

*Pain management interventions for women of  
reproductive age with chronic primary pain:  
a systematic review*

## **Background**

Chronic pain refers to pain lasting at least 3 months, with ‘chronic primary pain’ being defined as “chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) or functional disability (interference in daily life activities and reduced participation in social roles).” (1) The etiology of chronic primary pain is multifactorial, involving a complex interplay of biological, psychological and social factors. Diagnosis is made independently of biological or psychological contributors and only made if no other “diagnosis would better account for the presenting symptoms.” (1)

Among the most frequently diagnosed forms of chronic primary pain are chronic nonspecific low back pain and fibromyalgia. Episodic low back pain is common among the general population, with 11-84% of adults experiencing at least one episode during their lifetime. Of these individuals, approximately 40% will develop chronic low back pain. (2) The point prevalence of fibromyalgia among the general population has been estimated to be 1.78%, being significantly higher in women (3.98%) than men (0.01%). (3)

Chronic primary pain poses a tremendous burden on the healthcare system. For example, when accounting for both direct and indirect costs, low back pain is associated with an expenditure of 12 billion British pounds in the United Kingdom. (4) Fibromyalgia is a significant cause of work disability, with the number of hours of work being often reduced by 50-75%. With regards to healthcare payer burden, a Canadian survey reported an average 6-month direct medical cost per patient of \$2298 CAD, the most significant components of this cost being medication (\$758 CAD), and diagnostic tests (\$356 CAD). (5)

There is a limited evidence base for informing clinical practice guidelines for the management of chronic primary pain. Pharmacological management often comprises

antidepressants, muscle relaxants, NSAIDs, and/or opioids. (6, 7) While some of these have direct pain relief qualities (e.g. NSAIDs and opioids), the mode of action of others (e.g. selective serotonin reuptake inhibitors) remain unclear and controversial. (6) Non-pharmacological interventions (e.g. exercise, physiotherapy, and complementary and alternative medicine interventions) have also been shown to be effective in many cases of chronic pain. For example, for chronic nonspecific low back pain, it is recommended that simple therapies (i.e. exercise) may be sufficient, but no single intervention is likely to be effective in treating all patients. (6)

Reports of adverse effects of therapies for chronic primary pain patients are sparse; especially in women of reproductive age who may be pregnant. Even so, there is strong evidence of the side-effects profiles of many commonly used pharmacological therapies. For instance, a fifth of patients taking antidepressives report have adverse reactions (e.g. drowsiness, dry mouth, dizziness, constipation), (6) NSAID use is associated with gastrointestinal complications (e.g. irritation, ulcers, bleeding) and muscle relaxants are often associated with drowsiness, dizziness, and addiction. The same also applies for opioids which may be associated with dependence, constipation, dizziness, and sweating; (6) not to mention an international dependence crisis. To our knowledge, no evidence-based guidelines are available for the management of chronic primary pain in women of reproductive age. As such, the objective of this systematic review was to identify, critically-appraise and analyze the best evidence on the efficacy and safety of both pharmacologic and nonpharmacologic interventions for managing pain in women of reproductive age diagnosed with chronic primary pain. The results of this work will support the production of an evidence-based guideline by the Society of Obstetricians and Gynaecologists of Canada (SOGC) on 'Chronic pain in women who are pregnant or planning pregnancy'.

## **Methods**

This systematic review was conducted in accordance to the methodological approaches outlined in the Cochrane Handbook for Systematic Reviewers and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria. We identified and developed a team of clinicians from different backgrounds and geographical location across Canada. The research group included experts in pain management, nursing, research methodology, statistical methods, and library sciences. Through a priori discussions between the research team and the knowledge users, we developed a clinical query, identified the details of the population, interventions, comparators, outcomes of interest to this review and appropriate study designs (PICOS). Please see Appendix 1-2 for the PICOS and analytic plan, respectively. Further, search strategies were developed by an experienced trial search expert (librarian) in consultation with an expert search strategist (who also peer-reviewed the final search strategies).

Following a preliminary search of the three commonly used bibliographic databases (Medline, Embase, and the Cochrane Library), we identified dozens of relevant published systematic reviews related to the clinical question being reviewed. As we further anticipated dozens more additional reviews being identified upon meticulous screening of these databases and other relevant bibliographic databases, we decided that for feasibility and decreasing research waste, we will identify previous systematic reviews, meta-analyses or pooled studies related to the clinical question and review their included trials to determine if they meet the inclusion criteria of the current evidence synthesis.

Detailed inclusion and exclusion criteria are reported in Appendix 1. In brief, for Key Question (KQ1), we included randomized controlled trials (RCTs) of pharmacological and/or nonpharmacological pain management (monotherapy or combination therapy). For KQ2, we

expanded the inclusion criteria to additional study designs (e.g. retrospective and cross-sectional studies) of clinical interviews or drug toxicology screening tests compared with another method of eliciting information on drug-seeking or dependence behavior. Further, for KQ2, due to lack of identifying any studies specifically in the population of interest to this review, we expanded the inclusion to any population defined as having chronic pain.

Titles and abstracts of citations, and relevant full-texts, from the bibliographic databases were screened by one reviewer, with clarifications provided by the team members on inclusion, as required. All studies selected for inclusion, data extractions and risk of bias assessments (using the Cochrane risk of bias tool for RCTs)/ quality assessment (for observational study designs) were conducted by one reviewer and double-checked for accuracy and completeness by a second reviewer. Discrepancies were resolved at all stages by discussion, consensus and discussing with a third team member (e.g. methods expert or clinical expert depending on the conflict).

