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SUMMARY WITH CRITICAL APPRAISAL

Capsaicin for Acute or Chronic Non-Cancer Pain: A Review of Guidelines

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Abbreviations

AAOS	American Association of Orthopedic Surgeons
ACOEM	American College of Occupational and Environmental Medicine
ACP	American College of Physicians
ACR	American College of Rheumatology
AGS	American Geriatric Society
ELAR	European League Against Rheumatism
GRADE	Grading of Recommendations Assessments, Development and Evaluation
NICE	National Institute of Health and Care Excellence
NP	neuropathic pain
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
RACGP	Royal Australian College of General Practitioners
RCP	Royal College of Physicians
SIGN	Scottish Intercollegiate Guideline Network

Context and Policy Issues

Pain is a common experience. Generally, acute pain is defined as lasting less than three months, and chronic pain is defined as pain lasting three months or longer.[1] Acute pain includes pain from sprains, strains, and tendonitis; and muscle aches. Chronic pain includes pain associated with osteoarthritis (OA), neuropathic pain (NP), and back pain.[1] According to the Canadian Community Health Survey of individuals during the period 2007 to 2008, the prevalence of chronic pain in adults over the age of 18 years was 18.9% in Canada, and ranged between 16% and 22% for the different provinces.[2] Pain is associated with reduced quality of life, absenteeism from work, and substantial healthcare costs.[1]

There are several treatment options for managing pain; both pharmacological and non-pharmacological options. Capsaicin, which is found in chili peppers, has been used as a topical agent to relieve pain.[3] It is a transient receptor potential vanilloid 1 receptor (TRPV1) agonist; it binds to nociceptors (sensory receptors responsible for sending signals that cause the perception of pain) in the skin, specifically to the TRVP1 receptor. This binding initially results in depolarization, initiation of action potential, and pain signal transmission to the spinal cord, and subsequently causes desensitization of the sensory axons and inhibition of pain transmission.[3-5] There are various formulations for capsaicin: cream, gel, lotion and patch.[4] It is available as low concentration (e.g., 0.025%, 0.075%, and 0.25%) and high concentration (e.g., 8%) product.[3-5] According to a report dated 2018, capsaicin is available in Canada as a cream (0.025%, 0.05%, and 0.075%), gel (0.025%), and patch (0.025%), as well as in creams, gels, or lotions (0.025% or 0.035%) in combination with

other active ingredients.[6] There appears to be some uncertainty regarding the therapeutic efficacy of capsaicin for the management of pain.[7]

The purpose of this report is to review the evidence-based guidelines regarding capsaicin products for the treatment of acute and chronic non-cancer pain. A subsequent report will review the comparative clinical effectiveness, safety, and cost-effectiveness regarding capsaicin products for the treatment of acute and chronic non-cancer pain.

Research Questions

What are the evidence-based guidelines regarding over-the-counter capsaicin products for the treatment of acute and chronic non-cancer pain?

Key Findings

Seven relevant publications were identified, these comprised two systematic reviews of guidelines, and two individual guideline reports on osteoarthritis (OA); and three individual guideline reports on neuropathic pain (NP).

There appears to be some variability in the recommendations for use of capsaicin for the management of pain in patients with OA. The two systematic reviews found that capsaicin was recommended for OA (two guidelines), hand OA (two guidelines), knee OA (three guidelines), and hip OA (one guideline); and capsaicin was not recommended for OA (one guideline). According to one guideline report, capsaicin is recommended for knee OA but not for hand OA (conditional recommendation); and the other guideline report does not recommend for or against use of capsaicin for treating glenohumeral joint OA (due to absence of reliable evidence).

For treatment of patients with NP, one guideline recommends high concentration capsaicin patch (weak recommendation); and two guidelines recommend capsaicin (8%) patch as second-line treatment (strength of recommendation: weak according to one guideline and based on high level evidence according to another guideline).

Findings need to be interpreted in the light of limitations (such as limited available evidence, and variability in the reported recommendations).

