Effective Health Care

Non-Opiate Treatments for Chronic Pain

Results of Topic Selection Process & Next Steps

The nominator sees managing opiate medications as a rapidly increasing problem and feels as though clinicians need to have evidence-based guidelines on alternative treatments for pain. However, the topic is not feasible for a full systematic review due to the limited data available for a review at this time. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

The following AHRQ systematic reviews may be useful to the nominator:

- Effectiveness of Treatments for Diabetic Peripheral Neuropathy (in-progress). https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2197
- Nonpharmacologic Treatment for Pain (in-progress). https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2314
- Treatment of Osteoarthritis of the Knee: An Update (in-progress). https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2247

Topic Brief

Topic Name: Non-Opiate Treatments for Chronic Pain

Topic #: 0690

Nomination Date: 06/30/2016

Topic Brief Date: 10/12/2016

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

Summary of Key Findings

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: An AHRQ product addressing off-label prescription medication (outside of opiates), OTCs, and herbal therapies would not be duplicative. A recent AHRQ review on low-back pain addresses aspects of key questions 1 and 2 for that specific condition. While there are many systematic reviews on treatments for pain, the scope tends to be focused on a single condition or treatment, and there is nothing that comprehensively addresses the nominator's needs.

- Impact: Because there is little high-quality evidence about effectiveness, the nomination has moderate to low impact potential to inform changes in practice or to reduce practice variation.
- Feasibility: An AHRQ evidence review on this topic is not feasible at this time.
    - *Size/scope of review:* From PubMed, we estimate that the number of relevant studies published between August 2011 and August 2016 may be 29 across all key questions. Most studies though are focused on a single condition.
    - *Detailed Feasibility Results:* An AHRQ product addressing off-label prescriptions, OTCs, and adjuvant interventions for chronic pain is feasible (KQ 1a-c). An AHRQ product addressing acute exacerbations of chronic pain (KQ 2a-c), and subgroup analysis of treatments for pain in the pediatric population (KQ 3a.i-a.iii), those with a history of substance abuse (KQ 3b.i-biii), and with mental health diagnoses (KQ 3c.i-c.iii) may not be feasible. There are very few recent trials or studies addressing key questions 2 and 3, and there are concerns about the quality of the identified studies for these questions.
    - *Clinicaltrials.*gov: We identified 13 trials relevant to the key questions, including 8 completed trials, 4 of which had results.

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Introduction

Over the past two decades there has been increased pressure on clinicians to minimize use of opioids for pain management. There are strong government and private policies and initiatives in place for reducing opiate use in the United States. However, for many providers, the lack of clear evidence about the comparative effectiveness of non-opioid treatments, and the lack of guidelines for using them, may hinder adherence to these policies. While the Centers for Disease Control and Prevention (CDC) has recently released guidelines[1] focused on treating chronic pain with opioids for pain lasting longer than three months, they do not cover over-the-counter (OTC) or herbal and thermal therapies. Additionally, the Patient Centered Outcomes Research Institute recently proposed research into reducing opioid prescribing.

Topic nomination #0690 was received on June 30, 2016. It was nominated by the American Academy of Physician Assistants (AAPA). Due to the broad scope of the original nomination, AAPA narrowed the scope to focus on specific interventions and populations. Additionally, they concentrated the nomination to interventions for pain, and withdrew a question regarding treatment options for opiate abuse. The questions for this nomination are:

Key Question 1. What are the benefits and harms of the following treatments for chronic pain:

a. Approved and off-label use of prescription medication
b. OTCs
c. Adjuvant interventions

Key Question 2. What are the benefits and harms of the following treatments for acute exacerbations of chronic pain:

a. Approved and off-label use of prescription medication
b. OTCs
c. Adjuvant interventions

Key Question 3. What are the benefits and harms of treatments for chronic pain in the following high-risk populations:

a. Pediatric
    i. Approved and off label use of prescription medication
    ii. OTCs
    iii. Adjuvant interventions
b. History of substance use
    i. Approved and off label use of prescription medication
    ii. OTCs
    iii. Adjuvant interventions
c. Mental health diagnoses
    i. Approved and off label use of prescription medication
    ii. OTCs
    iii. Adjuvant interventions

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes (PICOs) of interest. See Table 1.

