Chronic non malignant pain in the Older population: Rapid systematic review

Treatment recommendations

Version 1 11 2023

Center for Evidence, Research and Innovation for Health Decisions

PRESIDENCIA DE SALUD E INNOVACIÓN

Developer Group

Thematic Team

Olga Gómez
MD, Sp Family Medicine
Programs and clinical management Assistant Manager
Global Institute for Clinical Excellence
Presidency of Health and Innovation, Keralty

Nancy Yomayusa
M.D.,Sp. Internal Medicine and Nephrology
Vice president
Global Institute for Clinical Excellence
Presidency of Health and Innovation, Keralty

Hector Mauricio Cardenas
M.D.,Sp. Internal Medicine and Geriatrics.
Global Committee for the Elderly, Keralty

Wilson Daniel Ossa
Psychologist, MPH.
Global Institute for Clinical Cxcellence

Daniel Castrillón
M.D., Sp
Healthcare Analysis and Optimization Unit

Estefania Muñoz
M.D., Sp
Healthcare Analysis and Optimization Unit

Methodological Team

Kelly Chacón Acevedo
Physiotherapist., MSc.
Global Institute for clinical excellence

Adriana Rodriguez
Bacteriology., MSc.
Global Institute for clinical excellence

Santiago Saldarriaga
M.D., Sp
Healthcare Analysis and Optimization Unit

Doris Restrepo
M.D., Sp
Healthcare Analysis and Optimization Unit

Jairo Uparela
M.D., Sp
Healthcare Analysis and Optimization Unit

Santiago Ospina
M.D., Sp
Healthcare Analysis and Optimization Unit

Conflict of interest

The authors and experts who participated in the development of the document declare that under the methodology established by the Global Institute of Clinical Excellence – IGEC- there is no conflict of interest that prevents or invalidates the development process (financial, intellectual, affiliation or family).

Declaration of editorial Independence

Keralty, Global Institute of Clinical Excellence, Healthcare Analysis and Optimization Unit and the authors declare that the development of the technical-scientific document was carried out in a rigorous, independent, transparent and impartial manner by its members.

Funding

This paper was financed by the Keralty Group of companies.

Cite as:

Restrepo D, Saldarriaga S, Uparela J, Ospina S, Chacón K, Ossa D, et al. Center for evidence, research and innovation for Health Decision & Healthcare Analysis and Optimization Unit. Chronic non-malignant pain in the Older population: Rapid systematic review. v1. November2023.

Use Rights

This version applies to all Keralty Companies and Countries, the guidelines consolidated must be adapted or adjusted according to the public health policies and standards issued by regulatory bodies, Ministries of Health and other Organizations of the countries where Keralty is present. A dynamic document will evolve as new evidence emerges.

Some copyrights are reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 Intergovernmental Organizations license. (CC BY-NC-SA 4.0 IGO).

 CC BY-NC-SA 4.0

Subject to the terms of the license, copying, redistribution, and adaptation of the work for non-commercial purposes is permitted, as long as the same or equivalent Creative Commons license is used and proper citation is given, as indicated above.

No use of this work should imply that Keralty, Global Institute for Clinical Excellence, or Healthcare Analysis and Optimization Unit endorses any specific organization, product, or service.

Content

Contents

Acronyms and abbreviations

ADRB	Aberrant Drug-Related Behaviour
CNMP	Chronic non-malignant pain
COT	Chronic opioid therapy
DisDat	Disability Distress Assessment Tool
DMI	Drug Misuse Index
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HRQoL	Health-related quality of life
IASP	International Association for the Study of Pain
KOA	Knee osteoarthritis
KOOS	Knee Injury and Osteoarthritis Outcome Score
LBP	Low Back Pain
MA	Meta-analysis
MEED	Morphine Equivalent Daily Dose
MSP	Musculoskeletal Pain
MSKD	Musculoskeletal disorders
OMC	Opioid Monitoring Clinic
OTA	Opioid treatment agreements
OTC	Over the counter medications
PADE	Pain Assessment for the Dementing Elderly
PCP	Primary Care Providers
PICO	Population, intervention, comparator, and outcome
PMP	Prescription monitoring programme (PMP)
PRISMA-P	Preferred reporting items for systematic reviews and meta-analysis protocol
RCT	Randomized controlled trials
RoB	Risk of bias
RR	Risk ratio
SLR	Systematic Literature Review
SOAPP-R	Screener and Opioid Assessment for Pain Patients-Revised
UDS	Urine drug screening
WOMAC	Western Ontario and McMaster Universities Arthritis Index

❖ Summary

Introduction/background: Chronic non-malignant pain has a high incidence in older adults. Appropriate geriatric pharmacotherapy, global assessment of patients' clinical and functional parameters, and integration of skills from different healthcare professionals are needed to address the medical complexity of older adults.

Objective To identify and synthesize evidence on pharmacological treatment recommendations in older adults with chronic non-malignant pain, to have them as a resource in the development of chronic pain programs in Sanitas medical centers patients.

Methodology: The Pubmed, Embase, Google Scholar, NICE and Epistemonikos databases, were searched using the set of keywords and their combination related to the targeted and rapid review, as well as design, approach, and methodology. Of the 530 records retrieved, 8 references were included.

Results This report is organized so that the highest quality evidence is presented first. Therefore, included guidelines and then systematic reviews are presented first. No relevant health technology assessments were identified.

Conclusions: The available evidence recommends comprehensive programs for the management of non-malignant chronic pain, focused on the person and their families, composed of professionals from different areas, who provide both pharmacological and non-pharmacological care, education and support

key Words: Chronic non-malignant pain, chronic pain, pharmaceutical therapy, medication optimization, multimodal care, musculoskeletal disorders.

❖ Introduction/Background

The International Association for the Study of Pain (IASP) defines chronic non-malignant pain (CNMP) as pain that persists for over three months. CNMP is a complex and variable interplay between biological, psychological, and social factors. The IASP and World Health Organization (WHO) categorize it as a chronic disease because it may last a lifetime, can lead to functional impairment, is irreversible, and requires patient rehabilitation, frequent medical care, and supervision (1–3).

Chronic non-malignant pain originates from the musculoskeletal system, and the most common sites of pain for older adults are lower back issues, arms, hips, and legs, or arthritis (2). Many studies have shown obesity to be strongly associated with knee and hip pain. People with overweight are more likely to suffer from fatigue, depression, and chronic pain, in part due to the mechanical load on weight-bearing joints. This is especially relevant in patients with knee osteoarthritis, as the knee joint is most affected in the lower extremities. As a chronic degenerative disease that could permanently damage bone joints, osteoarthritis is the most common type of arthritis (4).

Pain management in older adults can be complex because of disease interactions. The use of analgesics is the most common method of relieving pain in older adults because of its effectiveness. When analgesics are prescribed and adjusted, the physician should consider the adverse effects. Some adverse effects of analgesics are gastrointestinal bleeding, oliguria, fluid retention, decreased excretion of sodium, renal failure, and prolonged bleeding can result from the use of non-steroidal anti-inflammatory drugs. Delirium, constipation, nausea, pupil constriction, and respiratory distress are the most common adverse effects brought about by morphine. In addition, changes in body composition, advanced age, and comorbidities can affect the pharmacokinetics and pharmacodynamics of analgesics. The physiological changes related to aging can affect an individual's absorption, excretion, and analgesic response. The pain reduction effect can be less than expected (2,5).

In Canada, Chronic pain affects about one in three seniors (age ≥ 65 years). It has considerable economic implications associated with managing many consultations and resources for managing chronic pain. It is very significant for all health systems and the patient, so clinical recommendations of high reliability and evidence focus on this population and reduce adverse events related to return visits, polypharmacy, and deterioration in the quality of life (4).

This document aims to review and summarize the relevant evidence to improve and optimize the best pharmacological interventions for chronic pain management in older adults. However, the idea is to start with conservative management through non-pharmacological interventions.

1 Objective

To identify and evaluate clinical treatment recommendations for chronic non-malignant pain in older adults, to have them as a resource in the development of chronic pain programs in Sanitas Medical Centers patients.

2 Question

In older adults, what is the recommended pharmacological management for non-malignant chronic pain?

3 Methodology

We carried out a rapid review according to the Keralty-IGEC's framework. A rapid review adheres to the essential principles of systematic reviews, including scientific rigor, transparency, and reproducibility. It uses "abbreviated" systematic review methodology, including limiting search criteria, faster data extraction, and using narrative synthesis methods.

3.1 Eligibility criteria:

Based on the research question, the eligibility criteria were defined (Table 1)

Table 1. Eligibility criteria - Non malignant chronic pain in adults: pharmacological management: a Rapid Evidence Review

Population:	Older adults (>63 years) with non-malignant chronic pain (>12 weeks) of different origins, musculoskeletal, postoperative, neuropathy, mechanical, inflammatory pain or psychogenic This includes chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain and chronic primary musculoskeletal pain other than orofacial pain.
Intervention:	Pharmacological treatment
Comparador:	• Non-pharmacological treatment • Pharmacological treatment plus non-pharmacological treatment • Standard treatment • Placebo or no treatment
Outcome of interest:	Pain Control, Quality of life, Functionality, Costs, Hospitalizations, Safety (dependency, adverse effects, Complications).
Timing:	From 2013 to 6 June, 2023

Study design:	Clinical Practice guidelines, systematic reviews of literature and health technology assessments.