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search was used for both this report and a subsequent related report. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were capsaicin or capsaicin and safety. A search filter was applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was limited to English language documents published between January 1, 2015 and May 19, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (18 years and older) with acute or chronic non-cancer pain (e.g., backache, lumbago, strains, sprains, pain of tendons and ligaments, neuropathic pain [e.g. diabetic neuropathy, post-herpetic neuralgia], osteoarthritis, rheumatoid arthritis, pruritic disorders [e.g., pruritic psoriasis, peripheral neuropathic itching disorders, intractable idiopathic pruritus ani])
Intervention	Topical capsaicin (e.g., cream, gel, lotion, or patch), as a single product formulation
Comparator	Not applicable
Outcomes	Recommendations on the use of capsaicin for acute or chronic non-cancer pain and its place in therapy
Study Designs	Systematic reviews of guidelines, and evidence-based guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[8] for systematic reviews, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[9] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 445 citations were identified in the literature search. Following screening of titles and abstracts, 416 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 31 potentially relevant articles, 24 publications were excluded for various reasons, and seven publications met the inclusion criteria and were included in this report. These comprised two systematic reviews[7,10] of evidence-based guidelines, and five evidence-based guidelines.[11-15] For the rest of the report, evidence-based guidelines will be simply referred to as guidelines, and systematic review of evidence-based guidelines will be referred to as systematic reviews. Appendix 1 presents the PRISMA[16] flowchart of the study selection.

Of the two systematic reviews[7,10] one systematic review[7] was exclusively on capsaicin; and the other systematic review[10] had a broad objective, and reported on treatments for OA pain with capsaicin as well as various other topical pharmacological agents. The five guidelines[11-15] had broad objectives and reported on capsaicin, as well as other treatment

options (which included one or more treatment modalities such as pharmacological therapies, psychological therapies, and surgical interventions) for the management of OA pain, neuropathic pain, or chronic pain. For the purpose of this current report, only information regarding capsaicin will be presented.

Summary of Study Characteristics

Two relevant systematic reviews,[7,10], and five relevant guidelines.[11-15] were identified. The study characteristics are summarized below. Additional details regarding the characteristics of included publications are provided in Appendix 2, Table 2 (systematic review of guidelines) and Table 3 (guidelines).

Study Design

In one systematic review[7] multiple databases were searched between 2004 to 2016. It included three relevant guidelines (produced by the American College of Occupational and Environmental Medicine [ACOEM], Royal Australian College of General Practitioners [RACGP], and Royal College of Physicians [RCP]) published between 2008 and 2011. In the second systematic review[10] multiple databases were searched up to January 2016. It included five relevant guidelines (produced by the National Institute of Health and Care Excellence [NICE], Osteoarthritis Research Society International [OARSI], American College of Rheumatology [ACR], American Geriatric Society [AGS], and European League Against Rheumatism [ELAR]) published between 2003 and 2014.

For the five included guidelines,[11-15] the guideline development group comprised a multidisciplinary team (various combinations of health care professionals such as rheumatologist, neurologist, neuro-surgeon, pain physician, general practitioner, clinical psychiatrist, physiotherapist, occupational therapist, pharmacist, and nurse). In addition, in three guidelines[11,14,15] a patient representative was included in the guideline development group. In three guidelines,[11,12,14] recommendations were graded using the Grading of Recommendations Assessments, Development and Evaluation (GRADE) method. In the GRADE method, evidence was graded as high, moderate, low, or very low; and recommendations were graded as strong or weak (some guideline panels may prefer terms such as conditional or discretionary).[17] In the fourth guideline[13] recommendations were graded using the American association of Orthopedic Surgeons (AAOS) method. In the AAOS method, the evidence levels were described as high, moderate, low or conflicting evidence, and no evidence; and the recommendation levels were described as strong, moderate, limited, and consensus which were also visually represented by stars (1 to 4) with the highest number of stars indicating the strongest recommendation.[13] In the fifth guideline,[15] the Scottish Intercollegiate Guidelines Network (SIGN) method was used. In the SIGN method, the evidence levels ranged from 1++ (highest level) to 4 (lowest level), and recommendation grades ranged from A (highest) to D (lowest).Recommendations were based on voting in three guidelines,[11,13,14] and by consensus in two guidelines.[12,15]

Country of Origin

One systematic review[7] was published by authors from Portugal in 2018, and the other systematic review[10] was published by authors from China in 2018.

