

# Systematic Review on Nonopioid Pharmacologic Treatments for Chronic Pain: Surveillance Report 2

Literature Update Period: October 2021 through December 2021

## Background and Purpose

This is the second update for the 2020 report *Nonopioid Pharmacologic Treatments for Chronic Pain* (<https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research>),<sup>1</sup> covering the period October through December 2021. 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 September 2021 and to determine how the new evidence impacts findings of the 2020 report and Surveillance Report 1, which added evidence from September 2019 through September 2021 and was published on the Agency for Healthcare Research and Quality (AHRQ) website (<https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research>). A subsequent update is planned for April 2022 (based on evidence published before March 2022).

## Scope

The scope and eligibility criteria established at the time of the original report<sup>1</sup> 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<sup>®</sup> MEDLINE<sup>®</sup>, Embase<sup>®</sup>, PsycINFO<sup>®</sup>, CINAHL<sup>®</sup>, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews to identify evidence published from October 2021 through December 2021. Search strategies from the original report were utilized.<sup>1</sup> In addition, to capture articles not yet indexed in MEDLINE, we supplemented the original search strategies with a previously developed<sup>2</sup> 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, to increase efficiency of abstract review, we utilized a machine learning classifier in conjunction with a second investigator to assist in conducting dual reviews. The machine learning classifier was previously shown to have 100 percent recall for identifying eligible studies in update searches for this review.<sup>2</sup> The machine learning classifier screened all citations; the second investigator performed dual review on all studies that the machine learning classifier did not classify as very low probability of eligibility. Any citation identified as potentially eligible by either investigator 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<sup>3</sup> and outlined in the AHRQ Methods Guide chapter “Assessing the Risk

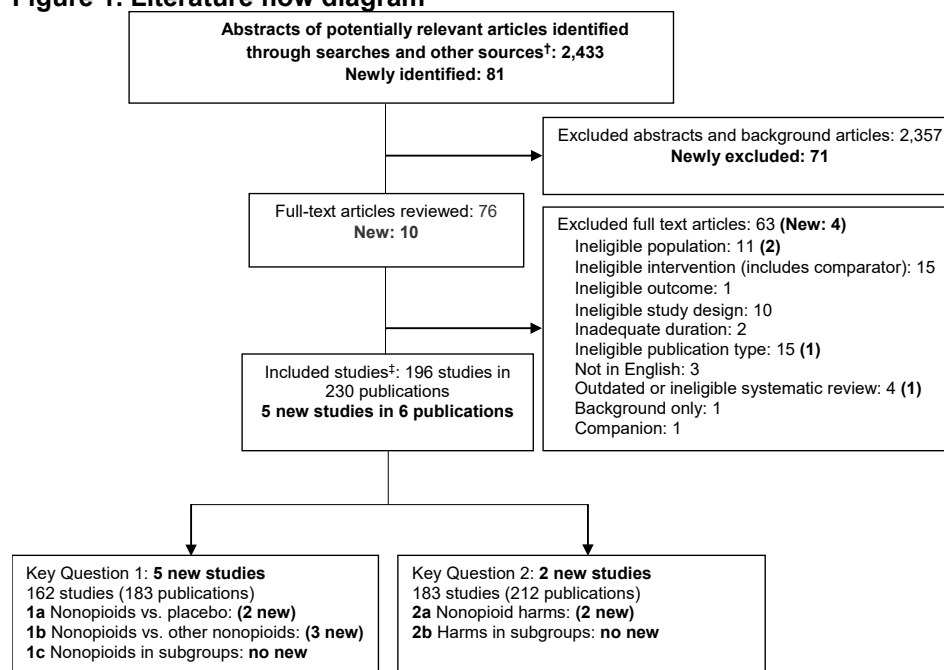
of Bias of Individual Studies When Comparing Medical Interventions.”<sup>4,5</sup> The decision to update meta-analyses from the original report was based on the number and sample sizes of new studies eligible for meta-analysis (meta-analysis performed if new evidence was large relative to the studies in the original meta-analysis); consistency in findings between the new studies and the original meta-analysis (meta-analysis performed if findings from new evidence appear inconsistent and new studies were appropriate for pooling based on similarity in populations, interventions, and comparisons, in order to determine whether new studies impact conclusions); or whether new evidence could impact the strength of evidence (SOE) (meta-analysis performed if the SOE based on the original meta-analysis was low or insufficient and new evidence could increase the SOE due to increased precision, quality, or other factors). The 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. Changes in the SOE assessments resulting from this current surveillance update are described separately from the findings reported in Surveillance Report 1.

