Systematic Review on Nonopioid Pharmacologic Treatments for Chronic Pain: Surveillance Report 3

Literature Update Period: January 2022 through April 1, 2022

Background and Purpose

This is the third surveillance report for the 2020 report *Nonopioid Pharmacologic Treatments for Chronic Pain (*https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research*)*,[1] covering the period January to April 1, 2022. This report addressed benefits and harms of nonopioid pharmacologic treatments in adults with chronic pain (e.g., neuropathic pain, fibromyalgia, osteoarthritis, inflammatory arthritis, low back and neck pain, chronic headache, and sickle cell disease). 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 December 2021 and to determine how the new evidence impacts findings of the 2020 report and Surveillance Reports 1 and 2, which added evidence from September 2019 through December 2021 and were published on the Agency for Healthcare Research and Quality (AHRQ) website (https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research). This is the final surveillance update planned for this topic.

Scope

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

Key Question 1a. In patients with chronic pain, what is the effectiveness of nonopioid pharmacologic agents versus placebo for outcomes related to pain, function, and quality of life after short-term treatment duration (3 to <6 months), intermediate-term treatment duration (6 to <12 months), and long-term treatment duration (≥12 months)?

Key Question 1b. In patients with chronic pain, what is the comparative effectiveness of nonopioid pharmacologic agents compared to other nonopioid pharmacologic agents for outcomes related to pain, function, and quality of life after short-term treatment duration (3 to <6 months), intermediate-term treatment duration (6 to <12 months), and long-term treatment duration (≥12 months)?

Key Question 1c. How does effectiveness or comparative effectiveness vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) dose of medication used, (5) duration of treatment, and (6) dose titration, including tapering?

Key Question 2a. In patients with chronic pain, what are the risks of nonopioid pharmacologic agents for harms including overdose, misuse, dependence, substance use disorder, withdrawals due to adverse events, and serious adverse events (including falls, fractures, motor vehicle accidents), and specific adverse events according to drug class?

Key Question 2b. How do harms vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) dose of medication used, (5) duration of treatment, and (6) dose titration, including tapering?

The protocol is available on the AHRQ website (https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol) and on the PROSPERO systematic reviews registry (CRD42019134249).

Methods

Update searches were conducted in Ovid® MEDLINE®, Embase®, PsycINFO®, CINAHL®, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews to identify evidence published from January to April 1, 2022. Search strategies from the original report were utilized.[1] In addition, to capture articles not yet indexed in MEDLINE, we supplemented the original search strategies with a previously developed[2] optimized (text-word only) search in preMEDLINE to identify studies not yet indexed with Medical Subject Headings (MeSH). As in the original report, searches on electronic databases were supplemented by review of reference lists of relevant articles. Search strategies are available in Appendix A.

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

The same inclusion and exclusion criteria were applied, based on the original report PICOTS (populations, interventions, comparators, outcomes, timing, and settings) (https://www.ncbi.nlm.nih.gov/books/NBK556271/#ch3.s1).

We utilized the same methods for data abstraction and quality assessment as for the original report. Risk of bias (quality) was assessed using criteria and methods developed by the Cochrane Back and Neck Group[3] and outlined in the AHRQ Methods Guide chapter "Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions."[4,5] Studies with at least 1 month of followup were included, and results were stratified according to short-term (1 to <6 months), intermediate term (6 to <12 months), and long-term (≥12 months) followup. We also classified the magnitude of effects for pain and function using the same approach as the original report. A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale or visual analog scale (VAS) and for function as a standardized mean difference (SMD) of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent. A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent. Large/substantial effects were defined as greater than moderate.

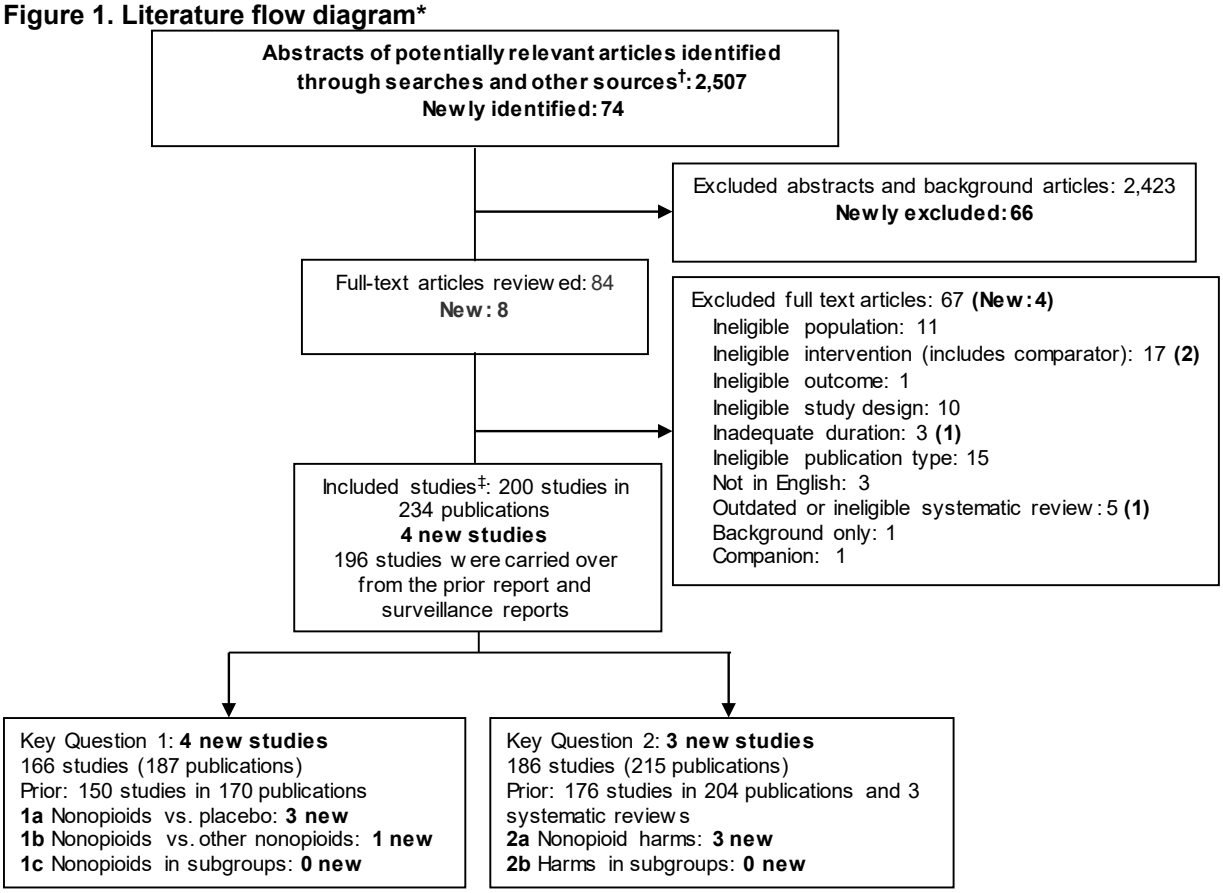
New data identified from surveillance were incorporated into the relevant meta-analyses from the original 2020 report and re-analyzed to provide updated estimates. We also ran new meta-analyses when data permitted. The strength of evidence (SOE) was based on the totality of evidence (evidence in the original report plus new evidence) and determined using the methods described in the original report. We highlighted any changes in the SOE assessments from this surveillance.

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

Results

The search for Surveillance Report 3 from January to April 1, 2022, yielded 71 citations. Of these, one new randomized controlled trial (RCT) in knee osteoarthritis (duloxetine added to oral nonsteroidal anti-inflammatory drugs [NSAIDs] vs. oral NSAIDs alone) met inclusion criteria;[6] in addition, three older placebo-controlled trials for low back pain also met inclusion criteria (2 NSAIDs[7,8] and 1 duloxetine) and were added (Figure 1).[9]

Figure 1. Literature flow diagram*



Note: New studies are those added since the original systematic review, Surveillance Report 1, and Surveillance Report 2.
*Search counts are for the update searches only, and the included studies totals are from the original report and surveillance reports combined.
†Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
‡Some studies were included for multiple Key Questions.

Summary of Findings

Osteoarthritis

- One newly published trial found improved pain response, but not function, with duloxetine compared with placebo in patients with knee osteoarthritis taking NSAIDS.

Low Back Pain

- One newly identified trial found improved pain and function with duloxetine compared with placebo.
- Two newly identified trials found mixed results for pain and no improvement in function with naproxen compared with placebo.

Summary of New Evidence

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 with new evidence since the original report; the original SOE table is available in the full report

(https://www.ncbi.nlm.nih.gov/books/NBK556268/#ch5.s1) and a table showing SOE ratings updated for areas with new evidence is show in Appendix I.

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

Type of Pain or Harm	Key Question	Conclusions From 2020 Report	Findings From Surveillance Reports	Assessment
Neuropathic pain	KQ1. THC/CBD versus placebo short-term	Cannabis was associated with a moderate improvement in short-term pain response versus placebo but no effect on pain improvement in neuropathic pain • SOE: Low, based on 2 RCTs	1 RCT (n=339) from Surveillance Report 1 found no difference in pain response or pain improvement with THC/CBD added to current treatment versus current treatment + placebo; sleep and health status were also not improved with THC/CBD.[10] New MA for pain response (2 RCTs): RR 1.30 (95% CI, 0.88 to 1.94, I^2=56%)	No effect on pain improvement (SOE: Low); small increase (previously moderate) in likelihood of pain response (SOE: Low)
	KQ1. Capsaicin patch versus placebo patch short-term	Capsaicin was associated with no effect on pain intensity or response • SOE: Moderate based on 3 RCTs	1 RCT (n=179) from Surveillance Report 1 found capsaicin patch associated with reduced pain intensity compared with placebo.[11]	No change in conclusions
	KQ1. Lidocaine patch versus placebo patch short-term	No studies	1 RCT (n=184) from Surveillance Report 1 found no difference in lidocaine patch versus placebo in pain improvement.[11]	Effect of lidocaine patch (SOE: Insufficient)
	KQ1. Pregabalin versus amitriptyline versus combination short-term	No studies	1 RCT (n=110) from Surveillance Report 1 found no differences between monotherapy with pregabalin or amitriptyline or combination therapy in pain improvement.[12]	Differences between pregabalin, amitriptyline, and combination therapy (SOE: Insufficient)
	KQ1. Pregabalin CR tablet versus pregabalin IR capsule short-term	No studies	1 RCT (n=352) from Surveillance Report 1 found no differences in pain improvement and pain response between the two formulations; sleep, anxiety, depression, and Patient and Clinical Global Impression of Change scores were also not different between treatments.[13]	Differences between pregabalin CR tablet and pregabalin IR capsule (SOE: Insufficient)
	KQ1. Pregabalin/ gabapentin versus duloxetine short-term	No difference between drugs • SOE: Insufficient based on 1 RCT	2 RCTs (N=247) from Surveillance Report 2 found mixed results for improvement in pain intensity between pregabalin/gabapentin and duloxetine.[14,15] New MA for pain improvement (3 RCTs): MD 0.22 (95% CI, -0.56 to 0.93, I^2=77%)	No difference between pregabalin/gabapentin and duloxetine (SOE: Low)†

Type of Pain or Harm	Key Question	Conclusions From 2020 Report	Findings From Surveillance Reports	Assessment
Fibromyalgia	KQ1. Pregabalin versus placebo short-term	Pregabalin was associated with a small reduction in pain intensity and a small increase in pain response and function • SOE: Moderate, based on 8 RCTs	1 RCT (n=343) from Surveillance Report 1 found pregabalin associated with improved pain, pain response, and sleep interference but no improvement in anxiety or depression scores versus placebo.[16] Updated MAs: • Pain improvement (9 RCTs): MD -0.59 (95% CI, -0.75 to -0.43, I^2=26%) • Pain response (9 RCTs): RR 1.31 (95% CI, 1.21 to 1.43, I^2=0%) • Function (9 RCTs): SMD -0.21 (95% CI, -0.28 to -0.15, I^2=0%)	No change in conclusions
Osteoarthritis	KQ1. Nortriptyline versus placebo short-term	No studies	1 RCT (n=205) from Surveillance Report 1 found no difference between nortriptyline versus placebo in pain improvement, function, or quality of life in knee osteoarthritis.[17]	Effect of nortriptyline (SOE: Insufficient)*
	KQ1. Duloxetine versus placebo short-term	***Small reduction in pain intensity with duloxetine*** • ***SOE: High based on 6 RCTs*** ***Moderate improvement in pain response with duloxetine*** • ***SOE: High based on 4 RCTs*** ***Small improvement in function with duloxetine*** • ***SOE: High based on 5 RCTs***	***1 RCT (n=128) for Surveillance Report 3 found improved pain response and pain severity, but not function, with duloxetine.[6]*** ***Updated MA for pain improvement (7 RCTs): MD -0.77 (95% CI, -1.01 to -0.58, I^2=12%)***	***No change in conclusions***
Low back pain	KQ1. Desipramine versus active placebo short-term	No overall improvement in pain with desipramine, but low desipramine plasma concentration associated with improved pain • SOE: Insufficient, based on 1 RCT	1 RCT (n=70) from Surveillance Report 1 found no effect of desipramine versus placebo on pain.[18]	No change in conclusions

Type of Pain or Harm	Key Question	Conclusions From 2020 Report	Findings From Surveillance Reports	Assessment
Low back pain	***KQ1. Duloxetine versus placebo short-term***	***Small reduction in pain intensity with duloxetine*** • ***SOE: Moderate based on 3 RCTs*** ***Small reduction in pain response*** • ***SOE: Low based on 3 RCTs*** ***No effect on function*** • ***SOE: Moderate based on 3 RCTs***	***1 RCT (n=236) for Surveillance Report 3 found improved pain outcomes and function with duloxetine.[9]*** ***Updated MAs:*** • ***Pain improvement (4 RCTs): MD -0.54 (95% CI, -0.76 to -0.34, I^2=0%)*** • ***Pain response (4 RCTs): RR 1.26 (95% CI, 1.13 to 1.39, I^2=0%)*** • ***Function (4 RCTs): MD -0.42 (95% CI, -0.77 to -0.14, I^2=36%)***	***No change in conclusions***
	KQ1. Naproxen versus placebo short-term	***No studies***	***2 RCTs (n=654) for Surveillance Report 3 found mixed results on pain outcomes and no effect on function with naproxen.[7,8]***	***Effect of naproxen (SOE: Insufficient)‡***
Chronic pelvic pain	KQ1. Gabapentin versus placebo	No studies	2 RCTs (n=366) from Surveillance Report 2 found mixed results on pain outcomes with gabapentin compared with placebo.[19-21] 1 RCT (n=306) from Surveillance Report 2 found no differences between gabapentin and placebo on quality of life and activity.[20,21]	Effect of gabapentin on pain (SOE: Insufficient)† No effect of gabapentin on quality of life and activity (SOE: Low) †
Inflammatory arthritis	KQ1. Diclofenac versus Meloxicam versus Celecoxib	No differences between diclofenac and celecoxib on pain improvement, pain response, or function • SOE: Moderate, based on 3 RCTs No differences between diclofenac and meloxicam on pain improvement • SOE: Low, based on 1 RCT No studies compared meloxicam and celecoxib	1 RCT (n=30) from Surveillance Report 2 found no differences between diclofenac and meloxicam and celecoxib on pain improvement and function.[22] Updated MAs for diclofenac versus celecoxib: • Pain improvement (4 RCTs): MD -0.07 (95% CI, -0.63 to 0.42, I^2=48%) • Function (4 RCTs): SMD -0.00 (95% CI, -0.12 to 0.13, I^2=0%)	No change in SOE for diclofenac versus celecoxib, and diclofenac versus meloxicam Meloxicam versus celecoxib (SOE: Insufficient)†
Harms	KQ2. TCAs short-term	Dry mouth more likely with amitriptyline • SOE: Insufficient, based on 1 RCT	1 RCT (n=70) from Surveillance Report 1 found no increase in SAEs, nausea, or sedation but a nonsignificant increase in dry mouth with desipramine;[18] 1 RCT (n=201) from Surveillance Report 2 found no difference in SAEs but increased dry mouth with nortriptyline.[17]	Increased dry mouth with TCAs (SOE: upgraded to Low)*,† Evidence for SAEs (SOE: Insufficient)*,†

Type of Pain or Harm	Key Question	Conclusions From 2020 Report	Findings From Surveillance Reports	Assessment
Harms	KQ2. Anticonvulsants short-term	No increased risk of SAEs • SOE: Low, based on 19 RCTs Moderate increase in WAEs • SOE: Moderate, based on 26 RCTs Large increase in cognitive AEs • SOE: Low. based on 8 RCTs Large increase in dizziness, peripheral edema, sedation, and weight gain • SOE: Moderate, based on 21-25 RCTs	1 RCT (n=334) from Surveillance Report 2 found no increase in risk of having any AE, SAE, or WAE, but increased risk of dizziness and somnolence.[16] 2 RCTs (n=366) from Surveillance Report 2 found increased risk of dizziness.[19-21] 1 RCT (n=306) from Surveillance Report 2 found increased risk of SAEs, sedation, and visual disturbances.[20,21] 1 RCT (n=60) from Surveillance Report 2 found increased risk of WAEs and nonsignificantly increased risk of sedation and cognitive effects.[19] Updated MAs for pregabalin/gabapentin: • SAEs (21 RCTs): RR 0.94 (95% CI, 0.63 to 1.40, I^2=21%) • WAEs (28 RCTs): RR 1.74 (95% CI, 1.51 to 2.02, I^2=3%) • Blurred vision (13 RCTs): RR 3.35 (95% CI, 2.09 to 6.07, I^2=30%) • Cognitive effects (9 RCTs): RR 3.14 (95% CI, 1.88 to 5.34, I^2=0%) • Dizziness (28 RCTs): RR 2.85 (95% CI, 2.43 to 3.34, I^2=36%) • Sedation (27 RCTs): RR 2.90 (95% CI. 2.47 to 3.52, I^2=23%)	No change in conclusions
	KQ2. Topical capsaicin short-term	Topical capsaicin resulted in moderate increase in application site erythema and a large increase in application site pain with no increase in SAEs, or application site pruritus • SOE: Moderate, based on 3 RCTs No increased risk of WAEs • SOE: Moderate based on 2 RCTs	1 RCT (n=179) from Surveillance Report 1 found capsaicin patch associated with increased withdrawals due to treatment-emergent AEs.[11] Updated MA of WAEs (3 RCTs): RR 2.20 (95% CI, 0.37 to 12.91, I^2=8%)	Large increase in risk of WAEs with capsaicin (SOE: Moderate)