3.2 Search, screening and selection:

We searched Pubmed, Embase, and Epistemonikos from 2013 to June 2023 based on keywords, MeSH terms and Entree terms according to the source of information for chronic pain and pharmacological management (e.g., "chronic pain," "nociceptive pain," "musculoskeletal pain," "pain postoperative," "pain management," "pharmacological treatment," "drug therapy," analgesics opioid," "anti-inflammatory agents non-steroidal," "NSAIDs", "aged," "aged people," "elderly" and others). We searched numerous other sources, such as Google Scholar and NICE, to identify existing clinical practice guides and systematic reviews. The search strategies are presented in Appendix 1. We found 530 articles; the references were screened through the Rayyan® application by two independent investigators, who screened the study abstracts according to the inclusion and exclusion criteria. A third investigator resolved any conflicts arising regarding the selection by discussing or obtaining the study's full text. Finally, seven relevant publications that met the criteria were selected. These comprised two guidelines and six systematic reviews. See Appendix 2, which presents the PRISMA flowchart of the study selection.

3.3 Evaluation of the quality of evidence

Study selection was based on the eligibility criteria described in (Table 1). The quality of evidence was assessed by two epidemiologists independently. Any disagreement was resolved through discussion or by a third epidemiologist in case of a significant discrepancy.

The AGREE II (Appraisal of Guidelines for Research and Evaluation) instrument was used to determine the methodological quality of clinical practice guides (Table 2). ROBIS to systematic reviews (Table 3).

Table 2. Guideline assessment according to the AGREE II instrument.

AGREE II					
Neuropathic pain in adults: pharmacological management in non-specialist settings. UK. 2013. Update 22 September 2020					
Domain 1	**Domain 2**	**Domain 3**	**Domain 4**	**Domain 5**	**Domain 6**
89%	83%	100%	100%	96%	100%
Overall Assessment 1		95%	**Overall Assessment 2**		Si
AGREE II					

Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. UK. 2021					
Domain 1	**Domain 2**	**Domain 3**	**Domain 4**	**Domain 5**	**Domain 6**
82%	97%	97%	92%	89%	100%
Overall Assessment 1		93%	**Overall Assessment 2**		Si

Table 3. Quality appraisal of the included systematic reviews

Name	Domain 1	Domain 2	Domain 3	Domain 4	Risk for bias -ROBIS
Role of pharmacists in optimizing opioid therapy for chronic non-malignant pain; A systematic review. UK. 2022 (6)	**Low**	**Low**	**Low**	**Low**	**Low**
Interventions to optimize prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review. UK. 2021 (1)	**Low**	**Low**	**Low**	**High**	**Low**
Paracetamol: A Review of Guideline Recommendations. Italia. 2021 (5)	**Low**	**High**	**High**	**High**	**High**
A systematic review of the evidence for the efficacy of opioids for chronic non-cancer pain in community-dwelling older adults. UK.2020 (7)	**Low**	**Low**	**Low**	**Low**	**Low**
Low-Dose Naltrexone for Chronic Non-Cancer Pain: Clinical Effectiveness. Canada. 2017 (8)	**High**	**High**	**High**	**High**	**High**
Selective serotonin reuptake inhibitors for fibromyalgia syndrome (Review). USA. 2015 (9)	**Low**	**Low**	**Low**	**Low**	**Low**

3.4 Extraction and synthesis of information

Information extraction

The characteristics of the selected evidence were summarized using a standardized format in Excel. A single reviewer extracted data using a pilot form. A second reviewer verified the accuracy and completeness of the extracted data. Two reviewers structured the extraction instrument. The information extracted from studies

included: Name, author, country, publication year, populations, objectives/goals, interventions, and outcomes. See Appendix 3 and Appendix 4.

Information synthesis

The synthesis of the information was narrative and effect measures were reported if it was available.

4 Results

4.1 Evidence synthesis

After a detailed selection, the eight references that met the criteria are reviewed, and the information is synthesized. See Appendix 3 and Appendix 4- Evidence synthesis.

Pharmacological management of chronic primary pain

Pain Control and quality of life

Pain management in older adults can be complex because of disease interactions. The use of analgesics is the most common method of relieving pain in older adults because of its effectiveness. When analgesics are prescribed and adjusted, special consideration and warnings have to be given to older persons who might be susceptible to the adverse effects of the analgesics (2). The construction of this rapid review focused on the pharmacological management of older adult patients with chronic non-palliative pain and identified some relevant considerations for managing pain in this population.

Paracetamol is the first and preferred long-term oral analgesic for the management of knee OA and the first-line treatment for mild-to-moderate OA pain because of its safety and effectiveness. But the American College of Rheumatology (ACR) conditionally recommended paracetamol for hand, hip, or knee OA at a maximum dose of 3 g/day, especially for patients with reduced therapeutic options because of contraindications to NSAIDs, with monitor liver function (5).

There is strong evidence for the paracetamol perioperative use of oral and intravenous paracetamol as a non-opioid adjunct for pain management of patients undergoing primary total joint arthroplasty during hospitalization and after discharge (5).

It is recommended to consider the use of paracetamol before NSAIDs, especially in the elderly, due to frequent adverse events in the gastrointestinal, cardiovascular, and renal systems and the increased risk of hospitalization, renal toxicity, myocardial infarction, stroke, and death. In addition, paracetamol is recommended as the initial

pharmacological treatment of persistent pain, particularly MSP, due to its effectiveness and safety profile (5,10).

The use of paracetamol is contraindicated in patients with liver failure or alcohol abuse, as it can cause significant damage to the liver. However, the use of paracetamol in this population should be considered, with 50 - 75% dose reduction for the management of persistent pain (5,10).

Osteoarthritis Research Society International (OARSI) 2019 guidelines for OA: paracetamol was conditionally not recommended; oral and transdermal opioids were strongly not recommended as well, and oral NSAIDs were not endorsed for cardiovascular or frail patients (5).

In chronic LBP, the use of paracetamol is contradictory; some authors advise against its use, and others, however, support it, especially in elderly patients or with gastrointestinal, cardiovascular, or renal comorbidities (5).

The guide suggests considering an antidepressant, either amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine, or sertraline, for people aged 18 years and over to manage chronic primary pain after a complete discussion of the benefits and harms (10):

Tricyclic, tetracyclic, and SNRI antidepressants (amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine, or sertraline) improved quality of life, pain, sleep, and psychological distress compared with placebo. In addition, the selected anticonvulsants (e.g., pregabalin, gabapentin enacarbil, oxcarbazepine) can be considered for neuropathic pain. Capsaicin and lidocaine patches can be considered for localized neuropathic pain, especially for those who cannot tolerate oral treatments. In older adults, decisions to use tricyclic antidepressants should be made judiciously on a case-by-case basis because of risks for confusion and falls (10). Duloxetine and pregabalin are for the treatment of diabetic peripheral neuropathy, and pregabalin and gabapentin are for the treatment of postherpetic neuralgia. Duloxetine (the only SNRI with evidence for chronic primary pain) had more long-term evidence of effectiveness (10).

In patients with fibromyalgia, tricyclic (e.g., amitriptyline), the evidence indicating benefit included very low doses of 5 mg per day. The NICE guide considers it appropriate to start amitriptyline at the lowest possible dose and titrate up to no more than 100 mg per day. The efficacy of antidepressants should be reviewed at 4 to 6 weeks, and SNRI antidepressants (e.g., duloxetine, milnacipran), NSAIDs (e.g., topical diclofenac), and specific anticonvulsants (i.e., pregabalin and gabapentin) are used to improve pain, function, and quality of life. Duloxetine, milnacipran, and pregabalin are for the treatment of fibromyalgia. In older adults, the decision to use tricyclic antidepressants should be based on a fully informed discussion with the person with chronic primary pain, taking into the risks and benefits because of risks for confusion and falls (10)

Antidepressants may be used to manage chronic pain might be especially likely to benefit from antidepressant medication because these medicines may help with quality of life, pain, sleep, and psychological distress, even in the absence of a diagnosis of depression (10)

The NICE guide says if an antidepressant is offered to manage chronic primary pain, these medicines may help with quality of life, pain, sleep, and psychological distress, even in the absence of a diagnosis of depression. However, when prescribing antidepressants, the risk of withdrawal symptoms should be considered, and those not be continued if they are not helped (6).

In patients affected by osteoarthritis who have an insufficient response to nonpharmacologic interventions such as exercise for arthritis pain, topical NSAIDs can be used in patients with pain in a single or few joints near the surface of the skin (e.g., knee). For patients with osteoarthritis pain in multiple joints or incompletely controlled with topical NSAIDs, duloxetine or systemic NSAIDs can be considered.

NSAIDs should be used at the lowest effective dose and the shortest duration needed and should be used with caution, particularly in older adults and in patients with cardiovascular comorbidities, chronic renal failure, or previous gastrointestinal bleeding.

In patients with chronic lower back pain who have had an insufficient response to nonpharmacologic approaches such as exercise, clinicians can consider NSAIDs or duloxetine for patients without contraindications.

In non-specialist settings, do not start to manage with the following medicine for neuropathic pain unless advised by a specialist to do so: cannabis sativa extract, capsaicin patch, lacosamide, lamotrigine, levetiracetam, morphine, oxcarbazepine, topiramate, tramadol, venlafaxine, sodium valproate (11)

As regards the effectiveness of the use of opioids, there is limited evidence supporting their long-term use. The lack of solid clinical trials in this population is a problem in light of the increase in its use and the significant harm associated with it. Research is urgently needed to inform age-specific guidelines, which address considerations for initial assessments of chronic pain, evidence-based indications for opioid use (i.e. which medical conditions), and assessment of broader outcomes than just pain relief, such as function, mood, and quality of life, adverse effects, procedures for monitoring and review of efficacy and procedures for weaning and ceasing opioids safely (7,11).

Opioids should not be considered first-line or routine therapy for chronic pain. This does not mean that patients should be required to fail nonpharmacologic sequentially and nonopioid pharmacologic therapy or be required to use any specific treatment before proceeding to opioid therapy. Instead, Clinicians should ensure that patients are aware of the expected benefits of, common risks of, severe dangers of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients in decisions about whether to start opioid therapy (10,12). The efficacy of opioids is demonstrated to have benefits for chronic back, spinal, or arthritis pain.

