Rep. 2021 Feb 25;25(3):18. doi: 10.1007/s11916-020-00934-z. PMID: 33630185. Exclusion reason: Systematic review used as source document
- 108. Esteve R, Reyes-Perez A, Ramirez-Maestre C, et al. Diagnostic and Predictive Capacity of the Spanish Versions of the Opioid Risk Tool and the Screener and Opioid Assessment for Patients with Pain-Revised: A Preliminary Investigation in a Sample of People with Noncancer Chronic Pain. Pain Ther. 2022doi: 10.1007/s40122-022-00356-2. Exclusion reason: Ineligible population
- 109. Falk J, Thomas B, Kirkwood J, et al. PEER systematic review of randomized controlled trials: Management of chronic neuropathic pain in primary care. Can Fam Physician. 2021 05;67(5):e130-e40. doi: 10.46747/cfp.6705e130. PMID: 33980642. Exclusion reason: Systematic review used as source document
- 110. Farabee D, Condon T, Hallgren KA, et al. A randomized comparison of extended-release naltrexone with or without patient navigation vs enhanced treatment-as-usual for incarcerated adults with opioid use disorder. J Subst Abuse Treat. 2020

- 10;117:108076. doi: 10.1016/j.jsat.2020.108076. PMID: 32811623. **Exclusion reason:** Ineligible population
- 111. Farrar JT, Bilker WB, Cochetti PT, et al. Evaluating the stability of opioid efficacy over 12 months in patients with chronic noncancer pain who initially demonstrate benefit from extended release oxycodone or hydrocodone: harmonization of Food and Drug Administration patient-level drug safety study data. Pain. 2021 Jul 12;12:12. doi: 10.1097/j.pain.0000000000002331. PMID: 34261978. Exclusion reason: Ineligible comparator
- 112. Feldman CA, Fredericks-Younger J, Lu S-E, et al. The Opioid Analgesic Reduction Study (OARS)-a comparison of opioid vs. non-opioid combination analgesics for management of post-surgical pain: a double-blind randomized clinical trial. Trials. 2022;23(1):160. doi: 10.1186/s13063-022-06064-8. Exclusion reason: Ineligible publication type
- 113. Feng B, Malloch YZ, Kravitz RL, et al. Assessing the effectiveness of a narrative-based patient education video for promoting opioid tapering. Patient Educ Couns. 2021;104(2):329-36. doi: https://doi.org/10.1016/j.pec.2020.08.019. PMID: 32900605. Exclusion reason: Ineligible outcome
- 114. Ferri CM, Natoli S, Sanz-Ayan P, et al.
 Quality of life and functional outcomes with
 tapentadol prolonged release in chronic
 musculoskeletal pain: post hoc analysis.
 Pain Manag. 2021 Mar;11(2):173-87. doi:
 10.2217/pmt-2020-0084. PMID: 33241725.
 Exclusion reason: Ineligible publication
 type
- 115. Ferris LM, Saloner B, Jackson K, et al.
 Performance of a Predictive Model versus
 Prescription-Based Thresholds in
 Identifying Patients at Risk of Fatal Opioid
 Overdose. Substance Use & Misuse.
 2021;56(3):396-403. doi:
 10.1080/10826084.2020.1868520. PMID:
 33446000. Exclusion reason: Ineligible
 population
- 116. Fishman M, Wenzel K, Scodes J, et al. Young Adults Have Worse Outcomes Than Older Adults: Secondary Analysis of a Medication Trial for Opioid Use Disorder. J

- Adolesc Health. 2020 12;67(6):778-85. doi: 10.1016/j.jadohealth.2020.07.038. PMID: 32873500. **Exclusion reason:** Ineligible population
- 117. Fishman MA, Antony AB, Hunter CW, et al. The Cost of Lost Productivity in an Opioid Utilizing Pain Sample. J Pain Res. 2021;14:2347-57. doi: 10.2147/JPR.S309691. PMID: 34377015. Exclusion reason: Ineligible comparator
- 118. Flynn D, Doorenbos AZ, Steffen A, et al. Pain Management Telementoring, Long-term Opioid Prescribing, and Patient-Reported Outcomes. Pain Med. 2020 02 01;21(2):266-73. doi: 10.1093/pm/pnz338. PMID: 31876948. Exclusion reason: Ineligible population
- 119. Freo U, Furnari M, Ambrosio F, et al. Efficacy and tolerability of tapentadol for the treatment of chronic low back pain in elderly patients. Aging Clin Exp Res. 2021 Apr;33(4):973-82. doi: 10.1007/s40520-020-01586-0. PMID: 32418129. Exclusion reason: Ineligible comparator
- 120. Frers A, Shaffer J, Edinger J, et al. The relationship between sleep and opioids in chronic pain patients. Journal of Behavioral Medicine. 2021 06;44(3):412-20. doi: 10.1007/s10865-021-00205-1. PMID: 33609232. Exclusion reason: Ineligible population
- 121. Freynhagen R, Elling C, Radic T, et al. Safety of tapentadol compared with other opioids in chronic pain treatment: network meta-analysis of randomized controlled and withdrawal trials. Curr Med Res Opin. 2021 01;37(1):89-100. doi: 10.1080/03007995.2020.1832977. PMID: 33032466. Exclusion reason: Systematic review used as source document
- 122. Friedman BW, Irizarry E, Feliciano C, et al. A randomized controlled trial of oxycodone/acetaminophen versus acetaminophen alone for emergency department patients with musculoskeletal pain refractory to ibuprofen. Acad Emerg Med. 2021 Feb 12;12:12. doi: 10.1111/acem.14231. PMID: 33576545. Exclusion reason: Ineligible population
- 123. Galindo SR, da Nobrega Marinho MH, Gatchel RJ, et al. Cross-cultural adaptation of the Pain Medication Questionnaire for use

- in Brazil. BMC Med Res Methodol. 2019 09 23;19(1):188. doi: 10.1186/s12874-019-0821-x. PMID: 31547804. Exclusion reason: Ineligible intervention
- 124. Garland EL, Brintz CE, Hanley AW, et al. Mind-Body Therapies for Opioid-Treated Pain: A Systematic Review and Meta-analysis. JAMA Intern Med. 2020 Jan 01;180(1):91-105. doi: 10.1001/jamainternmed.2019.4917. PMID: 31682676. Exclusion reason: Systematic review used as source document
- 125. Garland EL, Hanley AW, Nakamura Y, et al. Mindfulness-oriented recovery enhancement for opioid misuse and chronic pain in primary care: A full-scale randomized controlled trial. J Gen Intern Med. 2021;36(SUPPL 1):S122-S3. doi: 10.1007/s11606-021-06830-5. PMID: 34297318. Exclusion reason: Ineligible publication type
- 126. Garland EL, Hanley AW, Riquino MR, et al. Mindfulness-oriented recovery enhancement reduces opioid misuse risk via analgesic and positive psychological mechanisms: A randomized controlled trial. J Consult Clin Psychol. 2019 Oct;87(10):927-40. doi: 10.1037/ccp0000390. PMID: 31556669. Exclusion reason: Ineligible comparator
- 127. Garland EL, Hudak J, Hanley AW, et al. Mindfulness-oriented recovery enhancement reduces opioid dose in primary care by strengthening autonomic regulation during meditation. American Psychologist. 2020 09;75(6):840-52. doi: 10.1037/amp0000638. PMID: 32915027. Exclusion reason: Ineligible intervention
- 128. Garland El HAWKACNA. Mindfulness-Oriented Recovery Enhancement reduces opioid craving among individuals with opioid use disorder and chronic pain in medication assisted treatment: ecological momentary assessments from a stage 1 randomized controlled trial. Drug Alcohol Depend. 2019;203:61. Exclusion reason: Ineligible comparator
- 129. Gersch WD, Delate T, Bergquist KM, et al. Clinical Effectiveness of an Outpatient Multidisciplinary Chronic Pain Management Telementoring Service. Clin J Pain. 2021 Jul 12;12:12. doi: 10.1097/AJP.0000000000000967. PMID:

- 34265787. **Exclusion reason:** Ineligible intervention
- 130. Gibson CJ, Grasso J, Li Y, et al. An Integrated Pain Team Model: Impact on Pain-Related Outcomes and Opioid Misuse in Patients with Chronic Pain. Pain Med. 2020 09 01;21(9):1977-84. doi: 10.1093/pm/pnaa003. PMID: 32100002. Exclusion reason: Ineligible comparator
- 131. Gimbel JS, Rauck RL, Bass A, et al. Effects of naltrexone exposure observed in two phase three studies with ALO-02, an extended-release oxycodone surrounding sequestered naltrexone. J Opioid Manag. 2019 Sep/Oct;15(5):417-27. doi: 10.5055/jom.2019.0530. PMID: 31849032. Exclusion reason: Ineligible outcome
- 132. Gimelfarb Y, Shamir EZ, Ness Dabush K, et al. Methadone maintenance treatment and survival of schizophrenic patients with a lifetime comorbid substance use disorders: a long-term follow-up study. J Addict Dis. 2020 Oct-Dec;38(4):458-64. doi: 10.1080/10550887.2020.1782558. PMID: 32608328. Exclusion reason: Ineligible population
- 133. Girardot K, Hollister L, Zhu TH, et al. Effectiveness of Multimodal Pain Therapy on Reducing Opioid Use in Surgical Geriatric Hip Fracture Patients. J Trauma Nurs. 2020 Jul/Aug;27(4):207-15. doi: 10.1097/JTN.000000000000516. PMID: 32658061. Exclusion reason: Ineligible intervention
- 134. Green C, Eldabe SS, Taylor RS, et al.
 Resource Use and Cost of Subcutaneous
 Nerve Stimulation Versus Optimized
 Medical Management in Patients With
 Failed Back Surgery Syndrome: An
 Analysis of the SubQStim Study.
 Neuromodulation. 2021 Apr 27;27:27. doi:
 10.1111/ner.13405. PMID: 33905144.
 Exclusion reason: Ineligible intervention
- 135. Greiner RS, Boselli D, Patel JN, et al.
 Opioid Risk Screening in an Oncology
 Palliative Medicine Clinic. JCO Oncol
 Pract. 2020 11;16(11):e1332-e42. doi:
 10.1200/OP.20.00043. PMID: 32603251.
 Exclusion reason: Ineligible population
- 136. Groessl EJ, Liu L, Schmalzl L, et al.
 Secondary Outcomes from a Randomized
 Controlled Trial of Yoga for Veterans with