Type of Pain or Harm	Key Question	Conclusions From 2020 Report	Findings From Surveillance Reports	Assessment
Harms	KQ2. Topical lidocaine short-term	No studies	1 RCT (n=184) from Surveillance Report 1 found lidocaine patch associated with no increase in withdrawals due to treatment-emergent AEs.[11]	WAEs with lidocaine (SOE: Insufficient)*
	KQ2. Cannabis (oral/oromucosal) short-term	Dronabinol associated with a moderate increase in SAEs, WAEs, or nausea; oral THC/CBD associated with large increase in WAEs, dizziness, nausea, but no increase in SAEs or sedation • SOE: Low based on 2 RCTs	1 RCT (n=339) from Surveillance Report 1 found increased risk of any AE, dizziness, somnolence and a nonsignificant increase in risk of nausea with THC/CBD.[10] New MAs: • SAEs (2 RCTs): RR 1.54 (95% CI, 0.90 to 2.64, I^2=0%) • WAEs (2 RCTs): RR 2.25 (95% CI, 1.16 to 4.39, I^2=27%) • Dizziness (2 RCTs): RR 4.48 (95% CI, 2.77 to 7.22, I^2=0%) • Nausea (2 RCTs): RR 2.11 (95% CI, 1.20 to 3.72, I^2=0%) • Sedation (2 RCTs): RR 5.84 (95% CI, 1.90 to 17.92, I^2=0%)	No change in conclusions for WAEs, SAEs, dizziness, and nausea (SOE: Low); large effect of cannabis on sedation (SOE: Low)*
	KQ2. Duloxetine short-term	***SNRIs associated with no effect on SAEs*** • ***SOE: Low based on 19 RCTs*** ***SNRIs associated with moderate increase in WAEs*** • ***SOE: Moderate based on 24 RCTs***	***1 RCT (n=236) from Surveillance Report 3 found no effect of duloxetine on SAEs and a moderate effect on WAEs.[9]*** ***Updated MAs:*** • ***SAEs (20 RCTs): RR 0.92 (95% CI, 0.65 to 1.29, I^2=0%)*** • ***WAEs (25 RCTs): RR 2.00 (95% CI, 1.72 to 2.35, I^2=18%)***	***No change in conclusions***
	KQ2. Naproxen short-term	***NSAIDs associated with no effect on SAEs*** • ***SOE: Low based on 23 RCTs*** ***NSAIDS associated with small increase in WAEs*** • ***SOE: Moderate based on 38 RCTs***	***2 RCTs (n=654) from Surveillance Report 3 found no increased risk of SAEs or WAEs with naproxen.[7,8]*** ***New MAs:*** • ***SAEs (25 RCTs): RR 0.96 (95% CI, 0.73 to 1.27, I^2=0%)*** • ***WAEs (40 RCTs): RR 1.27 (95% CI, 1.11 to 1.46, I^2=18%)***	***No change in conclusions***

Abbreviations: AE=adverse event; CBD=cannabidiol; CI=confidence interval; CR=controlled release; IR=immediate release; KQ=Key Question; MA=meta-analysis; MD=mean difference; NSAID=nonsteroidal anti-inflammatory drug; RCT=randomized controlled trial; RR=relative ratio; SAE=serious adverse events; SMD=standard mean difference; SNRI= serotonin–norepinephrine reuptake inhibitor; SOE=strength of evidence; SR=Surveillance Report; TCAs=tricyclic antidepressants; THC=delta tetrahydrocannabinol; WAE=withdrawals due to adverse events

*Change in SOE for Surveillance Report 1

†New SOE or change in SOE for Surveillance Report 2

‡New SOE for Surveillance Report 3

Evidence Details

One newly published trial of duloxetine versus placebo in osteoarthritis, identified in update searches, was included in this Surveillance Report 3.[6] Three additional trials in low back pain that were inadvertently omitted from the original report were also included. One trial of duloxetine was wrongly excluded,[9] and two placebo-controlled trials of tanezumab (an excluded intervention) also contained a naproxen arm.[7,8]

Key Question 1: Benefits

Osteoarthritis

One new fair-quality RCT (n=128) found 3 months of duloxetine treatment associated with improved pain outcomes compared with placebo in patients with knee osteoarthritis and taking NSAIDS that was consistent with previous conclusions.[6] The likelihood of experiencing at least a 50-percent pain response in this trial (48.4% vs. 31.3%, relative ratio [RR] 1.55, 95% confidence interval [CI], 1.00 to 2.41) was consistent with previous pooled analysis of at least a 30-percent pain response that found a moderate benefit with duloxetine (4 RCTs, N=1,247, RR 1.37, 95% CI, 1.24 to 1.52, I^2=0%).[23-26] In meta-analysis updated with this new study, findings of a small beneficial effect of duloxetine on mean pain intensity were unchanged (7 RCTs, N=1,636, mean difference [MD] -0.77, 95% CI, -1.01 to -0.58, I^2=12%).[6,23-28] The new trial found no effect of duloxetine on function based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score (MD -0.02, p>0.05) in data that could not be pooled with other studies;[6] this is inconsistent with prior evidence of a small effect on function.

Low Back Pain

One fair-quality RCT (n=236) added to this update found duloxetine associated with improved pain outcomes compared with placebo, which was consistent with previous findings.[9] Function, based on the Brief Pain Inventory (BPI) Interference score, was also improved, which was inconsistent with the previous findings of no effect of duloxetine on function. Updated meta-analyses with this trial continued to show duloxetine associated with a small improvement in mean pain intensity (4 RCTs, N=1,462, MD -0.54, 95% CI, -0.76 to -0.34, I^2=0%)[9,29-31] and likelihood of pain response (4 RCTs, N=1,451, 58.3% vs. 47.3%, RR 1.26, 95% CI, 1.13 to 1.39, I^2=%),[9,29-31] and no effect on function based on the BPI Interference Score (4 RCTs, N=1,437, MD -0.42, 95% CI, -0.77 to -0.14, I^2=36%).[9,29-31]

Two fair-quality RCTs (N=654), added to this update, reported mixed results for pain outcomes with naproxen compared with placebo in low back pain.[7,8] One 16-week treatment trial (n=525) found a small but statistically significant reduction in pain intensity with naproxen (MD -0.41, p=0.037) and 30-percent or greater pain response (p=0.009) with baseline observation carried forward for missing data.[7] However, treatment with naproxen was not better than placebo with last observation carried forward analysis. There was no difference in function on the Roland-Morris Disability Questionnaire (RMDQ) between naproxen and placebo (MD -0.32, p=0.405). The second naproxen trial (n=129) found no differences between naproxen

and placebo on pain intensity (approximate MD -0.3, p=0.277), 30-percent or greater pain response (34.1% vs. 29.3%, p=0.369), or function on the RMDQ (approximate MD -0.4, p=0.305) after 12 weeks treatment.[8] SOE for these outcomes is rated insufficient due to inconsistency.

Key Question 2: Harms

Serotonin–Norepinephrine Reuptake Inhibitor

The addition of one trial of duloxetine (n=236)[9] to an updated meta-analysis did not change prior conclusions of no effect of serotonin–norepinephrine reuptake inhibitors (SNRIs) on the risk of serious adverse events (SAEs) (20 RCTs, N=9,059, 1.6% vs. 2.6%, RR 0.92, 95% CI, 0.65 to 1.29, I^2=0%)[9,23-26,29-43] and a moderate risk of withdrawals due to adverse events (WAEs) (25 RCTs, N=10,207, 15.2% vs. 7.4%, RR 2.00, 95% CI, 1.72 to 2.35, I^2=18%).[9,23-27,29-47]

NSAIDs

The addition of two trials of naproxen (N=654),[7,8] for this update, to an updated meta-analysis did not change prior conclusions showing no effect on SAEs (25 RCTs, N=13,736, 1.8% vs. 1.6%, RR 0.96, 95% CI, 0.73 to 1.27, I^2=0%)[7,8,48-68] and a small increased risk of WAEs (40 RCTs, N=20,714, 7.7% vs. 5.6%, RR 1.27, 95% CI, 1.11 to 1.46, I^2=18%).[7,8,48-83]

Conclusions

A systematic review and three subsequent surveillance updates have found nonopioid drugs (mainly SNRI antidepressants, pregabalin/gabapentin, and NSAIDs) associated with small to moderate improvements in pain and function outcomes in patients with specific types of noncancer chronic pain in the short term, with few differences between drugs in a class or doses of a drug (Table 1). Evidence on intermediate- and long-term effects on pain, function, and quality of life is limited. Nonopioid drugs were associated with increased risk of class-specific harms (e.g., gastrointestinal events with NSAIDS), with some patients withdrawing due to adverse events, suggesting that potential harms should be considered when selecting nonopioid drug treatments.

One new RCT from Surveillance Report 3 did not change conclusions regarding improved pain and function with duloxetine compared with placebo in osteoarthritis. One study of duloxetine in low back pain added to Surveillance Report 3 did not change previous conclusions of a small effect on pain outcomes with no effect on function. Two trials added for Surveillance Report 3 provided insufficient evidence on the effects of naproxen in low back pain.

Meta-analyses updated with trials identified in Surveillance Reports 1 and 2 were largely consistent with prior findings. Changes to prior conclusions as a result of new or updated meta-analyses occurred in neuropathic pain trials and include low SOE for a small reduction in pain intensity with cannabis (previously a moderate reduction), low SOE for a large risk of sedation with cannabis (previously insufficient evidence), and low SOE for no difference between gabapentin/pregabalin and duloxetine on pain intensity (previously insufficient evidence). An updated meta-analysis of capsaicin trials found moderate SOE of a large increased risk of WAEs compared with placebo (previously no increase in risk), although the absolute number of participants who withdrew due to adverse events was less than 1 percent.

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Disclaimers

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

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

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Afterword

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

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

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

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

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Appendix Contents

Appendix A. Literature Search Strategies

Randomized Controlled Trials

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclofenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,kw,sh,ti.
2 (carbamazepine or gabapentin or oxcarbazepine or pregabalin).ab,kw,sh,ti.
3 (desvenlafaxine or duloxetine or levomilnacipran or milnacipran or venlafaxine).ab,kw,sh,ti.
4 (amitriptyline or desipramine or doxepin or imipramine or nortriptyline or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarboamol or tizanidine).ab,kw,sh,ti.
5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,kw,sh,ti.
6 (topical adj2 lidocaine).ab,kw,ti.
7 or/1-6
8 exp Neuralgia/
9 Fibromyalgia/
10 exp Anemia, Sickle Cell/
11 Headache/
12 exp Headache Disorders/
13 Musculoskeletal Pain/
14 exp Osteoarthritis/
15 Low Back Pain/
16 Neck Pain/
17 exp Arthritis, Rheumatoid/
18 Spondylitis, Ankylosing/
19 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,kw,ti.
20 or/8-19
21 7 and 20
22 randomized controlled trial.pt.
23 controlled clinical trial.pt.
24 clinical trials as topic.sh.
25 (random* or trial or placebo).ti,ab.
26 clinical trials as topic.sh.
27 exp animals/ not humans.sh.
28 or/22-26
29 28 not 27
30 21 and 29
31 limit 21 to randomized controlled trial
32 30 or 31

33 limit 32 to (english language and humans)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclofenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,kw,sh,ti.
2 (carbamazepine or gabapentin or oxcarbazepine or pregabalin).ab,kw,sh,ti.
3 (desvenlafaxine or duloxetine or levomilnacipran or milnacipran or venlafaxine).ab,kw,sh,ti.
4 (amitriptyline or desipramine or doxepin or imipramine or nortriptyline or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarboamol or tizanidine).ab,kw,sh,ti.
5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,kw,sh,ti.
6 (topical adj2 lidocaine).ab,kw,ti.
7 or/1-6
8 exp Neuralgia/
9 Fibromyalgia/
10 exp Anemia, Sickle Cell/
11 Headache/
12 exp Headache Disorders/
13 Musculoskeletal Pain/
14 exp Osteoarthritis/
15 Low Back Pain/
16 Neck Pain/
17 exp Arthritis, Rheumatoid/
18 Spondylitis, Ankylosing/
19 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,kw,ti.
20 or/8-19
21 7 and 20
22 21 not acute.ti.
23 limit 22 to english language

Database: PsycINFO

1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclofenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,kw,sh,ti.
2 (carbamazepine or gabapentin or oxcarbazepine or pregabalin).ab,kw,sh,ti.
3 (desvenlafaxine or duloxetine or levomilnacipran or milnacipran or venlafaxine).ab,kw,sh,ti.
4 (amitriptyline or desipramine or doxepin or imipramine or nortriptyline or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or

flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarboamol or tizanidine).ab,kw,sh,ti.
5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,kw,sh,ti.
6 (topical adj2 lidocaine).ab,kw,ti.
7 or/1-6
8 exp NEURALGIA/
9 exp chronic pain/
10 exp headache/
11 exp Back Pain/
12 sickle cell disease/
13 exp ARTHRITIS/
14 fibromyalgia/
15 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,hw,ti.
16 or/8-15
17 7 and 16
18 17 and (random* or control* or trial).ti,ab.
19 limit 18 to english language

Database: Elsevier Embase
(celecoxib:ti OR diclofenac:ti OR diflunisal:ti OR etodolac:ti OR fenoprofen:ti OR flurbiprofen:ti OR ibuprofen:ti OR indomethacin:ti OR ketoprofen:ti OR ketorolac:ti OR meclofenamate:ti OR 'mefenamic acid':ti OR meloxicam:ti OR nabumetone:ti OR naproxen:ti OR oxaprozin:ti OR piroxicam:ti OR salsalate:ti OR sulindac:ti OR tenoxicam:ti OR 'tiaprofenic acid':ti OR tolmetin:ti OR celecoxib:ab OR diclofenac:ab OR diflunisal:ab OR etodolac:ab OR fenoprofen:ab OR flurbiprofen:ab OR ibuprofen:ab OR indomethacin:ab OR ketoprofen:ab OR ketorolac:ab OR meclofenamate:ab OR 'mefenamic acid':ab OR meloxicam:ab OR nabumetone:ab OR naproxen:ab OR oxaprozin:ab OR piroxicam:ab OR salsalate:ab OR sulindac:ab OR tenoxicam:ab OR 'tiaprofenic acid':ab OR tolmetin:ab OR carbamazepine:ti OR gabapentin:ti OR oxcarbazepine:ti OR pregabalin:ti OR carbamazepine:ab OR gabapentin:ab OR oxcarbazepine:ab OR pregabalin:ab OR desvenlafaxine:ti OR duloxetine:ti OR levomilnacipran:ti OR milnacipran:ti OR venlafaxine:ti OR desvenlafaxine:ab OR duloxetine:ab OR levomilnacipran:ab OR milnacipran:ab OR venlafaxine:ab OR amitriptyline:ti OR desipramine:ti OR doxepin:ti OR imipramine:ti OR nortriptyline:ti OR amitriptyline:ab OR desipramine:ab OR doxepin:ab OR imipramine:ab OR nortriptyline:ab OR alprazolam:ti OR chlordiazepoxide:ti OR clobazam:ti OR clonazepam:ti OR clorazepate:ti OR diazepam:ti OR estazolam:ti OR flurazepam:ti OR lorazepam:ti OR oxazepam:ti OR temazepam:ti OR triazolam:ti OR baclofen:ti OR carisoprodol:ti OR cyclobenzaprine:ti OR metaxalone:ti OR methocarboamol:ti OR tizanidine:ti OR alprazolam:ab OR chlordiazepoxide:ab OR clobazam:ab OR clonazepam:ab OR clorazepate:ab OR diazepam:ab OR estazolam:ab OR flurazepam:ab OR lorazepam:ab OR oxazepam:ab OR temazepam:ab OR triazolam:ab OR baclofen:ab OR carisoprodol:ab OR cyclobenzaprine:ab OR metaxalone:ab OR methocarboamol:ab OR tizanidine:ab OR acetaminophen:ti OR paracetamol:ti OR acetaminophen:ab OR paracetamol:ab OR capsaicin:ti OR capsaicin:ab OR methocarbamol;ti OR methocarbamol:ab OR marijuana:ti

OR cannabidiol:ti OR phytocannabinoid:ti OR dronabinol:ti OR nabilone:ti OR marijuana:ab OR cannabidiol:ab OR phytocannabinoid:ab OR dronabinol:ab OR nabilone:ab OR memantine:ti OR memantine:ab OR (lidocaine:ti AND topical) OR (lidocaine:ab AND topical)) AND ('neuropathic pain':ti OR fibromyalgia:ti OR 'sickle cell':ti OR headache:ti OR 'musculoskeletal pain':ti OR osteoarthrtis:ti OR 'low back pain':ti OR 'neck pain':ti OR 'inflammatory pain':ti OR 'rheumatoid arthritis':ti OR 'neuropathic pain':ab OR fibromyalgia:ab OR 'sickle cell':ab OR headache:ab OR 'musculoskeletal pain':ab OR osteoarthrtis:ab OR 'low back pain':ab OR 'neck pain':ab OR 'inflammatory pain':ab OR 'rheumatoid arthritis':ab) AND ('clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*) AND [humans]/lim AND [english]/lim AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Systematic Reviews

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclofenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,kw,sh,ti.
2 (carbamazepine or gabapentin or oxcarbazepine or pregabalin).ab,kw,sh,ti.
3 (desvenlafaxine or duloxetine or levomilnacipran or milnacipran or venlafaxine).ab,kw,sh,ti.
4 (amitriptyline or desipramine or doxepin or imipramine or nortriptyline or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarboamol or tizanidine).ab,kw,sh,ti.
5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,kw,sh,ti.
6 (topical adj2 lidocaine).ab,kw,ti.
7 or/1-6
8 exp Neuralgia/
9 Fibromyalgia/
10 exp Anemia, Sickle Cell/
11 Headache/
12 exp Headache Disorders/
13 Musculoskeletal Pain/
14 exp Osteoarthritis/
15 Low Back Pain/
16 Neck Pain/
17 exp Arthritis, Rheumatoid/
18 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthrtis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,kw,ti.
19 or/8-18