A list of included studies identified for this update is provided in [Appendix C](#). A list of articles excluded at full-text review along with reasons for exclusion is available in [Appendix D](#). Evidence tables providing data from included studies are available in [Appendixes E and F](#), and quality assessments for each study are shown in [Appendix G](#).

## Results

The search for Surveillance Report 2 from October through December 2021 yielded 81 citations, and identified five new eligible studies (in 6 publications): two good-quality<sup>6-8</sup> and three fair-quality<sup>9-11</sup> (Figure 1). All were randomized controlled trials (RCTs): two trials in neuropathic pain (gabapentin/pregabalin vs. duloxetine),<sup>8,11</sup> one in inflammatory arthritis (diclofenac vs. meloxicam vs. celecoxib),<sup>10</sup> and two in chronic pelvic pain (gabapentin vs. placebo).<sup>6,7,9</sup>

**Figure 1. Literature flow diagram\***



†Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.

‡Some studies were included for multiple Key Questions.

## Summary of Findings

- Five new, short-term RCTs were identified for Surveillance Report 2; four of the new trials (indicated by an asterisk in the bulleted list) evaluated comparisons not previously evaluated for specific pain conditions.

### Neuropathic Pain:

- One new trial was consistent with prior evidence that found no differences in pain intensity between gabapentin and duloxetine.
- One new trial found no differences in pain intensity between pregabalin and duloxetine.\*

### Chronic Pelvic Pain:

- One new trial found no differences between gabapentin and placebo on pain, while another new trial found gabapentin associated with improved pain intensity versus placebo.\* One trial found no improvement with gabapentin on quality of life and activity versus placebo\*

### Inflammatory Arthritis:

- One new trial found no differences in pain outcomes between diclofenac, meloxicam, and celecoxib.\*

## Harms:

- Two new trials reported harms of gabapentin versus placebo. Consistent with prior evidence, gabapentin was associated with increased risk of dizziness, sedation, visual disturbances, cognitive effects, and withdrawals due to adverse events in one or both trials. One trial found increased risk of serious adverse events with gabapentin. (The other new trial did not report serious adverse events.) This was inconsistent with a prior meta-analysis of 19 trials that found no effect (along with 1 additional RCT identified in Surveillance Report 1). Due to the small sample size relative to the prior meta-analysis, this study did not change conclusions.

## 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 report. 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>). New evidence identified for Surveillance Report 2 also included one new SOE rating where none existed before (no differences between gabapentin and placebo in quality of life and activity in chronic pelvic pain, SOE: low).

With the addition of one new RCT from Surveillance Report 2, the SOE rating for no difference between gabapentin and duloxetine in pain improvement in patients with neuropathic pain was changed from insufficient to low. Surveillance Report 2 also identified two studies in women with chronic pelvic pain, representing a new pain category for this report.