- Chronic Low-Back Pain. Int J Yoga Therap. 2020 Jan 01;30(1):69-76. doi: 10.17761/2020-D-19-00036. PMID: 31509451. **Exclusion reason:** Ineligible intervention
- 137. Gudin J, Mavroudi S, Korfiati A, et al.
 Reducing Opioid Prescriptions by
 Identifying Responders on Topical
 Analgesic Treatment Using an
 Individualized Medicine and Predictive
 Analytics Approach. J Pain Res.
 2020;13:1255-66. doi:
 10.2147/JPR.S246503. PMID: 32547186.
 Exclusion reason: Ineligible intervention
- 138. Guitart J, Vargas MI, De Sanctis V, et al. Effects of Age Among Elderly Cancer Patients on Breakthrough Pain Management with Sublingual Fentanyl Tablets. Drugs R D. 2019 Sep;19(3):247-54. doi: 10.1007/s40268-019-0276-x. PMID: 31177479. Exclusion reason: Ineligible population
- 139. Gupta R, Boehmer S, Giampetro D, et al. The Effect of the Prescription Drug Monitoring Program on Emergency Department Opioid Prescribing Habits. Postgrad Med. 2019;131(SUPPL 1):78-9. doi: 10.1080/00325481.2019.1655695. Exclusion reason: Ineligible publication type
- 140. Guy M, Juhel C, Rigaudier F, et al.
 Analgesic therapeutic sparing evidenced with the use of transcutaneous electrical neurostimulation for the relief of chronic joint and musculoskeletal pain: A controlled, randomized, open-label and cross-over trial. Douleurs. 2021;22(4):175-86. doi: 10.1016/j.douler.2021.05.004. Exclusion reason: Not in English
- 141. Hah JM, Trafton JA, Narasimhan B, et al. Efficacy of motivational-interviewing and guided opioid tapering support for patients undergoing orthopedic surgery (MI-Opioid Taper): A prospective, assessor-blind, randomized controlled pilot trial. EClinicalMedicine. 2020 Nov;28:100596. doi: 10.1016/j.eclinm.2020.100596. PMID: 33294812. Exclusion reason: Ineligible comparator
- 142. Hallvik SE, El Ibrahimi S, Johnston K, et al. Patient outcomes after opioid dose reduction among patients with chronic opioid therapy. Pain. 2022 Jan 01;163(1):83-90. doi:

- 10.1097/j.pain.0000000000002298. PMID: 33863865. **Exclusion reason:** Ineligible population
- 143. Hayes CJ, Krebs EE, Brown J, et al. Impact of transitioning from long-term to intermittent opioid therapy on the development of opioid-related adverse outcomes: A retrospective cohort study. Drug Alcohol Depend. 2022 Feb 01;231:109236. doi:10.1016/j.drugalcdep.2021.109236. PMID: 34974270. Exclusion reason: Ineligible comparator
- 144. He L, Tan K, Lin X, et al. Multicenter, randomized, double-blind, controlled trial of transcutaneous electrical nerve stimulation for pancreatic cancer related pain. Medicine (Baltimore). 2021 Feb 05;100(5):e23748. doi: 10.1097/MD.0000000000023748. PMID: 33592831. Exclusion reason: Ineligible population
- 145. Henningfield J, Markman J, Gudin J, et al.

 Measuring withdrawal in a phase 3 study of
 a new analgesic, nktr-181, in subjects with
 moderate to severe chronic low-back pain.
 Postgrad Med. 2017;129(SUPPL 1):25-6.
 doi: 10.1080/00325481.2017.1367065.
 Exclusion reason: Ineligible publication
 type
- 146. Henningfield JE, Gudin J, Rauck R, et al.

 Measuring Opioid Withdrawal in a Phase 3
 Study of a New Analgesic, NKTR-181
 (Oxycodegol), in Patients with Moderate to
 Severe Chronic Low Back Pain. Pain Med.
 2020 08 01;21(8):1553-61. doi:
 10.1093/pm/pnz326. PMID: 32150255.

 Exclusion reason: Ineligible intervention
- 147. Hetta DF, Mohamed AA, Hetta HF, et al. Radiofrequency Thoracic Sympathectomy for Sympathetically Maintained Chronic Post-Mastectomy Pain, a Preliminary Report: 6-Month Results. Pain Practice. 2021 01;21(1):54-63. doi: 10.1111/papr.12933. PMID: 32629535. Exclusion reason: Ineligible intervention
- 148. Hines KL, Garofoli GK, Garofoli MP, et al. Impact of naloxone education for patients receiving buprenorphine-containing prescriptions indicated for opioid use disorder at an independent community pharmacy. J Am Pharm Assoc (2003). 2020 Nov Dec;60(6):e205-e14. doi: 10.1016/j.japh.2020.07.015. PMID:

- 32800678. **Exclusion reason:** Ineligible study design
- 149. Hodges SE, Rahimpour S, Antezana LA, et al. Protocolized high-dose (HD) and low-dose (LD) spinal cord stimulation (SCS) workflow results in meaningful pain and opiate reduction. Clin Neurosurg.
 2019;66:59. doi: 10.1093/neuros/nyz310-190. Exclusion reason: Ineligible publication type
- 150. Hooten W, Biernacka JM, O'Brien TG, et al. Associations of catecholomethyltransferase (rs4680) single nucleotide polymorphisms with opioid use and dose among adults with chronic pain. Pain. 2019 Jan;160(1):263-8. doi: http://dx.doi.org/10.1097/j.pain.0000000000 001400. PMID: 30211780. Exclusion reason: Inadequate duration
- 151. Huang R, Jiang L, Cao Y, et al. Comparative Efficacy of Therapeutics for Chronic Cancer Pain: A Bayesian Network Meta-Analysis. J Clin Oncol. 2019 07 10;37(20):1742-52. doi: 10.1200/JCO.18.01567. PMID: 30939089. Exclusion reason: Ineligible population
- 152. Huang Y, Xu C, Zeng T, et al. Intravenous patient-controlled analgesia hydromorphone combined with pregabalin for the treatment of postherpetic Neuralgia: A multicenter, randomized controlled study. Korean J Pain. 2021;34(2):210-6. doi: 10.3344/KJP.2021.34.2.210. PMID: 33785673. Exclusion reason: Ineligible intervention
- 153. Hur J, Tang S, Gunaseelan V, et al.
 Predicting postoperative opioid use with
 machine learning and insurance claims in
 opioid-naive patients. Am J Surg.
 2021;222(3):659-65. doi:
 10.1016/j.amjsurg.2021.03.058. PMID:
 33820654. Exclusion reason: Ineligible
 intervention
- 154. Iheanacho T, Payne K, Tsai J. Mobile,
 Community-Based Buprenorphine
 Treatment for Veterans Experiencing
 Homelessness With Opioid Use Disorder: A
 Pilot, Feasibility Study. Am J Addict. 2020
 11;29(6):485-91. doi: 10.1111/ajad.13055.
 PMID: 32367557. Exclusion reason:
 Ineligible outcome

- 155. Imai H, Fumita S, Harada T, et al. Opioid-induced constipation in patients with cancer pain in Japan (OIC-J study): a post hoc subgroup analysis of patients with lung cancer. Japanese Journal of Clinical Oncology. 2021 Mar 03;51(3):444-50. doi: 10.1093/jjco/hyaa186. PMID: 33157554.

 Exclusion reason: Inadequate duration
- 156. Jackson HJ, Walters J, Raman R. Auricular Acupuncture to Facilitate Outpatient Opioid Weaning: A Randomized Pilot Study. Med Acupunct. 2021;33(2):153-8. doi: 10.1089/acu.2020.1450. PMID: 33820654. Exclusion reason: Ineligible intervention
- 157. Jan AL, Aldridge ES, Visser EJ, et al.
 Battlefield acupuncture added no benefit as an adjunct analgesic in emergency department for abdominal, low back or limb trauma pain. Emerg Med Australas. 2020 Sep 23;23:23. doi: 10.1111/1742-6723.13642. PMID: 32969169. Exclusion reason: Inadequate duration
- 158. Jantarada C, Silva C, Guimaraes-Pereira L.
 Prevalence of Problematic Use of Opioids in
 Patients with Chronic Noncancer Pain: A
 Systematic Review with Meta-analysis. Pain
 Practice. 2021 Jul;21(6):715-29. doi:
 10.1111/papr.13001. PMID: 33528858.
 Exclusion reason: Systematic review used
 as source document
- 159. Jasmine Silva M, Coffee Z, Ho Alex Yu C, et al. Anxiety and Fear Avoidance Beliefs and Behavior May Be Significant Risk Factors for Chronic Opioid Analgesic Therapy Reliance for Patients with Chronic Pain Results from a Preliminary Study. Pain Med. 2021 Sep;22(9):2106-16. doi: 10.1093/pm/pnab069. PMID: 33595642. Exclusion reason: Ineligible comparator
- 160. Jassal M, Egan G, Dahri K. Opioid
 Prescribing in the Elderly: A Systematic
 Review. The Journal of pharmacy
 technology: jPT: official publication of the
 Association of Pharmacy Technicians.
 2020;36(1):28-40. doi:
 10.1177/8755122519867975. Exclusion
 reason: Systematic review used as source
 document
- 161. Ji X, Haight SC, Ko JY, et al. Association Between State Policies on Improving Opioid Prescribing in 2 States and Opioid Overdose Rates Among Reproductive-aged Women. Med Care. 2021 02 01;59(2):185-92. doi:

