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

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), covering the period September 2019 through September 2021. This report addressed benefits and harms of nonopioid pharmacologic treatments in adults with chronic pain (i.e., 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 surveillance reports 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 report 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 (KQ):

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 (SUD),
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 to identify evidence published from September 2019 through September 2021. Search strategies from the original report were utilized. In addition, to capture articles not yet indexed in Medline, we supplemented the original search strategies with a previously developed optimized (text-word only) search in pre-Medline, to identify 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. 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) (Table 1).

<table>
<thead>
<tr>
<th>Table 1. PICOTS: Inclusion and exclusion criteria</th>
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<tbody>
<tr>
<td><strong>PICOTS</strong></td>
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<tr>
<td><strong>Populations and Conditions</strong></td>
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<tr>
<td>Adults (age ≥18 years) with chronic pain (pain lasting &gt;3 months).</td>
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<tr>
<td>Specific chronic pain populations:</td>
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<tr>
<td>o Neuropathic</td>
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<tr>
<td>o Musculoskeletal (e.g., low back pain, osteoarthritis)</td>
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<td>o Fibromyalgia (assessed using established criteria)</td>
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<td>o Sickle cell disease</td>
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<td>o Inflammatory arthritis (e.g., rheumatoid arthritis)</td>
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<td>o Chronic headache*</td>
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PICOTS

Inclusion Criteria

Exclusion Criteria

Interventions

Nonopioid pharmacologic drugs for chronic pain:
• Oral pharmacologic agents specifically used to treat chronic pain:
  o NSAIDs (e.g., celecoxib, diclofenac, ibuprofen)
  o Antidepressants SNRIs (i.e., duloxetine, milnacipran) and TCAs (e.g., amitriptyline)
  o Anticonvulsants: Carbamazepine, gabapentin, oxcarbazepine, pregabalin
  o Other: Acetaminophen, muscle relaxants (e.g., cyclobenzaprine, diazepam), memantine
  o Topical agents (diclofenac, capsaicin, and lidocaine)
  o Medical cannabis in all forms, including phytocannabinoids and synthetic cannabinoid

Injectable preparations, including biologic drugs, corticosteroids, etc.
• Other antidepressants (e.g., SSRIs, MAOIs)
• Other antiepileptics (e.g., topiramate, lamotrigine, levetiracetam, phenytoin)
• Drugs used for migraine prophylaxis (e.g., verapamil, beta-blockers) or treating acute migraine (e.g., triptans)
• Salicylates (topical and oral)
• Topical menthol preparations
• Disease-modifying drugs for rheumatoid arthritis (DMARDs, e.g., methotrexate)

Comparators

Placebo, another included nonopioid pharmacologic agent, dose, or treatment duration

Nonpharmacologic treatment (comparison to nonopioids included in review of nonpharmacologic treatments)
• Opioid treatment

Outcomes

• Pain, function, and quality of life using validated outcome measures.
  • Pain severity is the assessment of improvement in pain from baseline as a continuous measure. Pain response is the dichotomous assessment whether patients’ improvement meet an established threshold (e.g., 30% improvement).
  • Patient-reported pain assessments are prioritized. Pain response based on clinician assessments was also acceptable and noted where they are reported.
  • Secondary outcomes include mood, sleep, and global assessments using validated scales.
• All drug classes: Withdrawal from treatment due to adverse events (any adverse event, not specifically symptoms of withdrawal from an opioid or other drug), incidence of serious adverse events, overdose, misuse, addiction, and development of SUD.
• Key specific adverse events according to drug class (e.g., gastrointestinal and cardiovascular events, kidney and liver-related harms with NSAIDs).

Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)
• Indirect measurement of pain (e.g., quantitative sensory testing).

Timing

Short- (3 to <6 months), intermediate- (6 to <12 months), and long-term (≥12 months) treatment duration

Studies or outcomes reported with <3-month duration of treatment

Setting

Outpatient settings (e.g., primary care, pain clinics, emergency rooms, urgent care clinics)

Addiction treatment settings, inpatient settings

Study Design

• Randomized controlled trials
• High-quality, recent systematic reviews that best match the scope of this review
• English language publications

• Observational studies
• Outdated/out of scope systematic reviews
• Non-English language publications

DMARDs = disease-modifying antirheumatic drug; KQ = Key Question; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; SUD = substance use disorder; TCA = tricyclic antidepressant

Chronic headache defined as (International Classification of Headache Disorders, 3rd edition definition): Primary headaches attributed to the headache condition itself, not caused by another disease or medical condition. Chronic headache is defined as 15 or more days each month for at least 12 weeks or history of headache more than 180 days a year.

