

Systematic Review on Nonopioid Pharmacologic Treatments for Chronic Pain: Surveillance Report 1

Literature Update Period: September 2019 through September 2021

Background and Purpose

This is the first update for the 2020 report *Nonopioid Pharmacologic Treatments for Chronic Pain* (<https://effectivehealthcare.ahrq.gov/products/nonopioid-chronic-pain/research>),¹ covering the period September 2019 through September 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 since the 2020 report and to determine how the new evidence impacts findings of the 2020 report. Subsequent updates are planned for January 2022 (based on evidence published from October to December 2021) and April 2022 (based on evidence published from January to March 2022).

Scope

The scope and eligibility criteria established at the time of the original report¹ were utilized for this surveillance report; no changes were made. The report focused on use of nonopioids in patients with chronic pain 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 Agency for Healthcare Research and Quality 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 September 2019 through September 2021. 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 developed² optimized (text-word only) search in pre-Medline to identify studies not yet indexed with Medical Subject Headings (MeSH). As in the original report, searches on electronic databases were supplemented by review of reference lists of relevant articles. Search strategies are available in [Appendix A](#).

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

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 Group³ and outlined in the *AHRQ Methods Guide* chapter “Assessing the Risk of

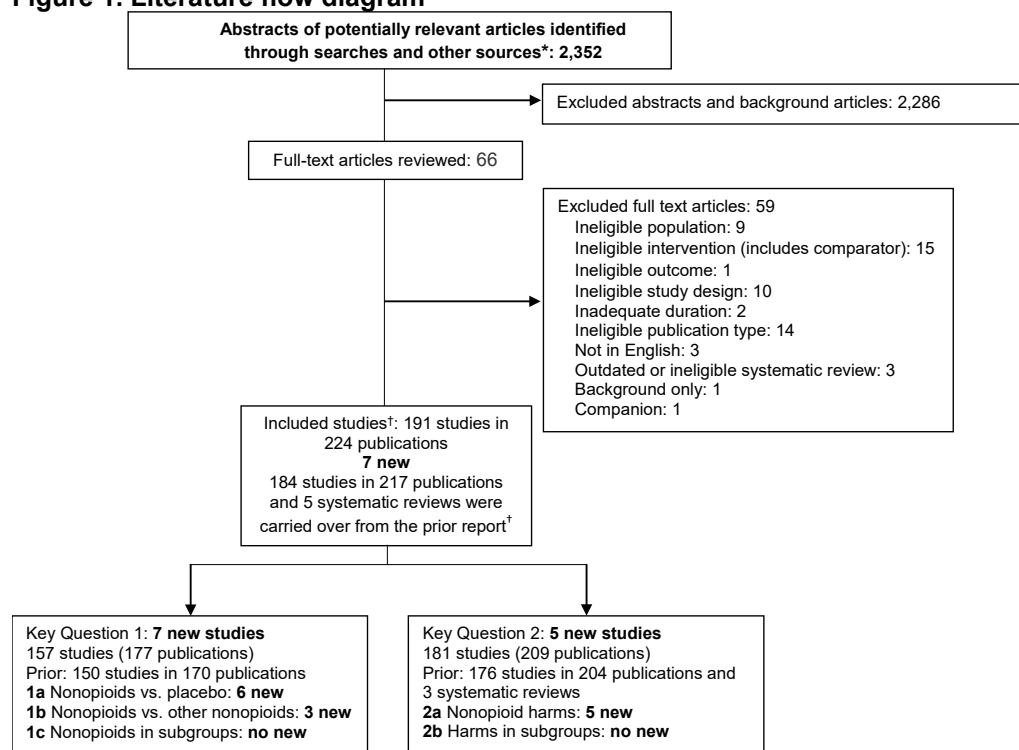
Bias of Individual Studies When Comparing Medical Interventions.”^{4,5} The decision to update meta-analyses from the original report was based on the number and sample sizes of new studies eligible for meta-analysis (meta-analysis performed if new evidence was large relative to the studies in the original meta-analysis); consistency in findings between the new studies and the original meta-analysis (meta-analysis performed if findings from new evidence appear inconsistent); or whether new evidence could impact the strength of evidence (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. We highlighted any changes in the SOE assessments.