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

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 <ul style="list-style-type: none"> <li>SOE: Low, based on 2 RCTs</li> </ul>	1 RCT (n=339) 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. <sup>12</sup>	No change in conclusions
	KQ1. Capsaicin patch versus lidocaine patch versus placebo patch short-term	No studies	1 RCT (n=179) found capsaicin patch associated with pain improvement compared with placebo. <sup>13</sup>	Improved pain with capsaicin patch compared with placebo (SOE: Low)*
	KQ1. Lidocaine patch versus placebo patch short-term	No studies	1 RCT (n=184) found no difference in lidocaine versus placebo in pain improvement. <sup>13</sup>	Effect of lidocaine patch (SOE: Insufficient)
	KQ1. Pregabalin versus amitriptyline versus combination short-term	No studies	1 RCT (n=110) found no differences between monotherapy with pregabalin or amitriptyline or combination therapy in pain improvement. <sup>14</sup>	Differences between pregabalin, amitriptyline, and combination therapy (SOE: Insufficient)

Type of Pain or Harm	Key Question	Conclusions From 2020 Report	Findings From Surveillance Reports	Assessment
Neuropathic pain	KQ1. Pregabalin CR tablet versus pregabalin IR capsule short-term	No studies	1 RCT (n=352) 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. <sup>15</sup>	Differences between pregabalin CR tablet and pregabalin IR capsule (SOE: Insufficient)
	<b>KQ1. Pregabalin versus duloxetine short-term: New evidence from SR 2</b>	<b>No studies</b>	<b>1 new RCT (n=161) found no differences in pain improvement between pregabalin and duloxetine.<sup>11</sup></b>	<b>Differences between pregabalin and duloxetine (SOE: Insufficient)</b>
	<b>KQ1. Gabapentin versus duloxetine short-term: New evidence from SR 2</b>	<b>No differences in pain improvement between gabapentin and duloxetine</b> <ul style="list-style-type: none"> <li>• <b>SOE: Insufficient, based on 1 RCT</b></li> </ul>	<b>1 new RCT (n=86) found no difference between gabapentin and duloxetine on pain improvement.<sup>8</sup></b>	<b>No differences between gabapentin and duloxetine (SOE: Low)<sup>†</sup></b>
Fibromyalgia	KQ1. Pregabalin versus placebo short-term	Pregabalin was associated a small reduction in pain <ul style="list-style-type: none"> <li>• SOE: Moderate, based on 8 RCTs</li> </ul>	1 new RCT (n=343) found pregabalin associated with improved pain, pain response, and sleep interference but no improvement in anxiety or depression scores versus placebo. <sup>16</sup>	No change in conclusions
Osteoarthritis	KQ1. Nortriptyline versus placebo short-term	No studies	1 RCT (n=205) found no difference between nortriptyline versus placebo in pain improvement, function, or quality of life in knee osteoarthritis. <sup>17</sup>	Effect of nortriptyline (SOE: Insufficient)
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 <ul style="list-style-type: none"> <li>• SOE: Insufficient, based on 1 RCT</li> </ul>	1 RCT (n=70) found no effect of desipramine versus placebo on pain. <sup>18</sup>	No change in conclusions
Chronic pelvic pain	<b>KQ1. Gabapentin versus placebo: New evidence from SR 2</b>	<b>No studies</b>	<b>2 new RCTs (n=366) found mixed results on pain outcomes with gabapentin compared with placebo.<sup>6,7,9</sup></b>  <b>1 new RCT (n=306) found no differences between gabapentin and placebo on quality of life and activity.<sup>6,7</sup></b>	<b>Effect of gabapentin on pain (SOE: Insufficient)<sup>†</sup></b>  <b>No effect of gabapentin on quality of life and activity (SOE: Low)<sup>†</sup></b>