- 10.1097/MLR.000000000001475. PMID: 33273289. **Exclusion reason:** Ineligible intervention
- Jiang J, Pan H, Chen H, et al. Comparative Efficacy of Pharmacological Therapies for Low Back Pain: A Bayesian Network Analysis. Frontiers in Pharmacology. 2022;13:811962. doi: 10.3389/fphar.2022.811962. PMID: 35250562. Exclusion reason: Systematic review used as source document
- 163. Jung JM, Chung CK, Kim CH, et al.
 Comparison of the use of opioids only and pregabalin add-on for the treatment of neuropathic pain in cervical myelopathy patients: a pilot trial. Sci Rep. 2020 05 15;10(1):8120. doi: 10.1038/s41598-020-65108-8. PMID: 32415211. Exclusion reason: Ineligible population
- 164. Kabore JL, Saidi H, Dassieu L, et al.
 Predictors of Long-Term Opioid
 Effectiveness in Patients With Chronic NonCancer Pain Attending Multidisciplinary
 Pain Treatment Clinics: A Quebec Pain
 Registry Study. Pain Practice. 2020
 07;20(6):588-99. doi: 10.1111/papr.12883.
 PMID: 32187793. Exclusion reason:
 Ineligible comparator
- 165. Kashyap K, Singh V, Mishra S, et al. The Efficacy of Scrambler Therapy for the Management of Head, Neck and Thoracic Cancer Pain: A Randomized Controlled Trial. Pain Physician. 2020 09;23(5):495-506. PMID: 32967392. Exclusion reason: Inadequate duration
- 166. Katzman C, Harker EC, Ahmed R, et al. The Association Between Preoperative Opioid Exposure and Prolonged Postoperative Use. Ann Surg. 2021;274(5):e410-e6. doi: 10.1097/SLA.0000000000003723. Exclusion reason: Ineligible comparator
- 167. Kern KU, Sohns M, Heckes B, et al.
 Tapentadol prolonged release for severe chronic osteoarthritis pain in the elderly: improvements in daily functioning and quality of life. Pain Manag. 2020
 Mar;10(2):85-95. doi: 10.2217/pmt-2019-0041. PMID: 31973627. Exclusion reason: Ineligible comparator
- 168. Khan NF, Bykov K, Glynn RJ, et al. Coprescription of Opioids With Other Medications and Risk of Opioid Overdose.

- Clin Pharmacol Ther. 2021 10;110(4):1011-7. doi: 10.1002/cpt.2314. PMID: 34048030. **Exclusion reason:** Ineligible comparator
- 169. Kim HS, Ciolino JD, Lancki N, et al. A
 Prospective Observational Study of
 Emergency Department-Initiated Physical
 Therapy for Acute Low Back Pain. Phys
 Ther. 2021 03 03;101(3):03. doi:
 10.1093/ptj/pzaa219. PMID: 33351942.
 Exclusion reason: Ineligible outcome
- 170. Kim MS, Koh IJ, Choi KY, et al. Efficacy of duloxetine compared with opioid for postoperative pain control following total knee arthroplasty. PLoS One. 2021;16(7 July)doi: https://doi.org/10.1371/journal.pone.025364 1. PMID: 34214098. Exclusion reason: Ineligible study design
- 171. Kirisci L, Tarter RE, Reynolds M, et al.
 Derivation and assessment of the opioid use
 disorder severity scale: prediction of health,
 psychological and social adjustment
 problems. Am J Drug Alcohol Abuse. 2020
 11 01;46(6):699-707. doi:
 10.1080/00952990.2019.1707840. PMID:
 31967913. Exclusion reason: Ineligible
 population
- 172. Knezevic NN, Aijaz T, Camacho-Ortega A, et al. A Retrospective Analysis of Gabapentinoid and Opioids to Opioid Monotherapy for Pain Relief in Patients with Chronic Neck and Low Back Pain. Pain Med. 2021;22(8):1760-6. doi: 10.1093/pm/pnab006. PMID: 33502505. Exclusion reason: Ineligible outcome
- 173. Koffel E, Kats AM, Kroenke K, et al. Sleep Disturbance Predicts Less Improvement in Pain Outcomes: Secondary Analysis of the SPACE Randomized Clinical Trial. Pain Med. 2020 06 01;21(6):1162-7. doi: 10.1093/pm/pnz221. PMID: 31529104. Exclusion reason: Ineligible outcome
- 174. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020 02;72(2):149-62. doi: 10.1002/acr.24131. PMID: 31908149. Exclusion reason: Systematic review used as source document

- 175. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol. 2020 02;72(2):220-33. doi: 10.1002/art.41142. PMID: 31908163. Exclusion reason: Systematic review used as source document
- 176. Kolber MR, Ton J, Thomas B, et al. PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care. Can Fam Physician. 2021 01;67(1):e20-e30. doi: 10.46747/cfp.6701e20. PMID: 33483410. Exclusion reason: Systematic review used as source document
- 177. Krebs E, Zhou C, Min JE, et al. Diagnosis of Opioid Use Disorder by Youths Assessed in Acute Care Settings in British Columbia, Canada. J Pediatr. 2021 05;232:243-50. doi: 10.1016/j.jpeds.2021.01.046. PMID: 33515555. Exclusion reason: Ineligible population
- 178. Kronborg-White S, Andersen CU, Kohberg C, et al. Palliation of chronic breathlessness with morphine in patients with fibrotic interstitial lung disease a randomised placebo-controlled trial. Respir Res. 2020;21(1):195. doi: https://doi.org/10.1186/s12931-020-01452-7. PMID: 32703194. Exclusion reason: Ineligible population
- 179. Kundal D, Raj R, Garg R, et al. Therapeutic Efficacy of Rhemercise: A Novel Mindfulness Technique in Patients With Opioid Use Disorder. The primary care companion for CNS disorders. 2022;24(1)doi: .org/10.4088/PCC.21m03064. Exclusion reason: Ineligible population
- 180. Lagisetty P, Garpestad C, Larkin A, et al. Identifying individuals with opioid use disorder: Validity of International Classification of Diseases diagnostic codes for opioid use, dependence and abuse. Drug Alcohol Depend. 2021 Apr;221doi: http://dx.doi.org/10.1016/j.drugalcdep.2021. 108583. PMID: 33662670. Exclusion reason: Ineligible population
- 181. Laigaard J, Bache N, Stottmeier S, et al.
 Cognitive Function During Opioid Tapering
 in Patients with Chronic Pain: A Prospective

- Cohort Study. J Pain Res. 2020;13:3385-94. doi: 10.2147/JPR.S273025. PMID: 33363405. **Exclusion reason:** Ineligible comparator
- 182. Langejan AI, de Kleijn L, Rijkels-Otters H, et al. Effectiveness of non-opioid interventions to reduce opioid withdrawal symptoms in patients with chronic pain: a systematic review. Fam Pract. 2021 Nov 26;26:26. doi: 10.1093/fampra/cmab159. PMID: 34849764. Exclusion reason: Systematic review used as source document
- 183. Latif Ze SKKOAKNBJSKPS-HKTL. No increased pain among opioid-dependent individuals treated with extended-release naltrexone or buprenorphine-naloxone: a 3-month randomized study and 9-month opentreatment follow-up study. The american journal on addictions. 2019;28(2):77.

 Exclusion reason: Ineligible intervention
- 184. Lawal OD, Gold J, Murthy A, et al. Rate and Risk Factors Associated With Prolonged Opioid Use After Surgery: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 06 01;3(6):e207367. doi: 10.1001/jamanetworkopen.2020.7367. PMID: 32584407. Exclusion reason: Systematic review used as source document
- 185. Lee B, Zhao W, Yang KC, et al. Systematic Evaluation of State Policy Interventions Targeting the US Opioid Epidemic, 2007-2018. JAMA Netw Open. 2021 02 01;4(2):e2036687. doi: 10.1001/jamanetworkopen.2020.36687. PMID: 33576816. Exclusion reason: Ineligible intervention
- 186. Lee C, Lin M, Martins KJB, et al. Opioid use in medical cannabis authorization adult patients from 2013 to 2018: Alberta, Canada. BMC Public Health. 2021 05 01;21(1):843. doi: 10.1186/s12889-021-10867-w. PMID: 33933061. Exclusion reason: Ineligible population
- 187. Lee CS, Kim D, Park SY, et al. Usefulness of the Korean Version of the CAGE-Adapted to Include Drugs Combined With Clinical Predictors to Screen for Opioid-Related Aberrant Behavior. Anesth Analg. 2019 09;129(3):864-73. doi: 10.1213/ANE.000000000003580. PMID: 31425231. Exclusion reason: Ineligible population