Older showed a reduction in the average numeric pain scale rating from 6.35 to 2.95 in carefully selected patients (people without contraindications and who were cognitively and physically able to take opioids or supervised) (7). However, amongst community dwellings, older people with cognitive impairment had limited pain reduction, with most subjects reporting ongoing pain despite opioid use (7).

Most of the studies identified that address pain management with opioids are adjusted to a supervision, education, and control program to avoid the abuse of this medication. A study that included daily patient visits to a primary care physician clinic showed that 8% elected to wean opioids, 53% continued opioid medication, and 9% transferred care. Patients maintaining opioid treatment showed no statistically significant change in clinical outcomes such as quality of life and depression scale point compared with the baseline. For that reason, the evidence indicates that the most promising approach to increase the appropriate use of prescribed pain medication among CNMP patients is a structured opioid clinic with a multidisciplinary approach. Clinicians need to attend more to the negative impact of psychiatric and behavioral issues on the use of opioids. Additionally, they should initiate discussions with patients who are being prescribed opioids to evaluate their medication-taking behaviors and treatment effectiveness, as well as to screen for their risk of prescription opioid misuse and provide intervention as needed. In other situations (e.g., headache or fibromyalgia), the expected benefits of initiating opioids are unlikely to outweigh the risks regardless of previous nonpharmacologic and nonopioid pharmacologic therapies used (1,6).

Opioid therapy should not be initiated without consideration by the clinician and patient of an exit strategy to be used if opioid therapy is unsuccessful (10).

Before opioid therapy is initiated for chronic pain, clinicians should determine jointly with patients how functional benefit will be evaluated and establish specific, measurable treatment goals (10).

Clinicians seeing new patients already receiving opioids should establish treatment goals, including functional goals, for continued opioid therapy. Clinicians should avoid rapid tapering or abrupt discontinuation of opioids (10).

Clinicians should ensure that patients are aware of the expected benefits of, common risks of, severe dangers of, and alternatives to opioids before starting or continuing opioid therapy and should involve patients in decisions about whether to start opioid therapy (10).

Carbamazepine is an initial treatment for trigeminal neuralgia.

Quality of life and functionality

Opioid use did not improve general activity, mood, or walking ability in older adults (7).

Hospitalizations

No relevant evidence was identified on hospitalizations for chronic pain in older adults.

Safety (adverse effects)

Paracetamol has a favorable safety profile that is of utmost importance, especially in the elderly with chronic pain, without clinically relevant adverse effects using the recommended doses (up to 4 g per day). However, long-term use increased the reporting of cardiovascular, gastrointestinal, and renal adverse events during acetaminophen therapy, especially in the high dose range (5).

Cost-effectiveness

Pharmacological management is just one of the many options that can be used in practice to help patients manage their chronic pain. The committee of guidelines acknowledged the high level of expenditure currently attributable to the use of drug treatments. It was recommended that the use of such interventions should be reduced from current levels in clinical practice (10).

Unit costs can vary depending on the drug. There is variation in the costs of antidepressants, and SNRIs are slightly more expensive than other types, such as tricyclic antidepressants. However, this depends on the dose the recommendations made should reduce the use of pharmacological interventions in managing chronic primary pain. The experts suggested that there could be further savings where potential harms are avoided through the reduced use of opioids and gabapentinoids (10).

Regarding the topic of pharmacological management, it was found that there is very low-quality evidence regarding the benefits of using SSRIs in fibromyalgia, so it would be inappropriate to suggest their use for this condition (9). Regarding the use of paracetamol vs NSAIDs in patients with chronic pain of musculoskeletal origin, paracetamol is slightly less effective than NSAIDs but is consistently associated with a better gastrointestinal safety profile (5). Regarding the effectiveness of the use of low doses of naltrexone, one randomized controlled trial on pain associated with fibromyalgia, in which the authors determined that there was a significant reduction in baseline pain in women receiving low-dose naltrexone when compared to placebo. The treatment also appeared to have benefits for patients regarding improved mood and life satisfaction (8).

Regarding pharmaceutical management programs for optimizing the prescription of medications for chronic pain, especially opioids, it is concluded that multidisciplinary teams of professionals are required to carry out multi-component interventions (based on chronic pain management guidelines from the United States, such as the clinical practice guideline for the management of opioid therapy of chronic pain from the Department of Defense) aimed at health professionals and patients for the reduction of problematic medication-taking behaviors, taking into account the states physical and psychological health of patients, as well as their satisfaction (6).

5 Additional considerations

5.1 General recommendations and non-pharmacological management of chronic pain

These are some recommendations to be considered in the non-pharmacological management of older adults with chronic pain (chronic primary pain, chronic secondary pain, or both) (10).

- An interdisciplinary pain management program should include, evaluate, and manage patients with chronic pain in accordance with the guidelines established in care programs focused on older adults, including telehealth tools, digital health, and flexible schedules (1).
- In all cases of chronic pain in older adults, the evaluation should begin with a complete clinical history that identifies the comprehensive needs, the characteristics of the pain, precipitating factors, concomitant diseases, pharmacological history, and response to previous treatments, among others. The use of clinical scales to evaluate pain, doses of analgesics, cognitive impairment, functionality, and quality of life, among others, should be standard practice for the objective management of the level of pain and the treatment plan (10).
- Non-pharmacological interventions are essential as an integral part of pain treatment, and they have demonstrated improvement in pain, activity, and functionality scales (2,10–12).
    - ✓ Exercise programmers and physical activity for chronic primary pain: encourage patients to remain physically active for overall health benefits.
    - ✓ Psychological therapy for chronic primary pain, delivered by healthcare professionals with appropriate training.
    - ✓ Acupuncture for chronic primary pain, delivered by healthcare professionals with appropriate training.
- Physical exercise is effective, particularly in the management of people with non-specific low back pain (12).
- It is recommended that exercise be combined with educational measures and that patients be encouraged to follow a healthy lifestyle, including weight control, regular physical exercise, and the need to stay active and avoid a sedentary lifestyle. At the same time, bed rest is not recommended as part of the treatment of chronic pain (4,12).
- Given the clinical effectiveness of anti-inflammatory diets in the management of chronic pain not related to cancer, it is recommended to evaluate their prescription within the comprehensive treatment guided by nutrition specialists

(i.e., diets that focus on eating anti-inflammatory foods or restricting inflammatory foods: Mediterranean diet DASH (Dietary Approaches to Stop Hypertension); AIP (autoimmune paleo) diet; Whole30 Weil's Anti-Inflammatory Diet) (13).

- Yoga can be an effective and safe practice to control chronic pain, mainly in patients with chronic lower back or neck pain. Compared to usual care, improved quality of life and mood of participants (14).
- Some studies were identified regarding the clinical effectiveness of body weight modification interventions for chronic non-cancer pain, in which no changes were found in pain measures or numerical effect measures. Yoga can be an effective and safe practice to control chronic and acute pain, primarily in patients with low back or chronic cervical pain. Otherwise, the results were not very consistent for people with pain associated with osteoarthritis, rheumatoid arthritis, fibromyalgia, carpal tunnel, and irritable bowel syndromes (14).
- Multimodal intervention that includes rehabilitation and exercises combined with usual medical care is an effective therapeutic option to reduce disabilities in older adults with chronic musculoskeletal pain (15).
- When prescribing opiates, the considerations and particular regulations for each state, as well as company policies, must be taken into account. (See sections 5.2 and 5.3).

5.2 Opioid Prescription

These policies contain and provide state-specific guidelines among the states Sanitas operates in due to statutes or other applicable state or local information and agreement to patients who will begin long-term treatment with opioid analgesics or other controlled substances (16,17).

- MED 6.053 - Prescribing of Controlled Substances by a Physician Assistant or an Advanced Nurse Practitioner (17).
- MED 6.049 - Long Term Controlled Substance for Patients (16).

5.3 Information and Federal Laws by state

The use of opioids must comply with the laws and regulations established by the states of Florida (18–20), Texas (21), Tennessee (22,23) and New Jersey (24), among other states in which the prescription is made.

6 Recommendations

Once the team of thematic experts has reviewed the evidence, the following recommendations and good practice guidelines are issued:

- Consider an antidepressant, either amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine, or sertraline, to manage chronic primary pain after a complete discussion of the benefits and harms (10).
- Paracetamol is recommended as first-line therapy for the pharmacological management of mild to moderate pain in older adults with osteoarthrosis, musculoskeletal pain, and low back pain due to its efficacy and safety profile (5).
- It is recommended that the dose of paracetamol be reduced by 50% in patients with liver failure and that the dose be monitored periodically (5).
- It is recommended to exercise extreme caution and limit the use of NSAIDs in older people due to the frequent adverse effects on the gastrointestinal, cardiovascular, and renal systems and the increased risk of hospitalization, nephrotoxicity, myocardial infarction, stroke, and death (5).
- The use of NSAIDs is contraindicated in patients with hepatic impairment, liver failure, chronic alcohol abuse, or dependence (5).
- In patients with neuropathic pain (except trigeminal neuralgia), management with any of the following drugs can be considered according to the patient's clinical conditions, taking into account side effects and drug interactions: amitriptyline, duloxetine, gabapentin or pregabalin as treatment initial for neuropathic pain. If the initial treatment is not practical or tolerated, offer one of the remaining three medications and consider switching again if the second and third medications tried are also ineffective or not tolerated. Consider tramadol only if acute rescue therapy is needed (11).

7 Conclusions

According to the articles considered for this rapid systematic review and based on the PICO question initially posed, we can conclude that in older adults, multimodal medication management for non-malignant chronic pain is significantly better than monotherapy. With respect to non-pharmacological therapies in this population, the evidence has demonstrated sustainable effects of pain reduction, but When recommending them, it is important to individualize each case and take into account the sustainability of each of them.