Summary data is presented graphically and using frequency analyses. No formal meta-analysis was conducted as the data was sparse, heterogeneous, or required complex meta-analytic techniques (e.g. network meta-analysis) to be properly analyzed; which outside the scope of this review.

## **Results**

For KQ1, from 3,677 citations retrieved from the bibliographic databases, we identified 83 RCTs, systematic reviews, meta-analyses, pooled analyses, and clinical practice guidelines of potential relevance (Figure 1). None of the secondary sources of evidence (e.g. systematic reviews) specifically provided evidence for this review question. Even so, we did identify 657 citations of potentially relevant RCTs that might be of interest to this review in their referenced citations. Upon reviewing the full-texts of these RCTs, we included 51 trial publications (47 primary plus four companion publications) that met the inclusion criteria for KQ1 (Appendix 3).

For KQ2, from 400 citations retrieved from the bibliographic databases, we identified 18 studies of potential relevance (Figure 2). Similar to KQ1, none provided direct evidence for this review question, but did provide a curated source of citations for further review. We identified four studies that met the broader inclusion criteria (e.g. not specifically in women of reproductive age) for KQ2 (Appendix 4).

None of the included trials included for either KQ were specifically in pregnant women and therefore, we performed a directed literature search to identify evidence on primary chronic pain and pregnancy. From 3,795 citations identified from the bibliographic databases, we included 17 studies of relevance. As this was beyond the scope of this review, we have provided the list of citations in Appendix 5 for review without any further assessment or analysis.

### ***Study demographics***

For KQ1, in summary, trials randomized between 21 and 393 participants to 40 different interventions/ combinations of interventions (Figure 3). We did not consider education alone as a pain management intervention and classified it as ‘no intervention’. Most arms included women

of reproductive age ranging from 75 – 100% of the participants in each trial arm. The mean age of women in each trial arm was 36.3 years old and the most common diagnoses were fibromyalgia and primary chronic low back/ neck pain. Most trials were at unclear/ high risk of bias due to lack of blinding of participants/ trial personnel.

For KQ2, the four included trials used the natural language processing (NLP) technique, a Prescription Drug Use Questionnaire - Patient Version (PDUQp), the PainCAS (Clinical Assessment System) and 1) completion of monthly electronic diaries; 2) monthly urine screens for 6 months; 3) monthly completion of the Opioid Compliance Checklist; 4) monthly group education sessions with worksheet handouts on topics related to substance misuse; and 5) participation in individual motivational compliance counseling. These were compared against clinician-documented violation of the opioid agreement, National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the Alcohol Use Disorder and Associated Disabilities Interview (AUDADIS), paper-and-pencil comprehensive pain assessments and electronic diaries.

### ***Outcome of interest***

For KQ1, the most commonly reported outcome was reduction of acute pain symptoms using self-reporting (27 trials) and functional status (21 trials). Far less trials followed up patients to determine if the intervention had an effect on reducing pain more than 30 days (12 trials), or its effect on their quality of sleep (n = 7), health-related quality of life (n = 1), and mental health status (n = 11). Additional pain medication use was allowed by most trials, even though it was not reported if there was any change in their use during the trial period. Details of the effect estimates per trial are available upon request.

The most commonly used interventions were based around exercise (e.g. increasing strength and/ endurance), coping with pain (e.g. cognitive behavioral therapy, stress reduction techniques) and physiotherapy. Interventions were usually compared against other active interventions, wait lists/ no intervention or sham/ placebo interventions. Less frequently were analgesics, antidepressants or muscle relaxants used in the included trials as a comparator.

Most trials showed small benefits reflected in reduced pain assessments and increased functionality. It is not clear if this resulted in less analgesic rescue, but could be expected to have done so. Further, as no trials were in pregnant women, it is unclear what the side effect profile is expected to be in this population. Even so, no trials reported high numbers of drop-outs due to side-effects or any severe adverse effects.

For KQ2, only two studies reported the diagnostic accuracy results of the tests. NLP had a high sensitivity, specificity, positive predictive value, and negative predictive value (96.1%, 92.8%, 92.6%, and 96.6%, respectively). PDUQp fared much less and depended on opioid misuse, prescription opioid use disorder (any) or prescription opioid use disorder (moderate to severe).

## **Conclusions**

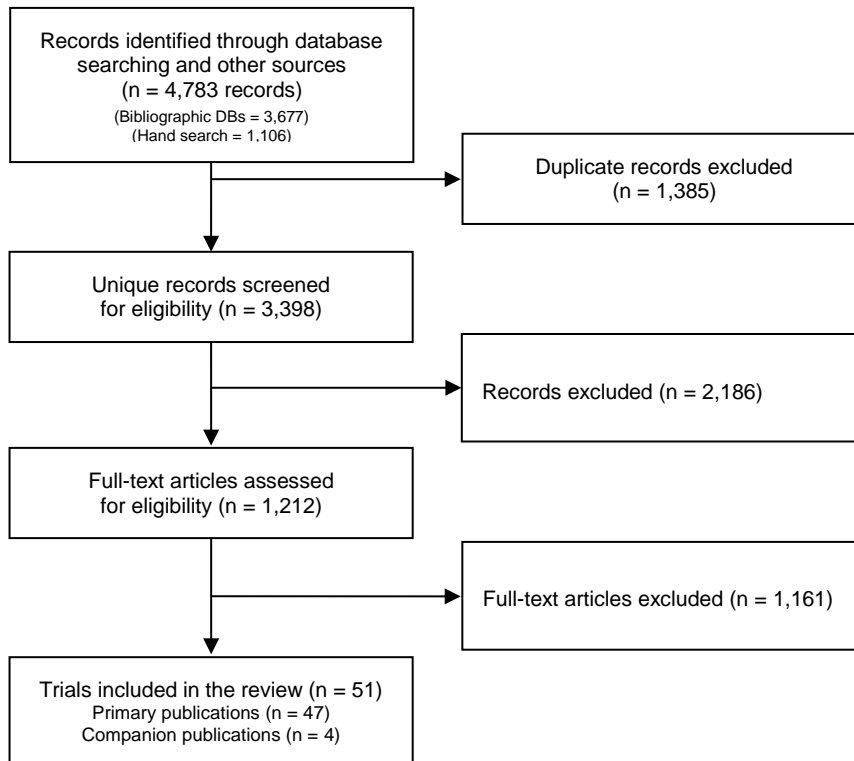
There is a dearth of evidence on pain management interventions in pregnant women and evidence to support this patient population will require indirect high quality evidence from other patient populations, lower quality study designs (e.g. cohort and registry-based studies) in this population and/ or expert opinion. Evidence from randomized trials of women of reproductive age, but not pregnant at the time of the trial shows promising results for non-pharmacological interventions that are expected to be safer on the pregnant mother and growing fetus than the traditional analgesic regimens or other pharmacological interventions (e.g. antidepressants).