- 188. Leng X, Zhang F, Yao S, et al. Prolonged-Release (PR) Oxycodone/Naloxone
 Improves Bowel Function Compared with Oxycodone PR and Provides Effective
 Analgesia in Chinese Patients with Non-malignant Pain: A Randomized, Double-Blind Trial. Adv Ther. 2020 03;37(3):1188-202. doi: 10.1007/s12325-020-01244-x.
 PMID: 32020565. Exclusion reason:
 Ineligible population
- 189. Leppert W, Nosek K. Comparison of the Quality of Life of Cancer Patients with Pain Treated with Oral Controlled-Release Morphine and Oxycodone and Transdermal Buprenorphine and Fentanyl. Curr Pharm Des. 2019;25(30):3216-24. doi: 10.2174/1381612825666190717091230. PMID: 31333114. Exclusion reason: Ineligible population
- 190. Li D, Sun RR, Li QL, et al. Acupuncture combined with opioid drugs on moderate and severe cancer pain: a randomized controlled trial. Zhongguo Zhen Jiu. 2020;40(3):257-61. doi: 10.13703/j.0255-2930.20190311-k0001. PMID: 32270637. Exclusion reason: Not in English
- 191. Liang J, Chen L, Yang S, et al. A 12-hour rapid titration method for cancer pain: a randomized, controlled, open-label study. Ann Palliat Med. 2021 Jan;10(1):88-96. doi: 10.21037/apm-20-2336. PMID: 33474955. Exclusion reason: Inadequate duration
- 192. Liu S, Gnjidic D, Nguyen J, et al.
 Effectiveness of interventions on the
 appropriate use of opioids for noncancer
 pain among hospital inpatients: A systematic
 review. Br J Clin Pharmacol. 2020
 02;86(2):210-43. doi: 10.1111/bcp.14203.
 PMID: 31863503. Exclusion reason:
 Ineligible setting
- 193. Lucas P, Boyd S, Milloy MJ, et al. Cannabis Significantly Reduces the Use of Prescription Opioids and Improves Quality of Life in Authorized Patients: Results of a Large Prospective Study. Pain Med. 2021 03 18;22(3):727-39. doi: 10.1093/pm/pnaa396. PMID: 33367882. Exclusion reason: Ineligible study design
- 194. Luo Z, Miao J, Shu S, et al.
 Pharmacokinetics and Bioequivalence
 Evaluation of a New Oxycodone TamperResistant Tablet Administered with an
 Opioid Antagonist in Patients with Chronic

- Pain. Clin Drug Investig. 2020 Feb;40(2):139-48. doi: 10.1007/s40261-019-00870-w. PMID: 31679120. **Exclusion reason:** Inadequate duration
- 195. Lynch M, Moulin D, Perez J. Methadone vs. morphine SR for treatment of neuropathic pain: A randomized controlled trial and the challenges in recruitment. Can J Pain. 2019;3(1):180-9. doi: 10.1080/24740527.2019.1660575. PMID: 35005408. Exclusion reason: Ineligible outcome
- 196. MacCallum CA, Eadie L, Barr AM, et al. Practical Strategies Using Medical Cannabis to Reduce Harms Associated With Long Term Opioid Use in Chronic Pain. Frontiers in Pharmacology. 2021;12:633168. doi: 10.3389/fphar.2021.633168. PMID: 33995035. Exclusion reason: Ineligible publication type
- 197. Machado-Alba JE, Serna-Echeverri LS, Valladales-Restrepo LF, et al. Use of Tramadol or Other Analgesics in Patients Treated in the Emergency Department as a Risk Factor for Opioid Use. Pain Res Manag. 2020;2020:8847777. doi: 10.1155/2020/8847777. PMID: 33273995. Exclusion reason: Ineligible population
- 198. Machado-Duque ME, Ramirez-Valencia DM, Murillo-Munoz MM, et al. Trends in Opioid Use in a Cohort of Patients with Rheumatoid Arthritis. Pain Res Manag. 2020;2020:3891436. doi: 10.1155/2020/3891436. PMID: 32724487. Exclusion reason: Ineligible comparator
- 199. Macintyre PE, Quinlan J, Levy N, et al.
 Current Issues in the Use of Opioids for the
 Management of Postoperative Pain: A
 Review. JAMA surgery. 2022;157(2):15866. doi: 10.1001/jamasurg.2021.6210.
 Exclusion reason: Background paper
- 200. Mackey K, Anderson J, Bourne D, et al. Benefits and Harms of Long-term Opioid Dose Reduction or Discontinuation in Patients with Chronic Pain: a Rapid Review. J Gen Intern Med. 2020 12;35(Suppl 3):935-44. doi: 10.1007/s11606-020-06253-8. PMID: 33145689. Exclusion reason: Systematic review used as source document
- 201. MacLean RR, Spinola S, Manhapra A, et al. Systematic Review of Pain Severity and Opioid Craving in Chronic Pain and Opioid

- Use Disorder. Pain Med. 2020 02 01;21(2):e146-e63. doi: 10.1093/pm/pnz228. PMID: 32034413. **Exclusion reason:** Systematic review used as source document
- 202. Madden K, Haider A, Rozman De Moraes A, et al. Frequency of Concomitant Use of Gabapentinoids and Opioids among Patients with Cancer-Related Pain at an Outpatient Palliative Care Clinic. Journal of Palliative Medicine. 2021 01;24(1):91-6. doi: 10.1089/jpm.2019.0614. PMID: 32486874. Exclusion reason: Ineligible population
- 203. Magee MR, McNeilage AG, Avery N, et al. mHealth Interventions to Support Prescription Opioid Tapering in Patients With Chronic Pain: Qualitative Study of Patients' Perspectives. JMIR Form Res. 2021 May 18;5(5):e25969. doi: 10.2196/25969. PMID: 34003133.
 Exclusion reason: Ineligible study design
- 204. Mahairas AD, Neff R, Craker N, et al. Trends in Opioid Usage Following Tympanoplasty and Mastoidectomy. Otol Neurotol. 2020 09;41(8):e1035-e40. doi: 10.1097/MAO.0000000000002709. PMID: 32558746. Exclusion reason: Ineligible population
- 205. Maheu E, Soriot-Thomas S, Noel E, et al. Wearable transcutaneous electrical nerve stimulation demonstrated better efficacy and safety than weak opioids in the treatment of moderate to severe, chronic nociceptive pain in knee osteoarthritis. A randomized, controlled, non-inferiority trial. Ann Rheum Dis. 2021;80(SUPPL 1):364-5. doi: 10.1136/annrheumdis-2021-eular.2086. Exclusion reason: Ineligible publication type
- 206. Mali J, Nascimento J, Atkinson J, et al. Chronic pain treatment satisfaction in musculoskeletal disease: Differences between osteoarthritis and chronic low back pain in medication switching, opioid use, and utilization of non-drug treatments. Postgrad Med. 2019;131(SUPPL 1):115-6. doi: 10.1080/00325481.2019.1655695. Exclusion reason: Ineligible publication type
- 207. Mallow PJ, Belk KW. Cost-utility analysis of single nucleotide polymorphism panelbased machine learning algorithm to predict risk of opioid use disorder. J. 2021

- 12;10(18):1349-61. doi: 10.2217/cer-2021-0115. PMID: 34672212. **Exclusion reason:** Ineligible population
- Maloy PE, Iacocca MO, Morasco BJ. CE: Implementing Guidelines for Treating Chronic Pain with Prescription Opioids. Am J Nurs. 2019 11;119(11):22-9. doi: 10.1097/01.NAJ.0000605344.99391.78. PMID: 31651495. Exclusion reason: Ineligible publication type
- 209. Manniche C, Stokholm L, Ravn SL, et al. Prevalence of long-term opioid therapy in spine center outpatients the spinal pain opioid cohort (SPOC). European Spine Journal. 2021 Apr 24;24:24. doi: 10.1007/s00586-021-06849-6. PMID: 33893870. Exclusion reason: Ineligible comparator
- 210. Markman J
 GJRRACRMAEGJKNDSKTMLLSS.
 SUMMIT-07: a randomized trial of NKTR181, a new molecular entity, full mu-opioid
 receptor agonist for chronic low-back pain.
 Pain. 2019;160(6):1374. Exclusion reason:
 Ineligible intervention
- 211. Markman JD, Rhyne AL, Sasso RC, et al. Association between Opioid Use and Patient-Reported Outcomes in a Randomized Trial Evaluating Basivertebral Nerve Ablation for the Relief of Chronic Low Back Pain. Neurosurgery. 2020;86(3):343-7. doi: https://doi.org/10.1093/neuros/nyz093. PMID: 31034561. Exclusion reason: Ineligible intervention
- 212. Martinson A, Craner J, Clinton-Lont J. Outcomes of a 6-week Cognitive-Behavioral Therapy for Chronic Pain Group for veterans seen in primary care. Translational Behavioral Medicine. 2020 Feb;10(1):254-66. doi: http://dx.doi.org/10.1093/tbm/iby127. PMID: 2020-73373-029. Exclusion reason: Ineligible study design
- 213. Mateos RG, Bernal DS, Morera LMT, et al. Long-Term Effectiveness and Tolerability of Pain Treatment with Tapentadol Prolonged Release. Pain Physician. 2021 01;24(1):E75-E85. PMID: 33400440. Exclusion reason: Ineligible comparator
- 214. Mathieson S, Maher C, Ferreira G, et al. Patient and clinician interventions for opioid