Systematic reviews of greater certainty are required, in addition to observational studies and randomized clinical trials with greater methodological attention that confer greater precision and reliability in the safety of pharmacological and non-pharmacological interventions in the management of non-palliative chronic pain,

which will allow us to reaffirm the recommendations and prioritize this type of special populations.

8 Bibliography

1. Alenezi A, Yahyouche A, Paudyal V. Interventions to optimize prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review. Eur J Clin Pharmacol [Internet]. 2021 [cited 2024 Mar 4];77(4):467–90. Available from: https://pubmed.ncbi.nlm.nih.gov/33123784/

2. Tang SK, Tse MMY, Leung SF, Fotis T. The effectiveness, suitability, and sustainability of non-pharmacological methods of managing pain in community-dwelling older adults: a systematic review. BMC Public Health [Internet]. 2019;19(1):1488. Available from: https://doi.org/10.1186/s12889-019-7831-9

3. Gauthier K, Dulong C, Argáez C. Multidisciplinary Treatment Programs for Patients with Chronic Non-Malignant Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines – An Update [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health [Internet]. 2019; Available from: www.ncbi.nlm.nih.gov/books/NBK545496/

4. Li Y, Argáez C. Body Weight Modification Interventions for Chronic Non-Cancer Pain: A Review of Clinical Effectiveness [Internet] [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. Ottawa (ON): CADTH Rapid Response Report: Summary with Critical Appraisal; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562950/

5. Freo U, Ruocco C, Valerio A, Scagnol I, Nisoli E. Paracetamol: A Review of Guideline Recommendations. J Clin Med [Internet]. 2021 Jul;10(15). Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC8347233/

6. Iqbal A, David Knaggs R, Anderson C, Toh LS. Role of pharmacists in optimising opioid therapy for chronic non-malignant pain; A systematic review. Research in Social and Administrative Pharmacy [Internet]. 2022;18(3):2352–66. Available from: https://www.sciencedirect.com/science/article/pii/S1551741120311992

7. O'Brien MDC, Wand APF. A systematic review of the evidence for the efficacy of opioids for chronic non-cancer pain in community-dwelling older adults. Age Ageing [Internet]. 2020 Feb 27;49(2):175–83. Available from: https://doi.org/10.1093/ageing/afz175

8. (CADTH Rapid response report: summary of abstracts). Low-Dose Naltrexone for Chronic Non-Cancer Pain: Clinical Effectiveness. CADTH [Internet]. 2017 [cited 2024 Mar 15]; Available from: https://www.cadth.ca/low-dose-naltrexone-chronic-non-cancer-pain-clinical-effectiveness-0

9. Walitt B, Urrútia G, Nishishinya MB, Cantrell SE, Häuser W. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. Cochrane Database of Systematic Reviews [Internet]. 2015;(6). Available from: https://doi.org//10.1002/14651858.CD011735

10. National Institute for Health and Care Excellence (NICE). 7 April 2021. 2021 [cited 2020 Sep 21]. p. 1–40 Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. Available from: https://www.nice.org.uk/guidance/ng193

11. National Institute for Health and Care Excellence (NICE). 20 november 2013 Update: 22 september 2020. 2013 [cited 2024 Feb 21]. p. 1–37 Overview | Neuropathic pain in adults: pharmacological management in non-specialist settings | Guidance | NICE. Available from: https://www.nice.org.uk/guidance/cg173

12. Peprah K, Loshak H. Exercise for Chronic, Non-Cancer Back Pain: A Review of Cost-Effectiveness and Guidelines | CADTH. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health [Internet]. 2019 [cited 2024 Feb 22];1–17. Available from: https://www.cadth.ca/exercise-chronic-non-cancer-back-pain-review-cost-effectiveness-and-guidelines

13. Kumar D, Grobelna A. Anti-inflammatory diets for chronic, non-cancer pain: clinical effectiveness and guidelines. Ottawa: CADTH. In: Ottawa (ON): Canadian Agency for Drugs and Technologies in Health [Internet]. Quebec.: Cadth rapid response reporr: Reference list; 2020. p. 1–7. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/2020/RA1099 Inflammatory diet pain Final.pdf

14. Melo RC de, Ribeiro AÂV, Jr CDL, Bortoli MC de, Toma TS, Barreto JOM. Effectiveness and safety of yoga to treat chronic and acute pain: a rapid review of systematic reviews. BMJ Open [Internet]. 2021 Dec 1;11(12):e048536. Available from: http://bmjopen.bmj.com/content/11/12/e048536.abstract

15. Kechichian A, Lafrance S, Matifat E, Dubé F, Lussier D, Benhaim P, et al. Multimodal Interventions Including Rehabilitation Exercise for Older Adults With Chronic Musculoskeletal Pain: A Systematic Review and Meta-analyses of Randomized Controlled Trials. Journal of Geriatric Physical Therapy [Internet]. 2022;45(1). Available from: https://journals.lww.com/jgpt/fulltext/2022/01000/multimodal_interventions_including_rehabilitation.4.aspx

16. MED 6.049. Opioid Prescription - Long Term Controlled Substance for Patients. PolicyStat ID13666703 [Internet]. Available from: https://sanitasusa-allstates.policystat.com/policy/10474513/latest

17. MED 6.053. Opioid Prescription - Prescribing of Controlled Substances by a Physician Assistant or an Advanced Nurse Practitioner. Policy ID 13785966 [Internet]. Available from: https://sanitasusa-allstates.policystat.com/policy/13785966/latest

18. Florida. Florida HB 423 – ARNP/PA Controlled Substance Prescribing [Internet]. HB 423. Available from: https://www.fana.org/florida-hb-423-arnppa-controlled-substance-prescribing

19. Florida. Opioid Laws and regulations [Internet]. Available from: http://www.leg.state.fl.us/statutes/index.cfm?App_mode=Display_Statute&URL=0400-0499/0456/Sections/0456.44.html%09

20. Florida. Important Legislative Update regarding HB 423 [Internet]. Available from: http://floridasnursing.gov/latest-news/new-legislation-impacting-your-profession/

21. Texas. Opioid laws and regulations - Prescribing Controlled Substances in Texas [Internet]. Available from: https://cnaptexas.com/aprn-practice/controlled-substances-prescribing/

22. Tennessee. Professions of the Healing Arts, Chapter 7 - Nursing, Part 1 - General Provisions § 63-7-123. Certified nurse practitioners, Drug prescriptions, Rules and regulations [Internet]. 2016. Available from: https://law.justia.com/codes/tennessee/2016/title-63/chapter-7/part-1/section-63-7-123

23. Tennessee. Controlled Substance Monitoring Database Program [Internet]. Available from: https://www.tn.gov/health/health-program-areas/health-professional-boards/csmd-board/csmd-board/faq.html

24. New Jersey. Opioid laws and regulations [Internet]. Available from: https://njafp.org/new-prescribing-law/

Appendix

Appendix 1. Searches reports in electronic databases.

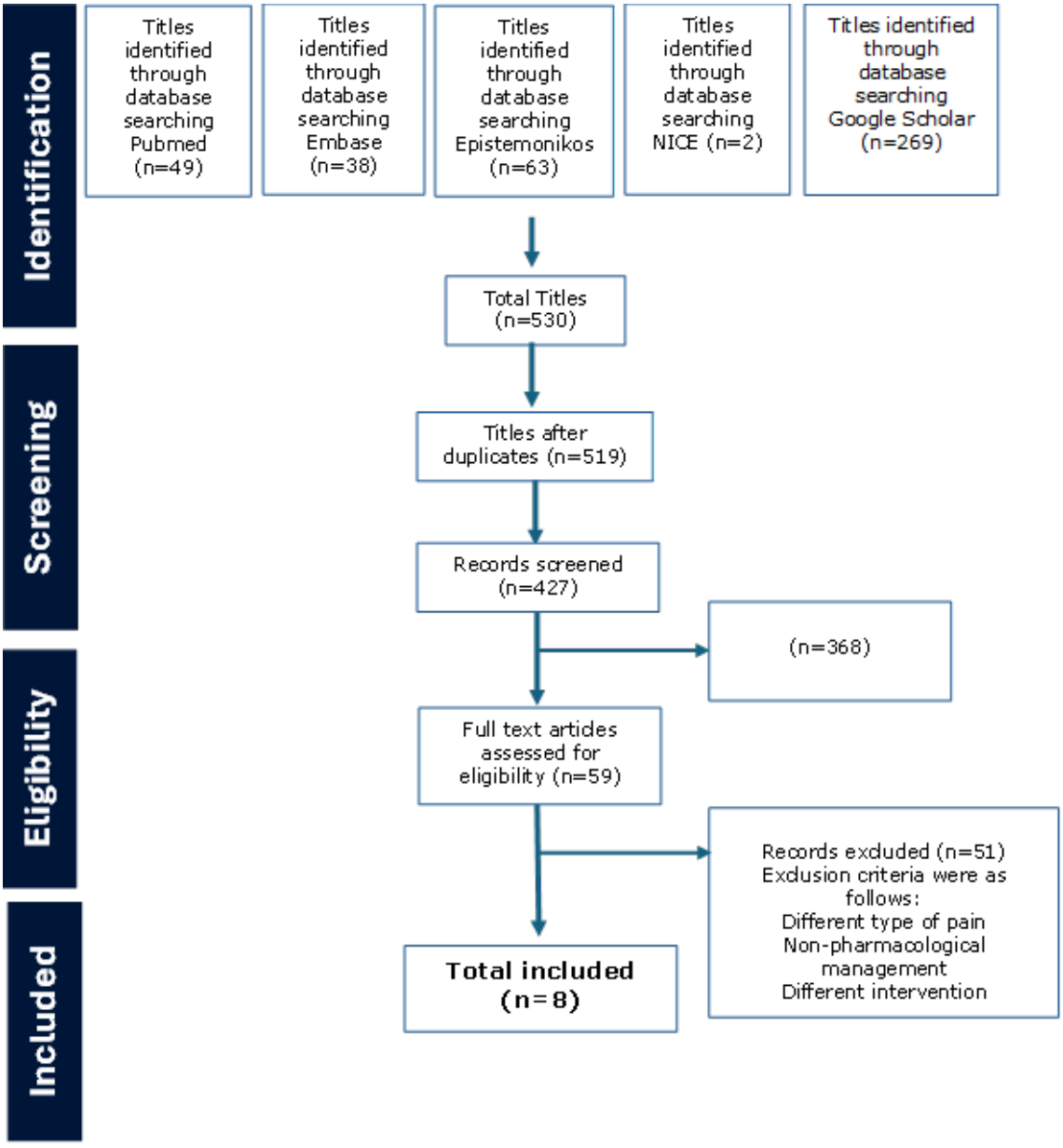
Search type	Rapid evidence review
Databases	Pubmed, Embase, Google Scholar, NICE, Epistemonikos
Search date/ search date range	June 6, 2023 Search horizon 10 years
Language restrictions	English, Spanish
Other limits	None
Identified references	**530 References were identified**