Type of Pain or Harm	Key Question	Conclusions From 2020 Report	Findings From Surveillance Reports	Assessment
Inflammatory arthritis	<b>KQ1. Diclofenac versus Meloxicam versus Celecoxib: New evidence from SR 2</b>	<p><i>No differences between diclofenac and celecoxib on pain improvement, pain response, or function</i></p> <ul style="list-style-type: none"> <li>• <i>SOE: Moderate, based on 3 RCTs</i></li> </ul> <p><i>No differences between diclofenac and meloxicam on pain improvement</i></p> <ul style="list-style-type: none"> <li>• <i>SOE: Low, based on 1 RCT</i></li> </ul> <p><i>No studies compared meloxicam and celecoxib</i></p>	<i>1 new RCT (n=30) found no differences between diclofenac and meloxicam and celecoxib on pain improvement and function.<sup>10</sup></i>	<p><i>No change in SOE for diclofenac versus celecoxib, and diclofenac versus meloxicam</i></p> <p><i>Meloxicam versus celecoxib (SOE: Insufficient)<sup>†</sup></i></p>
Harms	KQ2. TCAs short-term	<p>Dry mouth more likely with amitriptyline</p> <ul style="list-style-type: none"> <li>• <i>SOE: Insufficient, based on 1 RCT</i></li> </ul>	1 RCT (n=70) found no increase in SAEs, nausea, or sedation but a nonsignificant increase in dry mouth with desipramine; <sup>18</sup> 1 new RCT (n=201) found no difference in SAEs but increased dry mouth with nortriptyline. <sup>17</sup>	<p>Increased dry mouth with TCAs (SOE: Low)*</p> <p>Evidence on other adverse events (SOE: Insufficient)</p>
	<b>KQ2. Anticonvulsants short-term: New evidence from SR 2</b>	<p><i>No increased risk of SAEs</i></p> <ul style="list-style-type: none"> <li>• <i>SOE: Low, based on 19 RCTs</i></li> </ul> <p><i>Moderate increase in WAEs</i></p> <ul style="list-style-type: none"> <li>• <i>SOE: Moderate, based on 26 RCTs</i></li> </ul> <p><i>Large increase in cognitive AEs</i></p> <ul style="list-style-type: none"> <li>• <i>SOE: Low, based on 8 RCTs</i></li> </ul> <p><i>Large increase in dizziness, peripheral edema, sedation, and weight gain</i></p> <ul style="list-style-type: none"> <li>• <i>SOE: Moderate, based on 21-25 RCTs</i></li> </ul>	<p><i>1 RCT (n=334) found no increase in risk of having any AE or SAE, but increased risk of dizziness and somnolence.<sup>16</sup></i></p> <p><i>2 RCTs (n=366) found increased risk of dizziness.<sup>6,7,9</sup></i></p> <p><i>1 RCT (n=306) found increased risk of SAEs, sedation, and visual disturbances.<sup>6,7</sup></i></p> <p><i>1 RCT (n=60) found increased risk of WAEs and nonsignificantly increased risk of sedation and cognitive effects.<sup>9</sup></i></p>	<i>No change in conclusions</i>
	KQ2. Topical capsaicin short-term	<p>Topical capsaicin resulted in moderate increase in application site erythema and a large increase in application site pain with no increase in WAEs, SAEs, or application site pruritus</p> <ul style="list-style-type: none"> <li>• <i>SOE: Moderate, based on 3 RCTs</i></li> </ul>	1 RCT (n=179) found capsaicin patch associated with increased withdrawals due to treatment-emergent AEs. <sup>13</sup>	No change in conclusions
	KQ2. Topical lidocaine short-term	No studies	1 RCT (n=184) found lidocaine patch associated with no increase in withdrawals due to treatment-emergent AEs. <sup>13</sup>	WAEs with lidocaine (SOE: Insufficient)

Type of Pain or Harm	Key Question	Conclusions From 2020 Report	Findings From Surveillance Reports	Assessment
Harms	KQ2. Cannabis (oral/oromucosal) short-term	Dronabinol associated with no increase in SAEs, WAEs, or nausea; oral THC/CBD associated with large increase in WAEs, dizziness, nausea, but no increase in SAEs or sedation <ul style="list-style-type: none"> <li>• SOE: Low based on 2 RCTs</li> </ul>	1 RCT (n=339) found increased risk of any AE, dizziness, somnolence and a nonsignificant increase in risk of nausea with THC/CBD. <sup>12</sup>	No change in conclusions