20 7 and 19
21 meta-analysis.pt.
22 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
23 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
24 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
25 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
26 (data synthes* or data extraction* or data abstraction*).ti,ab.
27 (handsearch* or hand search*).ti,ab.
28 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
29 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
30 (meta regression* or metaregression*).ti,ab.
31 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
32 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
33 (cochrane or (health adj2 technology assessment) or evidence report).jw.
34 (meta-analysis or systematic review).ti,ab.
35 (comparative adj3 (efficacy or effectiveness)).ti,ab.
36 (outcomes research or relative effectiveness).ti,ab.
37 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
38 or/21-37
39 20 and 38
40 limit 20 to (meta analysis or systematic reviews)
41 39 or 40
42 limit 41 to yr="2008 -Current"
43 limit 42 to english language

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclofenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,ti.
2 (brivaracetam or carbamazepine or divalproex or "eslicarbazepine acetate" or ethotoin or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or perampanel or phenytoin or pregabalin or tiagabine or topiramate or "valproic acid" or zonisamide).ab,ti.
3 (bupropion or citalopram or desvenlafaxine or duloxetine or escitalopram or fluoxetine or fluvoxamine or levomilnacipran or mirtazapine or nefazodone or paroxetine or sertraline or trazodone or venlafaxine or vilazodone or vortioxetine).ab,ti.
4 (amitriptyline or desipramine or imipramine or nortriptyline or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarboamol or tizanidine or alprazolam or

chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam).ab,ti.
5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,ti.
6 (topical adj2 lidocaine).ab,ti.
7 or/1-6
8 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthrtis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,ti.
9 7 and 8

Database: Elsevier Embase

(celecoxib:ti OR diclofenac:ti OR diflunisal:ti OR etodolac:ti OR fenoprofen:ti OR flurbiprofen:ti OR ibuprofen:ti OR indomethacin:ti OR ketoprofen:ti OR ketorolac:ti OR meclofenamate:ti OR 'mefenamic acid':ti OR meloxicam:ti OR nabumetone:ti OR naproxen:ti OR oxaprozin:ti OR piroxicam:ti OR salsalate:ti OR sulindac:ti OR tenoxicam:ti OR 'tiaprofenic acid':ti OR tolmetin:ti OR celecoxib:ab OR diclofenac:ab OR diflunisal:ab OR etodolac:ab OR fenoprofen:ab OR flurbiprofen:ab OR ibuprofen:ab OR indomethacin:ab OR ketoprofen:ab OR ketorolac:ab OR meclofenamate:ab OR 'mefenamic acid':ab OR meloxicam:ab OR nabumetone:ab OR naproxen:ab OR oxaprozin:ab OR piroxicam:ab OR salsalate:ab OR sulindac:ab OR tenoxicam:ab OR 'tiaprofenic acid':ab OR tolmetin:ab OR carbamazepine:ti OR gabapentin:ti OR oxcarbazepine:ti OR pregabalin:ti OR carbamazepine:ab OR gabapentin:ab OR oxcarbazepine:ab OR pregabalin:ab OR desvenlafaxine:ti OR duloxetine:ti OR levomilnacipran:ti OR milnacipran:ti OR venlafaxine:ti OR desvenlafaxine:ab OR duloxetine:ab OR levomilnacipran:ab OR milnacipran:ab OR venlafaxine:ab OR amitriptyline:ti OR desipramine:ti OR doxepin:ti OR imipramine:ti OR nortriptyline:ti OR amitriptyline:ab OR desipramine:ab OR doxepin:ab OR imipramine:ab OR nortriptyline:ab OR alprazolam:ti OR chlordiazepoxide:ti OR clobazam:ti OR clonazepam:ti OR clorazepate:ti OR diazepam:ti OR estazolam:ti OR flurazepam:ti OR lorazepam:ti OR oxazepam:ti OR temazepam:ti OR triazolam:ti OR baclofen:ti OR carisoprodol:ti OR cyclobenzaprine:ti OR metaxalone:ti OR methocarboamol:ti OR tizanidine:ti OR alprazolam:ab OR chlordiazepoxide:ab OR clobazam:ab OR clonazepam:ab OR clorazepate:ab OR diazepam:ab OR estazolam:ab OR flurazepam:ab OR lorazepam:ab OR oxazepam:ab OR temazepam:ab OR triazolam:ab OR baclofen:ab OR carisoprodol:ab OR cyclobenzaprine:ab OR metaxalone:ab OR methocarboamol:ab OR tizanidine:ab OR acetaminophen:ti OR paracetamol:ti OR acetaminophen:ab OR paracetamol:ab OR capsaicin:ti OR capsaicin:ab OR methocarbamol;ti OR methocarbamol:ab OR marijuana:ti OR cannabidiol:ti OR phytocannabinoid:ti OR dronabinol:ti OR nabilone:ti OR marijuana:ab OR cannabidiol:ab OR phytocannabinoid:ab OR dronabinol:ab OR nabilone:ab OR memantine:ti OR memantine:ab OR (lidocaine:ti AND topical) OR (lidocaine:ab AND topical)) AND ('neuropathic pain':ti OR fibromyalgia:ti OR 'sickle cell':ti OR headache:ti OR 'musculoskeletal pain':ti OR osteoarthrtis:ti OR 'low back pain':ti OR 'neck pain':ti OR 'inflammatory pain':ti OR 'rheumatoid arthritis':ti OR 'neuropathic pain':ab OR fibromyalgia:ab OR 'sickle cell':ab OR headache:ab OR 'musculoskeletal pain':ab OR osteoarthrtis:ab OR 'low back pain':ab OR 'neck pain':ab OR 'inflammatory pain':ab OR 'rheumatoid arthritis':ab) AND ('systematic review' OR 'meta analysis') AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py

OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim

Appendix B. Key Questions and Inclusion Criteria

Key Questions

Key Question 1. Effectiveness and Comparative Effectiveness

a. In patients with chronic pain, what is the effectiveness of nonopioid pharmacologic agents versus placebo for outcomes related to pain, function, and quality of life after short-term treatment duration (3 to <6 months), intermediate-term treatment duration (6 to <12 months), and long-term treatment duration (≥12 months)?
b. In patients with chronic pain, what is the comparative effectiveness of nonopioid pharmacologic agents compared to other nonopioid pharmacologic agents for outcomes related to pain, function, and quality of life after short-term treatment duration (3 to <6 months), intermediate-term treatment duration (6 to <12 months), and long-term treatment duration (≥12 months)?
c. How does effectiveness or comparative effectiveness vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) the dose of medication used, (5) the duration of treatment, and (6) dose titration, including tapering.

Key Question 2. Harms and Adverse Events

a. In patients with chronic pain, what are the risks of nonopioid pharmacologic agents for harms including overdose, misuse, dependence, withdrawals due to adverse events, and serious adverse events (including falls, fractures, motor vehicle accidents), and specific adverse events according to drug class?
b. How do harms vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) the dose of medication used, (5) the duration of treatment, and (6) dose titration, including tapering.

Criteria for Inclusion/Exclusion of Studies in the Review

Population(s)

- For all Key Questions (KQs): Adults (age ≥18 years) with various types of chronic pain (defined as pain lasting >3 months), including patients with acute exacerbations of chronic pain, pregnant/breastfeeding women, and patients with opioid use disorder
- For KQs 1c, 2b: Subgroups of the above patient populations as defined by specific pain condition (neuropathic pain, musculoskeletal pain, fibromyalgia, inflammatory arthritis,

and chronic headache), patient demographics (e.g., age, race, ethnicity, and sex), comorbidities and degree of nociplasticity/central sensitization.

Interventions

- Oral pharmacologic agents: nonsteroidal anti-inflammatory drugs, acetaminophen, muscle relaxants (including benzodiazepines), antidepressants, and anticonvulsants
- Topical pharmacologic agents: diclofenac, capsaicin, and lidocaine
- Medical cannabis (any formulation)

Comparators

- For KQ 1a/c and KQ2: Placebo (effectiveness)
- For KQ 1b/c and KQ2: Another included nonopioid pharmacologic agent, different doses, or treatment durations (comparative effectiveness)

Outcomes

- KQ 1: Pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression)
    - Only validated scales for assessments of pain, function, and quality of life
- KQ 2: For all drug classes: overdose, misuse, dependence, withdrawals due to adverse events, and serious adverse events. Specific adverse events for each drug class, such as gastrointestinal events, cardiovascular events, and liver or kidney-related harms for non-steroidal anti-inflammatory drugs; weight gain, sedation, and cognitive effects for gabapentin and pregabalin, etc.

Timing

- Short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration (≥12 months)
- We will assess available literature to ensure that adequate evidence exists from studies of ≥3 months' treatment duration. If adequate evidence is not available for this shorter-duration, we will consider adding shorter-duration studies. If high-quality systematic reviews are available covering the scope of the review for shorter duration studies, we will summarize these in this case.

Settings

- Outpatient settings (e.g., primary care, pain clinics, other specialty clinics)

Appendix C. Included Studies

1. AbdelHafeez MA, Reda A, Elnaggar A, et al. Gabapentin for the management of chronic pelvic pain in women. Arch Gynecol Obstet. 2019 Nov;300(5):1271-7. doi: 10.1007/s00404-019-05272-z. PMID: 31435774.

2. Chakrabarty S, Biswas S, Maiti T, et al. Pregabalin and amitriptyline as monotherapy or as low-dose combination in patients of neuropathic pain: a randomized, controlled trial to evaluate efficacy and safety in an Eastern India teaching hospital. Ann Indian Acad Neurol. 2019 Oct-Dec;22(4):437-41. doi: 10.4103/aian.AIAN_144_18. PMID: 31736565.

3. Dixit A, Pandey P, Dhasmana DC. In vivo effects of nonselective, partially selective, and selective non steroidal anti-inflammatory drugs on lipid peroxidation and antioxidant enzymes in patients with rheumatoid arthritis: a clinical study. Int J Appl Basic Med Res. 2020 Jul-Sep;10(3):167-72. doi: 10.4103/ijabmr.IJABMR_344_19. PMID: 33088738.

4. Gould HM, Atkinson JH, Chircop-Rollick T, et al. A randomized placebo-controlled trial of desipramine, cognitive behavioral therapy, and active placebo therapy for low back pain. Pain. 2020 Jun;161(6):1341-9. doi: 10.1097/j.pain.0000000000001834. PMID: 32068667.

5. Hewitt CA, Vincent K, Middleton LJ, et al. Gabapentin to reduce pain in women aged between 18 and 50 years with chronic pelvic pain: the GaPP2 RCT. NIHR Journals Library. 2020 Nov;11:11. doi: 10.3310/eme07070. PMID: 33226738.

6. Horne AW, Vincent K, Hewitt CA, et al. Gabapentin for chronic pelvic pain in women (GaPP2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2020 Sep 26;396(10255):909-17. doi: 10.1016/S0140-6736(20)31693-7. PMID: 32979978.

7. Hudson B, Williman JA, Stamp LK, et al. Nortriptyline for pain in knee osteoarthritis: a double-blind randomised controlled trial in New Zealand general practice. Br J Gen Pract. 2021 Feb 10;10(10) doi: 10.3399/BJGP.2020.0797. PMID: 33571950.

8. Hussain N, Said ASA, Javaid FA, et al. The efficacy and safety profile of capsaicin 8% patch versus 5% lidocaine patch in patients with diabetic peripheral neuropathic pain: a randomized, placebo-controlled study of south Asian male patients. J Diabetes Metab Disord. 2021;20:271-8.

9.* Katz N, Borenstein DG, Birbara C, et al. Efficacy and safety of tanezumab in the treatment of chronic low back pain. Pain. 2011 Oct;152(10):2248-58. doi: 10.1016/j.pain.2011.05.003. PMID: 21696889.

10.* Khan Panezai MM, Gul S, Kakar ZE, et al. Comparison of NSAIDS versus NSAIDS plus duloxetine in knee osteoarthritis patients. Pakistan journal of medical and health sciences. 2021;15(10):2865-8. PMID: CN-02348308 NEW.

11. Khasbage S, Shukla R, Sharma P, et al. A randomized control trial of duloxetine and gabapentin in painful diabetic neuropathy. J Diabetes. 2021 Jul;13(7):532-41. doi: 10.1111/1753-0407.13148. PMID: 33340245.

12.* Kivitz AJ, Gimbel JS, Bramson C, et al. Efficacy and safety of tanezumab versus naproxen in the treatment of chronic low back pain. Pain. 2013 Jul;154(7):1009-21. doi: 10.1016/j.pain.2013.03.006. PMID: 23628600.

13. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013 Apr;260(4):984-97. doi: 10.1007/s00415-012-6739-4. PMID: 23180178.

14. Lee MK, Jeon Y, Choi SS, et al. Efficacy and safety of the controlled-release pregabalin tablet (GLA5PR GLARS-NF1) and immediate-release pregabalin capsule for peripheral neuropathic pain: a multicenter, randomized, double-blind, parallel-group, active-controlled, phase III clinical trial. Clin Ther. 2020 Dec;42(12):2266-79. doi: 10.1016/j.clinthera.2020.10.009. PMID: 33272643.

15. Shahid W, Kumar R, Shaikh A, et al. Comparison of the efficacy of duloxetine and pregabalin in pain relief associated with diabetic neuropathy. Cureus. 2019 Jul 31;11(7):e5293. doi: 10.7759/cureus.5293. PMID: 31579634.

16.* Skljarevski V, Desaiah D, Liu-Seifert H, et al. Efficacy and safety of duloxetine in patients with chronic low back pain. Spine. 2010b Jun 1;35(13):E578-85. doi: 10.1097/BRS.0b013e3181d3cef6. PMID: 20461028.

17. Zhang X, Xu H, Zhang Z, et al. Efficacy and safety of pregabalin for fibromyalgia in a population of Chinese subjects. J Pain Res. 2021;14:537-48. doi: 10.2147/JPR.S281483. PMID: 33658841.

*Studies identified since the last surveillance report

Appendix D. Excluded Studies

Table D-1. Key to exclusion codes

Exclusion Code	Exclusion Reason
2	Ineligible outcome
3	Ineligible intervention (including comparator)
4	Ineligible population
5	Ineligible publication type
6	Ineligible study design
7	Study not obtainable
8	Outdated or ineligible systematic review
9	Study duration <12 weeks
10	Foreign language
11	Companion to previously included study
12	Background

1. Abdel Fattah YH, Elnemr R. Efficacy of pregabalin as a monotherapy versus combined pregabalin and milnacipran in the management of fibromyalgia. Int J Rheum Dis. 2020 Nov;23(11):1474-80. doi: 10.1111/1756-185X.13953. PMID: 32886447. Exclusion: 3.

2. Abrams DI, Couey P, Dixit N, et al. Effect of inhaled cannabis for pain in adults with sickle cell disease: a randomized clinical trial. JAMA Netw Open. 2020 Jul 01;3(7):e2010874. doi: 10.1001/jamanetworkopen.2020.10874. PMID: 32678452. Exclusion: 4.

3. Akbas I, Kocak AO, Akgol Gur ST, et al. Lidocaine versus dexketoprofen in treatment of tension-type headache: a double-blind randomized controlled trial. Am J Emerg Med. 2021 Mar;41:125-9. doi: 10.1016/j.ajem.2020.12.057. PMID: 33423013. Exclusion: 3.

4. Alexander RC, Raudibaugh K, Spierings ELH, et al. A 3-way cross-over study of pregabalin, placebo, and the histamine 3 receptor inverse agonist AZD5213 in combination with pregabalin in patients with painful diabetic neuropathy and good pain-reporting ability. Clin J Pain. 2021 Jan;37(1):38-42. doi: 10.1097/AJP.0000000000000886. PMID: 33086238. Exclusion: 6.

5. Anonymous. Correction: postoperative intravenous parecoxib sodium followed by oral celecoxib post total knee arthroplasty in osteoarthritis patients (PIPFORCE): a multicentre, double-blind, randomised, placebo-controlled trial. BMJ Open. 2020 Mar 09;10(3):e030501corr1. doi: 10.1136/bmjopen-2019-030501corr1. PMID: 32152176. Exclusion: 6.

6. Argoff C, Eerdekens M, Engelen S, et al. Treatment outcomes in patients with post herpetic neuralgia: a controlled trial of capsaicin 8% patch versus oral pregabalin. Postgrad Med. 2020;132(Suppl 1):37-8. doi: 10.1080/00325481.2020.1824967. Exclusion: 5.

7. Arnold LM, Cappelleri JC, Clair A, et al. Interpreting Effect Sizes and Clinical Relevance of Pharmacological Interventions for Fibromyalgia. Pain Ther. 2013;2(1):65-71. doi: 10.1007/s40122-013-0011-1. Exclusion: 12.

8. Atzeni F, Bagnasco M, Lanata L, et al. Efficacy and safety of ketoprofen vs ibuprofen for the treatment of pain in rheumatoid arthritis: a systematic review and meta-analysis. Postgrad Med. 2017;129(Suppl 1):39. doi: 10.1080/00325481.2017.1367065. Exclusion: 5.

9. Aviram J, Pud D, Gershoni T, et al. Medical cannabis treatment for chronic pain: outcomes and prediction of response. Eur J Pain. 2021 Feb;25(2):359-74. doi: 10.1002/ejp.1675. PMID: 33065768. Exclusion: 6.

10. Ayeni F, Esan O, Ikem IC, et al. Early outcome of platelet rich plasma and non-steroidal anti-inflammatory agent alone and in combination on primary knee osteoarthritis. J Clin Diagn Res. 2019;13(11):RC06-RC8. doi: 10.7860/JCDR/2019/42135.13301. Exclusion: 3.

11. Bidari A, Moazen-Zadeh E, Ghavidel-Parsa B, et al. Comparing duloxetine and pregabalin for treatment of pain and depression in women with fibromyalgia: an open-label randomized clinical trial. Daru. 2019 Jun;27(1):149-58. doi: 10.1007/s40199-019-00257-4. PMID: 30877484. Exclusion: 9.