Table 1. Key Questions with PICOs

Key Question	1. What are the benefits and harms of the following treatments for chronic pain: a. approved and off-label use of	2. What are the benefits and harms of the following treatments for acute exacerbations of chronic pain: a. approved and off-label use of	3. What are the benefits and harms of treatments for chronic pain in the following high-risk populations: a. Pediatric i. approved and off label use of prescription medication ii. OTCs

	prescription medication b. OTCs c. Adjuvant interventions	prescription medication b. OTCs c. Adjuvant interventions	iii. Adjuvant interventions b. History of substance use i. approved and off label use of prescription medication ii. OTCs iii. Adjuvant interventions c. Mental health diagnoses i. approved and off label use of prescription medication ii. OTCs iii. Adjuvant interventions
Population	Adults with chronic pain (>3 months). Exclude: Cancer, palliative, end-of-life care, chronic pain disorders such as fibromyalgia, pregnant and breastfeeding women	Adults with acute exacerbation of chronic pain. Exclude: Cancer, palliative, end-of-life care, chronic pain disorders such as fibromyalgia, pregnant and breastfeeding women	a. Adolescents (10-17 years old) b. Adults with a history of drug and/or alcohol abuse c. Adults with diagnosed, MDD, Bipolar Disorder, PTSD, and/or Anxiety Exclude: Cancer, palliative, end-of-life care, chronic pain disorders such as fibromyalgia, pregnant and breastfeeding women
Interventions	a. Alpha blockers, anticonvulsants, antidepressants including tricyclics b. NSAIDs, acetaminophen, aspirin, topicals including topical agents c. Herbal supplements	a. Alpha blockers, anticonvulsants, antidepressants including tricyclics b. NSAIDs, acetaminophen, aspirin, topicals including topical agents c. Herbal supplements, ice/heat	a. Alpha blockers, anticonvulsants, antidepressants including tricyclics b. NSAIDs, acetaminophen, aspirin, topicals including topical agents c. Herbal supplements
Comparators	Placebo or other active intervention	Placebo or other active intervention	Placebo or other active intervention
Outcomes	Reduction of pain and adverse events (eg mortality, risk of overdose, organ damage/failure)	Reduction of pain and adverse events (eg mortality, risk of overdose, organ damage/failure)	Reduction of pain and adverse events (eg mortality, risk of overdose, organ damage/failure)

Abbreviations: KQ=Key Question; MDD=Major Depressive Disorder; NSAID=Non-Steroidal Anti-inflammatory Drug; OTC=Over-the-Counter; PTSD=Post-Traumatic Stress Disorder

Methods

To assess topic nomination *#0690 Non-Opiate Treatments for Pain,* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions. Appendix B includes the list of the sources searched and potentially relevant titles identified by our research librarian.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was hypothetically possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of a New Evidence Review

We conducted a literature search for randomized controlled trials in PubMed from August 2011-August 2016. Because a small number of articles were identified, we reviewed all abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. See *Table 2, Feasibility Column, Size/Scope of Review Section* for the citations of included studies. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This topic is highly appropriate and important. The CDC states that in 2012, 259 million prescriptions for opioid pain medication were written.[1] There have been efforts from multiple government and state agencies to reduce this number, and one way this can be done is to provide clear guidance on what else works. See Appendix A for details.

Desirability of New Review/Duplication

A comprehensive systematic review on non-opiate treatments for pain would not be duplicative. While we identified evidence reviews examining benefits and harms (KQ 1) of a few approved and off-label prescription medications (1a),[2-8] OTCs (1b),[2,9-14] and adjuvant interventions (1c) for a few examples of chronic pain.[15-17] Six of these evidence reviews also examine prescription, OTC, and adjuvant treatments for acute exacerbations of chronic pain.[2,10,14-16,18] We found no evidence reviews examining prescription, OTC, or adjuvant interventions for subgroups.