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 update search yielded 2,352 citations and identified seven new eligible studies. All the studies addressed benefits and five addressed harms. All were randomized controlled trials (RCTs): four trials in neuropathic pain, and one each in fibromyalgia, osteoarthritis, and low back pain) (Figure 1).

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

- Seven new, short-term RCTs were identified for this surveillance report; four of the new trials (indicated by an asterisk in the bulleted list) evaluated comparisons not previously evaluated for specific chronic pain conditions.

Neuropathic Pain:

- One new trial found no difference in pain with delta tetrahydrocannabinol (THC)/cannabidiol (CBD) versus placebo; this was inconsistent with the prior report, which found benefit on some pain outcomes.
- One new trial found a capsaicin patch associated with improved pain intensity versus placebo, but no difference between a lidocaine patch versus placebo.*
- One new trial found no difference in pain intensity between pregabalin, amitriptyline, or the combination of pregabalin and amitriptyline.*
- One new trial found no differences in pain outcomes between pregabalin controlled release (CR) and pregabalin immediate release (IR).*

Fibromyalgia:

- One new trial was consistent with previous evidence that found pregabalin associated with a small reduction in pain intensity versus placebo.

Osteoarthritis:

- One new trial found no statistically significant differences between nortriptyline versus placebo in pain or function, although some estimates favored nortriptyline.*

Low Back Pain:

- One new trial found no differences between desipramine versus placebo in pain or function.

Harms:

- One new trial of tricyclic antidepressants was consistent with a prior trial in finding an increased risk of dry mouth versus placebo.
- One new trial of THC/CBD was consistent with two prior trials in finding an increased risk of dizziness.

Summary of New Evidence

Table 1 provides the conclusions from the 2020 report and the new findings from studies identified in this surveillance report. Table 1 focuses on Key Questions with new evidence; the full SOE table is available in the full report (<https://www.ncbi.nlm.nih.gov/books/NBK556268/#ch5.s1>). The update includes one new SOE rating where none existed before (improved pain relief with capsaicin patch). With the addition of one new RCT, the SOE rating for increased dry mouth with tricyclic antidepressants (TCAs) was changed from insufficient to low. In Table 1 these changes in SOEs are bolded.

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

| Type of Pain or Harm | Key Question | Conclusions From 2020 Report | Findings From Surveillance Report | 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"> • SOE: Low, based on 2 RCTs | 1 new 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. | No change in conclusions |
| | KQ1. Capsaicin patch versus lidocaine patch versus placebo patch short-term | No studies | 1 new RCT (n=179) found capsaicin patch associated with pain improvement compared with placebo. | 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. | Effect of lidocaine patch (SOE: Insufficient) |
| | KQ1. Pregabalin versus amitriptyline versus combination short-term | No studies | 1 new RCT (n=110) found no differences between monotherapy with pregabalin or amitriptyline or combination therapy in pain improvement. | Differences between pregabalin, amitriptyline, and combination therapy (SOE: Insufficient) |
| | KQ1. Pregabalin CR tablet versus pregabalin IR capsule short-term | No studies | 1 new 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. | Differences between pregabalin CR tablet and pregabalin IR capsule (SOE: Insufficient due to high attrition) |
| Fibromyalgia | KQ1. Pregabalin versus placebo short-term | Pregabalin was associated a small reduction in pain <ul style="list-style-type: none"> • SOE: Moderate, based on 8 RCTs | 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. | No change in conclusions |