12. Braillon A. Efficacy and safety of duloxetine in osteoarthritis or chronic low back pain? The tip of an iceberg! Osteoarthritis Cartilage. 2020 Sep;28(9):1298-9. doi: 10.1016/j.joca.2020.04.019. PMID: 32446939. Exclusion: 5.

13. Chan FKL, Lanas A, Scheiman J, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet. 2010 Jul 17;376(9736):173-9. doi: 10.1016/S0140-6736(10)60673-3. PMID: 20638563. Exclusion: 3.

14. Chen B, Duan J, Wen S, et al. An Updated Systematic Review and Meta-analysis of Duloxetine for Knee Osteoarthritis Pain. The Clinical journal of pain. 2021 doi: https://dx.doi.org/10.1097/AJP.0000000000000975. Exclusion: 8.

15. Cheng BR, Chen JQ, Zhang XW, et al. Cardiovascular safety of celecoxib in rheumatoid arthritis and osteoarthritis patients: A systematic review and meta-analysis. PLoS ONE. 2021;16(12):e0261239. doi: https://dx.doi.org/10.1371/journal.pone.0261239. PMID: 34932581. Exclusion: 8.

16. 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: https://dx.doi.org/10.1136/bmj.n2321. PMID: 34642179. Exclusion: 8.

17. Dakin P, Kivitz AJ, Gimbel JS, et al. Efficacy and safety of fasinumab in patients with chronic low back pain: a phase II/III randomised clinical trial. Ann Rheum Dis. 2020 Nov 16;80(4):509-17. doi: 10.1136/annrheumdis-2020-217259 PMID: 33199274. Exclusion: 3.

18. Dolev A, Yaari L, Kittani M, et al. Efficacy of anti-inflammatory treatment versus rescue analgesia after arthroscopic partial meniscectomy in nonarthritic knees: a 3-arm controlled study. Orthop J Sports Med. 2021 Mar 19;9(3):2325967121991545. doi: 10.1177/2325967121991545. PMID: 33796593. Exclusion: 4.

19. Enomoto H, Fujikoshi S, Ogawa K, et al. Relationship between pain reduction and improvement in health-related quality of life in patients with knee pain due to osteoarthritis receiving duloxetine: exploratory post hoc analysis of a Japanese phase 3 randomized study. J Pain Res. 2020;13:181-91. doi: 10.2147/JPR.S211072. PMID: 32021407. Exclusion: 6.

20. Enomoto H, Sasaki N, Fujikoshi S, et al. Relationship between pain alleviation and disease-specific health-related quality of life measures in patients with chronic low back pain receiving duloxetine: exploratory post hoc analysis of a Japanese phase 3 randomized study. J. 2019 Nov;3(11):e10.5435. doi: 10.5435/JAAOSGlobal-D-18-00086. PMID: 31875196. Exclusion: 6.

21. Farag H, Yunusa I, Goswami H, et al. PMS6 effectiveness and acceptability of amitriptyline and Food and Drug Administration-approved treatments for fibromyalgia: a network meta-analysis Value Health. 2020 May;23(Suppl 1):S215. doi: 10.1016/j.jval.2020.04.693. Exclusion: 5.

22. Farpour HR, Estakhri F, Zakeri M, et al. Efficacy of piroxicam mesotherapy in treatment of knee osteoarthritis: a randomized clinical trial. Evid Based Complement Alternat Med. 2020 Aug 1;2020:6940741. doi: 10.1155/2020/6940741. PMID: 32831875. Exclusion: 3.

23. Freynhagen R, Argoff C, Eerdekens M, et al. Progressive response to repeat application of capsaicin 179 mg (8% w/w) cutaneous patch in peripheral neuropathic pain: comprehensive new analysis and clinical implications. Pain Med. 2021 Oct 8;22(10):2324-36. doi: 10.1093/pm/pnab113. PMID: 33871648. Exclusion: 3.

24. Gharibo C, Eerdekens M, Engelen S, et al. Long-term treatment with capsaicin 8% patches: a subgroup analysis in patients with postherpetic neuralgia from an open-label study. Postgrad Med. 2020;132(Suppl 1):36-7. doi: 10.1080/00325481.2020.1824967. Exclusion: 5.

25. Görür K, Gür H, İsmi O, et al. The effectiveness of propranolol, flunarizine, amitriptyline and botulinum toxin in vestibular migraine complaints and prophylaxis: a non-randomized controlled study. Braz J Otorhinolaryngol. 2021 Mar 7;S1808-8694(21):00026-4. doi: 10.1016/j.bjorl.2021.02.005. PMID: 33722518. Exclusion: 3.

26. Gul SK, Tepetam H, Gul HL. Duloxetine and pregabalin in neuropathic pain of lung cancer patients. Brain Behav. 2020 Mar;10(3):e01527. doi: 10.1002/brb3.1527. PMID: 31967742. Exclusion: 4.

27. Hermann GM, Iovoli AJ, Platek AJ, et al. A single-institution, randomized, pilot study evaluating the efficacy of gabapentin and methadone for patients undergoing chemoradiation for head and neck squamous cell cancer. Cancer. 2020 Apr 01;126(7):1480-91. doi: 10.1002/cncr.32676. PMID: 31869451. Exclusion: 4.

28. Inoue G, Kaito T, Matsuyama Y, et al. Comparison of the effectiveness of pharmacological treatments for patients with chronic low back pain: a nationwide, multicenter study in Japan. Spine Surg Relat Res. 2021;5(4):252-63. doi: 10.22603/SSRR.2020-0083. Exclusion: 6.

29. Itoh N, Tsuji T, Ishida M, et al. Efficacy of duloxetine for multisite pain in patients with knee pain due to osteoarthritis: an exploratory post hoc analysis of a Japanese phase 3 randomized study. J Orthop Sci. 2021 Jan;26(1):141-8. doi: 10.1016/j.jos.2020.02.013. PMID: 32245696. Exclusion: 6.

30. Itoh N, Uchio Y, Tsuji T, et al. Efficacy of duloxetine in patients with knee osteoarthritis or chronic low back pain with early pain reduction: an exploratory post-hoc analysis of Japanese phase 3, 1-year extension studies. J Orthop Sci. 2021 May 3;S0949-2658(21):00091-9. doi: 10.1016/j.jos.2021.02.016. PMID: 33958268. Exclusion: 6.

31. Jolly T, Mansuri Z, Trivedi C, et al. Are Psychotropic Medications Effective in Chronic Pain Management in Children and Adolescents? A Meta-Analysis of Randomized Control Trials. J Pain Res. 2021;14:1915-24. doi: https://dx.doi.org/10.2147/JPR.S310381. PMID: 34194243. Exclusion: 8.

32. Kataria D, Jumani L, Ahmed MU, et al. Comparison of pregabalin versus placebo in reduction of pain due to lumber disc herniation. Cureus. 2020 Aug 24;12(8):e9985. doi: 10.7759/cureus.9985. PMID: 32983686. Exclusion: 4.

33. Kim MS, Koh IJ, Sung YG, et al. Efficacy and safety of celecoxib combined with JOINS in the treatment of degenerative knee osteoarthritis: study protocol of a randomized controlled trial. Ther Adv Musculoskelet Dis. 2021 Jun;13:1759720X211024025. doi: 10.1177/1759720X211024025. PMID: 34262619. Exclusion: 5.

34. Levin OS, Skoromets AA, Tabeeva GR, et al. The efficacy and safety of naproxen in the treatment of nonspecific lumbalgia: the results of an open multi-center study (NEST). Zh Nevrol Psikhiatr Im S S Korsakova. 2019;119(5):27-31. doi: 10.17116/jnevro201911905127. PMID: 31317886. Exclusion: 10.

35. Mahmoud AMS, Ragab SG, Boules ML, et al. Comparison between two low doses of amitriptyline in the management of chronic neck pain: a randomized, double-blind, comparative study. Pain Res Manag. 2021 Jan 19;2021:8810178. doi: 10.1155/2021/8810178. PMID: 33532013. Exclusion: 3.

36. Ngo A, Yilmaz M, Gosalia N, et al. Novel advances in treatment of postherpetic neuralgia: topical film-forming spray with bupivacaine hydrochloride. Neuromodulation. 2020;23(3):e217. doi: 10.1111/ner.13133. Exclusion: 5.

37. Nikles J, Keijzers G, Mitchell G, et al. Pregabalin versus placebo to prevent chronic pain after whiplash injury in at-risk individuals: results of a feasibility study for a large randomised controlled trial. Pain. 2021 Jun 8 doi: 10.1097/j.pain.0000000000002362. PMID: 34108431. Exclusion: 4.

38. Nishida Y, Kano K, Nobuoka Y, et al. Sustained-release diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate) for knee osteoarthritis: a randomized phase 2 study. Rheumatology (Oxford). 2021 Mar 02;60(3):1435-44. doi: 10.1093/rheumatology/keaa605. PMID: 33006602. Exclusion: 3.

39. Nishida Y, Kano K, Nobuoka Y, et al. Efficacy and safety of diclofenac-hyaluronate conjugate (diclofenac etalhyaluronate) for knee osteoarthritis: a randomized phase 3 trial in Japan. Arthritis rheumatol. 2021 Sep;73(9):1646-55. doi: 10.1002/art.41725. PMID: 33749997. Exclusion: 3.

40. Nishida Y, Kano K, Osato T, et al. Open-label phase 3 study of diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate: ONO-5704/SI-613) for treatment of osteoarthritis: 1-year follow-up. BMC Musculoskelet Disord. 2021 Mar 01;22(1):233. doi: 10.1186/s12891-021-04108-9. PMID: 33648473. Exclusion: 3.

41. Parris W, Johnson B, Eriator I. A randomized placebo-controlled pilot study of a topical herbal analgesic for the management of chronic musculo-skeletal pain. Postgrad Med. 2019;131(Suppl 1):119. doi: 10.1080/00325481.2019.1655695. Exclusion: 5.

42. Parsons B, Fujii K, Nozawa K, ., et al. The efficacy of pregabalin for the treatment of neuropathic pain in Japanese subjects with moderate or severe baseline pain. J Pain Res. 2019 Mar 22;12:1061-8. doi: 10.2147/JPR.S181729. PMID: 30962707. Exclusion: 6.

43. Pelletier JP, Raynauld JP, Dorais M, et al. An international, multicentre, double-blind, randomized study (DISSCO): effect of diacerein vs celecoxib on symptoms in knee osteoarthritis. Rheumatology (Oxford). 2020 Dec 01;59(12):3858-68. doi: 10.1093/rheumatology/keaa072. PMID: 32521015. Exclusion: 3.

44. Pereira A, Marinho D. Clinical efficacy and safety profile of topical etofenamate in the treatment of patients with musculoskeletal disorders: results of a systematic review. Ann Rheum Dis. 2020;79(Suppl 1):1744. doi: 10.1136/annrheumdis-2020-eular.382. Exclusion: 5.

45. Privitera R, Anand P. Capsaicin 8% patch qutenza and other current treatments for neuropathic pain in chemotherapy-induced peripheral neuropathy (CIPN). Curr Opin Support Palliat Care. 2021 Jun 1;15(2):125-31. doi: 10.1097/SPC.0000000000000545. PMID: 33905384. Exclusion: 5.

46. Rayani M, Ansari B, Boroujeni SA, et al. Gabapentin versus pregabalin for management of chronic inflammatory demyelinating polyradiculoneuropathy. American journal of neurodegenerative diseases. 2021;10(4):50-6. PMID: CN-02326283 NEW. Exclusion: 3.

47. Romero V, Lara JR, Otero-Espinar F, et al. Capsaicin topical cream (8%) for the treatment of myofascial pain syndrome. Braz J Anesthesiol. 2019 Sep-Oct;69(5):432-8. doi: 10.1016/j.bjan.2019.06.008. PMID: 31519301. Exclusion: 10.

48. Ryder S, Buksnys T, Armstrong N, et al. PMU6 systematic review of the efficacy and safety of 5% lidocaine-medicated plaster vs. pregabalin Value Health. 2019 Nov 1;22(Suppl 3):S708. doi: 10.1016/j.jval.2019.09.1625. Exclusion: 5.

49. Schug SA, Parsons B, Almas M, et al. Effect of concomitant pain medications on response to pregabalin in patients with postherpetic neuralgia or spinal cord injury-related neuropathic pain. Pain physician. 2017;20(1):E53-E63. doi: 10.36076/ppj.2017.1.e53. Exclusion: 6.

50. Sharma C, Kaur I, Singh H, et al. A randomized comparative study of methylcobalamin, methylcobalamin plus pregabalin and methylcobalamin plus duloxetine in patients of painful diabetic neuropathy. Indian J Pharmacol. 2021;53(5):358-63. PMID: CN-02348394 NEW. Exclusion: 3.

51. Stubberud A, Tronvik E, Matharu M. Treatment of SUNCT/SUNA, paroxysmal hemicrania, and hemicrania continua: an update including single-arm meta-analyses. Curr Treat Options Neurol. 2020;22(12) doi: 10.1007/s11940-020-00649-x. Exclusion: 5.

52. Tabra SAA, Abu-Zaid MH, Hablas S. Vitamin D supplementation; is it effective in fibromyalgia patients? Ann Rheum Dis. 2020;79(Suppl 1):472-3. doi: 10.1136/annrheumdis-2020-eular.487. Exclusion: 5.

53. Tchaava K, Shavdia M, Gegeshidze N, et al. Management of diabetic neuropathic refractory pain. Diabetes Technol Ther. 2020;22:A189-A90. doi: 10.1089/dia.2020.2525.abstracts. Exclusion: 5.

54. Twelves C, Sabel M, Checketts D, et al. A phase 1b randomised, placebo-controlled trial of nabiximols cannabinoid oromucosal spray with temozolomide in patients with recurrent glioblastoma. Br J Cancer. 2021 Apr;124(8):1379-87. doi: 10.1038/s41416-021-01259-3. PMID: 33623076. Exclusion: 4.

55. Urquhart DM, Wluka AE, Heritier S, et al. Effect of low-dose amitriptyline on low back pain with a neuropathic component: a post hoc analysis. Spine J. 2021 Jun;21(6):899-902. doi: 10.1016/j.spinee.2021.01.012. PMID: 33460809. Exclusion: 11.

56. Vela J, Dreyer L, Petersen KK, et al. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. Pain. 2021 Aug 27 doi: 10.1097/j.pain.0000000000002466. PMID: 34510141. Exclusion: 4.

57. Vidhya A, Rao MVP, Geetha P. A comparative study of pregabalin and gabapentin combinations in type 2 diabetic neuropathy patients. Drug Invent Today. 2020;11(11):2845-9. Exclusion: 3.

58. Wade AG, Crawford GM, Young D, et al. Comparison of diclofenac gel, ibuprofen gel, and ibuprofen gel with levomenthol for the topical treatment of pain associated with musculoskeletal injuries. J Int Med Res. 2019 Sep;47(9):4454-68. doi: 10.1177/0300060519859146. PMID: 31353997. Exclusion: 4.

59. Wang Y, Xu T, Qiao Y, et al. Efficacy of duloxetine in treatment of central mediated abdominal pain syndrome. Chinese J Gastroenterol. 2020;25(11):666-9. doi: 10.3969/j.issn.1008-7125.2020.11.005. Exclusion: 10.

60. Wu W, Zhang B, Zhao T, et al. Efficacy and safety of pregabalin for chronic neuropathic pain: a meta-analysis. Neurol Asia. 2020;25(4):509-17. Exclusion: 8.

61. Xu Z, Chen L, Jin S, et al. The efficacy of memantine for the treatment of migraine: a meta-analysis of randomized controlled studies. Clin Neuropharmacol. 2021 May-Jun;44(3):94-8. doi: 10.1097/WNF.0000000000000425. PMID: 33961371. Exclusion: 3.

62. Yakushin S, Polyakova S, Shvarts Y, et al. Comparison of the efficacy and safety of ketoprofen plaster and diclofenac plaster for osteoarthritis-related knee pain: a multicenter, randomized, active-controlled, open-label, parallel-group, phase III clinical trial. Clin Ther. 2021 Aug 31;S0149-2918(21):00299-X. doi: 10.1016/j.clinthera.2021.08.002. PMID: 34479761. Exclusion: 9.

63. Yang X, Zhang Y, Yu H, et al. Efficacy of pregabalin in neuropathic pain after spinal cord injury. J Coll Physicians Surg Pak. 2020 Jan;30(1):106-7. doi: 10.29271/jcpsp.2020.01.106. PMID: 31931947. Exclusion: 5.

64. Yue L, Luo S, Wang Y, et al. Clinical meaningfulness of duloxetinea[Euro sign][TM]s effect in Chinese patients with chronic pain due to osteoarthritis: post hoc analyses of a phase 3 randomized trial. Open Access Rheumatol. 2019;11:67-76. Exclusion: 2.

65. Zajicek JP, Hobart JC, Slade A, et al. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32. doi: 10.1136/jnnp-2012-302468. PMID: 22791906. Exclusion: 4.

66. Zakerkish M, Raeisi D, Rafie S, et al. Comparison of efficacy of nortriptyline versus transcutaneous electrical nerve stimulation on painful peripheral neuropathy in patients with diabetes. Rom J Diabetes Nutr Metab Dis. 2019;26(4):401-11. Exclusion: 4.

67. Zhang J, Ge R, Yang Z. Effect of celecoxib combined with glucosamine hydrochloride in promoting the functional recovery and decreasing the inflammatory factor levels in patients with knee osteoarthritis. Pak. 2021 May;34(3(Special)):1277-82. PMID: 34602400. Exclusion: 9.