- analgesic deprescribing in chronic noncancer pain: A systematic review. BMJ Evid Based Med. 2019;24:A27-A8. doi: 10.1136/bmjebm-2019-POD.58. **Exclusion reason:** Ineligible publication type
- 215. Mathieson S, Maher CG, Ferreira GE, et al. Deprescribing Opioids in Chronic Noncancer Pain: Systematic Review of Randomised Trials. Drugs. 2020 Oct;80(15):1563-76. doi: 10.1007/s40265-020-01368-y. PMID: 32737739. Exclusion reason: Systematic review used as source document
- 216. Meske DS, Vaughn BJ, Kopecky EA, et al. Number Of Clinical Trial Study Sites Impacts Observed Treatment Effect Size: An Analysis Of Randomized Controlled Trials Of Opioids For Chronic Pain. J Pain Res. 2019;12:3161-5. doi: 10.2147/JPR.S201751. PMID: 31819600. Exclusion reason: Ineligible outcome
- 217. Migliorini F, Maffulli N, Baroncini A, et al. Opioids for chronic low back pain management: a Bayesian network meta-analysis. Expert Rev Clin Pharmacol. 2021 May;14(5):635-41. doi: 10.1080/17512433.2021.1903316. PMID: 33706636. Exclusion reason: Systematic review used as source document
- 218. Migliorini F, Maffulli N, Eschweiler J, et al. The pharmacological management of chronic lower back pain. Expert Opin Pharmacother. 2021 Jan;22(1):109-19. doi: 10.1080/14656566.2020.1817384. PMID: 32885995. Exclusion reason: Ineligible study design
- 219. Minozzi S, Amato L, Jahanfar S, et al. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev. 2020 11 09;11:CD006318. doi: 10.1002/14651858.CD006318.pub4. PMID: 33165953. Exclusion reason: Systematic review used as source document
- 220. Moisset X, Bouhassira D, Avez Couturier J, et al. Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. Revue Neurologique. 2020 May;176(5):325-52. doi: 10.1016/j.neurol.2020.01.361. PMID: 32276788. Exclusion reason: Background paper

- 221. Mollette LJ. Implementation and evaluation of an opioid risk assessment tool in the primary care setting. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2022;83(1-B):No Pagination Specified. PMID: 2021-80517-048.
 Exclusion reason: Ineligible publication type
- 222. Montgomery AD, Ottenbacher R. Battlefield Acupuncture for Chronic Pain Management in Patients on Long-Term Opioid Therapy. Med Acupunct. 2020 Feb 01;32(1):38-44. doi: 10.1089/acu.2019.1382. PMID: 32110262. Exclusion reason: Ineligible study design
- 223. Morasco BJ, Adams MH, Maloy PE, et al. Research methods and baseline findings of the improving the safety of opioid therapy (ISOT) cluster-randomized trial. Contemporary Clinical Trials. 2020 03;90:105957. doi: 10.1016/j.cct.2020.105957. PMID: 32061968. Exclusion reason: Ineligible outcome
- 224. Moreira de Barros GA, Baradelli R, Rodrigues DG, et al. Use of methadone as an alternative to morphine for chronic pain management: a noninferiority retrospective observational study. Pain rep. 2021 Nov-Dec;6(4):e979. doi: 10.1097/PR9.00000000000000979. PMID: 34938934. Exclusion reason: Inadequate duration
- 225. Morikawa N, Kasahara Y, Takahashi Y, et al. Risk Factors for Poor Pain Control after Opioid Switching from Oxycodone Tablet to Fentanyl Patch. Biol Pharm Bull. 2019;42(10):1674-8. doi: 10.1248/bpb.b19-00271. PMID: 31582655. Exclusion reason: Ineligible population
- 226. Moyo P, Simoni-Wastila L, Griffin BA, et al. Prescription drug monitoring programs: Assessing the association between "best practices" and opioid use in Medicare. Health Serv Res. 2019 10;54(5):1045-54. doi: 10.1111/1475-6773.13197. PMID: 31372990. Exclusion reason: Ineligible intervention
- 227. Muzzio K, Chandler M, Painter JT, et al. Characterizing Patients after Opioid Taper in a VA Medical Center. J Pain Pall Care Pharmacother. 2021 Jun;35(2):84-90. doi: 10.1080/15360288.2021.1900492. PMID:

- 33956566. **Exclusion reason:** Ineligible comparator
- 228. National Academies of Sciences E,
 Medicine, Health, et al. An Approach to
 Evaluate the Effects of Concomitant
 Prescribing of Opioids and Benzodiazepines
 on Veteran Deaths and Suicides. National
 Academies Press (US). 2019 09 24;09:24.
 doi: 10.17226/25532. PMID: 31596558.
 Exclusion reason: Ineligible publication
 type
- 229. Naylor JM, Buhagiar M, Johns N, et al. Prescription Opioids Higher Among Knee Arthroplasty Recipients Randomized to Inpatient Rehabilitation. ACR Open Rheumatol. 2021 Aug;3(8):573-7. doi: 10.1002/acr2.11304. PMID: 34245234. Exclusion reason: Ineligible intervention
- 230. Nicholas MK, Asghari A, Sharpe L, et al. Reducing the use of opioids by patients with chronic pain: an effectiveness study with long-term follow-up. Pain. 2020 03;161(3):509-19. doi: 10.1097/j.pain.000000000001763. PMID: 31764391. Exclusion reason: Ineligible population
- 231. Nielssen O, Karin E, Staples L, et al. Opioid use before and after completion of an online pain management program. J Consult Clin Psychol. 2019 Oct;87(10):904-17. doi: http://dx.doi.org/10.1037/ccp0000407. PMID: 31556667. Exclusion reason: Ineligible intervention
- 232. Noori A, Busse JW, Sadeghirad B, et al. Individual opioids, and long- versus short-acting opioids, for chronic noncancer pain: Protocol for a network meta-analysis of randomized controlled trials. Medicine (Baltimore). 2019 Oct;98(43):e17647. doi: 10.1097/MD.000000000017647. PMID: 31651885. Exclusion reason: Ineligible publication type
- 233. Nury E, Schmucker C, Nagavci B, et al. Efficacy and safety of strong opioids for chronic non-cancer pain and chronic low back pain: a systematic review and meta-analyses. Pain. 2021 Jul 28;28:28. doi: 10.1097/j.pain.0000000000002423. PMID: 34326292. Exclusion reason: Systematic review used as source document
- 234. O'Brien MDC, Wand APF. A systematic review of the evidence for the efficacy of

- opioids for chronic non-cancer pain in community-dwelling older adults. Age and Ageing. 2020 02 27;49(2):175-83. doi: 10.1093/ageing/afz175. PMID: 31971548. **Exclusion reason:** Systematic review used as source document
- 235. Odineal Dd MMTWDSCHCRSIWYWBDNHSGKR. Effect of Mobile Device-Assisted N-of-1 Trial Participation on Analgesic Prescribing for Chronic Pain: randomized Controlled Trial. J Gen Intern Med. 2020;35(1):102. Exclusion reason: Ineligible intervention
- 236. Oh TK, Song IA. Chronic Opioid Use and Risk of Cancer in Patients with Chronic Noncancer Pain: A Nationwide Historical Cohort Study. Cancer Epidemiol Biomarkers Prev. 2020 10;29(10):1962-7. doi: 10.1158/1055-9965.EPI-20-0206. PMID: 32699073. Exclusion reason: Ineligible outcome
- 237. Okusanya BO, Asaolu IO, Ehiri JE, et al. Medical cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review. Syst Rev. 2020 07 28;9(1):167. doi: 10.1186/s13643-020-01425-3. PMID: 32723354. Exclusion reason: Systematic review used as source document
- 238. Oliva EM, Bowe T, Manhapra A, et al. Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation. BMJ. 2020 Mar 4;368:m283. doi: 10.1136/bmj.m283. PMID: 32131996. Exclusion reason: Ineligible population
- 239. Osani M, Lohmander S, Bannuru R. Is there any role for opioids in the management of OA. Arthritis Rheumatol. 2019;71:1575-6. doi: 10.1002/art.41108. Exclusion reason: Ineligible publication type
- 240. Osani MC, Lohmander LS, Bannuru RR. Is There Any Role for Opioids in the Management of Knee and Hip Osteoarthritis? A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken). 2020 Jun 25;25:25. doi: 10.1002/acr.24363. PMID: 32583972. Exclusion reason: Systematic review used as source document

- 241. Otto JC, Forstenpointner J, Sachau J, et al. A Novel Algorithm to Identify Predictors of Treatment Response: Tapentadol Monotherapy or Tapentadol/Pregabalin Combination Therapy in Chronic Low Back Pain? Front Neurol. 2019;10:979. doi: 10.3389/fneur.2019.00979. PMID: 31572292. Exclusion reason: Ineligible study design
- 242. Pace M, Gannon K, Friedland M, et al. Influence of inpatient opioid consumption on persistent use following total knee arthroplasty. Reg Anesth Pain Med. 2021 02;46(2):99-103. doi: 10.1136/rapm-2020-101582. PMID: 33172905. Exclusion reason: Ineligible study design
- 243. Parchman ML, Penfold RB, Ike B, et al. Team-Based Clinic Redesign of Opioid Medication Management in Primary Care: Effect on Opioid Prescribing. Ann Fam Med. 2019 07;17(4):319-25. doi: 10.1370/afm.2390. PMID: 31285209. Exclusion reason: Ineligible intervention
- 244. Pergolizzi J, Cutter G. Consistent Efficacy of Buprenorphine Buccal Film in Opioid-Naive and Opioid-Experienced Patients with Moderate to Severe Chronic Low Back Pain. Postgrad Med. 2019;131(SUPPL 1):43-4. doi: 10.1080/00325481.2019.1655695. Exclusion reason: Ineligible publication type
- 245. Pergolizzi J, Kunkel T. Buprenorphine Buccal Film Improves Patient Global Impression of Change and Reduces the Prevalence of Anxiety and Insomnia in Patients with Chronic Low Back Pain. Postgrad Med. 2019;131(SUPPL 1):42-3. doi: 10.1080/00325481.2019.1655695. Exclusion reason: Ineligible publication type
- Pergolizzi JV, Raffa RB. Safety and efficacy of the unique opioid buprenorphine for the treatment of chronic pain. J Pain Res. 2019;12:3299-317. doi: 10.2147/JPR.S231948. PMID: 31997882. Exclusion reason: Systematic review used as source document
- 247. Petzke F, Klose P, Welsch P, et al. Opioids for chronic low back pain: An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks of double-blind duration. Eur J