For the five included guidelines,[11-15] countries indicated for the first author of the guideline document or of the guideline development group were France,[11,12] UK,[15] and USA.[13,14] The authors for one guideline[12] were from several European countries, UK, USA and Canada, while the remaining four guidelines[11,13-15] were produced by authors from the same country

or by a national guideline development group. Three guidelines[11,13,14] were dated 2020, one guideline[15] was dated 2019, and one guideline[12] was dated 2015.

Patient Population

Both systematic reviews[7,10] involved patients with OA. Of the five individual guideline reports, two guidelines[13,14] were on OA; and three guidelines were on NP.[11,12,15]

Interventions and Comparators

One systematic review[7] reported guideline recommendations on capsaicin, based on studies comparing capsaicin with placebo. The second systematic review[10] reported on guideline recommendations on capsaicin, but did not report on the studies which were used for evidence.

Of the five individual guideline reports,[11-15] two guidelines[13,14] reported on capsaicin (concentration was not specified); one guideline[11] reported on high concentration capsaicin and low concentration capsaicin (specific concentrations or ranges were not presented in the article); and two guidelines[12,15] reported on a high concentration capsaicin (8%) patch. The evidence was from studies that compared capsaicin with placebo, or high concentration capsaicin with low concentration capsaicin.

Outcomes

Both systematic reviews[7,10] presented recommendations for capsaicin; outcomes considered by each guideline panel when formulating recommendations were not mentioned for most of the included guidelines; one guideline mentioned outcomes (pain, function, quality of life, and adverse events).

For the five individual guideline reports,[11-15] the outcomes considered in formulating recommendations were pain,[11,12,14,15] function,[14,15] benefit[13] (not specified), and adverse events.[11-13,15]

Summary of Critical Appraisal

An overview of the critical appraisal of the included publications is summarized below. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 4 (systematic review of guidelines) and Table 5 (guidelines).

The two included systematic reviews[7,10] stated the objective, conducted a comprehensive literature search, and reported that the authors had no conflicts of interest. In one systematic review,[7] article selection was described (i.e., number of articles selected and flow chart of selection provided) and performed by two reviewers; data extraction was done by one reviewer and checked by another reviewer; and study characteristics were described. In the second systematic review,[10] there was a lack of information regarding article selection, data extraction and study characteristics. In both systematic reviews, the inclusion and exclusion criteria were unclear, quality assessment of the included studies (i.e., guidelines) was not conducted, and publication bias was not investigated. Hence it is not possible to comment on the reliability of the findings presented or if all relevant findings have been included.

In all the included guidelines[11-15] the scope and purpose were described, the target users were specified, the guideline development group comprised of individuals with relevant expertise, and in addition for three guidelines,[11,12,15] the guideline development group

included a patient representative. For all the guidelines, a systematic literature search was undertaken to identify evidence, the method for grading the recommendation was stated, the recommendations were clearly described, and the guideline was externally reviewed. In all the guidelines, recommendations were based on consensus; the method of achieving consensus was described in three guidelines[11,13,14] but not in two guidelines.[12,15] Applicability of the guidelines was not described. In one guideline[14] the funding body was not stated and in four guidelines[11-13,15] the funding body was stated, but it was unclear if the views of the funding body had any influence on the contents of the guidelines. In all the guidelines, conflicts of interest were declared or there was a process to declare conflicts; however, the procedure for addressing conflicts was not described.

Summary of Findings

The main findings are summarized below. Appendix 4, Table 6 (systematic review of guidelines) and Table 7 (guidelines) presents details of the main study findings and recommendations.

Guidelines

Seven relevant publications were identified, these comprised two systematic reviews[7,10] of guidelines, and five individual guideline reports.[11-15] Strengths of the recommendations are reported when available and the associated explanations are presented in Appendix 4, Table 6Table 7.

Osteoarthritis (OA)

Two systematic reviews[7,10] of guidelines, and two individual guideline reports[13,14] presented recommendations for the use of capsaicin in patients with OA.