Appendix E. Study Characteristics Evidence Tables

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

Appendix F. Meta-Analysis Evidence Tables

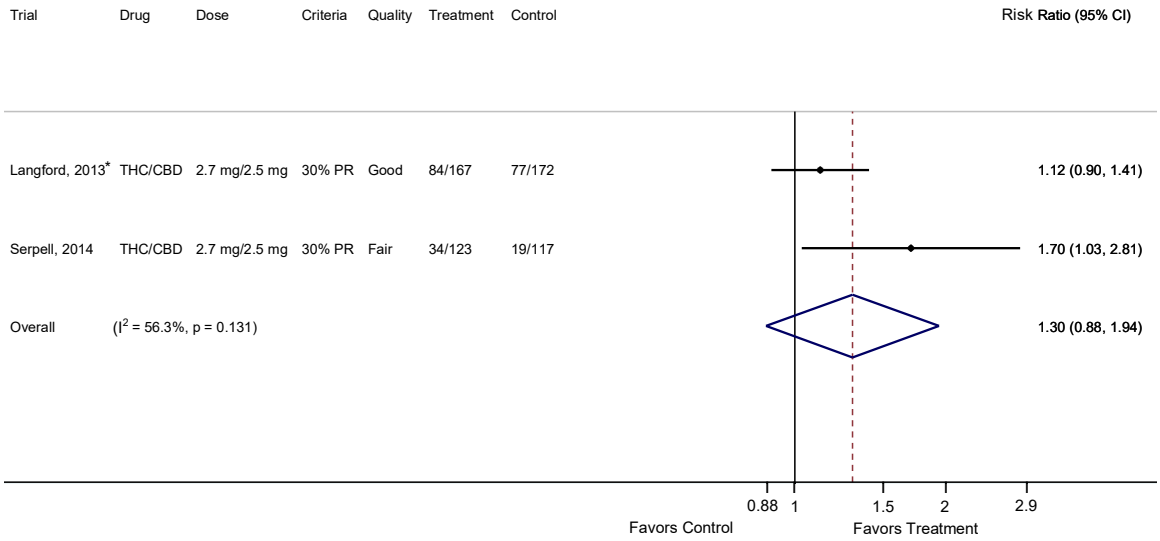
Shown in associated Excel files for Surveillance Report 3
at **https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research**.

Appendix G. Quality Assessment

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

Appendix H. Results of Updated Meta-Analyses

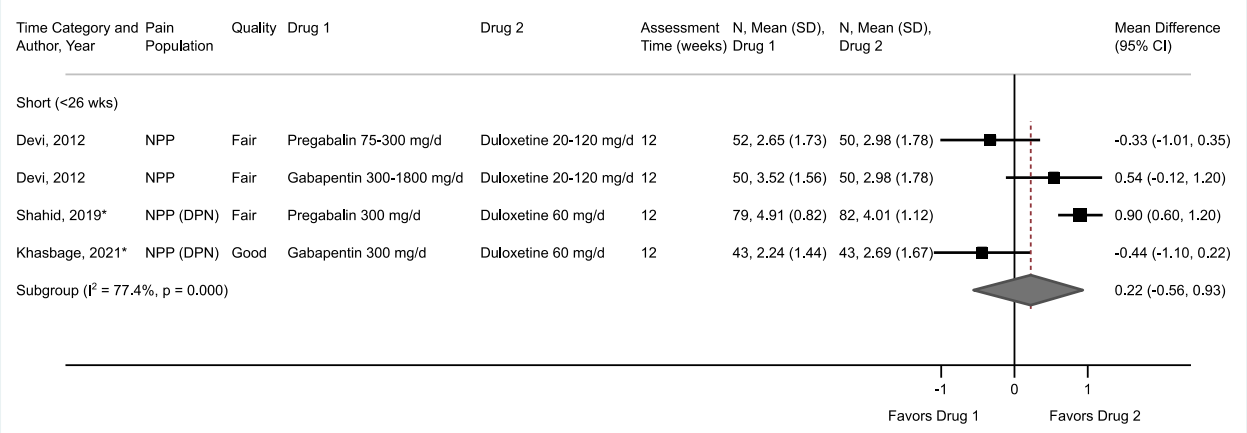
Figure H-1. NPP response, cannabis versus placebo



Abbreviations: CBD=cannabidiol; CI=confidence interval; mg=milligrams; NPP=neuropathic pain; PR=pain response; THC= delta tetrahydrocannabinol

*Newly included since the original 2020 systematic review.

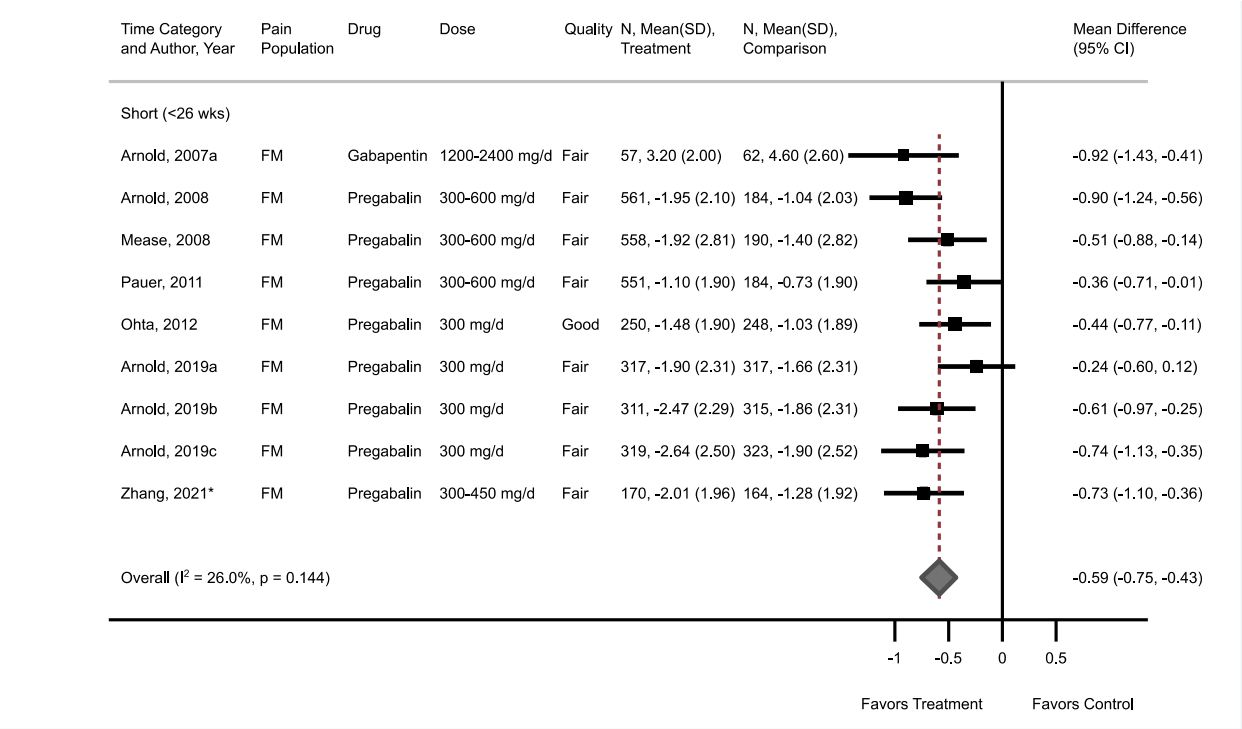
Figure H-2. NPP pain, gabapentin/pregabalin versus duloxetine



Abbreviations: CI=confidence interval; d=day; DPN=diabetic painful neuropathy; mg=milligrams; NPP=neuropathic pain; SD=standard deviation; wks=weeks

*Newly included since the original 2020 systematic review.

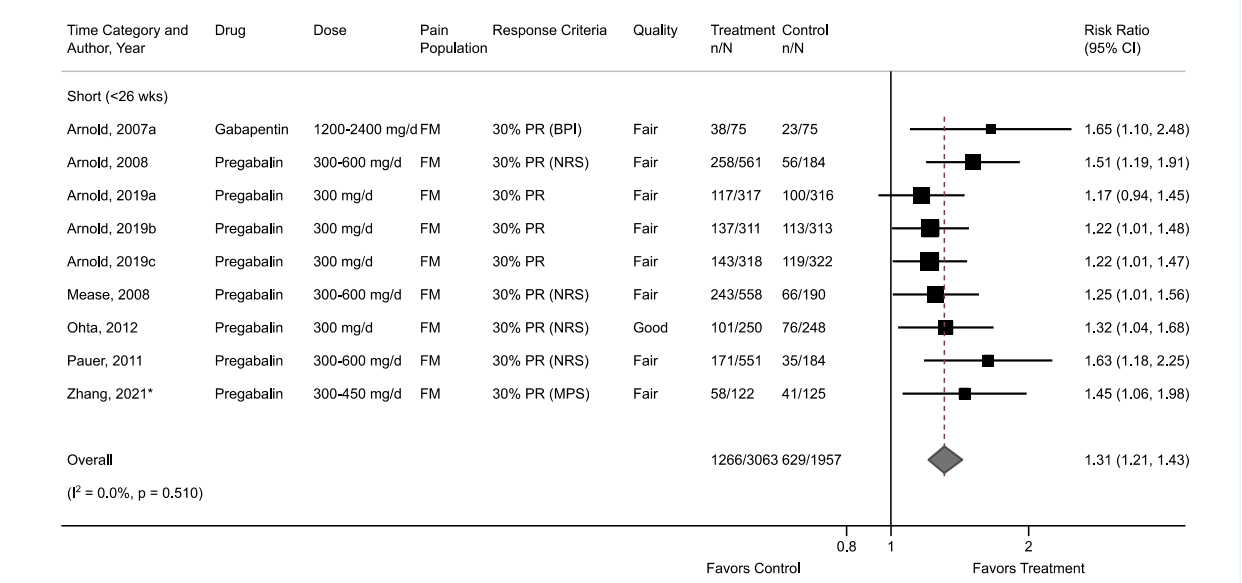
Figure H-3. FM pain, gabapentin/pregabalin versus placebo



Abbreviations: CI=confidence interval; d=day; FM=fibromyalgia; mg=milligrams; SD=standard deviation; wks=weeks

*Newly included since the original 2020 systematic review.

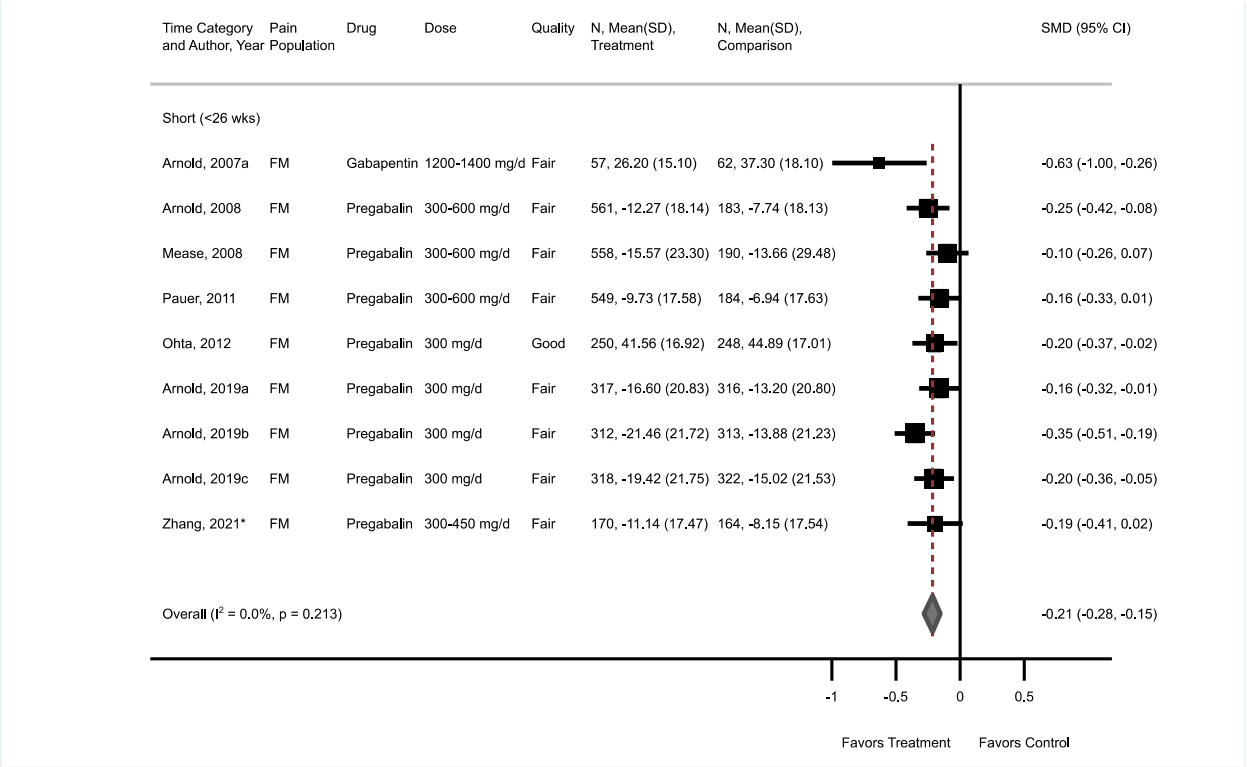
Figure H-4. FM response, gabapentin/pregabalin versus placebo



Abbreviations: BPI=Brief Pain Inventory; CI=confidence interval; d=day; FM=fibromyalgia; mg=milligrams; MPS=Mean Pain Score; NRS=Numeric Rating Scale; PR=pain response; SD=standard deviation; wks=weeks

*Newly included since the original 2020 systematic review.

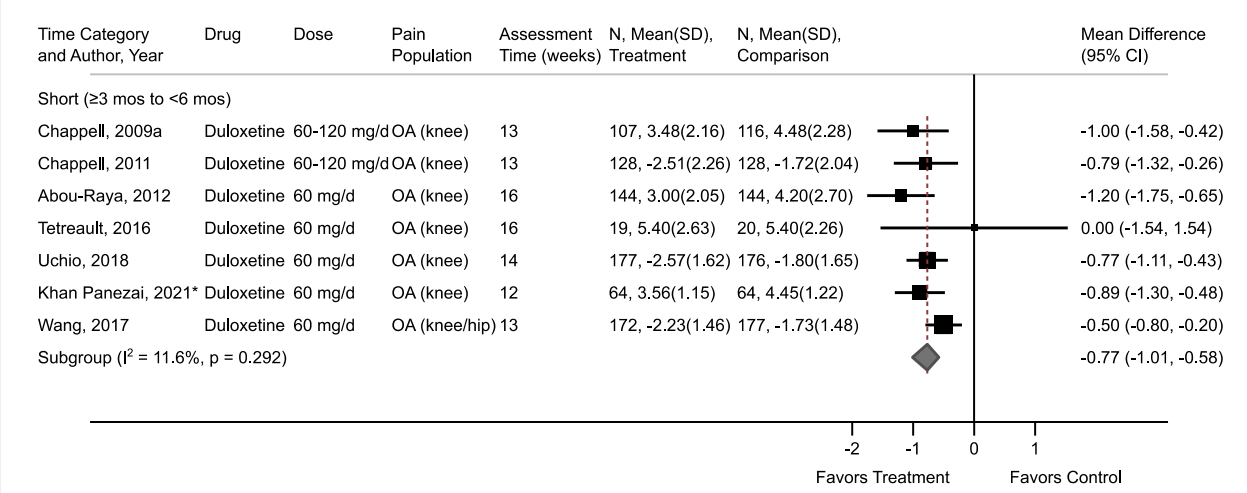
Figure H-5. FM function, gabapentin/pregabalin versus placebo



Abbreviations: CI=confidence interval; d=day; FM=fibromyalgia; mg=milligrams; SD=standard deviation; SMD=standardized mean difference; wks=weeks

*Newly included since the original 2020 systematic review.

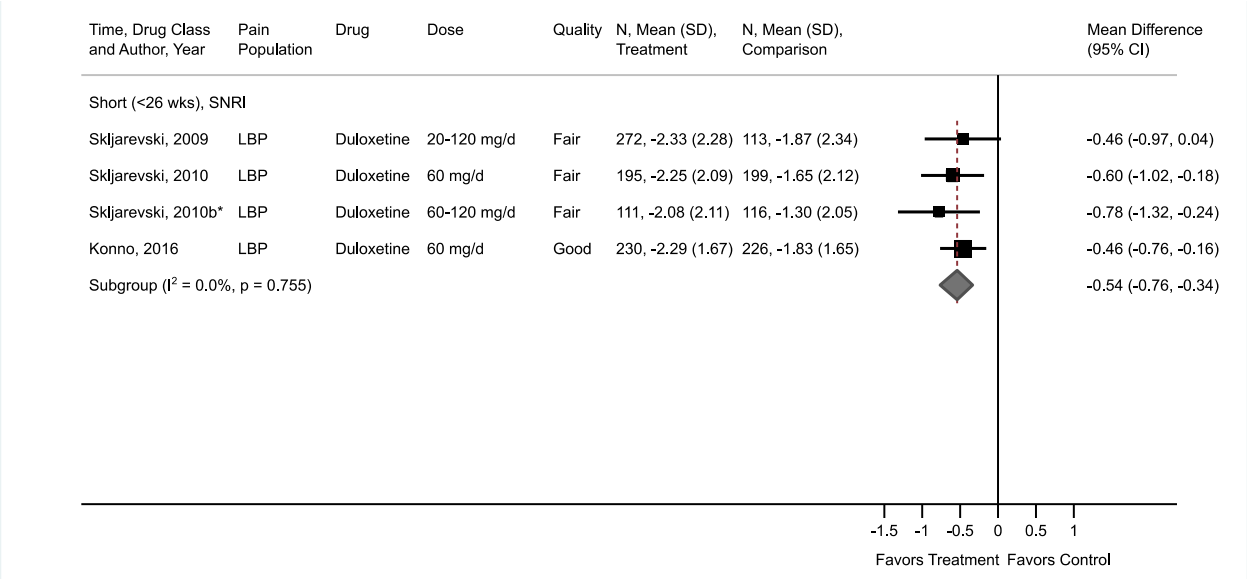
Figure H-6. OA pain, SNRI versus placebo



Abbreviations: CI=confidence interval; d=day; mg=milligrams; OA=osteoarthritis; SD=standard deviation; SNRI=selective serotonin and norepinephrine reuptake inhibitor; mos=months

*Newly included since the original 2020 systematic review.