Impact of a New Evidence Review

A new evidence review on non-opiate treatments for pain would have a limited impact. The standard of care is unclear. There are inconsistent guidelines for pain management outside of opiates. There is also vast practice variation. However, the partner organization does not currently have plans to create a practice guideline.

Feasibility of a New Evidence Review

A comprehensive AHRQ product covering all key questions may not be feasible at this time.

An AHRQ product addressing off-label prescriptions, OTCs, and adjuvant interventions for chronic pain is feasible (KQ 1a-c). An AHRQ product addressing acute exacerbations of chronic pain (KQ 2a-c), and subgroup analysis of treatments for pain in the pediatric population (KQ 3a.i-a.iii), those with a history of substance abuse (KQ 3b.i-biii), and with mental health diagnoses (KQ 3c.i-c.iii) may not be feasible. There are very few recent trials or studies addressing key questions 2 and 3, and there are concerns about the quality of the identified studies for these questions. Please see *Table 2, Original Research* for more details.

There are 13 in-process or recently completed clinical trials that may provide the additional data needed for a comprehensive evidence review in the coming years.

Table 2. Key questions with the identified corresponding evidence reviews and original research

Key Question	Completed and In-Process Evidence Reviews	Original Research (Published and Ongoing)
KQ 1a: Approved and Off-Label Prescription Medication	Total number of completed or in-progress systematic reviews - 7 • AHRQ Review – 1[2] • Cochrane Review – 4[3-6] • Other – 2[7,8]	<u>Size/Scope of Review</u> Relevant Studies Identified: 12 • RCT – 3[19-21] • Prospective open-label – 2[22,23] • Prospective cohort – 2[24,25] • Retrospective – 3[26-28] • Post-Hoc Analysis – 2[29,30] <u>Clinical Trials</u> Relevant Trials: 10 • Recruiting – 2[31,32] • Active, not recruiting – 1[33] • Complete – 7[34-40]
KQ 1b: OTCs	Total number of completed or in-progress systematic reviews – 7 • AHRQ Review – 1[2] • Cochrane Review – 5[9-13] • Other – 1[14]	<u>Size/Scope of Review</u> Relevant Studies Identified: 10 • RCT – 6[41-46] • nRCT – 1[47] • Prospective cohort – 1[48] • Prospective, non-randomized, open-label – 1[49] • Retrospective – 1[50] <u>Clinical Trials</u> Relevant Trials: 1 • Complete – 1[36]

KQ 1c: Adjuvant Interventions	Total number of completed or in-progress systematic reviews - 3 • Cochrane Review – 2[15,16] • Other (In-Process) – 1[17]	Size/Scope of Review Relevant Studies Identified: 11 • RCT – 3[51-53] • Prospective randomized – 1[54] • Prospective, non-randomized, open-label – 1[49] • Prospective Cohort – 2[55,56] • Open label, repeated-measures – 1[57] • Observational – 2[58,59] • Case series – 1[60] Clinical Trials Relevant Trials: 3 • Recruiting – 2[61,62] • Complete – 1[63]
KQ 2a: Approved and Off-Label Prescription Medication	Total number of completed or in-progress systematic reviews - 1 • AHRQ Review – 1[2]	Size/Scope of Review Relevant Studies Identified: 2 • RCT – 1[44] • Prospective Cohort – 1[27] • Retrospective – 1[28] Clinical Trials Relevant Trials: 2 • Recruiting – 1[32] • Complete – 1[36]
KQ 2b: OTCs	Total number of completed or in-progress systematic reviews - 3 • AHRQ Review – 1[2] • Cochrane Review – 1[10] • Other – 1[14]	Size/Scope of Review Relevant Studies Identified: 2 • RCT – 2[46,47] Clinical Trials Relevant Trials: 1 • Complete – 1[36]
KQ 2c: Adjuvant Interventions	Total number of completed or in-progress systematic reviews - 4 • AHRQ Review – 1[2] • Cochrane Review – 3[15,16,18]	Size/Scope of Review Relevant Studies Identified: • Observational – 1[58] Clinical Trials Relevant Trials: 1 • Complete – 1[63]
KQ 3a.i: Pediatric Approved and Off-Label Prescription Medication	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: 1 • Survey – 1[64] Clinical Trials Relevant Trials: 0
KQ 3a.ii: Pediatric OTCs	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: • Survey – 1[64] Clinical Trials Relevant Trials: 0
KQ 3a.iii: Pediatric Adjuvant Interventions	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: • RCT – 1[52] Clinical Trials Relevant Trials: 0