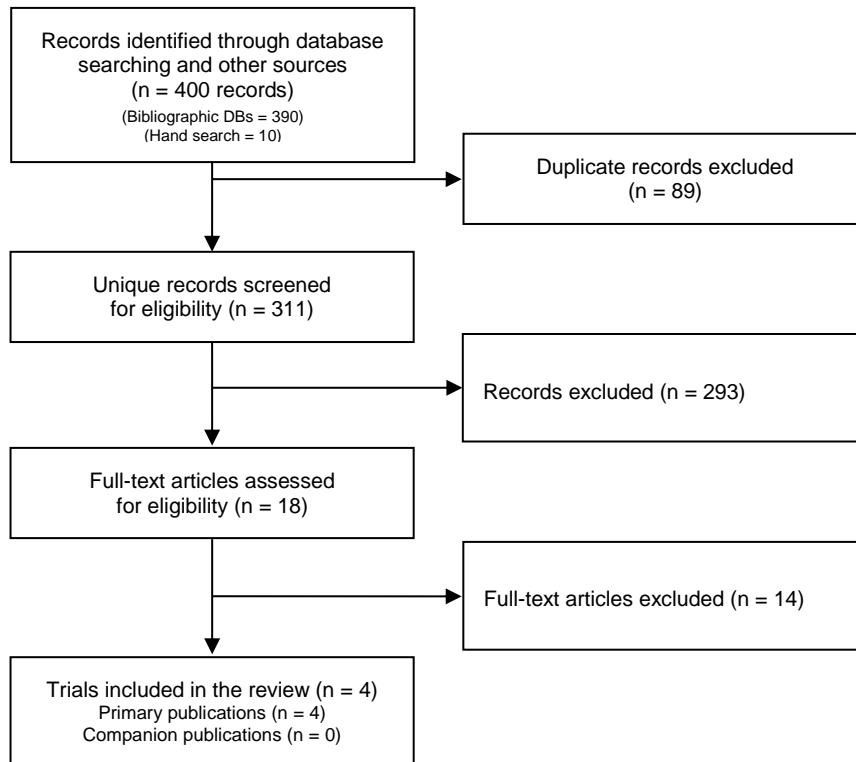
## References

1. ICD-11: International Classification of Diseases for Mortality and Morbidity Statistics [Internet]. 2018.
2. Miyamoto GC, Costa LO, Cabral CM. Efficacy of the Pilates method for pain and disability in patients with chronic nonspecific low back pain: a systematic review with meta-analysis. *Brazilian journal of physical therapy*. 2013;17(6):517-32.
3. Heidari F, Afshari M, Moosazadeh M. Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. *Rheumatology international*. 2017;37(9):1527-39.
4. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *The spine journal : official journal of the North American Spine Society*. 2008;8(1):8-20.
5. Penrod JR, Bernatsky S, Adam V, Baron M, Dayan N, Dobkin PL. Health services costs and their determinants in women with fibromyalgia. *The Journal of rheumatology*. 2004;31(7):1391-8.
6. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society*. 2006;15 Suppl 2:S192-300.
7. Chung JW, Zeng Y, Wong TK. Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. *Pain physician*. 2013;16(6):E685-704.
8. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. *Fertility and sterility*. 2017;108(3):393-406.
9. Provencher C, Milan A, S. H, D'Aoust C. Report on the Demographic Situation in Canada. Fertility: Overview, 2012 to 2016 Ottawa: Statistics Canada; 2018 [Available from: <https://www150.statcan.gc.ca/n1/pub/91-209-x/2018001/article/54956-eng.htm>].
10. Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*. 2019;160(1):28-37.