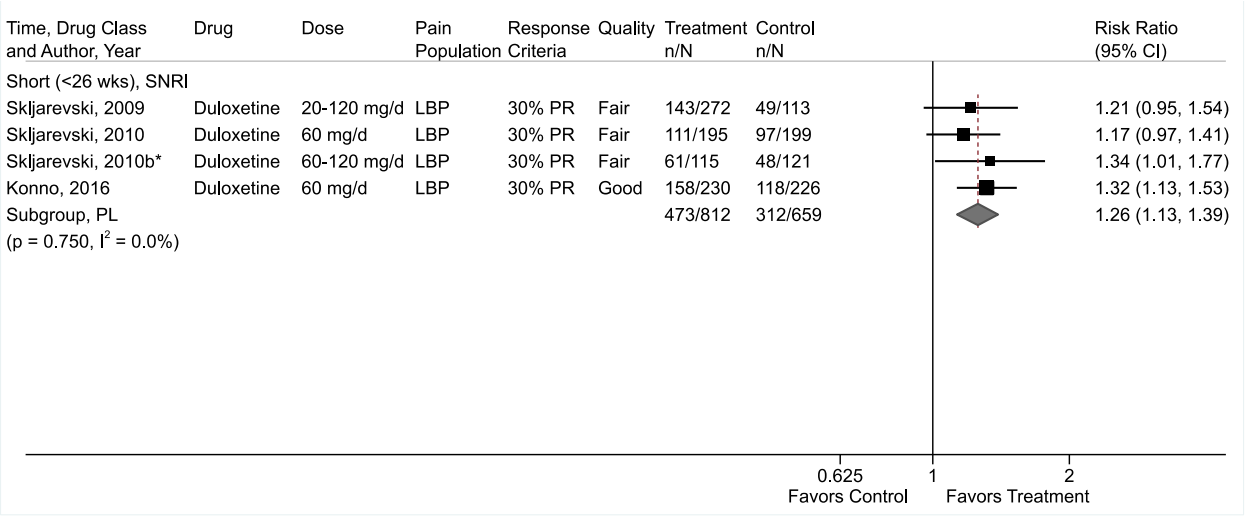
Figure H-7. LBP pain, SNRI versus placebo



Abbreviations: CI=confidence interval; d=day; mg=milligrams; LBP=low back pain; SD=standard deviation; SNRI=selective serotonin and norepinephrine reuptake inhibitor; wks=weeks

*Newly included since the original 2020 systematic review.

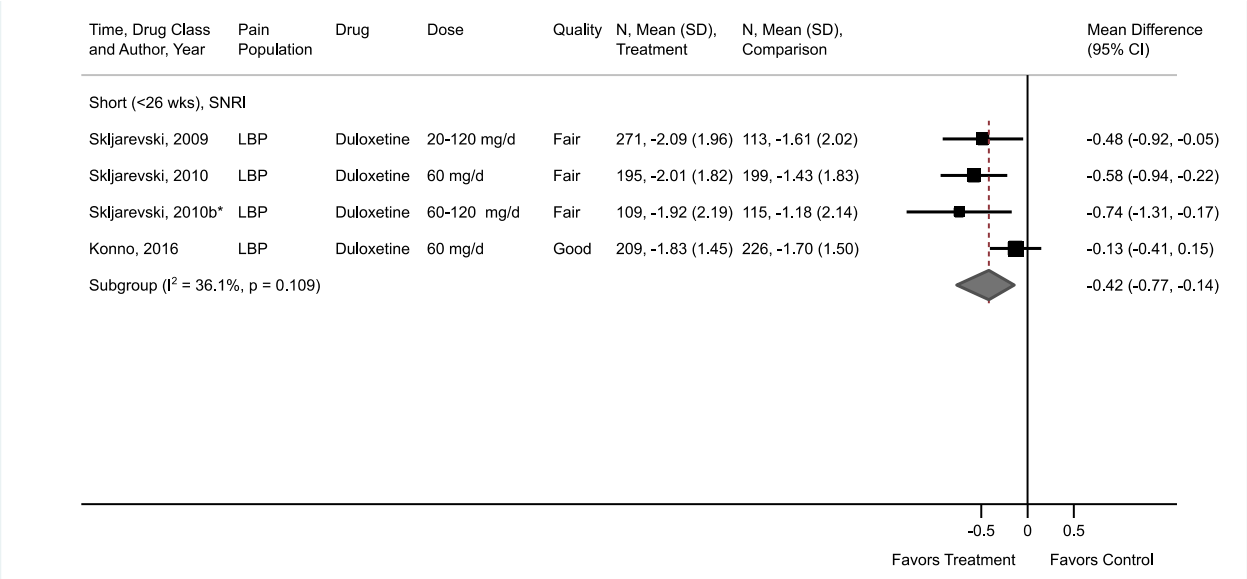
Figure H-8. LBP response, SNRI versus placebo



Abbreviations: CI=confidence interval; d=day; mg=milligrams; LBP=low back pain; PL=profile likelihood; PR=pain response; SNRI=selective serotonin and norepinephrine reuptake inhibitor; TCA=tricyclic antidepressants; wks=weeks

*Newly included since the original 2020 systematic review.

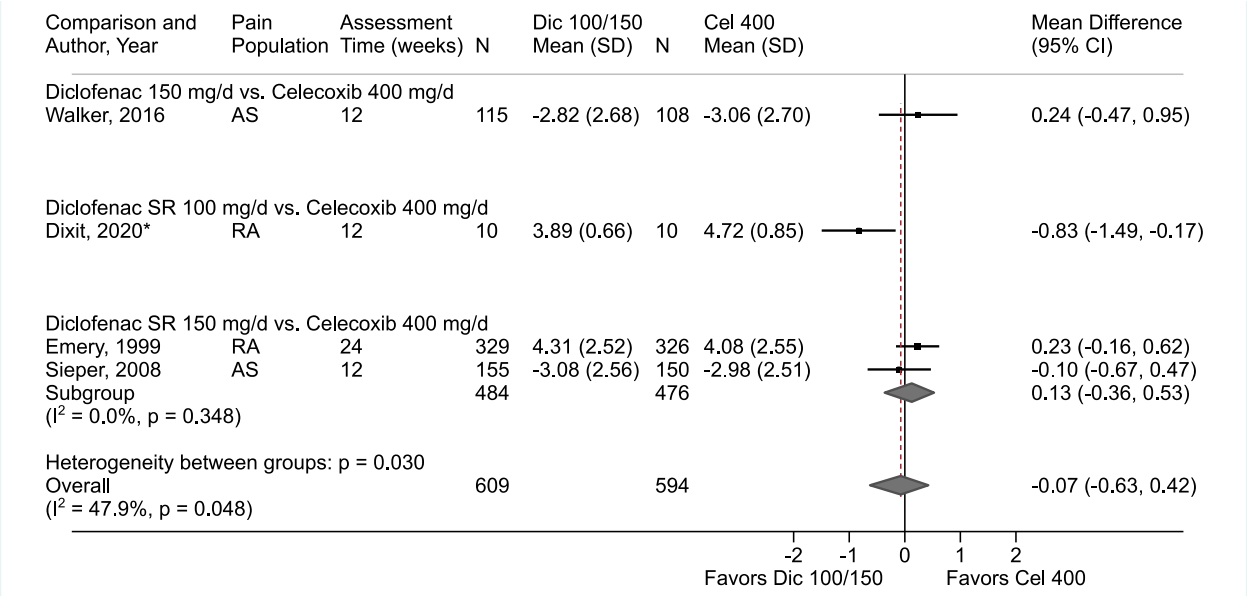
Figure H-9. LBP function, SNRI versus placebo



Abbreviations: CI=confidence interval; d=day; mg=milligrams; LBP=low back pain; SD=standard deviation; SNRI=selective serotonin and norepinephrine reuptake inhibitor; TCA=tricyclic antidepressants; wks=weeks

*Newly included since the original 2020 systematic review.

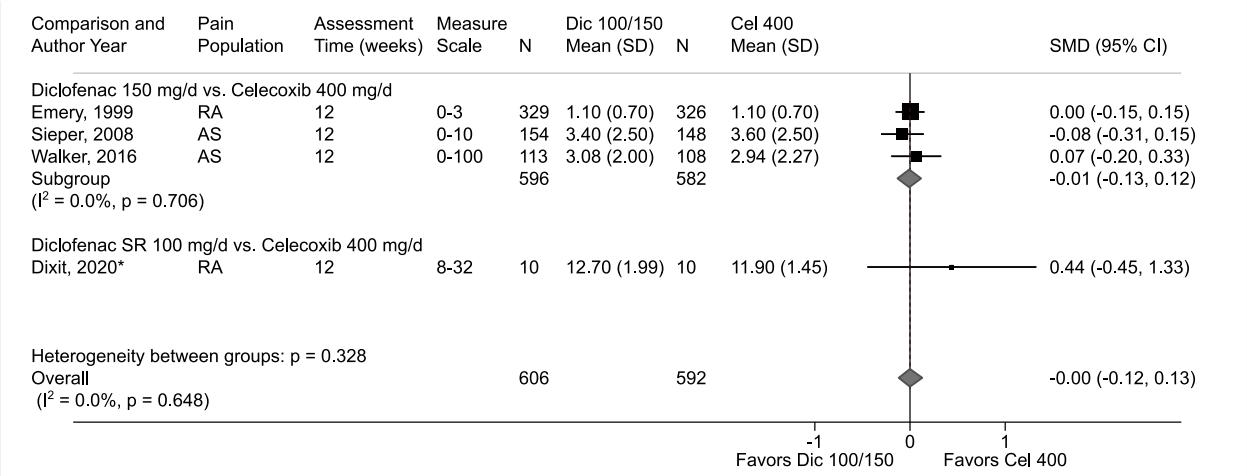
Figure H-10. RA head-to-head pain, Dic 100/150 versus Cel 400



Abbreviations: AS=ankylosing spondylitis; Cel=celecoxib; CI=confidence interval; d=day; mg=milligrams; Dic=diclofenac; RA=Rheumatoid arthritis; SD=standard deviation

*Newly included since the original 2020 systematic review.

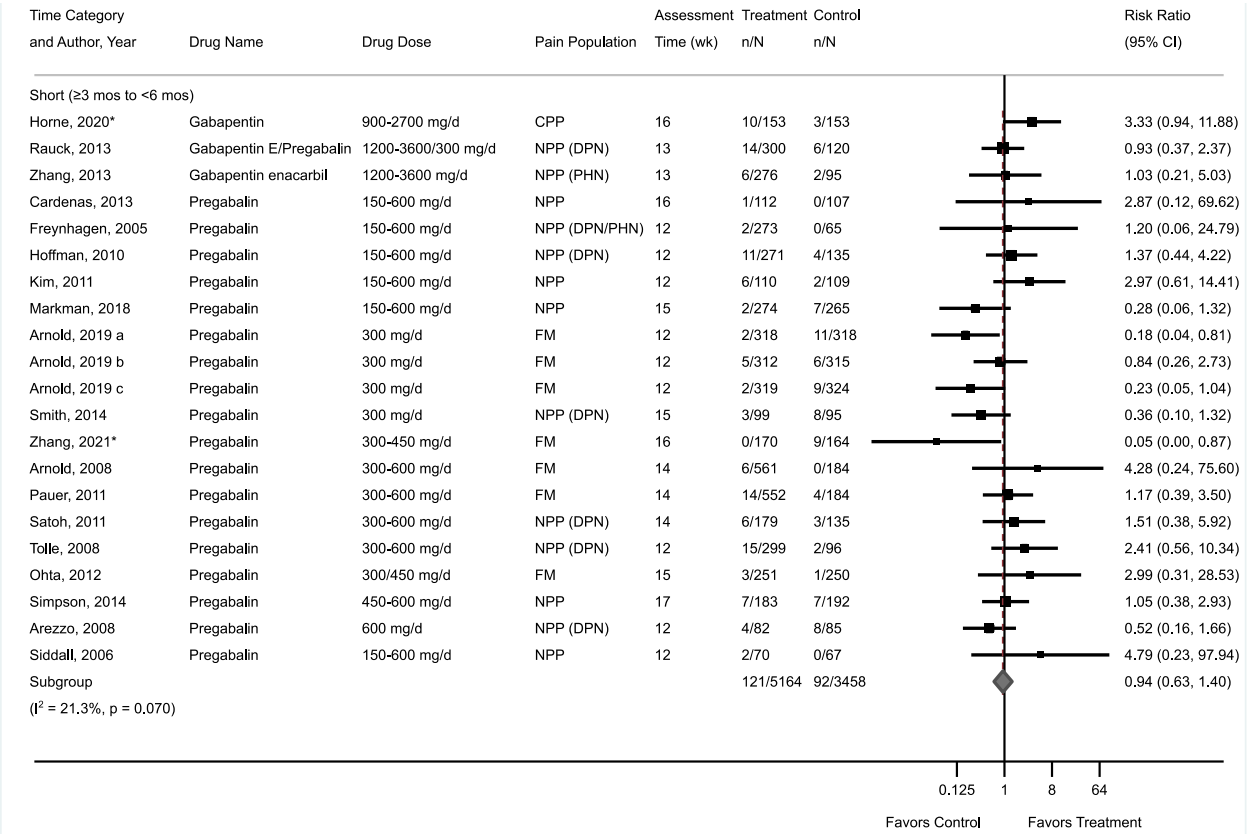
Figure H-11. RA head-to-head function, Dic 100/150 versus Cel 400



Abbreviations: AS=ankylosing spondylitis; Cel=celecoxib; CI=confidence interval; d=day; mg=milligrams; Dic=diclofenac; RA=Rheumatoid arthritis; SD=standard deviation; SMD=standardized mean difference

*Newly included since the original 2020 systematic review.

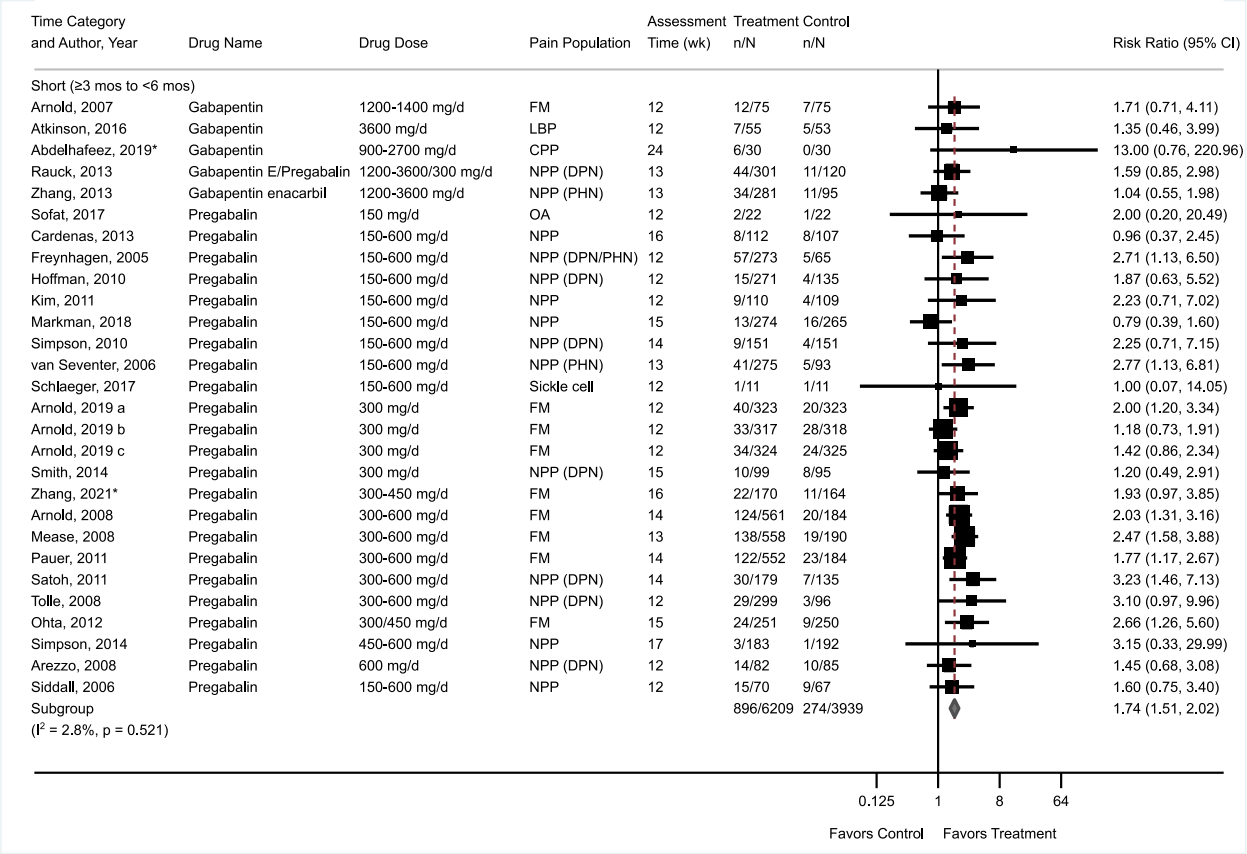
Figure H-12. Gabapentin/pregabalin harms, SAE



Abbreviations: CI=confidence interval; CPP=chronic pelvic pain; d=day; DPN=diabetic painful neuropathy; FM=fibromyalgia; LBP=low back pain; mg=milligrams; mos=months; NPP=Neuropathic pain; OA=osteoarthritis; SAE=serious adverse event; wk=weeks

*Newly included since the original 2020 systematic review.