- Pain. 2020 03;24(3):497-517. doi: 10.1002/ejp.1519. PMID: 31823442. **Exclusion reason:** Systematic review used as source document
- 248. Picco L, Lam T, Haines S, et al. How prescription drug monitoring programs influence clinical decision-making: A mixed methods systematic review and meta-analysis. Drug Alcohol Depend. 2021 11 01;228:109090. doi: 10.1016/j.drugalcdep.2021.109090. PMID: 34600255. Exclusion reason: Ineligible population
- 249. Picco L, Middleton M, Bruno R, et al. Validity and Reliability of the Computer-Administered Routine Opioid Outcome Monitoring (ROOM) Tool. Pain Med. 2020 12 25;21(12):3645-54. doi: 10.1093/pm/pnaa297. PMID: 33094345.
 Exclusion reason: Ineligible population
- 250. Picco L, Middleton M, Bruno R, et al. Validation of the OWLS, a Screening Tool for Measuring Prescription Opioid Use Disorder in Primary Care. Pain Med. 2020 11 01;21(11):2757-64. doi: 10.1093/pm/pnaa275. PMID: 32869062.
 Exclusion reason: Ineligible population
- 251. Pope JE, Fishman MA, Gunn JA, et al. Cross-Validation of the Foundation Pain Index with PROMIS-29 in Chronic Pain Patients. J Pain Res. 2021;14:2677-85. doi: 10.2147/JPR.S314021. PMID: 34512007. Exclusion reason: Ineligible intervention
- 252. Pope JE, Lee YC, Curtis JR, et al. Pain Reduction in Rheumatoid Arthritis Patients Who Use Opioids: A Post Hoc Analysis of Phase 3 Trials of Baricitinib. ACR Open Rheumatol. 2021 Dec 16;16:16. doi: 10.1002/acr2.11380. PMID: 34913611. Exclusion reason: Ineligible intervention
- 253. Portier A, Breville P, Groupe Agrhum A. Are guidelines for the management of osteoarthritis adapted to very old patients: How to manage opioids in the elderly in osteoarthritis? Osteoporos Int. 2019;30(SUPPL 2):S228-S9. doi: 10.1007/s00198-019-04986-9. PMID: 31289870. Exclusion reason: Ineligible publication type
- 254. Price-Haywood EG, Burton J, Burstain T, et al. Clinical Effectiveness of Decision Support for Prescribing Opioids for Chronic

- Noncancer Pain: A Prospective Cohort Study. Value in Health. 2020 02;23(2):157-63. doi: 10.1016/j.jval.2019.09.2748. PMID: 32113620. **Exclusion reason:** Ineligible intervention
- Pudney D, Arnold P. Analgesic prescribing in wales following unsupervised cluster analysis of primary care practices.
 Pharmacoepidemiol Drug Saf.
 2021;30(SUPPL 2):6. doi:
 10.1002/pds.5315. PMID: 34350651.
 Exclusion reason: Ineligible publication type
- 256. Punches BE, Ali AA, Brown JL, et al.
 Opioid-Related Risk Screening Measures for the Emergency Care Setting. Adv Emerg
 Nurs J. 2021 Oct-Dec 01;43(4):331-43. doi: 10.1097/TME.000000000000377. PMID: 34699423. Exclusion reason: Systematic review used as source document
- 257. Reps JM, Cepeda MS, Ryan PB. Wisdom of the CROUD: Development and validation of a patient-level prediction model for opioid use disorder using population-level claims data. PLoS ONE. 2020;15(2):e0228632. doi: 10.1371/journal.pone.0228632. PMID: 32053653. Exclusion reason: Ineligible population
- 258. Rhon DI, Greenlee TA, Gill NW, et al. Does Engaging Patients with Relevant Education About Long-Term Opioid Use Before Spine Surgery Affect Long-term Opioid Use? A Randomized Controlled Trial. Spine. 2022 Jan 01;47(1):5-12. doi: 10.1097/BRS.00000000000004186. PMID: 34341321. Exclusion reason: Ineligible population
- 259. Rife T, Tighe J, Li Y, et al. Improving chronic pain care and opioid safety in va primary care: Implementation and evaluation of the integrated pain team clinic. Postgrad Med. 2017;129(SUPPL 1):77-8. doi: 10.1080/00325481.2017.1367065. Exclusion reason: Ineligible publication type
- 260. Rossom RC, Sperl-Hillen JM, O'Connor PJ, et al. A pilot study of the functionality and clinician acceptance of a clinical decision support tool to improve primary care of opioid use disorder. Addict Sci Clin Pract. 2021 06 15;16(1):37. doi: 10.1186/s13722-021-00245-7. PMID: 34130758. Exclusion reason: Ineligible population

- 261. Rowe CL, Eagen K, Ahern J, et al. Evaluating the Effects of Opioid Prescribing Policies on Patient Outcomes in a Safety-net Primary Care Clinic. J Gen Intern Med. 2022;37(1):117-24. doi: 10.1007/s11606-021-06920-4. Exclusion reason: Ineligible population
- 262. Ruddell JH, Reid DBC, Shah KN, et al. Larger Initial Opioid Prescriptions Following Total Joint Arthroplasty Are Associated with Greater Risk of Prolonged Use. J Bone Joint Surg Am. 2021 Jan 20;103(2):106-14. doi: 10.2106/JBJS.20.00732. PMID: 33074953. Exclusion reason: Ineligible population
- 263. Rudolph KE, Diaz I, Luo SX, et al.
 Optimizing opioid use disorder treatment with naltrexone or buprenorphine. Drug
 Alcohol Depend. 2021 11 01;228:109031.
 doi: 10.1016/j.drugalcdep.2021.109031.
 PMID: 34534863. Exclusion reason:
 Ineligible intervention
- 264. Ruggeri M, Signorini A, Caravaggio S, et al. Cost-Effectiveness Analysis of Tapentadol Versus Oxycodone/Naloxone in both Branded and Generic Formulations in Patients with Musculoskeletal Pain. Clin Drug Investig. 2021;41(10):875-83. doi: 10.1007/s40261-021-01074-x. PMID: 34524651. Exclusion reason: Ineligible population
- 265. Samet JH, Tsui JI, Cheng DM, et al.
 Improving the Delivery of Chronic Opioid
 Therapy among People Living with HIV: A
 Cluster Randomized Clinical Trial. Clin
 Infect Dis. 2020 Jul 22;22:22. doi:
 10.1093/cid/ciaa1025. PMID: 32697847.
 Exclusion reason: Ineligible intervention
- 266. Samimi PA, Panza J, Heft J, et al. The impact of state legislation on opioid prescriptions in female pelvic reconstructive surgery. International Urogynecology Journal. 2019;30(1):S146. doi: 10.1007/s00192-019-04125-2. PMID: 31555841. Exclusion reason: Ineligible publication type
- 267. Sandhu HK, Abraham C, Alleyne S, et al. Testing a support programme for opioid reduction for people with chronic nonmalignant pain: the I-WOTCH randomised controlled trial protocol. BMJ Open. 2019;9(8)doi: 10.1136/bmjopen-2019-

- 028937. PMID: 31399456. **Exclusion reason:** Ineligible outcome
- 268. Scherrer JF, Tucker J, Salas J, et al.
 Comparison of Opioids Prescribed for
 Patients at Risk for Opioid Misuse Before
 and After Publication of the Centers for
 Disease Control and Prevention's Opioid
 Prescribing Guidelines. JAMA Netw Open.
 2020 12 01;3(12):e2027481. doi:
 10.1001/jamanetworkopen.2020.27481.
 PMID: 33263762. Exclusion reason:
 Ineligible study design
- 269. Schirle L, Jeffery A, Yaqoob A, et al. Two data-driven approaches to identifying the spectrum of problematic opioid use: A pilot study within a chronic pain cohort. Int J Med Inf. 2021 12;156:104621. doi: 10.1016/j.ijmedinf.2021.104621. PMID: 34673309. Exclusion reason: Ineligible intervention
- 270. Seal KH, Rife T, Li Y, et al. Opioid Reduction and Risk Mitigation in VA Primary Care: Outcomes from the Integrated Pain Team Initiative. J Gen Intern Med. 2020 04;35(4):1238-44. doi: 10.1007/s11606-019-05572-9. PMID: 31848861. Exclusion reason: Ineligible intervention
- 271. Seal Kh
 BBTJCBEDKMBJLYSEALWECMJ.
 Optimizing pain treatment interventions
 (OPTI): a pilot randomized controlled trial
 of collaborative care to improve chronic
 pain management and opioid safetyRationale, methods, and lessons learned.
 Contemporary clinical trials. 2019;77:76.
 Exclusion reason: Ineligible outcome
- 272. Sexton SM, Armstrong A, Gatton O, et al. A standardized team-based approach for identifying naloxone-eligible patients in a grocery store pharmacy. J Am Pharm Assoc (2003). 2019 Jul Aug;59(4S):S95-S100. doi: 10.1016/j.japh.2019.03.015. PMID: 31231001. Exclusion reason: Ineligible intervention
- 273. Seyedzadeh Sabounchi S, Seyedzadeh Sabounchi S, Cosler LE, et al. Opioid prescribing and misuse among dental patients in the US: a literature-based review. Quintessence Int. 2020;51(1):64-76. doi: 10.3290/j.qi.a43697. PMID: 31813941. Exclusion reason: Ineligible publication type