Databases	Strategies	Results
Pubmed	((((("Aged"[Title/Abstract] OR "elderly"[Title/Abstract]) NOT "children"[Title/Abstract]) NOT "adolescent"[Title/Abstract]) AND (("chronic pain"[Title/Abstract] OR "nociceptive pain"[Title/Abstract] OR "musculoskeletal pain"[Title/Abstract] OR "pain postoperative"[Title/Abstract]) NOT "palliative care"[Title/Abstract]) AND ("pain management"[Title/Abstract] OR "pharmacological treatment"[Title/Abstract] OR "drug therapy"[Title/Abstract] OR "analgesics opioid"[Title/Abstract] OR "anti inflammatory agents non steroidal"[Title/Abstract] OR "NSAIDs"[Title/Abstract] OR "Anticonvulsants"[Title/Abstract] OR "antidepressive agents tricyclic"[Title/Abstract] OR "selective serotonin reuptake inhibitors"[Title/Abstract] OR "neuromuscular agents"[Title/Abstract] OR "Steroids"[Title/Abstract] OR "anesthetics local"[Title/Abstract])) AND ((y_10[Filter]) AND (guideline[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))	49

Databases	Strategies	Results
Embase	(('aged'/exp OR 'aged' OR 'aged patient' OR 'aged people' OR 'aged person' OR 'aged subject' OR 'elderly' OR 'elderly patient' OR 'elderly people' OR 'elderly person' OR 'elderly subject' OR 'senior citizen' OR 'senium') AND 'chronic pain'/exp OR 'non cancer pain'/exp) NOT ('child'/exp OR 'child' OR 'children') NOT 'adolescent'/exp AND ('analgesia'/exp OR 'analgaesia' OR 'analgesia' OR 'pain management' OR 'pain relief' OR 'sequential analgetic analgesia' OR 'surgical analgesia' OR 'drug therapy'/exp OR 'drug therapy' OR 'drug treatment' OR 'medicament therapy' OR 'medicament treatment' OR 'medication' OR 'medicinal therapy' OR 'medicinal treatment' OR 'pharmaceutical therapy' OR 'pharmaceutical treatment' OR 'pharmaco-therapy' OR 'pharmaco-treatment' OR 'pharmacological therapy' OR 'pharmacological treatment' OR 'pharmacotherapy' OR 'pharmacotreatment' OR 'therapeutic uses' OR 'therapy, drug' OR 'therapy, pharmacological' OR 'treatment, drug' OR 'treatment, pharmacological') AND ('systematic review'/exp OR 'review, systematic' OR 'systematic review' OR 'practice guideline'/exp OR 'clinical practice guidelines' OR 'guidelines' OR 'guidelines as topic' OR 'practice guideline' OR 'practice guidelines' OR 'practice guidelines as topic') AND [2018-2023]/py	389
Epistemonikos	chronic pain non-malignant AND elderly AND pharmacological treatment	63
NICE	chronic pain	3
Google Scholar	non-malignant pain AND elderly patient AND pharmacologic treatment AND (guidelines OR systematic review)	26
	TOTAL	**530**

Appendix 2. Preferred reporting items for systematic reviews and meta-analysis protocol.

PRISMA diagram of literature search and inclusion process.



Appendix 3. Evidence synthesis of clinical guidelines

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain. UK. NICE, 2021 (10)	People aged 16 years and over with chronic pain (chronic primary pain, chronic secondary pain, or both)	This guideline covers assessing all chronic pain (chronic primary pain, chronic secondary pain, or both) and managing chronic primary pain in people aged 16 years and over. Inform a care and support plan by setting out a comprehensive person-centered assessment of the causes and effects of pain and agreeing possible management strategies, including self-management.	***Intervention:*** • Oral paracetamol • Non-steroidal anti-inflammatory drugs (by any route) • Ketamine (by any route) • Topical or intravenous local anaesthetics • Local anaesthetics and/or corticosteroids by injection (trigger point) • Oral or transdermal, intrathecal opioids (morphine, oxycodone, hydromorphone, buprenorphine, fentanyl, methadone, meptazinol, tapentadol, targinact, codeine, dihydrocodeine, tramadol, cocodamol, codydramol, naltrexone) • Oral anti-epilepsy drugs (gabapentin, pregabalin, sodium valproate, carbamazepine, oxcarbazepine, topiramate, lamotrigine, lacosamide, levetiracetam) • Oral anti-depressants - Tricyclic antidepressants (e.g. Amitriptyline, nortriptyline, clomipramine, imipramine) - Selective serotonin re-uptake inhibitors (e.g. Fluoxetine, citalopram) - Serotonin norepinephrine re-uptake inhibitors (e.g. Duloxetine, venlafaxine)	***Anti-epileptics (gabapentinoids) versus placebo*** **Pain reduction:** MD -0,56 (-0,77 to -0,35) the study did not show clinically important difference between gabapentinoids and placebo at >3 months (fibromyalgia subgroup) in pain severity score (Moderate quality evidence). **Quality of life:** MD -11,10 (-17,07 to -5,13): the study did not show clinically important difference between gabapentinoids and placebo at ≤3 months in fibromyalgia impact (Low quality evidence). **Physical function:** MD 6,40 (-8,35 to 21,15) the study did not show clinically important difference between gabapentinoids and placebo at ≤3 months or MD 3,6 (-12,50 to 19,70) >3 months in pain disability (Low to moderate quality evidence). **Safety-adverse**	**Pharmacological management of chronic primary pain** "Consider an antidepressant, either amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine or sertraline, for people aged 18 years and over to manage chronic primary pain, after a full discussion of the benefits and harms: Evidence indicated that antidepressants (amitriptyline, citalopram, duloxetine, fluoxetine, paroxetine and sertraline) improved quality of life, pain, sleep and psychological distress compared with placebo. But there were some limitations in the quality and amount of the evidence. Duloxetine (the only SNRI with evidence for chronic primary pain) had a larger amount of long-term evidence of effectiveness. However, due to the lack of head-to-head comparisons between the antidepressant classes, the committee could not recommend duloxetine in preference to the other antidepressants for which	**93%**