KQ 3b.i: Approved and Off-Label Prescription Medication for those with History of Substance Abuse	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: • Observational – 1[65] Clinical Trials Relevant Trials: 1 • Complete – 1[66]
KQ 3b.ii: OTCs for those with History of Substance Abuse	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: 0 Clinical Trials Relevant Trials: 0
KQ 3b.iii: Adjuvant Interventions for those with History of Substance Abuse	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: 0 Clinical Trials Relevant Trials: 0
KQ 3c.i: Approved and Off-Label Prescription Medication for those with Mental Health Diagnoses	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: • Prospective naturalistic – 1[67] • Prospective, open-label – 1[23] • Retrospective – 1[68] • Post-hoc analysis – 1[30] Clinical Trials Relevant Trials: 4 • Complete – 4[37-40]
KQ 3c.ii: OTCs for those with Mental Health Diagnoses	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: 0 Clinical Trials Relevant Trials: 0
KQ 3c.iii: Adjuvant Interventions for those with Mental Health Diagnoses	Total number of completed or in-progress systematic reviews – none.	Size/Scope of Review Relevant Studies Identified: 0 Clinical Trials Relevant Trials: 0

Abbreviations: KQ=Key Question; OTC=Over-the-Counter; RCT=Randomized Controlled Trial

Summary of Findings

- Appropriateness and importance: The nomination is both appropriate and important.
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Appendices

Appendix A: Selection Criteria Summary

Appendix B: Search for Systematic Reviews (Duplication)

Appendix C: Search Strategy & Results (Feasibility)

Appendix A. Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents a health care drug and intervention available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. The CDC states that in 2012, 259 million prescriptions for opioid pain medication were written.[1]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large, vulnerable population and there is not a clearly established indication for screening and diagnosis.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	This nomination addresses benefits and harms of prescription, OTC, and adjuvant medication for pain.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this topic represents common infections, and increasing medical care costs.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	An AHRQ product addressing off-label prescription medication (outside of opiates), OTCs, and adjuvant interventions for chronic pain (including subgroups) would not be duplicative. While there are many systematic reviews on treatments for pain, the scope tends to be very narrow, and there is nothing that comprehensively addresses the nominator's needs.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear. There are inconsistent guidelines for pain management outside of opiates.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation.
5. Primary Research	

5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	*Size/scope of review:* Our searches of PubMed resulted in a total of 295 unique titles. Upon title and abstract review, we identified a total of 29 published studies potentially relevant to the key questions in the nomination. Based on an inclusion percentage of 100%, the expected number of relevant studies published between August 2011 and August 2016 may be 29 across all key questions. *Clinicaltrials.*gov: We identified 13 trials on ClinicalTrials.gov relevant to the key questions. *Detailed Feasibility Results:* An AHRQ product addressing off-label prescriptions, OTCs, and adjuvant interventions for chronic pain is feasible (KQ 1a-c). An AHRQ product addressing acute exacerbations of chronic pain (KQ 2a-c), and subgroup analysis of treatments for pain in the pediatric population (KQ 3a.i-a.iii), those with a history of substance abuse (KQ 3b.i-biii), and with mental health diagnoses (KQ 3c.i-c.iii) may not be feasible. There are very few recent trials or studies addressing key questions 2 and 3, and there are concerns about the quality of the identified studies for these questions.

Appendix B. Search for Systematic Reviews (Duplication)

Listed below are the sources searched and results of our search for existing guidance. A research librarian conducted the search and selected potentially relevant evidence based on the key question in the nomination and the associated PICOTS. An investigator reviewed each of the links to evidence below for inclusion. The links below do not represent the evidence selected for inclusion (see main topic brief).