One systematic review[7] reported recommendations from three guidelines (ACOEM, 2011; RACGP, 2009; and RCP, 2008). The ACOEM guideline recommends topical capsaicin for chronic hand OA and for acute flares (strength of recommendation: C). The RACGP guideline recommends topical capsaicin (alone or in conjunction with other drugs) for short-term treatment for mild to moderate persistent symptoms of hip and knee OA and for acute flares (strength of recommendation: D). The RCP guideline recommends topical capsaicin be considered as an adjunct to core treatment for knee and hand OA (strength of recommendation: B). Details regarding recommendations strengths B, C, and D are presented in Table 7.

One systematic review[10] reported recommendations from five guidelines (NICE, 2014; OARSI, 2014; ACR, 2012; AGS, 2009; and ELAR, 2003) for treatment for knee OA. The NICE guideline recommends that topical capsaicin be considered as an adjunct to core treatment. The OARSI guideline recommends that capsaicin is appropriate only for knee OA without relevant comorbidities. The ACR guideline conditionally recommends against use of topical capsaicin. The AGS guideline recommends that topical capsaicin be considered for treatment of regional pain syndrome (strength of recommendation: weak). The ELAR guideline mentioned that there is evidence for efficacy of capsaicin for treatment of knee OA and that capsaicin has a good safety record; it was unclear if this was intended as a recommendation for use of capsaicin.

The guideline by Kolasinski et al.[14] recommends the use of capsaicin for knee OA and recommends against the use of capsaicin for hand OA (strength of recommendation: conditional). Recommendation against the use of capsaicin for hand OA was because of

the lack of direct evidence to support its use, and the potential risk of contamination of the eye. The AAOS guideline[13] does not recommend for or against the use of capsaicin for treating glenohumeral joint OA, due to lack of credible evidence.

In summary, there appears to be some variability in the recommendations for use of capsaicin for the management of pain in patients with OA. From the two systematic reviews[7,10] of guidelines, capsaicin is recommended for OA (two guidelines), hand OA (two guidelines), knee OA (three guidelines), and hip OA (one guideline); and capsaicin was not recommended for OA (one guideline). From the included individual guideline reports: according to the guideline by Kolasinski et al.[14] capsaicin is recommended for knee OA but not for hand OA (conditional recommendation); and the AAOS guideline does not recommend for or against use of capsaicin for treating glenohumeral joint OA.

Neuropathic pain (NP)

Three individual guideline reports[11,12,15] presented recommendations for NP. The guideline by Moisset et al.[11] recommends the use of high concentration capsaicin patch for treating peripheral NP including diabetic NP (strength of recommendation: weak). This guideline also reported that the evidence for low concentration capsaicin is inconclusive. The SIGN guideline[15] recommends capsaicin (8%) patch for treating peripheral NP, when first line pharmacological treatments were ineffective or not tolerated (strength of recommendation: A [recommendation strengths range from A to D, with A indicating recommendations based on the highest level of evidence, and D the lowest level of evidence]). The guideline by Finnerup et al.[12] recommends capsaicin (8%) patch as second line treatment for peripheral NP (strength of recommendation: weak).

Limitations

Evidence regarding capsaicin is limited in quantity and quality. There is variability in the recommendations from the different guidelines. The two systematic reviews of guidelines did not present details regarding the included guidelines, hence commenting on the reliability of the reported recommendations is difficult. In many cases, the recommendations did not specify the capsaicin concentration.

No guidelines on the use of capsaicin in treatment of conditions such as back pain, pain associated with rheumatoid arthritis, tendon and ligament pain, and pruritic disorders were identified.

The guidelines were from USA, UK, and France, hence generalizability to the Canadian context is unclear. Different countries have different health systems, but as all the guidelines were from developed countries this may not be a major limitation.

Conclusions and Implications for Decision or Policy Making

Seven relevant publications were identified on recommendations for the use of capsaicin for the treatment of acute or chronic non-cancer pain; these comprised two systematic reviews[7,10] of guidelines, and two individual guideline reports[13,14] on OA, and three individual guideline reports[11,12,15] on NP.