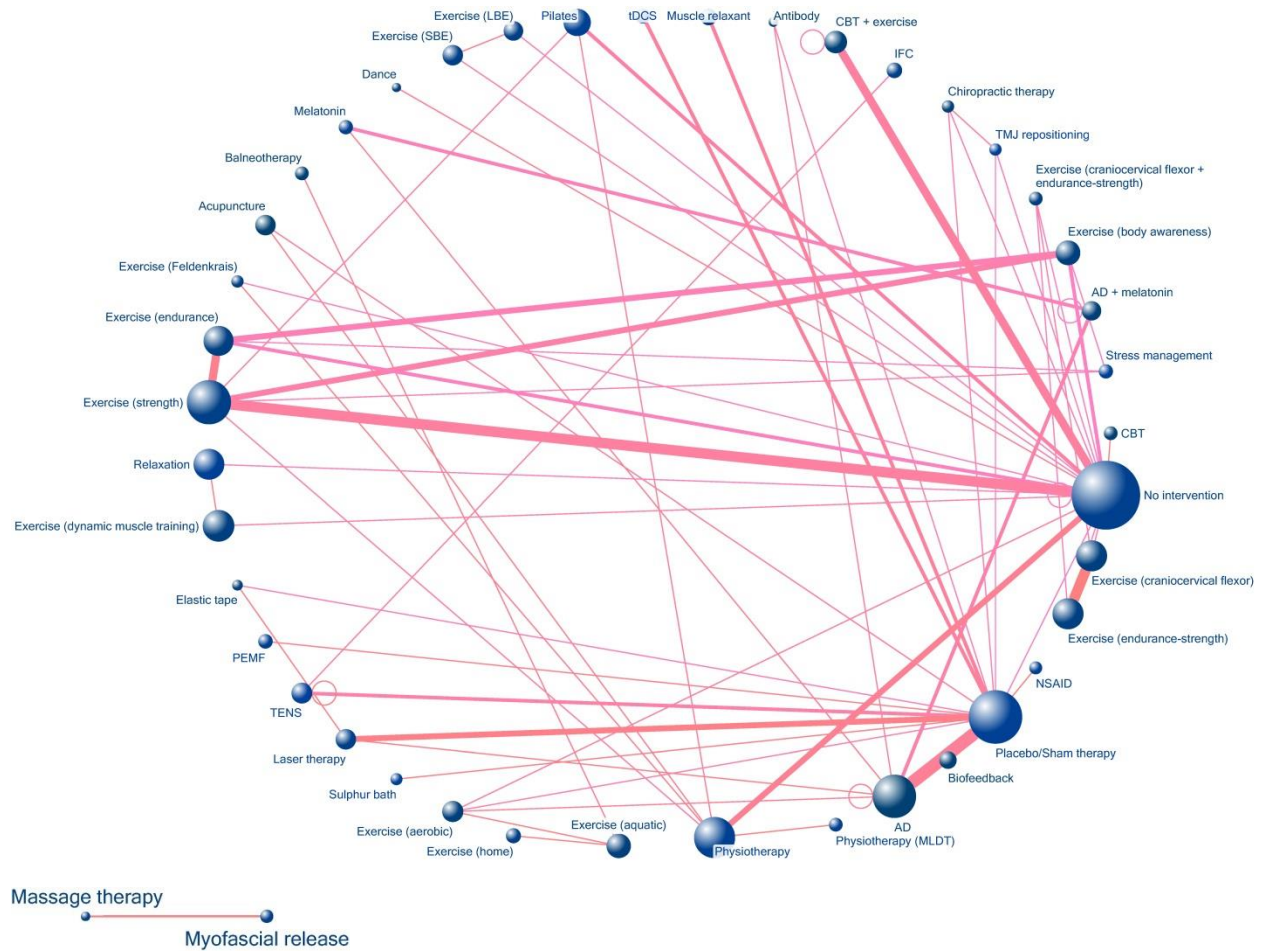
**Figure 1. Modified PRISMA flow diagram for KQ1.**



**Figure 2. Modified PRISMA flow diagram for KQ2.**



**Figure 3. Network plot for all pain management interventions included in this review (KQ1).**



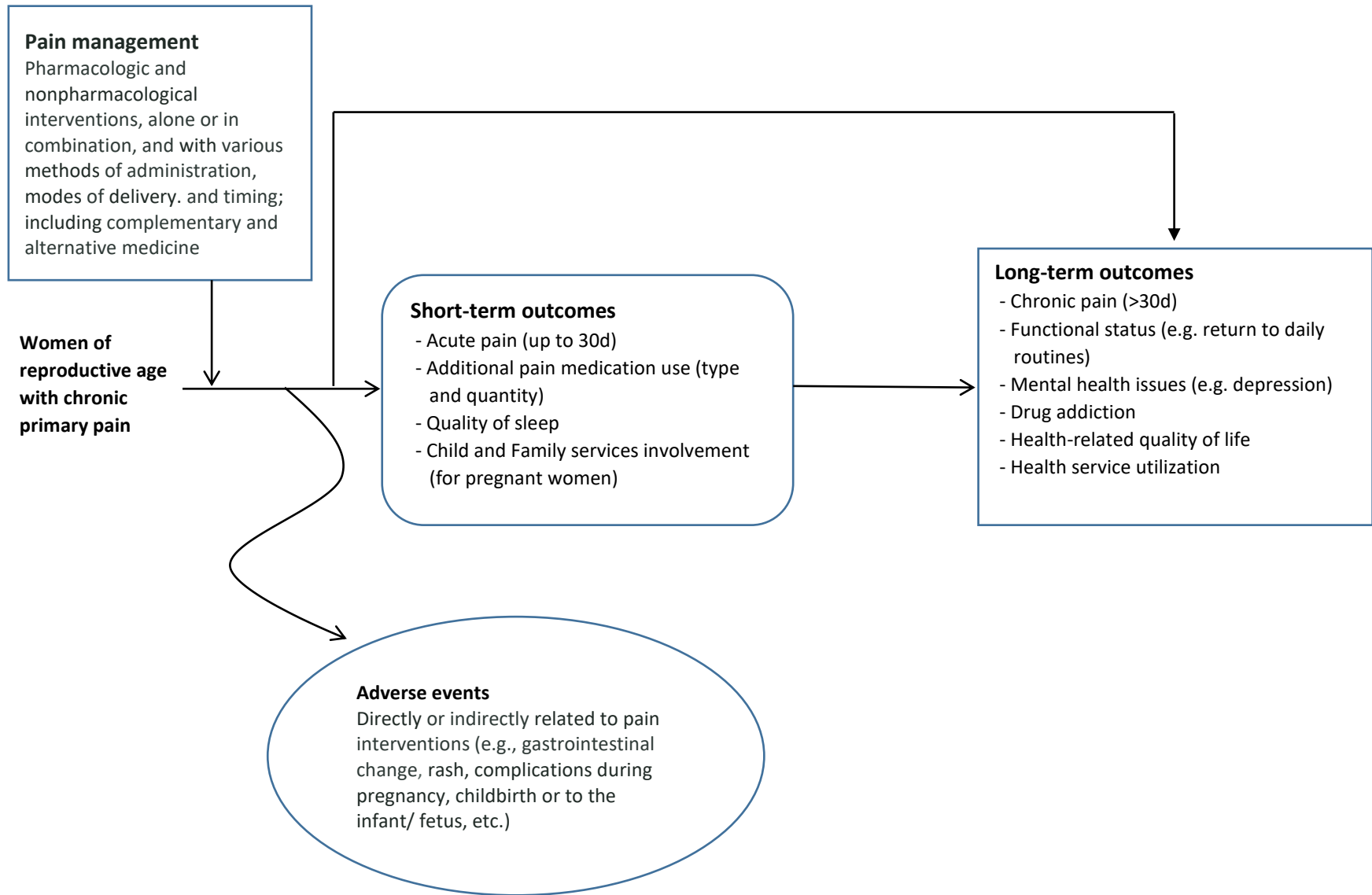
AD = anti-depressant; CBT = cognitive behavioral therapy; IFC = interferential current; LBE = long bouts of exercise; NSAID = non-steroidal anti-inflammatory drugs; MLDT = manual lymph drainage therapy; PEMF = pulsed electromagnetic field therapy; SBE = short bouts of exercise; tDCS = transcranial direct current stimulation; TENS = transcutaneous electrical nerve stimulation; TMJ = temporomandibular joint.

