

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

**Database: PsycINFO**

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

flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarbamol or tizanidine).ab,kw,sh,ti.

5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid\* or dronabinol or nabilone or memantine).ab,kw,sh,ti.

6 (topical adj2 lidocaine).ab,kw,ti.

7 or/1-6

8 exp NEURALGIA/

9 exp chronic pain/

10 exp headache/

11 exp Back Pain/

12 sickle cell disease/

13 exp ARTHRITIS/

14 fibromyalgia/

15 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,hw,ti.

16 or/8-15

17 7 and 16

18 17 and (random\* or control\* or trial).ti,ab.

19 limit 18 to english language

### **Elsevier Embase**

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

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

### Systematic reviews

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

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

**Database: EBM Reviews - Cochrane Database of Systematic Reviews**

- 1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclufenamate 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

### **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

DRAFT FINAL

# Appendix B. Key Questions and Inclusion Criteria

## Key Questions

### Key Question 1. Effectiveness and Comparative Effectiveness

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

### Key Question 2. Harms and Adverse Events

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

## Criteria for Inclusion/Exclusion of Studies in the Review

### Population(s):

- For all Key Questions (KQs): Adults (age  $\geq 18$  years) with various types of chronic pain (defined as pain lasting  $>3$  months), including patients with acute exacerbations of chronic pain, pregnant/breastfeeding women, and patients with opioid use disorder
- For KQs 1c, 2b: Subgroups of the above patient populations as defined by specific pain condition (neuropathic pain, musculoskeletal pain, fibromyalgia, inflammatory arthritis, and chronic headache), patient demographics (e.g., age, race, ethnicity, and sex), comorbidities and degree of nociplasticity/central sensitization.

### Interventions:

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



## **Comparators:**

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

## **Outcomes:**

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

## **Timing:**

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

## **Settings:**

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

## Appendix C. Included Studies

1. 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, Javid 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.
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## **Appendix E. Study Characteristics Evidence Tables**

Shown in associated Excel files.

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## Appendix F. Meta-Analysis Evidence Tables

Shown in associated Excel files.

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## **Appendix G. Quality Assessment**

Shown in associated Excel file.

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