- 274. Sheikh S, Booth-Norse A, Holden D, et al. Opioid Overdose Risk in Patients Returning to the Emergency Department for Pain. Pain Med. 2021 09 08;22(9):2100-5. doi: 10.1093/pm/pnab047. PMID: 33560418. Exclusion reason: Ineligible population
- 275. Shigematsu-Locatelli M, Kawano T, Koyama T, et al. Therapeutic experience with tramadol for opioid dependence in a patient with chronic low back pain: a case report. JA Clin Rep. 2019;5(1)doi: 10.1186/s40981-019-0289-z. PMID: 32026047. Exclusion reason: Ineligible study design
- Shilpakar R, Paudel BD, Shah A, et al. Comparison of the effectiveness of oral morphine versus oral tramadol on early pain control in opioidnaive patients with moderate cancer pain. J Clin Oncol. 2019;37doi: 10.1200/JCO.2019.37.15_suppl.11581.
 Exclusion reason: Ineligible population
- 277. Shulman M, Luo SX, Campbell ANC, et al. Secondary Analysis of Pain Outcomes in a Large Pragmatic Randomized Trial of Buprenorphine/Naloxone Versus Methadone for Opioid Use Disorder. J Addict Med. 2020 Sep/Oct;14(5):e188-e94. doi: 10.1097/ADM.000000000000030. PMID: 32039934. Exclusion reason: Ineligible outcome
- 278. Silverman S, Rice JB, White AG, et al. Clinical and economic burden of prescribing tramadol and other opioids for patients with osteoarthritis in a commercially insured population in the United States. Pain. 2022 Jan 01;163(1):75-82. doi: 10.1097/j.pain.0000000000002300. PMID: 34924552. Exclusion reason: Ineligible comparator
- 279. Simoni AH, Nikolajsen L, Olesen AE, et al. The association between initial opioid type and long-term opioid use after hip fracture surgery in elderly opioid-naive patients. Scand J Pain. 2020;20(4):755-64. doi: 10.1515/sjpain-2019-0170. PMID: 32853173. Exclusion reason: Ineligible intervention
- 280. Skoy E, Werremeyer A, Steig J, et al.
 Patient acceptance of naloxone resulting
 from targeted intervention from community
 pharmacists to prevent opioid misuse and
 accidental overdose. Substance Abuse.

- 2021;42(4):672-7. doi: 10.1080/08897077.2020.1827126. PMID: 33044896. **Exclusion reason:** Ineligible outcome
- 281. Smith DM, Wietzel KW, Elsey AR, et al. CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. Genet Med. 2019doi: https://doi.org/10.1038/s41436-018-0431-8. PMID: 30670877. Exclusion reason: Ineligible comparator
- 282. Smith WR, McClish DK, Roberts JD, et al. Prescription Opioid Misuse Index in sickle cell patients: a brief questionnaire to assess at-risk for opioid abuse. J Opioid Manag. 2019 Jul/Aug;15(4):323-31. doi: 10.5055/jom.2019.0517. PMID: 31637684. Exclusion reason: Ineligible population
- 283. Soin A, Soin Y, Dann T, et al. Low-Dose Naltrexone Use for Patients with Chronic Regional Pain Syndrome: A Systematic Literature Review. Pain Physician. 2021 Jul;24(4):E393-E406. PMID: 34213865.

 Exclusion reason: Ineligible intervention
- 284. Sommer C, Klose P, Welsch P, et al.
 Opioids for chronic non-cancer neuropathic pain. An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration. Eur J Pain. 2020 01;24(1):3-18. doi: 10.1002/ejp.1494. PMID: 31705717.

 Exclusion reason: Systematic review used as source document
- 285. Sridharan K, Sivaramakrishnan G. Adjuvant interventions with opioids for vaso-occlusive crisis in sickle cell disease: A mixed treatment network meta-analysis of randomized controlled clinical trials. J Opioid Manag. 2020 Jul/Aug;16(4):267-75. doi: 10.5055/jom.2020.0580. PMID: 32885834. Exclusion reason: Systematic review used as source document
- 286. Stack M, LaRouche V, Zhang Y, et al.
 Effects of Implementing a Comprehensive
 Opioid Reduction Protocol on Overall
 Opioid Prescribing Among Patients with
 Chronic, Non-Cancer Pain in a Rural Family
 Medicine Clinic: a Controlled Cross-over
 Trial. J Am Board Fam Med.
 2020;33(4):502-11. doi:
 https://doi.org/10.3122/jabfm.2020.04.2000

- 60. PMID: 32675261. **Exclusion reason:** Ineligible outcome
- 287. Steele GL, Dudek AZ, Gilmore GE, et al. Impact of Pain, Opioids, and the Mu-opioid Receptor on Progression and Survival in Patients With Newly Diagnosed Stage IV Pancreatic Cancer. Am J Clin Oncol. 2020 08;43(8):591-7. doi: 10.1097/COC.00000000000000714. PMID: 32482952. Exclusion reason: Ineligible population
- 288. Sturgeon JA, Sullivan MD, Parker-Shames S, et al. Outcomes in Long-term Opioid Tapering and Buprenorphine Transition: A Retrospective Clinical Data Analysis. Pain Med. 2020 12 25;21(12):3635-44. doi: 10.1093/pm/pnaa029. PMID: 32163149. Exclusion reason: Ineligible comparator
- 289. Su WC, Chuang CH, Chen FM, et al. Effects of Good Pain Management (GPM) ward program on patterns of care and pain control in patients with cancer pain in Taiwan.

 Support Care Cancer. 2021 Apr;29(4):1903-11. doi: 10.1007/s00520-020-05656-x.

 PMID: 32803728. Exclusion reason:
 Ineligible intervention
- 290. Sud A, Armas A, Cunningham H, et al. Multidisciplinary care for opioid dose reduction in patients with chronic noncancer pain: A systematic realist review. PLoS One. 2020;15(7):e0236419. doi: 10.1371/journal.pone.0236419. PMID: 32716982. Exclusion reason: Systematic review used as source document
- 291. Sulistio M, Wojnar R, Key S, et al. The role of methadone in cancer-induced bone pain: a retrospective cohort study. Support Care Cancer. 2021 Mar;29(3):1327-35. doi: 10.1007/s00520-020-05606-7. PMID: 32627056. Exclusion reason: Ineligible study design
- 292. Svanberg M, Stalnacke BM, Quinn PD, et al. Opioid Prescriptions in Chronic Pain Rehabilitation. A Prospective Study on the Prevalence and Association between Individual Patient Characteristics and Opioids. J Clin Med. 2021 May 14;10(10):14. doi: 10.3390/jcm10102130. PMID: 34069098. Exclusion reason: Ineligible outcome
- 293. Tam CA, Dauw CA, Ghani KR, et al. New Persistent Opioid Use After Outpatient

- Ureteroscopy for Upper Tract Stone Treatment. Urology. 2019 12;134:103-8. doi: 10.1016/j.urology.2019.08.042. PMID: 31536742. **Exclusion reason:** Ineligible population
- 294. Tarsitano A, Cortese M, Barile M, et al.
 Tapentadol prolonged release and the longterm management of chronic
 musculoskeletal pain in the elderly focus
 on anxiety, depression, cognitive status and
 life quality: the TaPE study. Eur Rev Med
 Pharmacol Sci. 2019 Nov;23(4 Suppl):35-9.
 doi: 10.26355/eurrev_201911_19374.
 PMID: 31755081. Exclusion reason:
 Ineligible study design
- 295. Terrett G, Mercuri K, Pizarro-Campagna E, et al. Social cognition impairments in long-term opiate users in treatment. J Psychopharmacol. 2020 02;34(2):254-63. doi: 10.1177/0269881119875981. PMID: 31556782. Exclusion reason: Ineligible comparator
- 296. Tolle T, Fitzcharles MA, Hauser W. Is opioid therapy for chronic non-cancer pain associated with a greater risk of all-cause mortality compared to non-opioid analgesics? A systematic review of propensity score matched observational studies. Eur J Pain. 2021 07;25(6):1195-208. doi: 10.1002/ejp.1742. PMID: 33533519. Exclusion reason: Systematic review used as source document
- 297. Tseregounis IE, Tancredi DJ, Stewart SL, et al. A Risk Prediction Model for Long-term Prescription Opioid Use. Med Care. 2021 12 01;59(12):1051-8. doi: 10.1097/MLR.0000000000001651. PMID: 34629423. Exclusion reason: Ineligible outcome
- 298. Tuan WJ, Spotts H, Zgierska AE, et al. COVID-19 outcomes among adult patients treated with long-term opioid therapy for chronic non-cancer pain in the USA: a retrospective cohort study. BMJ Open. 2021 11 26;11(11):e056436. doi: 10.1136/bmjopen-2021-056436. PMID: 34836910. Exclusion reason: Ineligible outcome
- 299. Uebelacker La VNDTGBGAASM. A pilot study assessing acceptability and feasibility of hatha yoga for chronic pain in people receiving opioid agonist therapy for opioid use disorder. J Subst Abuse Treat.