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
			- Tetracyclic antidepressants (mirtazapine) • Oral cannabinoids (nabilone, nabiximols oromucosal spray) • Antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole) • Benzodiazepines (diazepam, oxazepam, lorazepam, temazepam, nitrazepam, clonazepam) ***Comparator:*** • Placebo • Each other (drug class)	**events:** RR 1,86 (1,16 to 2,00) The studies did not show clinically important difference between gabapentinoids and placebo in discontinuation due to adverse events at >3 months (Low quality evidence) **SSRIs versus placebo** **Pain reduction:** SMD -0,65 (-1,16 to -0,15) the study showed a clinically important benefit of SSRIs compared to placebo at >3 months in pain reduction final values (Very low quality evidence). **Quality of life:** MD -11,50 (-19,22 to -3,78) The study showed a clinically important benefit of SSRIs compared to placebo at ≤3 months in total scores (Very low quality evidence). **Safety-adverse events:** RR 0,60 (0,04 to 8,46) the study showed a clinically important benefit of SSRIs compared to placebo at ≤3 months in discontinuation due to adverse events (Very low quality evidence).	there was evidence. The decision of which antidepressant to try should be based on a fully informed discussion with the person with chronic primary pain, taking into account the risks and benefits." *"The committee agreed that doses of SSRIs and SNRIs should be in line with BNF recommendations for depression.* For amitriptyline, the evidence indicating benefit included very low doses of 5 mg per day. The committee therefore agreed it was appropriate to start amitriptyline at the lowest possible dose and titrate up to no more than 100 mg per day. Efficacy of antidepressants should be reviewed at 4 to 6 weeks." The committee agreed that the risk of withdrawal symptoms should be considered when prescribing antidepressants and these should not be continued if they were not effective. "If an antidepressant is offered to manage chronic primary pain, explain that this is because these medicines may help with quality of life, pain, sleep	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				SNRIs versus placebo **Pain reduction:** MD -0,69 (-0,91 to -0,47) the studies did not show clinically important difference between SNRIs and placebo at >3 months (Moderate quality evidence). **Quality of life:** MD 3,17 (2,15 to 4,18) the study showed a clinically important benefit of SSRIs compared to placebo at ≤3 months (Very low quality evidence) **Physical function:** SMD -0,02 (-0,14 to 0,1) the studies did not show clinically important difference between SNRIs and placebo at >3 months (Low quality evidence) **Safety-adverse events:** RR 1,17 (1,35 to 2,15) the studies showed that more people discontinued from SNRIs compared to placebo at >3 months (Low quality evidence). **Tricyclic antidepressants versus placebo at >3 months.** **Pain reduction:** MD -2,1 (-7,68 to 3,48) the	and psychological distress, even in the absence of a diagnosis of depression." "Do not initiate any of the following medicines to manage chronic primary pain in people aged 16 years and over: antiepileptic drugs including gabapentinoids, unless gabapentinoids are offered as part of a clinical trial for complex regional pain syndrome (since CRPS is sometimes understood as a neuropathic pain disorder.), antipsychotic drugs, benzodiazepines, corticosteroid trigger point injections, ketamine, local anesthetics (topical or intravenous), unless as part of a clinical trial for complex regional pain syndrome, local anesthetic/corticosteroid combination trigger point injections,non-steroidal anti-inflammatory drugs,opioids,paracetamol. " When making shared decisions about whether to stop antidepressants, opioids, gabapentinoids or benzodiazepines, discuss with the person any problems associated with withdrawal. Others: Social interventions: for	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				study did not show clinically important difference (Very low quality evidence) **Physical function:** MD -0,17(-0,40 to 0,06) The study did not show clinically important difference (Very low quality evidence). **Adverse events:** RR 2,68 (0,72 to 9,93) the studies demonstrated that more people discontinued from tricyclic antidepressants compared to placebo (Low quality evidence) **Tetracyclic antidepressants versus placebo at >3 months** **Pain reduction:** RR 1,54 (0,72 to 3,28) the study showed a clinically important benefit of tetracyclic antidepressants compared to placebo (Very low quality evidence). **Quality of life:** MD 8,5 (-41,50 to 58,58) the study showed a clinically important benefit of tetracyclic antidepressants compared to placebo (Low quality evidence).	chronic pain (chronic primary pain and chronic secondary pain): could not make a recommendation for chronic pain without evidence on clinical and cost effectiveness. **Pain management** programmes: Most of the evidence showed no difference in quality of life "Cannabis-based medicinal products: No evidence was identified on the effectiveness of cannabis-based products for chronic primary pain, and some evidence suggested that the treatment could cause adverse events in the short term. However, this was limited evidence from a small study." **Opioids** This Guideline did not evidence was identified for the clinical effectiveness of opioids. the committee refers that even short-term use of opioids could be harmful for a chronic condition. The lack of evidence for effectiveness of opioids, along with evidence of long-term harm, persuaded the committee to recommend against opioid use for people with chronic primary pain. **NSAIDs**	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				Adverse events: RR 0,81 (0,15 to 4,28) the study did not show clinically important difference between tetracyclic antidepressants and placebo (Low quality evidence). **Benzodiazepines versus placebo at ≤3 months** **Pain reduction:** MD -0,38 (-0,82 to 0,06) the studies did not clinically important difference between benzodiazepines and placebo (moderate quality evidence). **Physical function:** MD 0,10 (0,03 to 0,17) the study showed clinically important harm of benzodiazepiness compared to placebo (Low quality evidence). **NSAIDs versus placebo at < 3 months.** **Pain reduction**: MD -0,28 (-0,66 to 0,1) the studies did no show clinically important difference between NSAIDs and placebo (Moderate quality evidence)	Evidence showed no difference in pain reduction, quality of life, psychological distress or discontinuation between NSAIDs and placebo. The committee agreed that the lack of evidence of the effectiveness of NSAIDs, coupled with evidence of harm, was sufficient to recommend against its use in clinical practice. **Benzodiazepines** The committee considered the addictive properties of this group of drugs in the long term and they recommended against the use of benzodiazepines for chronic primary pain. **Antiepileptics:** The evidence (less than 3 months and over 3 months) did not show clinically important benefit of gabapentinoids in terms of pain reduction, quality of life, physical function, psychological distress and sleep. The committee agreed there was insufficient evidence to justify the routine use of gabapentinoids for chronic primary pain. **Local anaesthetics** The committee did not recommend the use of local anesthetics.	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				Quality of life: MD -1,9 (-11,71 to 7,91) the study showed no clinically important difference between NSAIDs and placebo (Very low quality evidence). **Physical function**: MD 0,1 (0,03 to 0,17) the study showed clinically important harm of NSAIDs compared to placebo (Low quality evidence). **Adverse events:** OR 7,63 (0,47 to 124,75) the study showed no clinically important difference between NSAIDs and placebo (Low quality evidence). **Cannabinoids versus placebo at ≤ 3 months** **Adverse events**: RR 3(0,34 to 26,45) the study compared cannabinoids with placebo showed a clinically important harm of cannabinoids for chronic primary pain in terms of greater discontinuation due to adverse events (Very low quality evidence). **Local anaesthetics versus placebo**	**Paracetamol, corticosteroids, local anaesthetics corticosteroid combinations, ketamine and antipsychotics** The committee did not recommend the use of these treatments because the lack of evidence and possible associated harms. **Cost effectiveness** Pharmacological management is just one of the many options that can be used in practice to help patients manage their chronic pain. The committee acknowledged the high level of expenditure currently attributable to the use of drug treatments. the committee referred that the use of such interventions should be reduced from current levels in clinical practice. Unit costs can vary depending on the drug. There is variation in the costs of antidepressants, and SNRIs are slightly more expensive than other types such as trycyclic antidepressants. However, this does depend on dose. the recommendations made should reduce the use of pharmacological interventions in the	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				Evidence did not show difference between local anaesthetics and placebo in psychological distress and discontinuation and harm of local anaesthetics in relation to pain reduction (low and very low quality evidence).	management of chronic primary pain. the committee suggested that there could be further savings where potential harms are avoided through the reduced use of opioids and gabapentinoids.	
Neuropathic pain in adults: pharmacological management in non-specialist settings. UK. NICE, 2013, Update 2020 (11)	Adults with neuropathic pain in non-specialist settings	This guideline covers managing neuropathic pain (nerve pain) with pharmacological treatments (drugs) in adults in non-specialist settings. To improve quality of life for people with conditions such as neuralgia, shingles and diabetic neuropathy by reducing pain and promoting increased participation in all aspects of daily living. The guideline sets out how drug treatments for neuropathic pain differ from traditional pain	***Interventions*** *Pharmacological treatments:* Antidepressants: *tricyclic antidepressants (TCAs)*: Amitriptyline, Clomipramine, Dosulepin (dothiepin), Doxepin, Imipramine, Lofepramine, Nortriptyline, Trimipramine, Antidepressants: *selective serotonin reuptake inhibitors (SSRIs)*: Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline. Others antidepressants: Duloxetine, Mirtazapine, Reboxetine, Trazodone, Venlafaxine, Antiepileptic (anticonvulsant): Carbamazepine, Gabapentin, Lacosamide, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenytoin, Pregabalin, Valproate, Topiramate, Opioid analgesics: Buprenorphine, Co-codamol, Co-dydramol, Dihydrocodeine, Fentanyl, Morphine, Oxycodone, Oxycodone with naloxone, Tapentadol, Tramadol, Other Treatments: Cannabis sativa extract, Flecainide 5-HT_1-receptor agonists, Topical capsaicin, Topical lidocaine. **Comparator:** Placebo	Critical outcomes - Patient-reported improvement - Function - Adverse effects Important outcomes - Pain intensity - Adverse effects **Neuropathic pain**: Patient-reported improvement at least moderate improvement (28±7 days): cannabis sativa extract, levetiracetam, pregabalin, tramadol (Very low quality evidence). Patient-reported improvement at least moderate improvement (56±7 days): capsaicin patch, duloxetine, gabapentin, pregabalin, valproate (Very low quality evidence). Patient-reported improvement at least moderate improvement (84±14 days): capsaicin	***Treatment*** All neuropathic pain (except trigeminal neuralgia) Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain - Amitriptyline demonstrated pain reduction compared with placebo. The advers effects such as sedation may be considered intolerable by some patients, but may be considered beneficial by patients who have problems with sleeping. - Duloxetine and gabapentin – the analyses appeared consistent that duloxetine reduces pain compared with placebo. If the initial treatment is not effective or is not	**92%**