From the two systematic reviews of guidelines, there appears to be some variability in the recommendations for use of capsaicin for the management of pain in patients with OA. Capsaicin was recommended for OA (two guidelines), hand OA (two guidelines), knee OA (three guidelines), and hip OA (one guideline); and capsaicin was not recommended for OA

(one guideline). According to the guideline by Kolasinski et al.[14] capsaicin is recommended for knee OA but not for hand OA; and the AAOS guideline does not recommend for or against use of capsaicin for treating glenohumeral joint OA.

For treatment of patients with NP, one guideline[11] recommends high concentration capsaicin patch; and two guidelines[12,15] recommend capsaicin (8%) patch as second-line treatment (strength of recommendation: weak according to one guideline, and based on high level evidence according to another guideline).

The evidence base for capsaicin as a pain-relieving agent may need to be expanded. High quality studies are needed to have a better understanding of the efficacy and safety of capsaicin. Studies comparing capsaicin with other active agents would be useful to determine the place of capsaicin in the armamentarium of treatment options for management of pain. Also, studies investigating the role of capsaicin in treating other pain conditions such as sprains, muscle ache, back ache, pain due to rheumatoid arthritis, and pruritic disorder, would be useful.

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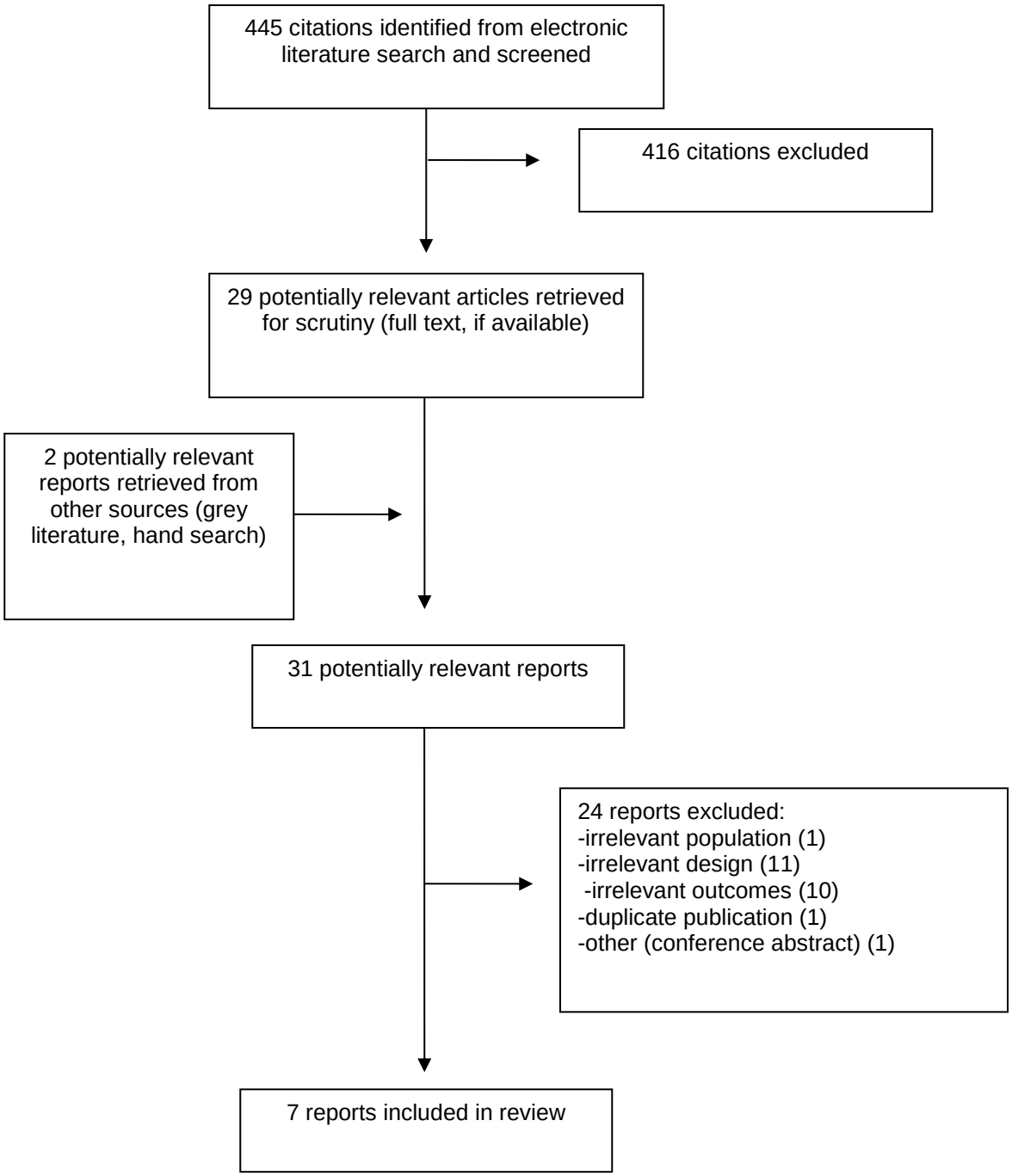
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Guedes et al., 2018,[7] Portugal. The authors declared that there was no funding.	Systematic review including 3 systematic reviews (published between 2009 and 2014) and 3 guidelines published between 2008 and 2011). Literature search: Multiple databases were searched between January 2004 and January 2016 to identify relevant systematic reviews, RCTs, and guidelines. Only the 3 guidelines which are relevant for this report will be discussed	Patients with pain from OA. The RCP guideline provided recommendations for treatment of knee and hand OA. The RACGP guideline provided recommendations for nonsurgical management of hip and knee OA. The ACOEM guideline provided recommendations for chronic hand OA or acute flares of OA	All the guidelines based recommendations on placebo-controlled capsaicin studies.	Recommendations from guidelines (outcomes considered by guideline development group included pain intensity, functional capacity, quality of life, and adverse events)
Meng and Huang, 2018,[10] China. Supported by the National Natural Science Foundation of China	Systematic review included 6 guidelines published between 2003 and 2014. Literature search: Multiple databases were searched up to January 2016. The report had a broad focus; only the 5 guidelines relevant for this current report are described. These 5 guidelines were published between 2003 and 2014.	Patients with knee OA	Recommendations for capsaicin were presented. Studies used for the preparation of the guidelines were not presented, hence information on the comparators were not available	Recommendations from guidelines (outcomes considered when formulating recommendations were not reported)