Abbreviations: AE = adverse event; CBD = cannabidiol; CR = controlled release; IR = immediate release; KQ = Key Question; RCT = randomized controlled trial; SAE = serious adverse events; 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

## Evidence Details

### Key Question 1: Benefits

#### Neuropathic Pain

One new good-quality head-to-head RCT (n=86) found no differences between gabapentin and duloxetine in pain improvement in patients with diabetic neuropathy (mean difference [MD] on the 0–100 Visual Analogue Scale [VAS] 5.23, 95% confidence interval [CI], -1.70 to 12.17).<sup>8</sup> Results were similar for the diabetic neuropathic examination score, the diabetic neuropathic score, and the neuropathic disability score. These results are consistent with a prior RCT included in the original report.

One new fair-quality head-to-head RCT (n=161) found no differences between pregabalin and duloxetine in pain improvement in patients with diabetic neuropathy (MD on the 0–10 VAS 0.72, p=0.90).<sup>11</sup> There was no evidence comparing pregabalin and duloxetine for neuropathic pain in the prior report.

#### Chronic Pelvic Pain

Two new RCTs compared gabapentin versus placebo for chronic pelvic pain in women. One good-quality RCT (n=306) found no differences in worst and average numerical rating scale score (adjusted MD -0.20, 97.5% CI, -0.81 to 0.42; adjusted MD -0.18, 97.5% CI, -0.71 to 0.35, respectively).<sup>6,7</sup> There were also no differences in quality of life and activity scores.

The second, fair-quality RCT (n=60) found gabapentin associated with decreased pain intensity (MD on the 0–10 VAS -1.63, p<0.001) and increased likelihood of 30-percent improvement in pain (95% vs. 35.7%, relative risk [RR] 0.50, 95% CI, 0.34 to 0.75) versus placebo, but attrition was high.<sup>9</sup>

The SOE for pain outcomes is insufficient due to inconsistency between the two trials. The SOE (based on 1 RCT) for no difference between gabapentin and placebo on quality of life and activity is low. There were no studies in chronic pelvic pain patients in the prior report.



## Inflammatory Arthritis

One fair-quality RCT (n=30) compared diclofenac versus meloxicam versus celecoxib in patients with rheumatoid arthritis.<sup>10</sup> There were no differences between diclofenac, meloxicam, and celecoxib on pain (% change VAS: 35.0% vs. 34.5% vs. 27.7%, p value not reported) and function (% change Modified Health Assessment Questionnaire: 25.3% vs. 28.2% vs. 25.8%, p value not reported).

## Key Question 2: Harms

### Anticonvulsants

One good-quality RCT (n=306)<sup>6,7</sup> and one fair-quality RCT (n=60)<sup>9</sup> of gabapentin versus placebo were consistent with previous evidence that found gabapentin associated with increased risk of dizziness (54% vs. 28%,  $p<0.001$ ;<sup>6,7</sup> 26.7% vs. 3.3%,  $p=0.03$ ,<sup>9</sup> respectively). New evidence was also consistent with previous evidence in finding gabapentin associated with increased risk of study withdrawal due to adverse events (1 RCT, 20% vs. 0%,  $p<0.05$ ),<sup>9</sup> visual disturbances (1 RCT, 22% vs. 11%,  $p=0.01$ ),<sup>6,7</sup> and sedation (2 RCTs, 52% vs. 29%,  $p=0.002$ ; 10% vs. 3.3%,  $p=0.605$ ).<sup>6,7,9</sup> One RCT found gabapentin associated with increased risk of serious adverse events compared with placebo (7% vs. 2%,  $p=0.04$ ).<sup>6,7</sup> A prior meta-analysis of 19 trials found no association between gabapentin/pregabalin and risk of serious adverse events (n=7,982, 2.3% vs. 2.5%, RR 0.90, 95% CI, 0.63 to 1.30,  $I^2=0\%$ ), and the new evidence was judged to not change these conclusions due to inconsistency in the new RCTs and small sample size relative to the studies in the meta-analysis.<sup>1</sup> One RCT found increased risk of poor concentration (10% vs. 3.3%,  $p=0.605$ ) with gabapentin versus placebo that was not statistically significant<sup>9</sup> but is consistent with a prior meta-analysis of eight trials that found increased cognitive effects (n=3,801, 4.8% vs. 1.3%, RR 3.15, 95% CI, 1.86 to 5.51,  $I^2=0\%$ ) with gabapentin/pregabalin.<sup>1</sup> Due to the number of trials and sample sizes of pooled estimates, conclusions and SOE regarding gabapentin/pregabalin and increased risk of cognitive effects and sedation were unchanged (low SOE for large increase in risk for cognitive effects, moderate SOE for large increase in risk for sedation).