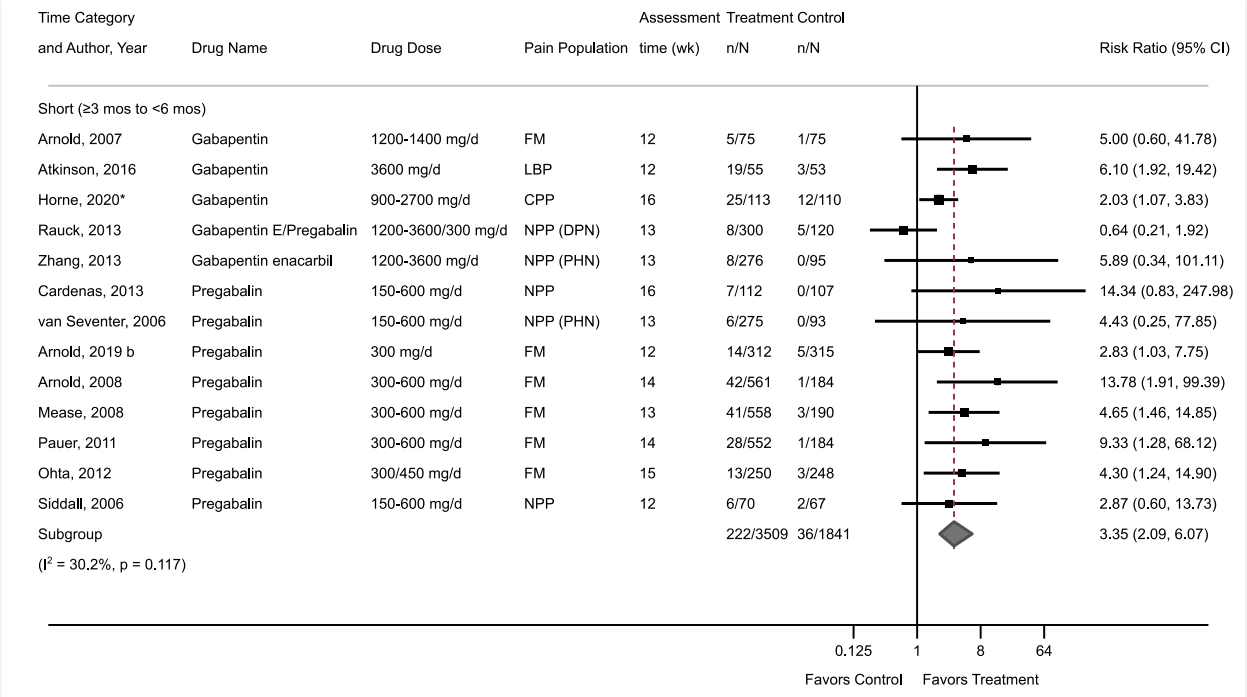
Figure H-13. Gabapentin/pregabalin harms, WAE



Abbreviations: CI=confidence interval; CPP=chronic pelvic pain; d=day; DPN=diabetic painful neuropathy; FM=fibromyalgia; LBP=low back pain; mg=milligrams; mos=months; NPP=Neuropathic pain; OA=osteoarthritis; PHN=postherpetic neuralgia; WAE=withdrawal due to adverse event; wk=weeks

*Newly included since the original 2020 systematic review.

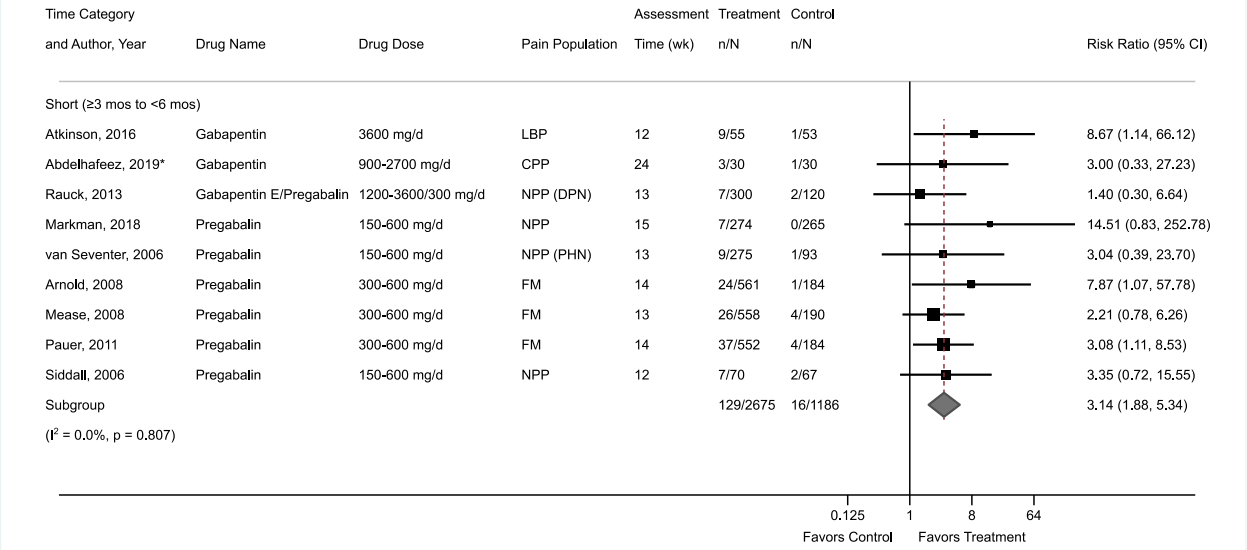
Figure H-14. Gabapentin/pregabalin harms, blurred vision



Abbreviations: CI=confidence interval; CPP=chronic pelvic pain; d=day; DPN=diabetic painful neuropathy; FM=fibromyalgia; LBP=low back pain; mg=milligrams; mos=months; NPP=Neuropathic pain; PHN=postherpetic neuralgia; wk=weeks

*Newly included since the original 2020 systematic review.

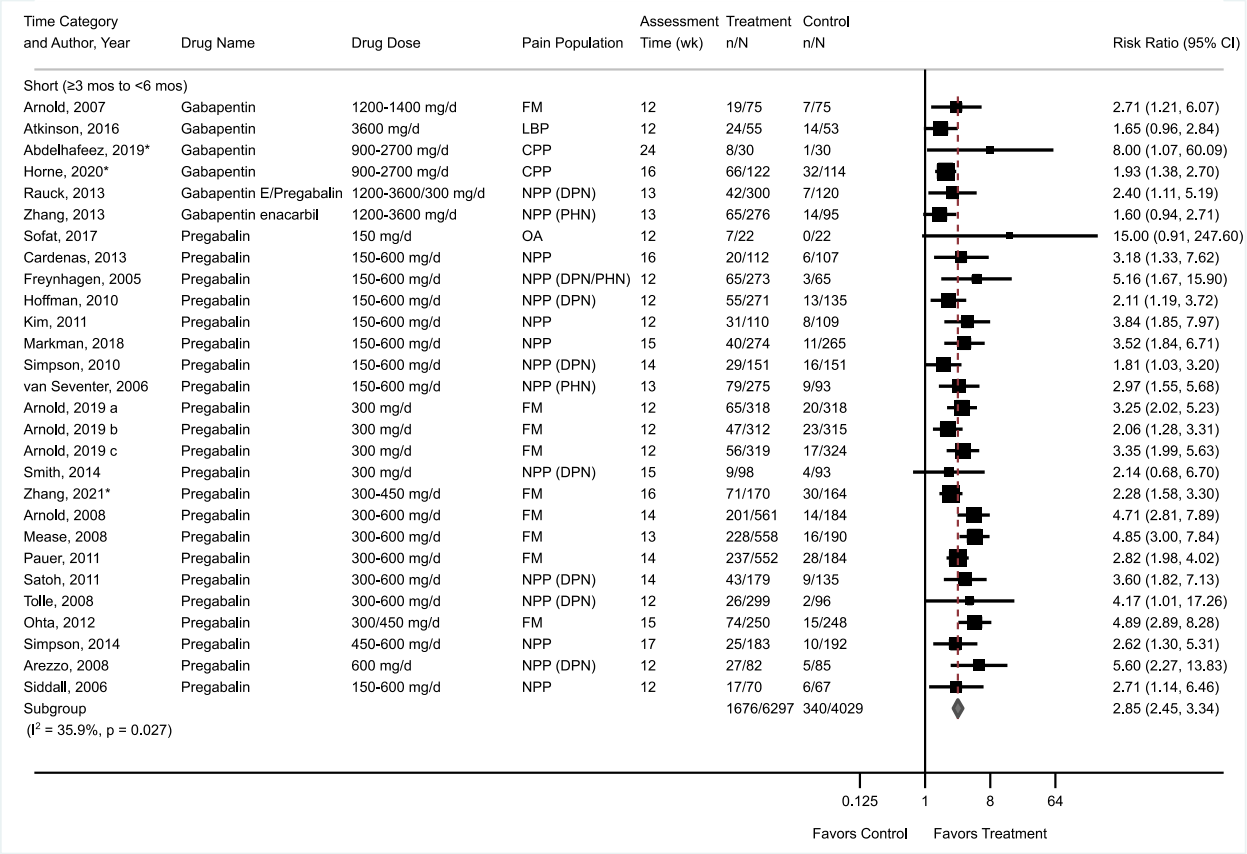
Figure H-15. Gabapentin/pregabalin harms, cognitive effects



Abbreviations: CI=confidence interval; CPP=chronic pelvic pain; d=day; DPN=diabetic painful neuropathy; FM=fibromyalgia; LBP=low back pain; mg=milligrams; mos=months; NPP=Neuropathic pain; PHN=postherpetic neuralgia; wk=weeks

*Newly included since the original 2020 systematic review.

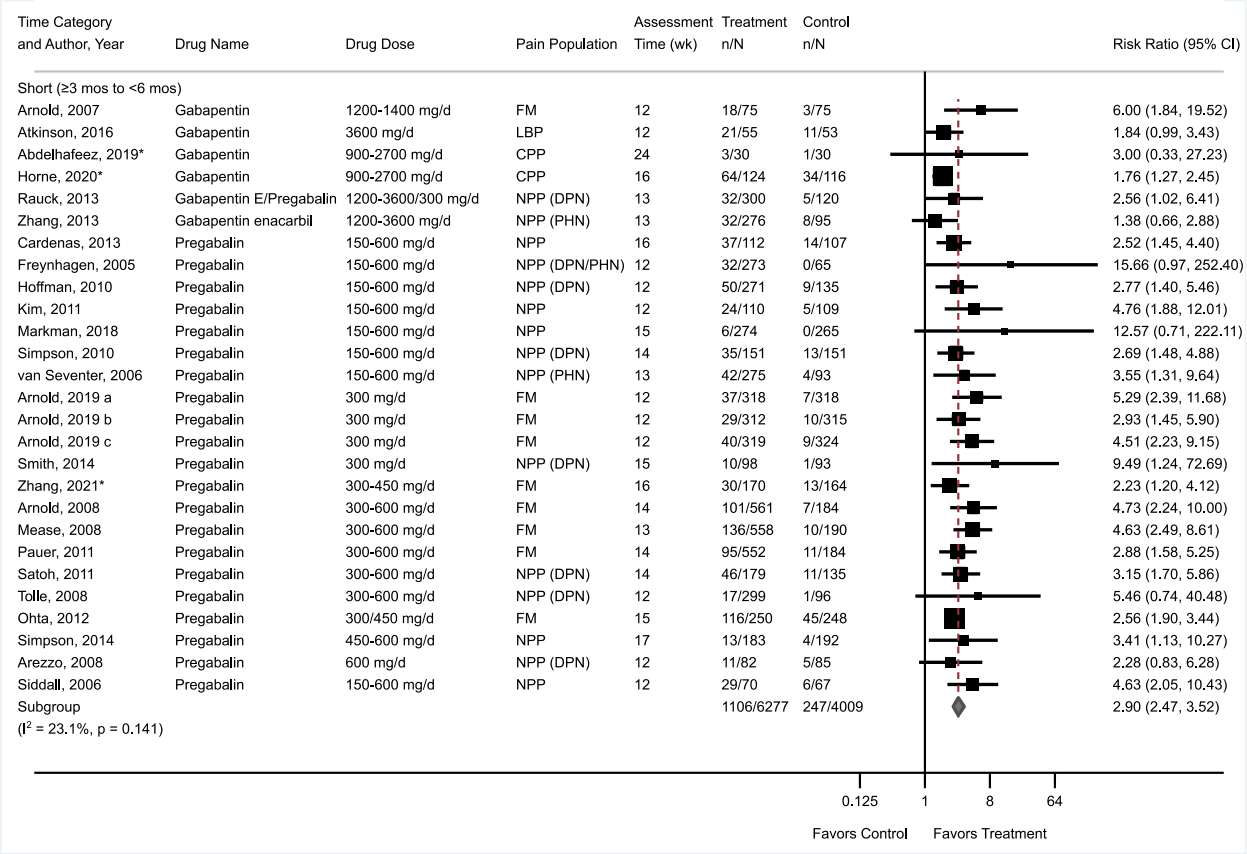
Figure H-16. Gabapentin/pregabalin harms, dizziness



Abbreviations: CI=confidence interval; CPP=chronic pelvic pain; d=day; DPN=diabetic painful neuropathy; FM=fibromyalgia; LBP=low back pain; mg=milligrams; mos=months; NPP=Neuropathic pain; OA=osteoarthritis; PHN=postherpetic neuralgia; wk=weeks

*Newly included since the original 2020 systematic review.

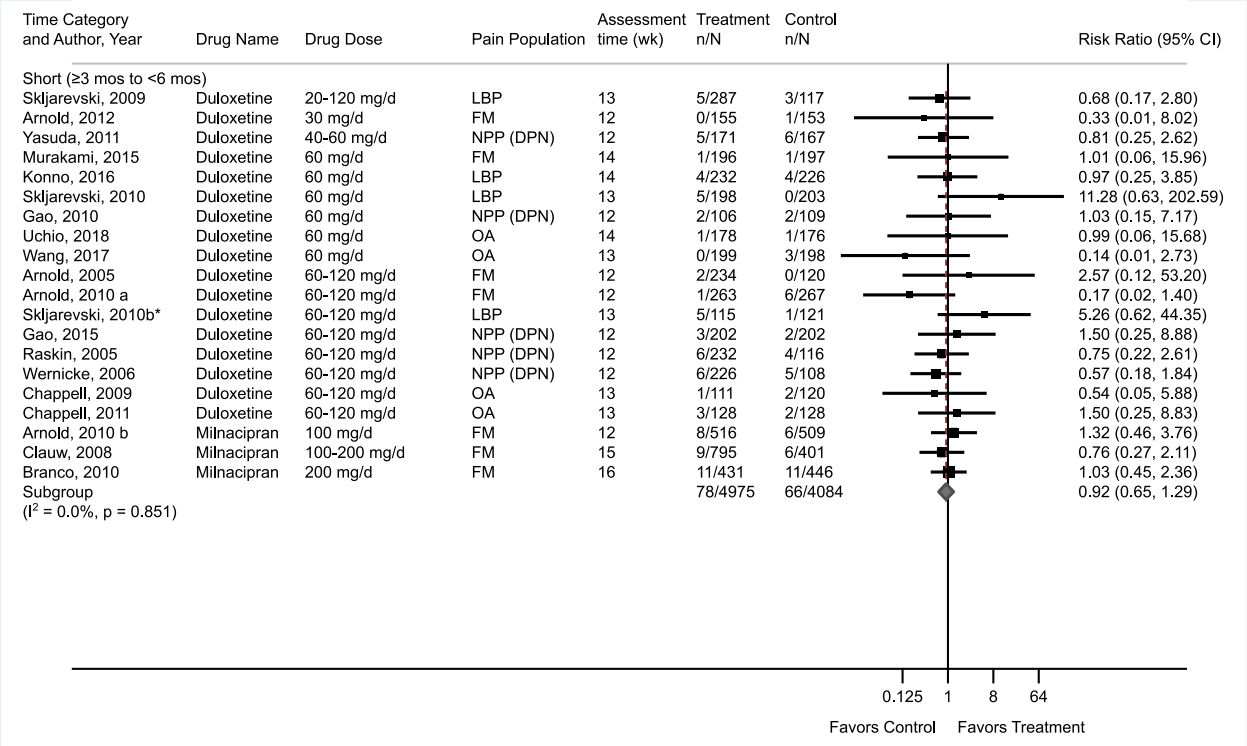
Figure H-17. Gabapentin/pregabalin harms, sedation



Abbreviations: CI=confidence interval; CPP=chronic pelvic pain; d=day; DPN=diabetic painful neuropathy; FM=fibromyalgia; LBP=low back pain; mg=milligrams; mos=months; NPP=Neuropathic pain; PHN=postherpetic neuralgia; wk=weeks

*Newly included since the original 2020 systematic review.

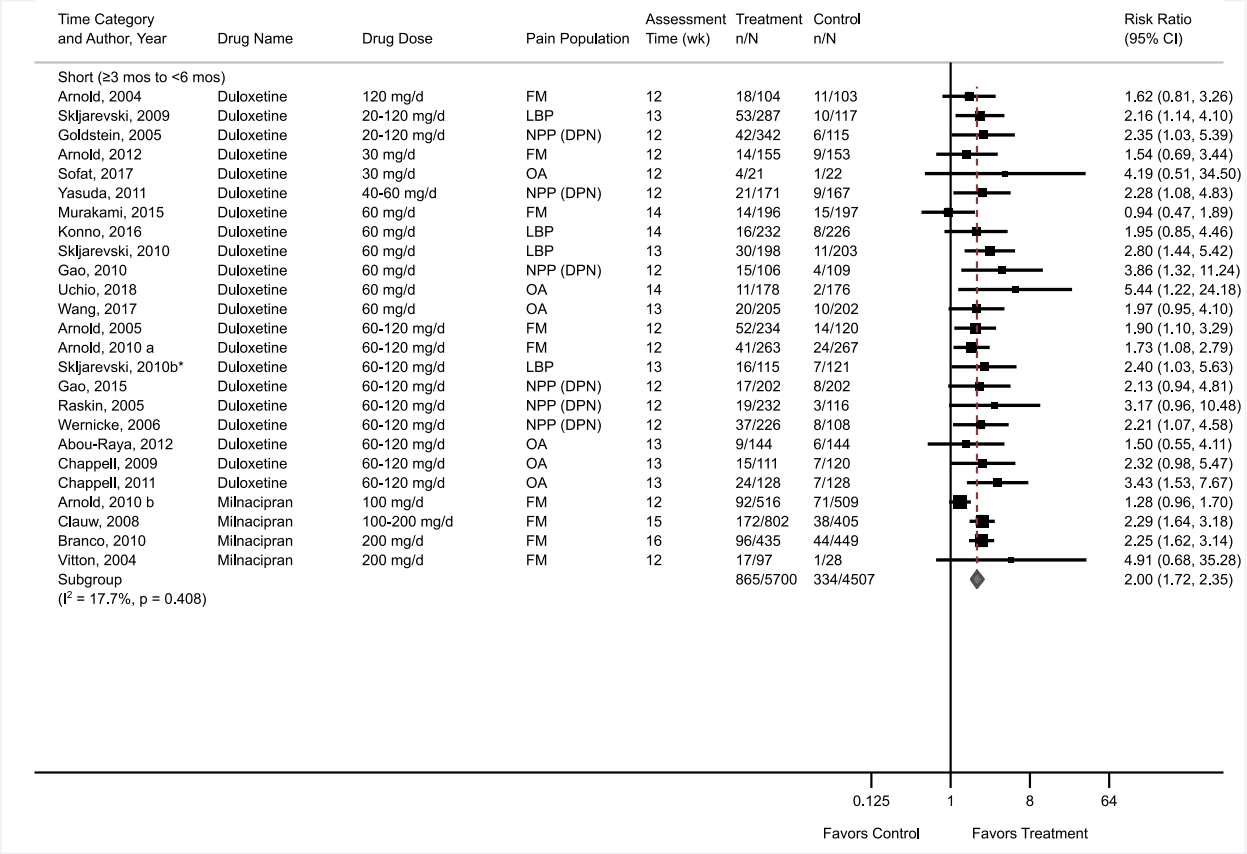
Figure H-18. SNRI harms, SAE



Abbreviations: CI=confidence interval; d=day; DPN=diabetic painful neuropathy; FM=fibromyalgia; LBP=low back pain; mg=milligrams; mos=months; NPP=Neuropathic pain; OA=osteoarthritis; SAE=serious adverse event; SNRI=selective serotonin and norepinephrine reuptake inhibitor; wk=weeks

*Newly included since the original 2020 systematic review.