Note: Size of the spheres represents the sample size; thickness of the lines represents the relative number of included trials directly comparing the two interventions.

## Appendix 1: PICOS (Population, Interventions, Comparator, Outcomes, Study Design)

- **Population:** Women of reproductive age (>80% between the ages of 15 - 49)(8, 9) with chronic primary pain (ICD-11 classification MG30.0)(10). Women may be pregnant or not at the time of study enrollment. Pain must have been present for at least 3 months and must not be cancer-related pain (MG30.1), postsurgical pain or post traumatic pain (MG30.2), secondary musculoskeletal pain (MG30.3), secondary visceral pain (MG30.4), neuropathic pain (MG30.5), or secondary headache/ orofacial pain (MG30.6). The pain may be also be classified as chronic primary visceral pain (MG30.00), chronic widespread pain (MG30.01), chronic primary musculoskeletal pain (MG30.02), Chronic primary headache or orofacial pain (MG30.03), Complex regional pain syndrome (8D8A.0), Other specified chronic primary pain (MG30.0Y), or chronic primary pain, unspecified (MG30.0Z). If ICD-11 classification is not used by the definitions used by the study authors will be matched to the closest ICD-11 definition.
- **Interventions:**
  - **KQ1:** Pharmacological and/or nonpharmacological pain management (monotherapy or combination therapy, regardless of mode of administration or time point during the care pathway). Additional pain management therapies may be provided as long as it given to both treatment arms.
  - **KQ2:** Clinical interviews or drug toxicology screening tests
- **Comparators:**
  - **KQ1:** Usual care (as defined by study authors) or another intervention(s) for pain management, administered as monotherapy or combination therapy.
  - **KQ2:** Another method of eliciting information on drug-seeking or dependence behavior.
- **Outcomes:** Please see the analytic framework (below).
- **Study designs:**
  - **KQ1:** Properly randomized controlled trials
  - **KQ2:** Cross-sectional studies
- **Subgroups:**
  - **Population:** Pregnant vs. Non-pregnant
  - **Interventions/ comparators: Different types, doses and frequency of administration of intervention/ comparator**
- **Settings:** Hospital/ care facility vs. Outpatient