| Type of Pain or Harm | Key Question | Conclusions From 2020 Report | Findings From Surveillance Report | Assessment |
|----------------------|---|--|--|--|
| Osteoarthritis | KQ1. Nortriptyline versus placebo short-term | No studies | 1 new RCT (n=205) found no difference between nortriptyline versus placebo in pain improvement, function, or quality of life in knee osteoarthritis. | 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"> SOE: Insufficient based on 1 RCT | 1 new RCT (n=70) found no effect of desipramine versus placebo on pain. | No change in conclusions |
| Harms | KQ2. TCAs short-term | Dry mouth more likely with amitriptyline <ul style="list-style-type: none"> SOE: Insufficient based on 1 RCT | 1 new RCT (n=70) found no increase in SAEs, nausea, or sedation but a nonsignificant increase in dry mouth with desipramine; 1 new RCT (n=201) found no difference in SAEs but increased dry mouth with nortriptyline. | Increased dry mouth with TCAs (SOE: Low);* evidence on other adverse events (SOE: Insufficient) |
| | KQ2. Anticonvulsants short-term | No increased risk of SAEs, moderate increase in WAEs <ul style="list-style-type: none"> SOE: Moderate based on 19 RCTs Large increase in cognitive AEs <ul style="list-style-type: none"> SOE: Low based on 8 RCTs Large increase in dizziness, peripheral edema, sedation, and weight gain <ul style="list-style-type: none"> SOE: Moderate based on 25 RCTs | 1 RCT (n=334) found no increase in risk of having any AE or SAE but increased risk of dizziness and somnolence. | 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 WAEs, SAEs, or application site pruritus <ul style="list-style-type: none"> SOE: Moderate based on 3 RCTs | 1 new RCT (n=179) found capsaicin patch associated with increased withdrawals due to treatment-emergent AEs. | No change in conclusions |

| Type of Pain or Harm | Key Question | Conclusions From 2020 Report | Findings From Surveillance Report | Assessment |
|----------------------|--|---|---|---|
| | KQ2. Topical lidocaine short-term | No studies | 1 new RCT (n=184) found lidocaine patch associated with no increase in withdrawals due to treatment-emergent AEs. | WAEs with lidocaine (SOE: Insufficient) |
| | 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"> SOE: Low based on 2 RCTs | 1 new RCT (n=339) found increased risk of any AE, dizziness, somnolence and a nonsignificant increase in risk of nausea with THC/CBD. | 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; TCA=tricyclic antidepressants; THC= delta tetrahydrocannabinol; WAE=withdrawals due to adverse events

*Change in SOE

Evidence Details

Key Question 1: Benefits

Neuropathic Pain

Four new RCTs (N=1,092) evaluated anticonvulsants,^{4,5} antidepressants,⁴ topical pain patches,⁶ and THC/CBD⁷ at short-term followup in patients with neuropathic pain.

One good-quality RCT (n=339)⁷ found no differences between THC/CBD oromucosal spray versus placebo in likelihood of at least a 30 or 50 percent improvement in pain severity (p=0.234; p=0.714, respectively) or pain intensity (mean difference [MD] -0.19 on a 0 to 10 Numerical Rating Scale [NRS], 95% confidence interval [CI], -0.62 to 0.29) among patients with multiple sclerosis.⁷ The prior report included a RCT of patients with allodynic (caused by stimuli not normally painful) neuropathic pain that found THC/CBD oromucosal spray associated with a moderate effect on the likelihood of achieving at least a 30 percent pain response versus placebo.⁸ While both RCTs used the same concentration of THC/CBD, the doses differed: the trial of patients with allodynia permitted 24 sprays in 24 hours,⁸ and the RCT of patients with multiple sclerosis allowed only 12 sprays in 24 hours.⁷ Another potential explanation for the discrepancy in THC/CBD's effect on pain response may be the differences in patient populations, as allodynia may not be present in all patients with multiple sclerosis and neuropathic pain. The new RCT⁷ also found no differences between THC/CBD versus placebo in sleep quality (p=0.83) or quality of life (EQ-5D (p=0.40), consistent with the prior report.