We utilized the same methods for data abstraction and quality assessment as the original report. 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 if new evidence could impact the strength of evidence (meta-analysis performed if the strength of evidence based on the original meta-analysis was low or insufficient and new evidence could increase the strength of evidence due to increased precision, high quality, or other factors). The strength of evidence 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 strength of evidence assessments.

A list of included studies identified for this update is provided in Appendix C. A list of articles excluded at full-text along with reasons for exclusion is available in Appendix D. Evidence tables providing data from included studies are available in Appendix 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 (all addressed benefits and 5 addressed harms) new eligible studies (all randomized controlled trials [RCTs], four trials in neuropathic pain, and one each in fibromyalgia, osteoarthritis, and low back pain) (**Figure 1**).

*Abstracts of potentially relevant articles identified through searches and other sources*: 2,352

Excluded abstracts and background articles: 2,286

Full-text articles reviewed: 66

Excluded full text articles: 59
- Ineligible population: 9
- Ineligible intervention (includes comparator): 15
- Ineligible outcome: 1
- Ineligible study design: 10
- Inadequate duration: 2
- Ineligible publication type: 14
- Not in English: 3
- Outdated or ineligible systematic review: 3
- Background only: 1
- Companion: 1

*Ineligible population*: 9
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*Companion*: 1

**Included studies**: 191 studies (7 new) in 224 publications
184 studies in 217 publications and 5 systematic reviews were carried over from the prior report

**Key Question 1**: 157 studies (177 publications)
Prior: 150 studies in 170 publications
New: 7 studies

**Key Question 2**: 181 studies (209 publications)
Prior: 176 studies in 204 publications and 3 systematic reviews
New: 5 studies

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

†Some studies were included for multiple KQs.
Evidence Summary
- Seven new, short-term RCTs were identified for this surveillance report; four of the new trials (indicated by asterisk) 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 that 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 intensity 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, though 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 2 provides the conclusions from the 2020 report and the new findings from studies identified in this surveillance report. The update includes one new strength of evidence (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 TCAs was changed from insufficient to low.
Table 2. Summary of Conclusions and Assessments

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Conclusions from 2020 report</th>
<th>Findings from Surveillance Report</th>
<th>Assessment</th>
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<tbody>
<tr>
<td><strong>Neuropathic Pain</strong></td>
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<tr>
<td>KQ1. THC/CBD vs. placebo short-term</td>
<td>Cannabis was associated with a moderate improvement in short-term pain response versus placebo but no effect on pain improvement in neuropathic pain.</td>
<td>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</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ1. Capsaicin patch vs. lidocaine patch vs. placebo short-term</td>
<td>No studies</td>
<td>1 new RCT (n=179) found capsaicin patch associated with pain improvement compared with placebo.</td>
<td>Improved pain with capsaicin patch compared with placebo (SOE: Low)</td>
</tr>
<tr>
<td>KQ1. Lidocaine patch vs. placebo short-term</td>
<td>No studies</td>
<td>1 RCT (n=184) found no difference in lidocaine versus placebo in pain improvement</td>
<td>Effect of lidocaine patch (SOE: Insufficient)</td>
</tr>
<tr>
<td>KQ1. Pregabalin vs. amitriptyline vs. combination short-term (neuropathic pain)</td>
<td>No studies</td>
<td>1 new RCT (n=110) found no differences between monotherapy with pregabalin or amitriptyline or combination therapy in pain improvement.</td>
<td>Differences between pregabalin, amitriptyline, and combination therapy (SOE: Insufficient)</td>
</tr>
<tr>
<td>KQ1. Pregabalin CR tablet vs pregabalin IR capsule short-term (neuropathic pain)</td>
<td>No studies</td>
<td>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.</td>
<td>Differences between pregabalin CR tablet and pregabalin IR capsule (SOE: Insufficient due to high attrition)</td>
</tr>
<tr>
<td><strong>Fibromyalgia</strong></td>
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<tr>
<td>KQ1. Pregabalin vs. placebo short-term</td>
<td>Pregabalin was associated with a small reduction in pain.</td>
<td>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</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td><strong>Osteoarthritis</strong></td>
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<tr>
<td>KQ1. Nortriptyline vs. placebo short-term</td>
<td>No studies</td>
<td>1 new RCT (n=205) found no difference between nortriptyline vs. placebo in pain improvement, function, or quality of life in knee osteoarthritis</td>
<td>Effect of nortriptyline (SOE: Insufficient)</td>
</tr>
<tr>
<td><strong>Low Back Pain</strong></td>
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<tr>
<td>KQ1. Desipramine vs. active placebo short-term</td>
<td>No overall improvement in pain with desipramine, but low desipramine plasma concentration associated with improved pain.</td>
<td>1 new RCT (n=70) found no effect of desipramine versus placebo on pain</td>
<td>No change in conclusions</td>
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</tbody>
</table>
**Key Question 2: Harm**