## Appendix 2. Analytic framework.



### **Appendix 3. Citations of randomized trials meeting the inclusion criteria of KQ1.**

1. Acedo AA, Antunes ACL, Dos Santos AB, De Oliveira CB, Dos Santos CT, Colonezi GLT, et al. Upper trapezius relaxation induced by tens and interferential current in computer users with chronic nonspecific neck discomfort: An electromyographic analysis. *Journal of Back and Musculoskeletal Rehabilitation*. 2015;28(1):19-24.
2. Ahlgren C, Waling K, Kadi F, Djupsjöbacka M, Thornell LE, Sundelin G. Effects on physical performance and pain from three dynamic training programs for women with work-related trapezius myalgia. *Journal of Rehabilitation Medicine*. 2001;33(4):162-9.
3. Alexandre NMC, De Moraes MAA, Corrêa Filho HR, Jorge SA. Evaluation of a program to reduce back pain in nursing personnel. *Revista de Saude Publica*. 2001;35(4):356-61.
4. Altan L, Bingöl U, Aykaç M, Koç Z, Yurtkuran M. Investigation of the effects of pool-based exercise on fibromyalgia syndrome. *Rheumatology International*. 2004;24(5):272-7.
5. Armagan O, Tascioglu F, Ekim A, Oner C. Long-term efficacy of low level laser therapy in women with fibromyalgia: A placebo-controlled study. *Journal of Back and Musculoskeletal Rehabilitation*. 2006;19(4):135-40.
6. Borisut S, Vongsirinavarat M, Vachalathiti R, Sakulsriprasert P. Effects of strength and endurance training of superficial and deep neck muscles on muscle activities and pain levels of females with chronic neck pain. *Journal of Physical Therapy Science*. 2013;25(9):1157-62.
7. Carette S, McCain GA, Bell DA, Fam AG. Evaluation of amitriptyline in primary fibrositis. A double-blind, placebo-controlled study. *Arthritis and rheumatism*. 1986;29(5):655-9.
8. De Meulemeester KE, Castelein B, Coppieters I, Barbe T, Cools A, Cagnie B. Comparing Trigger Point Dry Needling and Manual Pressure Technique for the Management of Myofascial Neck/Shoulder Pain: A Randomized Clinical Trial. *Journal of Manipulative and Physiological Therapeutics*. 2017;40(1):11-20.
9. DeVocht JW, Goertz CM, Hondras MA, Long CR, Schaeffer W, Thomann L, et al. A pilot study of a chiropractic intervention for management of chronic myofascial temporomandibular disorder. *Journal of the American Dental Association (1939)*. 2013;144(10):1154-63.
10. Donnell A, Nascimento TD, Lawrence M, Gupta V, Zieba T, Truong DQ, et al. High-definition and non-invasive brain modulation of pain and motor dysfunction in chronic TMD. *Brain Stimulation*. 2015;8(6):1085-92.
11. Ekici G, Bakar Y, Akbayrak T, Yuksel I. Comparison of manual lymph drainage therapy and connective tissue massage in women with fibromyalgia: a randomized controlled trial. *J Manipulative Physiol Ther*. 2009;32(2):127-33.
12. Evcik D, Yigit I, Pusak H, Kavuncu V. Effectiveness of aquatic therapy in the treatment of fibromyalgia syndrome: A randomized controlled open study. *Rheumatology International*. 2008;28(9):885-90.

13. Falla D, Jull G, Hodges P, Vicenzino B. An endurance-strength training regime is effective in reducing myoelectric manifestations of cervical flexor muscle fatigue in females with chronic neck pain. *Clin Neurophysiol.* 2006;117(4):828-37.
14. Falla D, Jull G, Russell T, Vicenzino B, Hodges P. Effect of neck exercise on sitting posture in patients with chronic neck pain. *Physical Therapy.* 2007;87(4):408-17.
15. Ginsberg F, Joos E, Géczy J, Bruhwyler J, Vandekerckhove K, Famaey JP. A pilot randomized placebo-controlled study of pirlindole in the treatment of primary fibromyalgia. *Journal of Musculoskeletal Pain.* 1998;6(2):5-17.
16. Giordano N, Geraci S, Santacroce C, Mattii G, Battisti E, Gennari C. Efficacy and tolerability of paroxetine in patients with fibromyalgia syndrome: A single-blind study. *Current Therapeutic Research - Clinical and Experimental.* 1999;60(12):696-702.
17. Goebel A, Baranowski A, Maurer K, Ghiai A, McCabe C, Ambler G. Intravenous immunoglobulin treatment of the complex regional pain syndrome: a randomized trial. *Annals of internal medicine.* 2010;152(3):152-8.
18. Groeneweg G, Huygen FJPM, Niehof SP, Wesseldijk F, Bussmann JBJ, Schasfoort FC, et al. Effect of tadalafil on blood flow, pain, and function in chronic cold Complex Regional Pain Syndrome: A randomized controlled trial. *BMC Musculoskeletal Disorders.* 2008;9.
19. Gür A, Karakoc M, Nas K, Cevik R, Sarac A, Ataoglu S. Effects of low power laser and low dose amitriptyline therapy on clinical symptoms and quality of life in fibromyalgia: A single-blind, placebo-controlled trial. *Rheumatology International.* 2002;22(5):188-93.
20. Hagberg M, Harms-Ringdahl K, Nisell R, Wigaeus Hjelm E. Rehabilitation of neck-shoulder pain in women industrial workers: A randomized trial comparing isometric shoulder endurance training with isometric shoulder strength training. *Archives of Physical Medicine and Rehabilitation.* 2000;81(8):1051-8.
21. Häkkinen A, Häkkinen K, Hannonen P, Alen M. Strength training induced adaptations in neuromuscular function of premenopausal women with fibromyalgia: Comparison with healthy women. *Annals of the rheumatic diseases.* 2001;60(1):21-6.
22. Häkkinen K, Pakarinen A, Hannonen P, Häkkinen A, Airaksinen O, Valkeinen H, et al. Effects of strength training on muscle strength, cross-sectional area, maximal electromyographic activity, and serum hormones in premenopausal women with fibromyalgia. *Journal of Rheumatology.* 2002;29(6):1287-95.
23. Hussain SA, Al K, II, Jasim NA, Gorial FI. Adjuvant use of melatonin for treatment of fibromyalgia. *J Pineal Res.* 2011;50(3):267-71.
24. Jaromi M, Nemeth A, Kranicz J, Laczko T, Betlehem J. Treatment and ergonomics training of work-related lower back pain and body posture problems for nurses. *Journal of clinical nursing.* 2012;21(11-12):1776-84.
25. Jensen KB, Kosek E, Wicksell R, Kemani M, Olsson G, Merle JV, et al. Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. *Pain.* 2012;153(7):1495-503.