## Conclusions

A systematic review and two subsequent surveillance updates have found nonopioid drugs (mainly serotonin-norepinephrine reuptake inhibitor antidepressants, pregabalin/gabapentin, and nonsteroidal anti-inflammatory drugs [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. 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.

New evidence from Surveillance Report 2 was largely consistent with the original report. However, two RCTs for chronic pelvic pain were identified, which represents a new pain category for this review. These two RCTs suggest no difference between gabapentin and placebo on quality of life and activity (low SOE).

New evidence found that there may be no difference in pain improvement between gabapentin and duloxetine in patients with neuropathic pain (SOE upgraded from insufficient to low).

The next surveillance report is scheduled for April 2022.

## References

1. McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid Pharmacologic Treatments for Chronic Pain. Comparative Effectiveness Review No. 228. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC010. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.
2. Chou R, Dana T, Shetty KD. Testing a Machine Learning Tool for Facilitating Living Systematic Reviews of Chronic Pain Treatments. Methods Research Report. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I and the Southern California Evidence-based Practice Center-RAND Corporation under Contract No. 290-2015-00010-I.) AHRQ Publication No. 21-EHC004. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.
3. Furlan AD, Malmivaara A, Chou R, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)*. 2015 Nov;40(21):1660-73. doi: 10.1097/BRS.0000000000001061. PMID: 26208232.
4. Viswanathan M, Patnode CD, Berkman ND, et al. Assessing the risk of bias in systematic reviews of health care interventions. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research and Quality; 2017.
5. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research Quality; Jan 2014. <https://effectivehealthcare.ahrq.gov/topics/ce-r-methods-guide/overview> Accessed February 1, 2019. PMID: 21433403.
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. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.

14. 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.
15. 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.
16. 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.
17. 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.
18. 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.

# Authors

Shelley Selph, M.D., M.P.H.  
Marian McDonagh, Pharm.D.  
Miranda Pappas, M.A.  
Erica Hart, M.S.T.  
Tracy Dana, M.L.S.  
Kim Mauer, M.D.  
Roger Chou, M.D.

# Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: research associate Christina Bougatsos, M.P.H., and student research assistant Jacqueline Boyd, M.P.H., both from Oregon Health & Science University; and Task Order Officer Suchitra Iyer, Ph.D., at the Agency for Healthcare Research and Quality.

# Disclaimers

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

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

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

This report is made available to the public under the terms of a licensing agreement between the author and the Agency for Healthcare Research and Quality. This report may be used and reprinted without permission except those copyrighted materials that are clearly noted in the report. Further reproduction of those copyrighted materials is prohibited without the express permission of copyright holders.

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

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

**Suggested citation:** Selph S, McDonagh M, Pappas M, Hart E, Dana T, Mauer K, Chou R. Systematic Review on Nonopioid Pharmacologic Treatments for Chronic Pain: Surveillance Report 2. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 22-EHC015. Rockville, MD: Agency for Healthcare Research and Quality; March 2022.