One fair-quality RCT (n=291) found a capsaicin patch associated with improved pain relief versus placebo on the 11-point Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN) question 4 mean daily pain rating (change in rating for capsaicin -2.2, 95% CI, -2.45 to -1.5, change in rating for placebo not reported, p<0.01).⁶ There was no difference between the 5 percent lidocaine patch versus placebo (p-value not reported). All patients in the trial were pretreated with 4 percent lidocaine cream.⁶ There was no evidence on the effect of topical pain relief patches in neuropathic pain in the prior report.

One fair-quality head-to-head RCT (n=110) found no differences between pregabalin 150 mg, amitriptyline 25 mg, or combination treatment (pregabalin 75 mg + amitriptyline 10 mg) in likelihood of pain improvement on the 0 to 100 Neuropathic Pain Symptom Inventory (p=0.09).⁴ The prior report did not evaluate these comparisons for neuropathic pain.

One fair-quality RCT found no difference between pregabalin CR versus IR in pain intensity (n=352, MD in the 11-point Daily Pain Rating Scale [DPRS] score -0.11, 95% CI, -0.05 to 0.30). There were also no differences between pregabalin formulations on DPRS 30 and 50 percent pain reduction, sleep, and depression or anxiety.⁵ There was no evidence comparing these pregabalin formulations in the prior report.

Fibromyalgia

One fair-quality RCT (n=343) found pregabalin associated with greater improvement in pain intensity on an 11-point NRS (MD -0.73, 95% CI, -1.10 to -0.36), likelihood of 30 percent or more pain improvement (47.5% vs. 32.7%, p=0.004) and 50 percent or more pain improvement (27.2% vs. 17.0%, p=0.019) versus placebo.⁹ This finding is consistent with prior evidence from eight RCTs that found pregabalin associated with a small reduction in pain versus placebo. The new RCT found no difference between pregabalin versus placebo in sleep disturbance (p=0.09),

but pregabalin was associated with improved sleep interference ($p<0.001$).⁹ There was also no difference between pregabalin versus placebo on the Hospital Anxiety and Depression Scale (HADS) anxiety scale, but pregabalin was associated with improved HADS depression score ($p=0.02$).⁹

Osteoarthritis

One good-quality RCT ($n=205$) found no statistically significant differences between nortriptyline versus placebo in Western Ontario and McMaster Universities (WOMAC) pain (0 to 20 scale, MD -6.2, 95% CI, -0.26 to 12.56),¹⁰ WOMAC function (0 to 68 scale, MD -4.4, 95% CI, -10.48 to 1.79), or quality of life (all Short-form (SF)-36 subscales $p>0.05$ except bodily pain [$p=0.02$]), though some estimates favored nortriptyline.¹⁰ There was no evidence on the effect of nortriptyline on osteoarthritis in the prior report.

Low Back Pain

One fair-quality RCT ($n=70$)¹¹ found no difference between desipramine versus active placebo (benztropine mesylate 0.125mg) in pain intensity on the Descriptor Differential Scale (0 to 20 scale, Cohen's d 0.46 vs. 0.64, $p>0.05$, $p=0.72$). This was inconsistent with a previous RCT¹² that found desipramine associated with decreased pain intensity versus placebo. Due to inconsistency, the new RCT does not alter the prior report's findings of insufficient evidence for desipramine on low back pain.