26. Jentoft ES, Kvalvik AG, Mengshoel AM. Effects of pool-based and land-based aerobic exercise on women with fibromyalgia/chronic widespread muscle pain. *Arthritis and rheumatism*. 2001;45(1):42-7.
27. Jull GA, Falla D, Vicenzino B, Hodges PW. The effect of therapeutic exercise on activation of the deep cervical flexor muscles in people with chronic neck pain. *Man Ther*. 2009;14(6):696-701.
28. Kayiran S, Dursun E, Dursun N, Ermutlu N, Karamürsel S. Neurofeedback intervention in fibromyalgia syndrome; A randomized, controlled, rater blind clinical trial. *Applied Psychophysiology Biofeedback*. 2010;35(4):293-302.
29. Kempnaers C, Simenon G, Vander Elst M, Fransolet L, Mingard P, de Maertelaer V, et al. Effect of an antidiencephalon immune serum on pain and sleep in primary fibromyalgia. *Neuropsychobiology*. 1994;30(2-3):66-72.
30. Kofotolis N, Kellis E, Vlachopoulos SP, Gouitas I, Theodorakis Y. Effects of Pilates and trunk strengthening exercises on health-related quality of life in women with chronic low back pain. *Journal of Back & Musculoskeletal Rehabilitation*. 2016;29(4):649-59.
31. Kwanchuay P, Petchnumsin T, Yiemsiri P, Pasuk N, Srikanok W, Hathaiareerug C. Efficacy and Safety of Single Botulinum Toxin Type A (Botox(R)) Injection for Relief of Upper Trapezius Myofascial Trigger Point: A Randomized, Double-Blind, Placebo-Controlled Study. *Journal of the Medical Association of Thailand = Chotmai het thangphaet*. 2015;98(12):1231-6.
32. Lauretti GR, Chubaci EF, Mattos AL. Efficacy of the use of two simultaneously TENS devices for fibromyalgia pain. *Rheumatology International*. 2013;33(8):2117-22.
33. Lundblad I, Elert J, Gerdle B. Randomized controlled trial of physiotherapy and Feldenkrais interventions in female workers with neck-shoulder complaints. *Journal of Occupational Rehabilitation*. 1999;9(3):179-94.
34. Mengshoel AM, Førre Ø. Physical Fitness Training in Patients with Fibromyalgia. *Journal of Musculoskeletal Pain*. 2010;1(3-4):267-72.
35. Mengshoel AM, Komnaes HB, Forre O. The effects of 20 weeks of physical fitness training in female patients with fibromyalgia. *Clinical and Experimental Rheumatology*. 1992;10(4):345-9.
36. Michelotti A, Steenks MH, Farella M, Parisini F, Cimino R, Martina R. The additional value of a home physical therapy regimen versus patient education only for the treatment of myofascial pain of the jaw muscles: Short-term results of a randomized clinical trial. *Journal of Orofacial Pain*. 2004;18(2):114-25.
37. Miyamoto GC, Oliveira Pena Costa L, Galvanin T, Nunes Cabral CM. Efficacy of the Addition of Modified Pilates Exercises to a Minimal Intervention in Patients With Chronic Low Back Pain: A Randomized Controlled Trial. *Physical therapy*. 2013;93(3):309-21.
38. Nugraha B, Neues-Lahusen M, Candir F, Gutenbrunner C. Effect of a Series of H2S Mineral Water Bathing on Pain in Patients with Fibromyalgia Syndrome – A Pilot Study. *Physikalische Medizin, Rehabilitationsmedizin, Kurortmedizin*. 2011;21(06):284-9.

39. O'Leary S, Falla D, Hodges PW, Jull G, Vicenzino B. Specific therapeutic exercise of the neck induces immediate local hypoalgesia. *The journal of pain : official journal of the American Pain Society*. 2007;8(11):832-9.
40. Oliveira LB, Lopes TS, Soares C, Maluf R, Goes BT, Sá KN, et al. Transcranial direct current stimulation and exercises for treatment of chronic temporomandibular disorders: A blind randomised-controlled trial. *Journal of Oral Rehabilitation*. 2015;42(10):723-32.
41. Pecos-Martín D, Montañez-Aguilera FJ, Gallego-Izquierdo T, Urraca-Gesto A, Gómez-Conesa A, Romero-Franco N, et al. Effectiveness of dry needling on the lower trapezius in patients with mechanical neck pain: A randomized controlled trial. *Archives of Physical Medicine and Rehabilitation*. 2015;96(5):775-81.
42. Rajpal N, Arora M, Chauhan V. A study on efficacy of Pilates and McKenzie exercises in postural low back pain: A rehabilitative protocol. *Physiother Occup Ther J*. 2008;1(1):33-56.
43. Schachter CL, Busch AJ, Peloso PM, Sheppard MS. Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: a randomized controlled trial. *Phys Ther*. 2003;83(4):340-58.
44. Sencan S, Ak S, Karan A, Muslumanoglu L, Ozcan E, Berker E. A study to compare the therapeutic efficacy of aerobic exercise and paroxetine in fibromyalgia syndrome. *Journal of Back and Musculoskeletal Rehabilitation*. 2004;17(2):57-61.
45. Sutbeyaz ST, Sezer N, Koseoglu F, Kibar S. Low-frequency pulsed electromagnetic field therapy in fibromyalgia: a randomized, double-blind, sham-controlled clinical study. *The Clinical journal of pain*. 2009;25(8):722-8.
46. van Koulil S, van Lankveld W, Kraaimaat FW, van Helmond T, Vedder A, van Hoorn H, et al. Tailored cognitive-behavioral therapy and exercise training for high-risk patients with fibromyalgia. *Arthritis Care Res (Hoboken)*. 2010;62(10):1377-85.
47. Vayvay ES, Tok D, Turgut E, Tunay VB. The effect of Laser and taping on pain, functional status and quality of life in patients with fibromyalgia syndrome: A placebo- randomized controlled clinical trial. *J Back Musculoskelet Rehabil*. 2016;29(1):77-83.
48. Viljanen M, Malmivaara A, Uitti J, Rinne M, Palmroos P, Laippala P. Effectiveness of dynamic muscle training, relaxation training, or ordinary activity for chronic neck pain: Randomised controlled trial. *British Medical Journal*. 2003;327(7413):475-7.
49. Waling K, Jarvholm B, Sundelin G. Effects of training on female trapezius Myalgia: An intervention study with a 3-year follow-up period. *Spine*. 2002;27(8):789-96.
50. Waling K, Sundelin G, Ahlgren C, Jarvholm B. Perceived pain before and after three exercise programs - a controlled clinical trial of women with work-related trapezius myalgia. *Pain*. 2000;85(1-2):201-7.
51. Yunus MB, Masi AT, Aldag JC. Short term effects of ibuprofen in primary fibromyalgia syndrome: a double blind, placebo controlled trial. *The Journal of rheumatology*. 1989;16(4):527-32.