Non-Opioid Treatment for Pain	
Source	**Evidence**
Search for Duplication: August 16, 2016	
AHRQ and Other Federal Products	
AHRQ: Evidence reports and technology assessments, USPSTF recommendations, and related DEcIDE projects, and Horizon Scan	*Noninvasive Treatments for Low Back Pain 2016* http://www.ncbi.nlm.nih.gov/books/NBK350276/ *Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review 2011* https://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=805
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program	*Duloxetine (an antidepressant) for Chronic Pain Conditions Recommendations for Use 2015* http://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations/Duloxetine_for_Chronic_Pain_Conditions_Recommendations_for_Use.pdf
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/	*Herbal medicine for low-back pain 2014* http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004504.pub4/full *Topical NSAIDs for chronic musculoskeletal pain in adults 2016*. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007400.pub3/full *Vitamin D for the treatment of chronic painful conditions in adults 2015* http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007771.pub3/full *Non-steroidal anti-inflammatory drugs for chronic low back pain 2016* http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012087/full *Desipramine* for neuropathic pain in adults 2014* http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011003.pub2/full *antidepressant *Topical capsaicin (low concentration) for chronic neuropathic pain in adults 2012* http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010111/full *Salicylate-containing rubefacients* for acute and chronic musculoskeletal pain in adults 2014*

	http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007403.pub3/full
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/	*Literature review of pain management for people with chronic pain. 2015* http://www.ncbi.nlm.nih.gov/pubmed/25407249
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/	*Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. 2011* http://www.ncbi.nlm.nih.gov/pubmed?term=21426373
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/	*Cannabis for the management of symptoms of chronic pain and/or PTSD* http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016033623 *Inhaled Cannabis for chronic painful neuropathy* http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42011001182 *Polyunsaturated fatty acids and chronic pain: a systematic review and meta-analysis* http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014010064 *Treating chronic pain with SSRI, what do we know?* http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014013777
CADTH (Canadian Agency for Drugs & Technologies in Health) https://www.cadth.ca/	None identified.
DoPHER (Database of promoting health effectiveness reviews) http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9	None identified.
ECRI institute https://www.ecri.org/Pages/default.aspx	None identified.
Secondary Sources checked on an as needed basis	
BlueCross BlueShield Foundation Massachusetts http://bluecrossfoundation.org/	None identified.
Campbell Collaboration http://www.campbellcollaboration.org/	None identified.
CMS Policies https://www.cms.gov/	None identified.
Hayes http://www.hayesinc.com/hayes/	None identified.
IOM (Institute of Medicine) http://iom.nationalacademies.org/	None identified.
McMaster Health System Evidence https://www.healthsystemsevidence.org/	None identified.

Robert Wood Johnson http://www.rwjf.org/	None identified.
Systematic Reviews (Journal) : protocols and reviews http://systematicreviewsjournal.biomedcentral.com/	None identified.
UBC Centre for Health Services and Policy Research http://chspr.ubc.ca/	None identified.
WHO Health Evidence Network http://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/health-evidence-network-hen	None identified.
National Heart, Lung, and Blood Institute http://www.nhlbi.nih.gov/	None identified.
National Cancer Institute http://www.cancer.gov/	None identified.
CINAHL (EBSCO)	None identified.
PsycINFO (Ovid)	None identified.

Appendix C. Search Strategy & Results (Feasibility)