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
		management.		patch, lacosamide, lamotrigine, pregabalin (Low quality evidence). Functionality with 10-point sleep scale (28±7 days): cannabis sativa extract, escitalopram, gabapentin, gabapentin+nortriptyline, nortriptyline (Low quality evidence). Functionality with 10-point sleep scale (56±7 days): Gabapentin (Moderate quality evidence). Functionality with 10-point sleep scale (84±14 days): duloxetine, pregabalin, topiramate (Low quality evidence). Adverse events: peripherical oedema, (low quality evidence) Adverse events: vertigo, somnolence, fatigue, lethargy, constipation, nauseas, vomiting, pruritus, burning pain, rash, blurred vision, confusion, cognitive impairment, mood disturbance, dry mouth, urine retention, weight gain, gait disturbance (Very low quality evidence) 30% pain relief (28±7	tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated. Consider tramadol only if acute rescue therapy is needed: The tramadol should only be considered as a rescue medication when people are awaiting referral to specialist pain services after initial treatment has failed. Consider capsaicin cream for people with localized neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments: The capsaicin cream is effective compared with placebo than other topical treatments. However, it important to apply the cream correctly (they noted that using gloves and/or avoiding particularly sensitive areas such as the eyes is often advised). ***Treatments that should not be used:*** "Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so: • cannabis sativa extract: decreases pain compared with placebo, but it	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				days): cannabis sativa extract, capsaicin cream, gabapentin, levetiracetam, pregabalin, tramadol (Very low quality evidence) 30% pain relief (56±7 days): amitriptyline, capsaicin patch, gabapentin, pregabalin (very low quality evidence) 30% pain relief (84±14 days): cannabis sativa extract, capsaicin patch, duloxetine, lacosamide, lamotrigine, pregabalin, topiramate (Very low quality evidence) 50% pain relief (28±7 days): amitriptyline, cannabis sativa extract, gabapentin, levetiracetam, morphine, pregabalin, tramadol (Very low quality evidence) 50% pain relief (56±7 days): gabapentin, lamotrigine, nortriptyline, pregabalin (Very low quality evidence) 50% pain relief (84±14 days): capsaicin patch, duloxetine, pregabalin, topiramate (Very low quality evidence)	appeared consistently worse than other treatments at reducing pain. • capsaicin patch: decreases pain compared with placebo, but it worse than other treatments at reducing pain. • lamotrigine: it did not demonstrate that lamotrigine is effective compared with placebo. In addition, it appears to be associated with high withdrawals due to adverse effects. • morphine: the morphine reduced pain compared with placebo, but it is associated with significant adverse effects and higher rates of withdrawal due to adverse effects. The NICE-GDG considered risk of opioid dependency. As a result, the GDG agreed it was not appropriate to consider this in non-specialist settings. • oxcarbazepine: the results were conflicting about effective compared with placebo; Also, this showed many adverse effects. • topiramate: the results appeared inconsistent about whether topiramate is effective compared with placebo. topiramate is associated with a range of adverse effects, it is not appropriate to be	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				Pain relief (continuous) (28±7 days): Cannabis Sativa Extract, Levetiracetam, Pregabalin, Tramadol, (Very low quality evidence) Pain relief (continuous) (56±7 days): Capsaicin Patch, Duloxetine, Gabapentin, Pregabalin, Valproate (Very low quality evidence) Pain relief (continuous) (84±14 days): Cannabis, Sativa Extract, Escitalopram, Gabapentin, Gabapentin+Nortriptyline, Nortriptyline (Low quality evidence) **Cost:** Treatment with amitriptyline was associated with lower net costs than treatment with gabapentin in 100%, and it was found to have greater net benefit than placebo 85% of the time. Therefore, the NICE-Guideline Development Group was satisfied that it was appropriate to recommend amitriptyline as an alternative first-line treatment Duloxetine and pregabalin, mean cost-perQALY estimates from	considered in non-specialist settings. • tramadol (this is referring to long-term use • Gabapentin + nortriptyline, gabapentin + oxycodone, imipramine, lacosamide, levetiracetam, oxycodone, venlafaxine: the analyses showed that these drugs either do not appear more effective than placebo. ***Trigeminal neuralgia*** Offer carbamazepine as initial treatment for trigeminal neuralgia. Carbamazepin has been the standard treatment for trigeminal neuralgia since the 1960s. Despite the lack of trial evidence, it is perceived by clinicians to be efficacious. Further research should be conducted: NICE-GDG felt that it was important to discuss dosage titration and how the titration process works, different self-management strategies for pain and coping with the pain, rehabilitation (such as lifestyle changes or adaptations in work life), and that other non-pharmacological treatments are available. "If initial treatment with carbamazepine is not effective, is not tolerated	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				the model suggested poor value for money in comparison with gabapentin and amitriptyline. **Peripheral neuropathic pain** Patient-reported improvement at least moderate improvement (28±7 days): pregabalin (moderate quality evidence). Patient-reported improvement at least moderate improvement (56±7 days): capsaicin patch, gabapentin, pregabalin, valproate (Very low quality evidence). Patient-reported improvement at least moderate improvement (84±14 days): capsaicin patch, lacosamide, lamotrigine, pregabalin (Low quality evidence). Adverse events: peripherical oedema, (low to very low quality evidence) 30% pain relief (28±7 days): cannabis sativa extract, capsaicin cream, gabapentin, pregabalin, tramadol (Very low quality evidence)	or is contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service." ***Additional information*** In November 2013, duloxetine was licensed for diabetic peripheral neuropathic pain only, and gabapentin was licensed for peripheral neuropathic pain only, so use for other conditions was off label. "Pregabalin and gabapentin are Class C controlled substances and Schedule 3 under the Misuse of Drugs Regulations 2001. Evaluate patients carefully for a history of drug abuse before prescribing and observe patients for development of signs of abuse and dependence" "In November 2013), capsaicin cream (Axsain) was licensed for post-herpetic neuralgia and painful diabetic peripheral polyneuropathy only, so use for other conditions was off label. The SPC states that this should only be used for painful diabetic peripheral polyneuropathy 'under the direct supervision of a	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				30% pain relief (56±7 days): capsaicin patch, pregabalin (very low quality evidence) 30% pain relief (84±14 days): cannabis sativa extract, capsaicin patch, duloxetine, lacosamide, lamotrigine, pregabalin, topiramate (Very low quality evidence) 50% pain relief (28±7 days): amitriptyline, cannabis sativa extract, gabapentin, pregabalin, tramadol (Very low quality evidence) 50% pain relief (56±7 days): capsaicin patch, gabapentin, lamotrigine, nortriptyline, pregabalin (Very low quality evidence) 50% pain relief (84±14 days): capsaicin patch, duloxetine, pregabalin, topiramate (Very low quality evidence) **Central neuropathic pain** Patient-reported improvement at least moderate improvement (28±7 days): cannabis sativa extract (very low quality evidence). Patient-reported	hospital consultant who has access to specialist resources'." <u>Monotherapy versus combination therapy for neuropathic pain:</u> Combination therapy is commonly prescribed for neuropathic pain. It may also be a helpful option as a stepwise approach if initially used drugs are insufficient at reducing pain. Combination therapy may also result in better tolerability because smaller doses of individual drugs are often used when combined with other drugs. "Side effects: Pharmacological agents for neuropathic pain are associated with various adverse effects. However, there is little evidence about how this affects cost of the quality of life of patients receiving treatment." "Misuse: There has been some suggestion that some pharmacological agents for neuropathic pain are associated with increased potential for misuse. However, there had not been enough high-quality evidence to adequately explore this issue."	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	AGREE II
				improvement at least moderate improvement (56±7 days): duloxetine (Low quality evidence). Adverse events: (low to very low quality evidence) 30% pain relief (84±14 days): lamotrigine, pregabalin (Very low quality evidence) 50% pain relief (84±14 days): pregabalin (Very low quality evidence)		

Appendix 4. Evidence synthesis of systematic reviews

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
Role of pharmacists in optimizing opioid therapy for chronic non-malignant pain; A systematic review. UK. Iqbal, 2022 (6)	Adults with pain originating from any origin except cancer pain and should be present for at least 3 months Age 46,5 (22-86)	Evaluate effectiveness of interventions in optimising opioid medicine use or reduction in pain intensity	Optimising opioid therapy for people with CNMP	Reduction in mean BPI (Brief Pain Inventory) pain interference = 7.1 to 6.1 (P = 0.02) BPI pain intensity: • Worst pain = 8 to 7.5 (P = 0.02) • Least pain = 5 to 4 (P = 0.12) • Average pain = 7 to 6 (P = 0.02) Chronic Pain Grade: • Median pain intensity score = 76.66 to 73.33 (P = 0.02) • Median disability score = 70 to 73.33 (P = 0.89) No improvement in CPG score was observed in majority of the patients = 21 (61.7%)	In individual domains scores, statistically significant improvements were found in physical role (P = 0.01), bodily pain (P = 0.01) and social functioning (P = 0.03).	**Low**
Interventions to optimize prescribed medicines and reduce their misuse in chronic non-malignant pain: a systematic review. UK. Alenazi, 2021 (1)	Adult patients (≥18 years old) with CNMP using pain medication for 3 months or more. Mean age 45 - 86 years old, with	Medicines optimization goals Medication taking behavior	**Single component interventions** Opioid treatment contract (OTC) with or without urine drug screening (UDS) Behavioral interventions Educational interventions	**Medicine optimization:** Optimizing the appropriate usage of prescribed pain medication among adults with CNMP using pain medication for 3 months or more *Two outcomes were*	Requiring a report of behavioral issues and urine toxicology screens creates a more comprehensive monitoring system than either alone. Significant reductions in overall illicit drug use with adherence monitoring combined with	**Low**

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
	nociceptive, neuropathic and osteomuscular chronic pain in treatment with opioids		**Multi-component interventions** Urine drug screening and opioid treatment contract within multicomponent intervention Monthly clinical/pain assessment Risk assessment Prescription monitoring programme (PMP) Opioid dose adjustments Prescribing, dispensing small quantities, pill count Team-based approach Patient education within a multi-component intervention Provider education within a multicomponent interventi Behavioral interventions within a multicomponent intervention Psychiatric consultation Electronic diaries	*evaluated:* -Appropriate use of pain medication -Inappropriate use of pain medication	random urine drug testing. The Opioid Contract is not enough to generate treatment adherence. Cognitive behavioral intervention: Correlations of the working alliance with treatment: outcomes failed to reveal statistically significant relationships between either patient or therapist alliance scores and average pain. Electronic diaries for ratings opioid craving at monthly clinic visits: Craving Index (CI mean values): at baseline high risk control HRC=26.7, High risk experimental HCE =11.0, at the end of study mean CI values (HRC = 24.5, HRE = 9.6)the differences were statistically significant. p = <.05. Targeting craving may be an important intervention to decrease misuse and improve compliance. Patients on opioids were able to engage and demonstrate positive outcomes using an Internet-based self-management program. Motivational Interviewing on Prescription Opioid Adherence shows a reduction in opioid abuse,	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
					a better self-efficacy on medication use, depression reduced and no reduction or increase of pain, and conclude that incorporating MI techniques can enhance prescription opioid adherence.	
Paracetamol: A Review of Guideline Recommendations. Italia. Freo, 2021 (5)	Adults with chronic pain Musculoskeletal (MSP)and headache	To conduct a scoping literature to summarize the evidence and the guideline recommendations on paracetamol for pain.	Paracetamol use versus placebo or NSAID	Recommendations on paracetamol for management of recurrent and chronic pain	"For the management of knee OA, the European League against Rheumatism (EULAR) recommended paracetamol as the first and preferred long-term oral analgesic, also as the first-line treatment for mild-to-moderate OA pain because of its safety and effectiveness." "The American College of Rheumatology (ACR) conditionally recommended paracetamol for hand, hip, or knee OA at a maximum dose of 3 g/day, especially for patients with reduced therapeutic options because of contraindications to NSAIDs, monitor liver function" NICE 2020: Recommended paracetamol to be considered ahead of NSAIDs "Osteoarthritis Research Society International (OARSI) 2019 guidelines for OA: paracetamol was conditionally not recommended; oral and	**High**