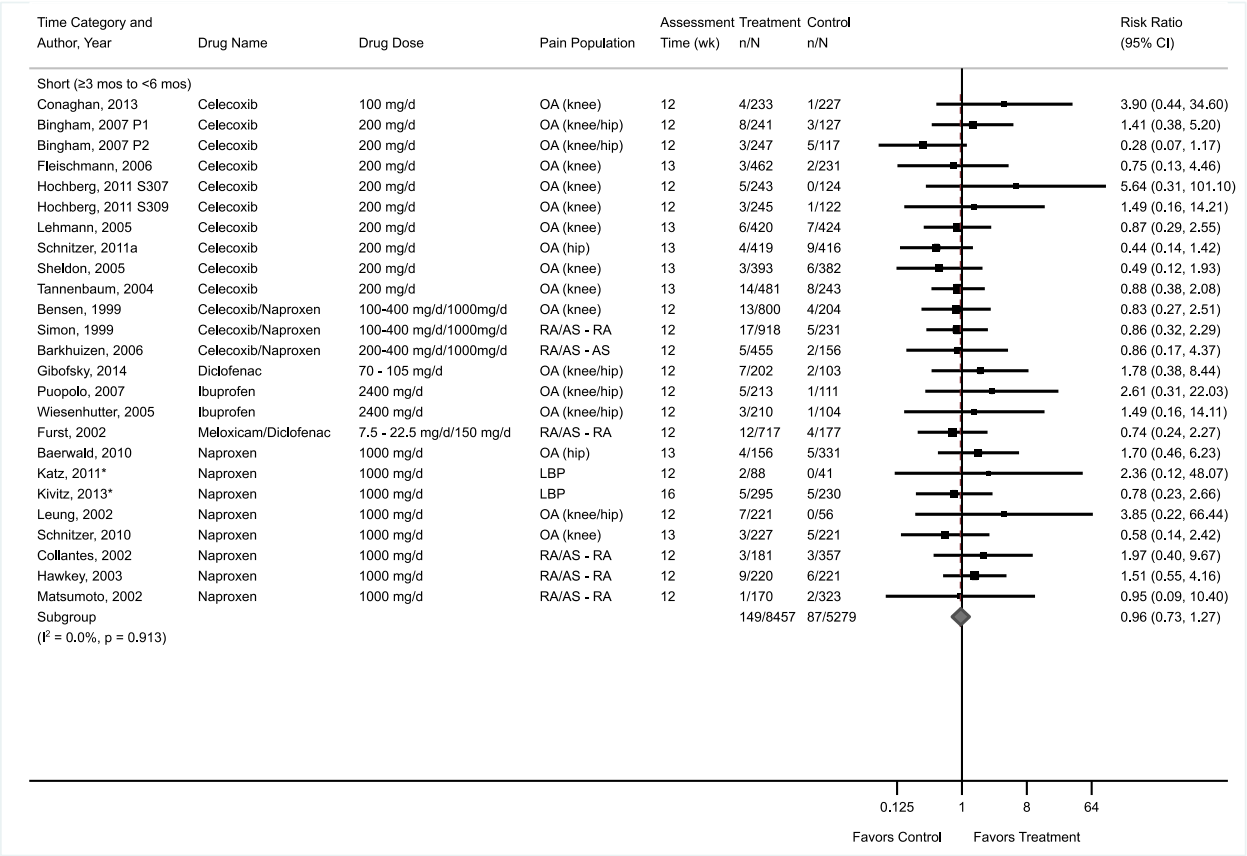
Figure H-19. SNRI harms, WAE



Abbreviations: CI=confidence interval; d=day; DPN=diabetic painful neuropathy; FM=fibromyalgia; LBP=low back pain; mg=milligrams; mos=months; NPP=Neuropathic pain; OA=osteoarthritis; SNRI=selective serotonin and norepinephrine reuptake inhibitor; WAE=withdrawal due to adverse event; wk=weeks

*Newly included since the original 2020 systematic review.

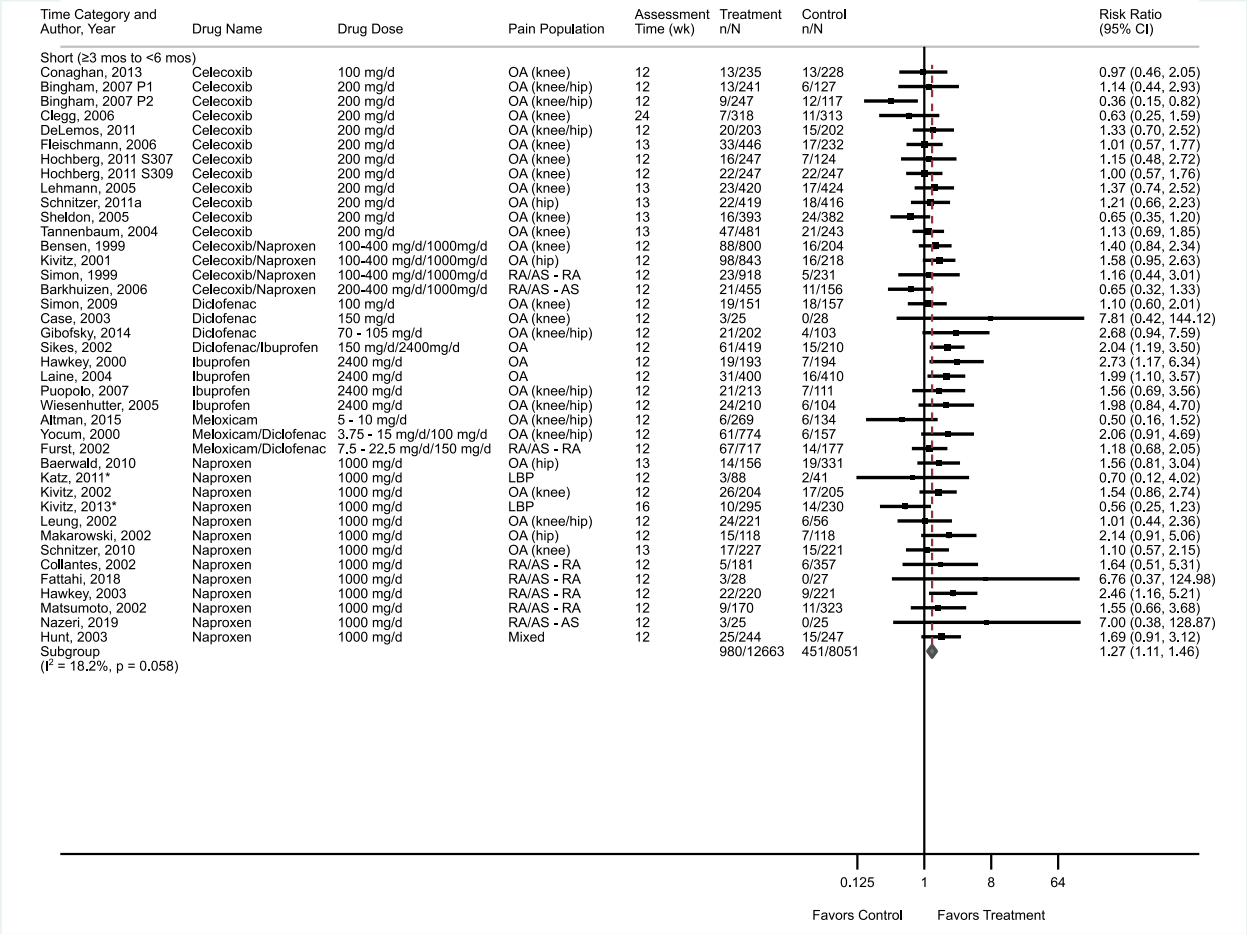
Figure H-20. NSAID harms, SAE



Abbreviations: AS=ankylosing spondylitis; CI=confidence interval; d=day; LBP=low back pain; mg=milligrams; mos=months; NSAID=non-steroidal anti-inflammatory drugs; OA=osteoarthritis; RA=rheumatoid arthritis; SAE=serious adverse event; wk=weeks

*Newly included since the original 2020 systematic review.

Figure H-21. NSAID harms, WAE



Abbreviations: AS=ankylosing spondylitis; CI=confidence interval; d=day; LBP=low back pain; mg=milligrams; mos=months; NSAID=non-steroidal anti-inflammatory drugs; OA=osteoarthritis; RA=Rheumatoid arthritis; WAE=withdrawal due to adverse event; wk=weeks

*Newly included since the original 2020 systematic review.

Appendix I. Strength of Evidence Table

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

Type of Pain; Comparison	Outcome	Duration	Number of Studies (n Participants)	Study Quality†	Directness	Consistency	Precision	Main Findings Effect Size (95% CI)	SOE
Neuropathic pain Cannabis vs. placebo	Pain Improvement (Continuous)	Short	3 (825)	Fair	Direct	Consistent	Imprecise	No effect (NRS) Cannabis vs. placebo Effect less than -0.2 points improvement in all studies	Low
	Pain Response‡ (Dichotomous)	Short	2 (585)	Fair	Direct	Consistent	Imprecise	Small effect (≥30%) Cannabis vs. placebo: 40.3% vs. 33.2%; RR 1.30 (0.88 to 1.94), I^2=59%	Low
	Pain Response‡ (Dichotomous)	Short	2 (585)	Fair	Direct	Consistent	Imprecise	No effect (BPI) Cannabis vs. placebo p=0.18, p=0.56	Low
Neuropathic pain Gabapentin/ pregabalin vs. duloxetine	Pain Improvement (Continuous)	Short	3 (449)	Fair	Direct	Inconsistent	Precise	Small effect Gabapentin/pregabalin vs. duloxetine; MD 0.22 (-0.56 to 0.93) I^2=78%	Low
Fibromyalgia Pregabalin vs. placebo	Pain Improvement (Continuous)	Short	9 (5,081)	Fair	Direct	Consistent	Precise	Small effect (0-10 scale) MD -0.59 (-0.75 to -0.43), I^2=26%	Moderate
	Pain Response‡ (Dichotomous)	Short	9 (5,020)	Fair	Direct	Consistent	Precise	Small effect (≥30%) 41.3% vs. 32.1%; RR 1.31 (1.21 to 1.43), I^2=0%	Moderate
	Function	Short	9 (5,074)	Fair	Direct	Consistent	Precise	Small effect (FIQ 0-80 or 0-100) SMD -0.21 (-0.28 to -0.15), I^2=0%	Moderate
Osteoarthritis Duloxetine vs. placebo	Pain Improvement (Continuous)	Short	7 (1,636)	Good	Direct	Consistent	Precise	Small effect (0 to10 scale) MD -0.77 (-1.01 to -0.58), I^2=12%	High
Low back pain Duloxetine vs. placebo	Pain Improvement (Continuous)	Short	4 (1,462)	Fair	Direct	Consistent	Precise	Small effect (BPI Pain Scale) MD -0.54 (-0.76 to -0.34), I^2=0%	Moderate
	Pain Response‡ (Dichotomous)	Short	4 (1,451)	Fair	Direct	Consistent	Imprecise	Small effect RR 1.26 (1.13 to 1.39), I^2=0%	Low
	Function	Short	4 (1,437)	Fair	Direct	Consistent	Precise	No effect (BPI Interference Scale) MD -0.42 (-0.77 to -0.14), I^2=36%	Moderate

Type of Pain; Comparison	Outcome	Duration	Number of Studies (n Participants)	Study Quality†	Directness	Consistency	Precision	Main Findings Effect Size (95% CI)	SOE
Low back pain NSAIDs vs. placebo	Pain Improvement (Continuous)	Short	2 (654)	Fair	Direct	Inconsistent	Imprecise	Naproxen vs. placebo (p=0.037, p=0.277)	Insufficient
	Pain Response‡ (Dichotomous)	Short	2 (654)	Fair	Direct	Consistent	Imprecise	Naproxen vs. placebo (p=0.009, p=0.369)	Insufficient
	Function	Short	2 (654)	Fair	Direct	Consistent	Imprecise	Naproxen vs. placebo (p=0.405, p=0.305)	Insufficient
Inflammatory arthritis Diclofenac vs. celecoxib	Pain Improvement (Continuous)	Short	4 (1,203)	Fair	Direct	Consistent	Precise	No effect (0-10 scale) Diclofenac 100/150 mg/day vs. celecoxib 400 mg/day: MD -0.07 (-0.63 to 0.42), I^2=48%	Moderate
	Function	Short	4 (1,198)	Fair	Direct	Consistent	Precise	No effect (mHAQ; BASFI) Diclofenac 100/150 mg/d vs. celecoxib 400 mg/d: SMD -0.00 (-0.12 to 0.13), I^2=0%	Moderate
Pregabalin/ Gabapentin vs. Placebo	SAE	Short	21 (8,622)	Fair	Direct	Consistent	Imprecise	No effect 2.3% vs. 2.7%; RR 0.94 (0.63 to 1.40), I^2=21%	Low
	WAE	Short	28 (10,148)	Fair	Direct	Consistent	Precise	Moderate effect 14.4% vs. 7.0%; RR 1.74, (1.51 to 2.02), I^2=3%	Moderate
	Blurred Vision	Short	13 (5,350)	Fair	Direct	Consistent	Imprecise	Large effect 6.3% vs. 2.0%; RR 3.35 (2.09 to 6.07), I^2=30%	Low
	Cognitive Effects	Short	9 (3,861)	Fair	Direct	Consistent	Imprecise	Large effect 4.8% vs. 1.3%; RR 3.14 (1.88 to 5.34), I^2=0%	Low
	Dizziness	Short	28 (10,326)	Fair	Direct	Consistent	Precise	Large effect 26.6% vs. 8.4%; RR 2.85 (2.43 to 3.34, I^2=36%	Moderate
	Sedation	Short	27 (10,286)	Fair	Direct	Consistent	Precise	Large effect 17.6% vs. 6.2%; RR 2.90 (2.47 to 3.52), I^2=23%	Moderate
Capsaicin vs. placebo	WAE	Short	3 (1,075)	Good	Direct	Consistent	Imprecise	Large effect 0.96% vs. 0.22%; RR 2.20 (0.37 to 12.91), I^2=8%	Moderate

Type of Pain; Comparison	Outcome	Duration	Number of Studies (n Participants)	Study Quality†	Directness	Consistency	Precision	Main Findings Effect Size (95% CI)	SOE
Cannabis (THC 2.7m/microL + CBD 2.5gm/microL) vs. placebo	SAE	Short	2 (585)	Fair	Direct	Consistent	Imprecise	No effect 10.5% vs. 6.9%; RR 1.54 (0.90 to 2.64), I^2=0%	Low
	WAE	Short	2 (585)	Fair	Direct	Consistent	Imprecise	Large effect 12.9% vs. 5.5%; RR 2.25 (1.16 to 4.39), I^2=27%	Low
	Dizziness	Short	2 (585)	Fair	Direct	Consistent	Imprecise	Large effect 28.5% vs. 6.2%; RR 4.48 (2.77 to 7.22), I^2=0%	Low
	Nausea	Short	2 (585)	Fair	Direct	Consistent	Imprecise	Large effect 11.9% vs. 5.5%; RR 2.11 (1.20 to 3.72), I^2=0%	Low
	Sedation	Short	2 (585)	Fair	Direct	Consistent	Imprecise	Large effect 6.8% vs. 1.0%; RR 5.84 (1.90 to 17.92), I^2=0%	Low
SNRIs vs. Placebo	SAE	Short	20 (9,059)	Fair	Direct	Consistent	Imprecise	No effect 1.6% vs. 2.6%; RR 0.92 (0.65 to 1.29), I^2=0%	Low
	WAE	Short	25 (10,207)	Fair	Direct	Consistent	Precise	Moderate effect 15.2% vs. 7.4%; RR 2.00 (1.72 to 2.35), I^2=18%	Moderate
NSAIDs vs. Placebo	SAE	Short	25 (13,736)	Fair	Direct	Consistent	Imprecise	No effect 1.8% vs. 1.6%; RR 0.96 (0.73 to 1.27), I^2=0%	Low
	WAE	Short	40 (20,714)	Fair	Direct	Consistent	Precise	Small effect 7.7% vs, 5.6%; RR 1.27 (1.11 to 1.46), I^2=18%	Moderate

Abbreviations: BASFI=Bath Ankylosing Spondylitis Functional Index; BPI=Brief Pain Inventory; CBD=cannabidiol; CI=confidence interval; MD=mean difference; mHAQ=modified Health Assessment Questionnaire; NRS=numeric rating scale; RR=risk ratio; SAE=serious adverse events; SMD=standard mean difference; SOE=strength of evidence; THC=delta tetrahydrocannabinol; WAE=withdrawals due to adverse events

* Reporting bias was undetected or unknown for all Key Questions/outcomes

†Study Quality: poor-quality studies not synthesized, however none of the studies identified for the surveillance were rated poor-quality.

‡Pain Response main findings, percentages represent threshold for Pain Response