There was no difference between desipramine versus active placebo in function (0 to 24 scale Roland Morris Disability Questionnaire Cohen's d 0.77 vs. 0.75, $p>0.05$).¹¹

Key Question 2: Harms

Tricyclic Antidepressants

Two new RCTs reported harms associated with TCAs versus placebo. One good-quality RCT ($n=201$) found nortriptyline associated with increased likelihood of dry mouth (86.9% vs. 51.0%, $p<0.001$),¹⁰ consistent with a prior RCT of amitriptyline.¹² A fair-quality RCT ($n=70$) found desipramine associated with a non-statistically significant increased risk of dry mouth versus the active placebo benztropine mesylate (13.1% vs. 3.0%, $p=0.12$).¹¹

One of the RCTs found nortriptyline associated with increased likelihood of constipation (58.6% vs. 31.4%, $p<0.01$) and sweating (31.3% vs. 20.6%, $p=0.033$).¹⁰

Anticonvulsants

Consistent with the prior report, one new fair-quality RCT, described above ($n=334$), found pregabalin associated with increased likelihood of dizziness (41.8% vs. 18.3%, $p<0.05$) and somnolence (17.6% vs. 7.9%, $p<0.05$) but no increased likelihood of serious adverse events (SAEs) (0% vs. 5.5%, $p>0.05$) or withdrawal due to adverse events (WAEs) (12.9% vs. 6.7%, $p>0.05$).⁹ There were no differences between pregabalin CR and IR in frequency of treatment-emergent adverse events (AEs) (66.5% vs. 65.3%, $p=0.91$), SAEs (1.7% vs. 1.1%, $p=0.99$), or WAEs (6.8% vs. 4.0%, $p=0.35$).⁵

Topical Pain Patches

One new fair-quality RCT, described above ($n=273$), found an 8 percent capsaicin patch associated with increased risk of WAEs versus a placebo patch (4.5% vs. 0%, $p<0.05$). In this

RCT, a 5 percent lidocaine patch with 4 percent lidocaine cream premedication was not associated with increased risk of withdrawal versus placebo (2.1% vs. 0%, $p>0.05$).⁶

The most common adverse event in the RCT was application site pain (36.6% overall; not reported by treatment group).⁶ Due to the small number of WAEs in the new RCT, there is no change to prior conclusions.

Cannabis

One new RCT ($n=339$)⁷ was consistent with findings from two prior RCTs^{8,13} that found cannabis associated with increased risk of dizziness, nausea, somnolence, and any AE.

Conclusions

Nonopioid drugs (mainly serotonin-norepinephrine reuptake inhibitor [SNRI] antidepressants, pregabalin/gabapentin, and nonsteroidal anti-inflammatory drugs [NSAIDs]) resulted in 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. Increased incidence of drug class-specific adverse events led to withdrawal from treatment in some patients, suggesting that careful consideration of patient characteristics is needed in selecting nonopioid drug treatments. Additional research is needed on longer term followup, quality of life, direct comparisons of nonopioid drugs, and use in older patients, nonwhite patients, and patients with more severe pain and with comorbidities.

Most new evidence for nonopioids for chronic pain evaluated new comparisons for specific chronic pain conditions but resulted in insufficient SOE assessments due to small sample size, high attrition, and lack of intention-to-treat analysis. Changes in SOE ratings from the prior report based on new evidence include low SOE (upgraded from insufficient) for increased risk of dry mouth with TCAs.

The next surveillance report is scheduled for January 2022.

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

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

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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 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 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 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 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 (≥ 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. 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.
2. 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.
3. 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;71(10) doi: 10.3399/BJGP.2020.0797. PMID: 33571950.
4. 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.
5. 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.
6. 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.
7. 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 |
|----------------|--|
| 1 | Included primary or secondary publication |
| 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, Lan 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. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.

22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.

35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. 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.
46. 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.
47. 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.
48. 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.
49. 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.

50. 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.
51. 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.
52. 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.
53. 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.
54. 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.
55. 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.
56. 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.
57. 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.
58. 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.
59. 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 files for Surveillance Report 1

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

Appendix F. Meta-Analysis Evidence Tables

Shown in associated Excel files for Surveillance Report 1

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

Appendix G. Quality Assessment

Shown in associated Excel file for Surveillance Report 1

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