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
					transdermal opioids were strongly not recommended as well, and oral NSAIDs were not endorsed for cardiovascular or frail patients" "The American Association of Hip and Knee Surgeons, American Academy of Orthopedic Surgeons (AAOS), Hip Society, Knee Society, and American Society of Regional Anesthesia and Pain Managements (ASRA): supports with strong evidence the perioperative use of oral and intravenous paracetamol as a non-opioid adjunct for pain management of patients undergoing primary total joint arthroplasty both during hospitalization and following discharge " "Guideline reviews primarily focus on the analgesic efficacy in young patients and pay less attention to potential adverse events especially in the much less studied older patient population. Nevertheless, when potential benefits and risks of harm are considered, paracetamol continues to be investigated and recommended as a first-line analgesic for older adults with mild-to-moderate pain" NICE recommended	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
					paracetamol and/or topical NSAIDs for OA and to be considered before oral NSAIDs, COX-2 inhibitors, or opioids "Makris et al. carried out a clinical review based on graded evidence from 92 studies on pharmacological and nonpharmacologic interventions, which were mostly primarily focused on older adults with OA. Given the scarcity of RCTs on older adults, the authors included reviews, guidelines, and consensus statements and concluded supporting a stepwise approach with paracetamol as first-line therapy for pain in the elderly" **Musculoskeletal pain (MSP)** "The American Geriatric Society (AGS) recommends extreme caution in the use of NSAIDs in the elderly because of frequent adverse events on the gastrointestinal, cardiovascular, and renal systems and the increased risk of hospitalization, renal toxicity, myocardial infarction, stroke, and death; they recommend paracetamol as initial pharmacological therapy in the treatment of persistent pain, particularly MSP, because of its efficacy and	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
					safety profile **(high quality of evidence; strong recommendation)**" Paracetamol over other medication: "The AGS considered a liver failure as an absolute contraindication **(high quality of evidence, strong recommendation)** and hepatic insufficiency, chronic alcohol abuse, or dependence as relative contraindications **(moderate quality of evidence, strong recommendation**)" The AGS recommends paracetamol as a first-line treatment for persistent pain with a 50–75% dose reduction in patients with liver failure. The British Geriatric Society (BGS) and British Pain Society (BPS): indicate in the first UK guideline paracetamol as first-line treatment in older patients, particularly for MSP. **Chronic Low back pain (LBP)** NICE 2020: not recommended paracetamol alone, recommended in association with opioids Evidence Based Medicine (EBM) 2019:	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
					recommended paracetamol for chronic LBP "Although paracetamol has long been recommended as the first-line treatment, recent systematic reviews found insufficient evidence to support its use in LBP. Most recent guidelines advise against its use in chronic LBP . Still, Morlion et al. recommend paracetamol as a first-line treatment for LBP in patients of advanced age or with gastrointestinal, cardiovascular, or renal comorbidities" Others: "The 2016 ASAS-EULAR guidelines: recommend paracetamol for patients with axial spondyloarthritis, an autoimmune disease of the spine, and who present failure, contraindications or poor tolerance to first-line recommended treatments"	
				Safety and Toxicity	Paracetamol has a favorable safety profile that is be of utmost importance across all ages and especially in the elderly with no clinically relevant adverse effects using recommended doses (up to 4 g per day). Although it underwent intense scrutiny of its	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
					efficacy and safety, paracetamol is recommended by guidelines for the treatment in diverse acute and chronic pain." Almost all RCTs and meta-analyses reported numbers of adverse events from paracetamol that were inferior to those of NSAIDs and comparable to those of placebo. "Reviews on long-term observational data reported increased cardiovascular, gastrointestinal, and renal adverse events during therapy with paracetamol, especially in the high dose range; cases of acute liver failure have been reported after accidental and unintentional overdose of paracetamol" Acute liver failure is infrequent with an approximate incidence for all causes of 1/million/year and is declining. Thusius et al. reported that the vast majority of patients survived and recovered without lasting medical sequelae. The liver transplant rate was 1.5% and the death rate <1%; the majority of both intentional and unintentional overdose patients underwent inpatient medical and	

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
					psychiatric treatment.	
A systematic review of the evidence for the efficacy of opioids for chronic non-cancer pain in community-dwelling older adults. UK. O´Brien, 2020 (7)	Chronic pain in older people (>65 years old)	To review of the evidence for the efficacy of opioids for chronic non-cancer pain in community-dwelling people aged 65 years or more	effectiveness of opioids for chronic pain in older people Intervention: opioids	**Pain reduce** Opioid use not associated with pain intensity: 73% of participants reported pain relief after taking opioids. However, opioid use was not associated with pain intensity, and on average, the majority of people still experienced moderate levels of pain, despite taking regular opioids Chronic osteoarthritis (OA) of the knee and/or hip: Patients with extreme OA used non-opioids (72.2 versus 16.7% P = 0.01) Opioid use occurred more with severe OA. Amongst 652 community-dwelling individuals suffering chronic osteoarthritis of the knee/hip, people with severe osteoarthritis were more likely to be taking opioids, and despite this, reported ongoing severe pain Older showed a reduction in the average Numeric Pain Scale rating from 6.35 to 2.95 in carefully selected patients (people without contraindications and who were cognitively and physically able to take opioids or supervised). Diabetic neuropathy,	**Primary aim: efficacy of opioids** opioids demonstrated have benefits over for chronic back, spinal or arthritis pain Efficacy amongst community-dwelling older people with cognitive impairment was limited, with most subjects reporting ongoing pain despite opioid use In people with chronic osteoarthritis the pain was present notwithstanding long-term opioid use Efficacy of opioids in nursing home residents was limited with the majority of analgesic users reporting persistent pain, despite regular opioids Subjects suffered neuropathic pain (80%) and were co-administered a gabapentinoid agent. **Secondary aims: Correlation of opioid use**: Opioid use was more likely in people with severe osteoarthritis pain and a history of coronary artery disease Amongst nursing home residents, opioid use at baseline was associated	**Low**

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
				peripheral neuropathy, radiculopathy, Mechanical back and neck pain: All patients reported an overall reduction of pain with use of liquid morphine **Quality of life** Opioid use did not improve general activity, mood, walking ability	with daily pain, severe pain, severe ADL impairment and a diagnosis of depression The same data shows the risk combination of depression and use of concurrent antidepressants and benzodiazepines was increased in those experiencing daily pain.	
Low-Dose Naltrexone for Chronic Non-Cancer Pain: Clinical Effectiveness. Canada. 2017 (8)	Adult patients experiencing chronic non-cancer pain (e.g., but not limited to, inflammation, fibromyalgia, Crohn's disease, multiple sclerosis, complex regional pain syndrome, etc.)	Finding what is the clinical effectiveness of low-dose naltrexone for the treatment of adults with chronic non-cancer pain?	Low-dose naltrexone (no specific doses are described)	Clinical effectiveness (e.g., reduction in pain, improved functioning, improved quality of life, etc.)	One randomized controlled trial (RCT) and one non-randomized study were identified regarding low-dose naltrexone for chronic, non-cancer pain. Both studies examined pain associated with fibromyalgia. The authors of the identified RCT1 determined that there was a significant reduction in baseline pain in women receiving low-dose naltrexone when compared to placebo. The treatment also appeared to have benefits for the patients with regards to improved mood and satisfaction with life. The authors of the identified blinded non-randomized study concluded that low-dose naltrexone reduce fibromyalgia symptoms in their cohort of women, with additional improvement in	**High**

NAME	POPULATION	OBJECTIVE / GOALS	TYPE OF INTERVENTIONS/COMPARATORS	OUTCOME	CONCLUSIONS	Risk of bias (ROBIS)
					mechanical and heat pain thresholds	
Selective serotonin reuptake inhibitors for fibromyalgia syndrome (Review). USA. Walitt, 2015 (9)	Adults (>18 years) on treatment of fibromyalgia symptoms	To assess the benefits and harms of selective serotonin reuptake inhibitors (SSRIs) in the treatment of fibromyalgia.	Intervention: Selective serotonin re-uptake inhibitor (SSRIs): citalopram, fluoxetine, escitalopram, fluvoxamine, paroxetine, and sertraline. Comparator: placebo	**At least 30% pain reduction** SSRIs were statistically significantly superior to placebo (P = 0.04); RD 0.10, 95% CI 0.01 to 0.20; 56/172 (32.6%) of patients with SSRIs and 39/171 (22.8%) of patients with placebo reported at least 30% pain reduction resulting in a NNTB of 10 (95% CI 5 to 100) **Global improvement** SSRIs were statistically significantly superior to placebo (P = 0.001); RD 0.14, 95% CI 0.06 to 0.23; 50/168 (29.8%) of patients with SSRIs and 26/162 (16.0%) of patients with placebo reported a clinically important global improvement resulting in a NNTB of 7 (95% CI 4 to 17) **Safety (adverse events)** There was no statistically significant or clinically important difference between SSRIs and placebo (P = 0.46); RD -0.01, 95% CI -0.07 to 0.05	The use of SSRIs in fibromyalgia had no appreciable clinical benefit compared to placebo. The quality of evidence was very low. The use of SSRIs in fibromyalgia had an appreciable clinical benefit compared to placebo. The quality of evidence was very low Serious adverse events were reported by 3/84 (3.6%) patients with SSRIs and by 4/84 (4.8%) of patients with placebo. The quality of evidence was very low	**Low**