DOI: <https://doi.org/10.23970/AHRQEPNONOPIOIDPHARMASURVEILLANCE2>. Posted final reports are located on the Effective Health Care Program [search page](#).

# Afterword

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

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

This and future quarterly progress reports will provide up-to-date information about the evidence base to inform health plans, providers, purchasers, government programs, and the healthcare system as a whole on the state of the science. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website ([www.effectivehealthcare.ahrq.gov](http://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](mailto:epc@ahrq.hhs.gov). They will be considered in the next update of the report.

Robert “Bob” Otto Valdez, Ph.D., M.H.S.A.  
Director  
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.  
Director  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Craig A. Umscheid, M.D., M.S.  
Director  
Evidence-based Practice Center Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D.  
Task Order Officer  
Evidence-based Practice Center Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

## Appendix Contents

Appendix A. Literature Search Strategies .....	A-1
Randomized Controlled Trials .....	A-1
Systematic Reviews .....	A-4
Appendix B. Key Questions and Inclusion Criteria.....	B-1
Key Questions.....	B-1
Key Question 1. Effectiveness and Comparative Effectiveness .....	B-1
Key Question 2. Harms and Adverse Events.....	B-1
Criteria for Inclusion/Exclusion of Studies in the Review .....	B-1
Population(s) .....	B-1
Interventions .....	B-2
Comparators .....	B-2
Outcomes .....	B-2
Timing.....	B-2
Settings.....	B-2
Appendix C. Included Studies .....	C-1
Appendix D. Excluded Studies .....	D-1
Appendix E. Study Characteristics Evidence Tables.....	E-1
Appendix F. Meta-Analysis Evidence Tables .....	F-1
Appendix G. Quality Assessment .....	G-1

# 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 chlorthalidone 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 methocarbamol 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 methocarbamol 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 methocarbamol 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 methocarbamol: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 methocarbamol: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 osteoarthritis: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 osteoarthritis: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 ('randomized 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 methocarbamol 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 osteoarthritis 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 syntheses\*)) 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 syntheses\* 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 methocarbamol 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 osteoarthritis 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 methocarbamol: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 methocarbamol: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 osteoarthritis: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 osteoarthritis: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 ( $\geq 12$  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 ( $\geq 12$  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  $\geq 18$  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 ( $\geq 12$  months)
- We will assess available literature to ensure that adequate evidence exists from studies of  $\geq 3$  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. 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.
10. 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.
11. 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.
12. 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.
13. 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.

## 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 dextropropofol 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, Lanis 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.00000000000000975>. Exclusion: 8.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.

23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. Kataria D, Jumani L, Ahmed MU, et al. Comparison of pregabalin versus placebo in reduction of pain due to lumbar disc herniation. *Cureus.* 2020 Aug 24;12(8):e9985. doi: 10.7759/cureus.9985. PMID: 32983686. Exclusion: 4.
32. 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.
33. 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.
34. 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.

35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. Privitera R, Anand P. Capsaicin 8% patch quenza 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.
45. 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.
46. 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.
47. 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.
48. 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.

49. 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.
50. 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.
51. 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.
52. 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.
53. 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.
54. 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.
55. 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.
56. 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.
57. 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.
58. 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.
59. 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.
60. 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.
61. Yue L, Luo S, Wang Y, et al. Clinical meaningfulness of duloxetine[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.
62. 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.
63. 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.

## Appendix E. Study Characteristics Evidence Tables

Shown in associated Excel file for Surveillance Report 2

at <https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research>.

## **Appendix F. Meta-Analysis Evidence Tables**

Shown in associated Excel files for Surveillance Report 2

at <https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research>.



## **Appendix G. Quality Assessment**

Shown in associated Excel file for Surveillance Report 2

at <https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research>.