- 2019;105:19. **Exclusion reason:** Ineligible population
- 300. Ueberall MA, Mueller-Schwefe G. COMET
 effectiveness and tolerability of
 methocarbamol versus oral opioidanalgesics as add-on measure in patients
 with non-specific low back pain refractory
 to recommended 1st line treatments. A
 retrospective analysis of depersonalized
 propensity score matched open-label realworld 4-week data from the German Pain eRegistry. Curr Med Res Opin. 2021 Dec
 14:1-17. doi:
 10.1080/03007995.2021.2003105. PMID:
 34767467. Exclusion reason: Ineligible
 study design
- 301. Veazie S, Mackey K, Peterson K, et al. Managing Acute Pain in Patients Taking Medication for Opioid Use Disorder: a Rapid Review. J Gen Intern Med. 2020 12;35(Suppl 3):945-53. doi: 10.1007/s11606-020-06256-5. PMID: 33145688. Exclusion reason: Ineligible population
- 302. Villarreal YR, Stotts AL, Paniagua SM, et al. Mindfulness predicts current risk of opioid analgesic misuse in chronic low back pain patients receiving opioid therapy. J Contextual Behav Sci. 2020 Oct;18:111-6. doi: http://dx.doi.org/10.1016/j.jcbs.2020.08.011. Exclusion reason: Ineligible study design
- 303. Visconti C, Mastroluca A, Varano L, et al. Tapentadol prolonged release in association with analgesic radiofrequency for the treatment of chronic lumbar radicular pain: an observational, prospective study. Eur Rev Med Pharmacol Sci. 2019 Nov;23(4 Suppl):27-34. doi: 10.26355/eurrev_201911_19375. PMID: 31755082. Exclusion reason: Ineligible study design
- 304. Vowles KE, Witkiewitz K, Cusack KJ, et al. Integrated Behavioral Treatment for Veterans With Co-Morbid Chronic Pain and Hazardous Opioid Use: A Randomized Controlled Pilot Trial. Journal of Pain. 2020 Jul Aug;21(7-8):798-807. doi: 10.1016/j.jpain.2019.11.007. PMID: 31760109. Exclusion reason: Ineligible population
- 305. Vraa ML, Myers CA, Young JL, et al. More Than 1 in 3 Patients With Chronic Low

- Back Pain Continue to Use Opioids Longterm After Spinal Fusion: A Systematic Review. The Clinical journal of pain. 2021;38(3):222-30. doi: 10.1097/AJP.000000000001006. **Exclusion reason:** Systematic review used as source document
- 306. Vunikili R, Glicksberg BS, Johnson KW, et al. Predictive Modelling of Susceptibility to Substance Abuse, Mortality and Drug-Drug Interactions in Opioid Patients. Front. 2021;4:742723. doi: 10.3389/frai.2021.742723. PMID: 34957391. Exclusion reason: Ineligible population
- 307. Walsh DA, Boeri M, Abraham L, et al. Exploring patient preference heterogeneity for pharmacological treatments for chronic pain: A latent class analysis. Eur J Pain. 2021 Dec 01;01:01. doi: 10.1002/ejp.1892. PMID: 34854164. Exclusion reason: Ineligible intervention
- 308. Watson A, Guay K, Ribis D. Assessing the impact of clinical pharmacists on naloxone coprescribing in the primary care setting. Am J Health Syst Pharm. 2020 Mar 24;77(7):568-73. doi: 10.1093/ajhp/zxaa007. PMID: 32207821. Exclusion reason: Ineligible outcome
- 309. Webster L, Henningfield J, Buchhalter AR, et al. "Human abuse potential of the new opioid analgesic molecule NKTR-181 compared with oxycodone": Erratum. Pain Med. 2019 Jul;20(7):1457. doi: https://doi.org/10.1093/pm/pnx080. PMID: 28340145. Exclusion reason: Ineligible publication type
- 310. Webster LR, Hansen E, Cater J, et al. A
 Phase I Placebo-Controlled Trial Comparing
 the Effects of Buprenorphine Buccal Film
 and Oral Oxycodone Hydrochloride
 Administration on Respiratory Drive. Adv
 Ther. 2020 11;37(11):4685-96. doi:
 10.1007/s12325-020-01481-0. PMID:
 32978722. Exclusion reason: Ineligible
 population
- 311. Wegwarth O, Ludwig WD, Spies C, et al.
 The role of simulated-experience and
 descriptive formats on perceiving risks of
 strong opioids: a randomized controlled trial
 with chronic noncancer pain patients. Patient
 Educ Couns. 2021 PMID: CN-02338737

- NEW. **Exclusion reason:** Ineligible intervention
- 312. Wei J, Wood MJ, Dubreuil M, et al.
 Association of tramadol with risk of
 myocardial infarction among patients with
 osteoarthritis. Osteoarthritis Cartilage. 2020
 02;28(2):137-45. doi:
 10.1016/j.joca.2019.10.001. PMID:
 31629022. Exclusion reason: Ineligible
 comparator
- 313. Welsch P, Petzke F, Klose P, et al. Opioids for chronic osteoarthritis pain: An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration. Eur J Pain. 2020 04;24(4):685-703. doi: 10.1002/ejp.1522. PMID: 31876347. Exclusion reason: Systematic review used as source document
- 314. Welsch P, Petzke F, Klose P, et al. "Opioids for chronic osteoarthritis pain: An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration": Erratum. Eur J Pain. 2020 Aug;24(7):1420. doi: http://dx.doi.org/10.1002/ejp.1603. PMID: 32716610. Exclusion reason: Ineligible publication type
- 315. Whedon JM, Kizhakkeveettil A, Toler A, et al. Long-Term Medicare Costs Associated With Opioid Analgesic Therapy vs Spinal Manipulative Therapy for Chronic Low Back Pain in a Cohort of Older Adults. J Manipulative Physiol Ther. 2021 Dec 05;05:05. doi: 10.1016/j.jmpt.2021.09.001. PMID: 34876298. Exclusion reason: Ineligible outcome
- 316. Whedon JM, Kizhakkeveettil A, Toler AW, et al. Initial Choice of Spinal Manipulative Therapy for Treatment of Chronic Low Back Pain Leads to Reduced Long-term Risk of Adverse Drug Events Among Older Medicare Beneficiaries. Spine. 2021 Apr 19;19:19. doi: 10.1097/BRS.0000000000004078. PMID: 33882542. Exclusion reason: Ineligible intervention
- 317. White R, Bruggink L, Hayes C, et al. Feasibility of patient-focused behavioral interventions to support adults experiencing chronic noncancer pain during opioid

- tapering: a systematic literature review. Translational Behavioral Medicine. 2021 08 13;11(8):1481-94. doi: 10.1093/tbm/ibab007. PMID: 33677606. **Exclusion reason:** Systematic review used as source document
- 318. Widenka M, Leppert W. Assessment of analgesic effects of different initial doses of transdermal buprenorphine in the treatment of chronic pain in the elderly diagnosed with osteoarthritis. J Physiol Pharmacol. 2020 Oct;71(5)doi: 10.26402/jpp.2020.5.13. PMID: 33571966. Exclusion reason: Inadequate duration
- 319. Widenka M, Leppert W. Acta poloniae pharmaceutica drug researchAssessment of the quality of life in elderly patients with osteoarthritis during the treatment of chronic pain with transdermal buprenorphine. Acta Pol Pharm. 2021;78(4):573-82. PMID: CN-02348213 NEW. Exclusion reason: Ineligible study design
- 320. Wilson JD, Abebe KZ, Kraemer K, et al.
 Trajectories of Opioid Use Following First
 Opioid Prescription in Opioid-Naive Youths
 and Young Adults. JAMA Netw Open. 2021
 04 01;4(4):e214552. doi:
 10.1001/jamanetworkopen.2021.4552.
 PMID: 33885777. Exclusion reason:
 Ineligible population
- 321. Wilson JG, Bass A, Pixton GC, et al. Safety and tolerability of ALO-02 (oxycodone hydrochloride and sequestered naltrexone hydrochloride) extended-release capsules in older patients: a pooled analysis of two clinical trials. Curr Med Res Opin. 2020 01;36(1):91-9. doi: 10.1080/03007995.2019.1661679. PMID: 31456431. Exclusion reason: Ineligible study design
- 322. Wilson L, Fiasconaro M, Liu J, et al. Risk of chronic opioid use after simultaneous versus staged bilateral knee arthroplasty. Reg Anesth Pain Med. 2021 05;46(5):405-9. doi: 10.1136/rapm-2020-102060. PMID: 33219103. Exclusion reason: Ineligible population
- 323. Xie J, Strauss VY, Martinez-Laguna D, et al. Association of Tramadol vs Codeine Prescription Dispensation With Mortality and Other Adverse Clinical Outcomes. JAMA. 2021 10 19;326(15):1504-15. doi:10.1001/jama.2021.15255. PMID:

- 34665205. **Exclusion reason:** Ineligible population
- 324. Yu Y, Chen Z, Wang Y, et al. Clinical effects of relaxation training combined with paracetamol and tramadol hydrochloride tablets on patients with chronic pain. Int J Clin Exp Med. 2020;13(9):6902-8.

 Exclusion reason: Ineligible population
- 325. Zhang X, Li X, Xiong Y, et al. Efficacy and safety of tramadol for knee or hip osteoarthritis: a systematic review and network meta-analysis of randomized controlled trials. Arthritis Care Res (Hoboken). 2021 Jul 12;12:12. doi: 10.1002/acr.24750. PMID: 34251756.

 Exclusion reason: Systematic review used as source document
- 326. Zhao D, Luo MH, Pan JK, et al. Based on minimal clinically important difference values, a moderate dose of tanezumab may be a better option for treating hip or knee osteoarthritis: a meta-analysis of randomized controlled trials. Ther.
 2022;14:1759720X211067639. doi: 10.1177/1759720X211067639. PMID:

- 35069811. **Exclusion reason:** Ineligible intervention
- 327. Zheng Z
 GSHRDWYLDSACHMSAADCCXCC.
 Effects of Electroacupuncture on Opioid
 Consumption in Patients with Chronic
 Musculoskeletal Pain: a Multicenter
 Randomized Controlled Trial. Pain Med.
 2019;20(2):397. Exclusion reason:
 Ineligible population
- 328. Zhou J, Wang Y, Jiang G. Oxycodone versus morphine for cancer pain titration: A systematic review and pharmacoeconomic evaluation. PLoS ONE.
 2020;15(4):e0231763. doi: 10.1371/journal.pone.0231763. PMID: 32302346. Exclusion reason: Systematic review used as source document
- 329. Ziadni M, Chen AL, Krishnamurthy P, et al. Patient-centered prescription opioid tapering in community outpatients with chronic pain: 2- to 3-year follow-up in a subset of patients. Pain rep. 2020 Sep-Oct;5(5):e851. doi: 10.1097/PR9.0000000000000851. PMID: 33490845. Exclusion reason: Ineligible population