Topic: Non-Opiate Treatments for Pain Date: August 19, 2016 Database Searched: MEDLINE (PubMed)	
Concept	Search String
Non-Opiate Treatments Alpha blockers Anticonvulsants Antidepressants (1st and 2nd gen) NSAIDs Acetaminophen Asprin Topicals Herbal Supplements Ice/heat	((((((((((((("Analgesics, Non-Narcotic"[Mesh]) OR ("Adrenergic alpha-Antagonists"[Mesh] OR "Adrenergic alpha-Antagonists" [Pharmacological Action])) OR ("Anticonvulsants"[Mesh] OR "Anticonvulsants" [Pharmacological Action])) OR "Analgesics, Non-Narcotic" [Pharmacological Action]) OR ("Antidepressive Agents"[Mesh] OR "Antidepressive Agents" [Pharmacological Action])) OR ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Anti-Inflammatory Agents, Non-Steroidal" [Pharmacological Action])) OR "Acetaminophen"[Mesh]) OR "acetylsalicylic acid lysinate" [Supplementary Concept]) OR "Administration, Topical"[Mesh]) OR ("Vitamins" [Pharmacological Action] OR "Vitamins"[Mesh])) OR ("Dietary Supplements"[Mesh] OR "dietary supplement, SPORT" [Supplementary Concept])) OR "Hot Temperature/therapy"[Mesh]) OR "Ice/therapy"[Mesh])) OR ((non-opiate[Title] OR non-opioid[Title] OR non-narcotic[Title] OR nonnarcotic[Title] OR nsaid[Title] OR nsaids[Title] OR herbal[Title]))
AND	
Chronic Non-Cancer Pain	("Chronic Pain/therapy"[Mesh]) OR (("non-cancer pain"[Title/Abstract] OR "chronic pain"[Title/Abstract]))
NOT	
Editorials, etc.	((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years ; English ; Human ; Adult	Filters activated: published in the last 5 years, Humans, English, Adult: 19+ years.
N=295	
Systematic Review N=25	PubMed subsection Systematic [sb]
Randomized Controlled Trials N=237	Cochrane Sensitive Search Strategy for RCT's (((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])
Other N=33	

ClinicalTrials.gov searched on August 19, 2016

40 studies found for: **Recruiting** | chronic pain | analgesics, non-narcotic OR Adrenergic alpha-Antagonists OR Anticonvulsants OR Antidepressive Agents OR Anti-Inflammatory Agents, Non-Steroidal OR Vitamins OR dietary supplements | Adult, Senior | Studies received from 08/19/2011 to 08/19/2016

https://clinicaltrials.gov/ct2/results?term=&recr=Recruiting&type=&rslt=&age_v=&age=1&age=2&gndr=&cond=chronic+pain&intr=analgesics%2C+non-narcotic+OR+Adrenergic+alpha-Antagonists+OR+Anticonvulsants+OR+Antidepressive+Agents+OR++Anti-Inflammatory+Agents%2C+Non-Steroidal+OR+Vitamins+OR+dietary+supplements&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=08%2F19%2F2011&rcv_e=08%2F19%2F2016&lup_s=&lup_e=

12 studies found for: **Active, not recruiting** | chronic pain | analgesics, non-narcotic OR Adrenergic alpha-Antagonists OR Anticonvulsants OR Antidepressive Agents OR Anti-Inflammatory Agents, Non-Steroidal OR Vitamins OR dietary supplements | Adult, Senior | Studies received from 08/19/2011 to 08/19/2016
https://clinicaltrials.gov/ct2/results?term=&recr=Active%2C+not+recruiting&type=&rslt=&age_v=&age=1&age=2&gndr=&cond=chronic+pain&intr=analgesics%2C+non-narcotic+OR+Adrenergic+alpha-Antagonists+OR+Anticonvulsants+OR+Antidepressive+Agents+OR++Anti-Inflammatory+Agents%2C+Non-Steroidal+OR+Vitamins+OR+dietary+supplements&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=08%2F19%2F2011&rcv_e=08%2F19%2F2016&lup_s=&lup_e=

37 studies found for: **Completed** | chronic pain | analgesics, non-narcotic OR Adrenergic alpha-Antagonists OR Anticonvulsants OR Antidepressive Agents OR Anti-Inflammatory Agents, Non-Steroidal OR Vitamins OR dietary supplements | Adult, Senior | Studies received from 08/19/2011 to 08/19/2016
https://clinicaltrials.gov/ct2/results?term=&recr=Completed&type=&rslt=&age_v=&age=1&age=2&gndr=&cond=chronic+pain&intr=analgesics%2C+non-narcotic+OR+Adrenergic+alpha-Antagonists+OR+Anticonvulsants+OR+Antidepressive+Agents+OR++Anti-Inflammatory+Agents%2C+Non-Steroidal+OR+Vitamins+OR+dietary+supplements&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=08%2F19%2F2011&rcv_e=08%2F19%2F2016&lup_s=&lup_e=