**Harms**

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Conclusions from 2020 report</th>
<th>Findings from Surveillance Report</th>
<th>Assessment</th>
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<tbody>
<tr>
<td>KQ2. TCAs short-term</td>
<td>Dry mouth more likely with amitriptyline • SOE: Insufficient based on 1 RCT</td>
<td>1 new RCT (n=70) found no increase in SAE, 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</td>
<td>Increased dry mouth with TCAs (SOE: Low); evidence on other adverse events (SOE: Insufficient)</td>
</tr>
<tr>
<td>KQ2. Anticonvulsants short-term</td>
<td>No increased risk of SAEs, moderate increase in WAEs • SOE: Moderate based on 19 RCTs Large increase in cognitive AEs • SOE: Low based on 8 RCTs Large increase in dizziness, peripheral edema, sedation, and weight gain • SOE: Moderate based on 25 RCTs</td>
<td>1 RCT (n=334) found no increase in risk of having any AE or SAE but increased risk of dizziness and somnolence</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ2. Topical Capsaicin short-term</td>
<td>Topical capsaicin resulted in moderate increase in application site erythema and a large increase in application site pain with no increase in WAE, SAE, or application site pruritus • SOE: Moderate based on 3 RCTs</td>
<td>1 new RCT (n=179) found capsaicin patch associated with increased withdrawals due to treatment-emergent AEs</td>
<td>No change in conclusions</td>
</tr>
<tr>
<td>KQ2. Topical Lidocaine short-term</td>
<td>No studies</td>
<td>1 new RCT (n=184) found lidocaine patch associated with no increase in withdrawals due to treatment-emergent AEs</td>
<td>WAEs with lidocaine (SOE: Insufficient)</td>
</tr>
<tr>
<td>KQ2. Cannabis (oral/oromucosal) short-term</td>
<td>Dronabinol associated with no increase in SAEs, WAEs, or nausea; oral THC/CBD associated in large increase in WAEs, dizziness, nausea, but no increase in SAEs or sedation • SOE: Low based on 2 RCTs</td>
<td>1 new RCT (n=339) found increased risk of any AE, dizziness, somnolence and a nonsignificant increase in risk of nausea with THC/CBD</td>
<td>No change in conclusions</td>
</tr>
</tbody>
</table>

Abbreviations: AE=adverse event; CBD=cannabidiol; CR=controlled release; IR=immediate release; RCT=randomized controlled trial; SAE=serious adverse events; SOE=strength of evidence; TCA=tricyclic antidepressants; THC=delta tetrahydrocannabinol; WAE=withdrawals due to adverse events

### Evidence Details

**Key Question 1: Benefits**

**Neuropathic Pain**

Four new RCTs (N=1,092) evaluated anticonvulsants, antidepressants, topical pain patches, and THC/CBD at short-term followup in patients with neuropathic pain.

One good-quality RCT (n=339) 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 (MD -0.19 on a 0 to 10 Numerical Rating Scale).
Scale [NRS], 95% CI, -0.62 to 0.29) among patients with multiple sclerosis. The prior report included a RCT of patients with allodynic (pain 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. 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 and the RCT of patients with multiple sclerosis allowed only 12 sprays in 24 hours. 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 RCT 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). 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. 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). 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, mean difference [MD] in the 11-point Daily Pain Rating Scale [DPRS] score -0.11, 95% confidence interval [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. 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 Numerical Rating Scale (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. 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). 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).

**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), WOMAC function (0 to 68 scale, MD -4.4, 95% CI, -10.48 to 1.79), or quality of life (all SF-36 subscales p>0.05 except bodily pain [p=0.02]).
though some estimates favored nortriptyline. There was no evidence on the effect of nortriptyline on osteoarthritis in the prior report.

**Low Back Pain**

One fair-quality RCT (n=70) 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 RCT that found desipramine associated with decreased pain intensity versus placebo. Due to inconsistency, the new RCT does not alter the prior reports 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).

**Key Question 2: Harms**

**Tricyclic Antidepressants (TCAs)**

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), consistent with a prior RCT of amitriptyline. The other 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).

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).

**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 (SAE) (0% vs. 5.5%, p>0.05) or withdrawal due to adverse events (WAE) (12.9% vs. 6.7%, p>0.05). There were no differences between pregabalin CR and IR in frequency of treatment-emergent 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).

**Topical Pain Patches**

One new fair-quality RCT described above (n=273) found an 8 percent capsaicin patch associated with increased risk of WAE versus 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).

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

**Cannabis**

One new RCT (n=339) was consistent with findings from two prior RCTs that found cannabis associated with increased risk of dizziness, nausea, somnolence, and any AE.
Conclusions

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 strength of evidence (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.

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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.

These 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 version of the report.

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