#### **Appendix 4. Citations of studies providing indirect evidence for KQ2.**

1. Haller IV, Renier CM, Juusola M, Hitz P, Steffen W, Asmus MJ, et al. Enhancing Risk Assessment in Patients Receiving Chronic Opioid Analgesic Therapy Using Natural Language Processing. *Pain medicine (Malden, Mass)*. 2017;18(10):1952-60.
2. Butler SF, Zacharoff KL, Charity S, Black RA, Chung E, Barreveld A, et al. Impact of an Electronic Pain and Opioid Risk Assessment Program: Are There Improvements in Patient Encounters and Clinic Notes? *Pain Medicine*. 2016;17(11):2047-60.
3. Beaudoin FL, Merchant RC, Clark MA. Prevalence and Detection of Prescription Opioid Misuse and Prescription Opioid Use Disorder Among Emergency Department Patients 50 Years of Age and Older: Performance of the Prescription Drug Use Questionnaire, Patient Version. *American Journal of Geriatric Psychiatry*. 2016;24(8):627-36.
4. Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD, et al. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: a randomized trial. *Pain (03043959)*. 2010;150(3):390-400.

#### **Appendix 5. Citations of studies on pregnancy and chronic pain.**

1. Anonymous. Substance use in pregnancy: No. 256, April 2011. *International Journal of Gynecology and Obstetrics*. 2011;114(2):190-202.
2. Fedoroff IC, Blackwell E, Malysh L, McDonald WN, Boyd M. Spinal cord stimulation in pregnancy: A literature review. *Neuromodulation*. 2012;15(6):537-41.
3. Jankiewicz A, Fielder A, Warland J. Chronic Pain Management in Pregnancy: A Review of the Literature. *Canadian Journal of Midwifery Research & Practice*. 2015;14(2):34-42.
4. Morsy KM, Osman AM, Shaaban OM, El-Hammady DH. Post Dural Puncture Headache in Fibromyalgia after Cesarean Section: A Comparative Cohort Study. *Pain physician*. 2016;19(6):E871-6.
5. Ostensen M, Rugelsjoen A, Horven Wigers S. The effect of reproductive events and alterations of sex hormone levels on the symptoms of fibromyalgia. *Scandinavian Journal of Rheumatology*. 1997;26(5):355-60.
6. Pritham UA, McKay L. Safe management of chronic pain in pregnancy in an era of opioid misuse and abuse. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN*. 2014;43(5):554-67.
7. Souzdalnitski D, Snegovskikh D. Analgesia for the parturient with chronic nonmalignant pain. *Techniques in Regional Anesthesia and Pain Management*. 2014;18(4):166-71.
8. Weimer MB, Chou R. Research gaps on methadone harms and comparative harms: Findings from a review of the evidence for an American Pain Society and College on Problems of drug dependence clinical practice guideline. *Journal of Pain*. 2014;15(4):366-76.

9. Kahan M, Srivastava A, Spithoff S, Bromley L. Prescribing smoked cannabis for chronic noncancer pain: preliminary recommendations. *Canadian family physician Medecin de famille canadien*. 2014;60(12):1083-90.
10. Andrade C. Safety of Pregabalin in Pregnancy. *The Journal of clinical psychiatry*. 2018;79(5).
11. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The journal of pain*. 2009;10(2):113-30.
12. Young AC, Lubenow TR, Buvanendran A. The parturient with implanted spinal cord stimulator: management and review of the literature. *Regional anesthesia and pain medicine*. 2015;40(3):276-83.
13. Task Force on the Low Back Pain Clinical Practice G. American Osteopathic Association Guidelines for Osteopathic Manipulative Treatment (OMT) for Patients With Low Back Pain. *The Journal of the American Osteopathic Association*. 2016;116(8):536-49.
14. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A. Canadian guideline for safe and effective use of opioids for chronic noncancer pain - Clinical summary for family physicians. Part 2: Special populations. *Canadian Family Physician*. 2011;57(11):1269-76.
15. Ray-Griffith SL, Wendel MP, Stowe ZN, Magann EF. Chronic pain during pregnancy: a review of the literature. *International journal of women's health*. 2018;10:153-64.
16. Gentile S, Fusco ML. Managing fibromyalgia syndrome in pregnancy no bridges between USA and EU. *Archives of Women's Mental Health*. 2019.
17. Hemsing N, Greaves L, Poole N, Schmidt R. Misuse of Prescription Opioid Medication among Women: A Scoping Review. *Pain research & management*. 2016;2016:1754195.