OA = osteoarthritis; RACGP = Royal Australian College of General Practitioners; ACOEM = American College of Occupational and Environmental medicine; RCP = Royal College of Physicians.

Table 3: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
AAOS, 2020,[13] USA						
Intended Users: Healthcare professionals (other than orthopedic surgeons) involved in the management of glenohumeral joint OA **Target Population:** Patients with glenohumeral joint OA	Non-surgical treatments (such as capsaicin, cannabis, opioid, acupuncture, TENS); and surgical procedures (such as total or hemi arthroplasty)	Benefits and harms	A systematic literature review was undertaken. Multiple databases were searched; search period between 2000 to June 2019	Strength of evidence and recommendations were reported based on AAOS criteria[13]	The GDG comprised of a multidisciplinary group (such as members from AAOS, AOSSM, and APTA; and literature review team and methodologist) Recommendations were voted on by the GDG members and disagreements were discussed in order to resolve them. Recommendations were approved with a majority of 60%.	Externally reviewed
Kolasinski et al., 2020,[14] USA						
Intended Users: Clinicians and patients making treatment decisions regarding management of OA **Target Population:** Patients with knee, hip or hand OA	Pharmacological treatments such as topical (e.g., capsaicin, lidocaine, NSAIDs); oral (e.g., acetaminophen, antidepressants, NSAIDs, tramadol); biologics (e.g., anti-nerve growth factor, tumor necrosis factor inhibitor); intra-articular (e.g., corticosteroids, mesenchymal stem cells, botulinum toxin). Non-pharmacological treatments such as acupuncture,	Pain (measures such as WOMAC, VAS, McGill pain questionnaire); and function (measures such as WOMAC, SF-36, ASES)	A systematic literature review was undertaken. Multiple databases were searched up to August 2018. Methodology used for the systematic review was that of the ACR guideline development process[18] which is a rigorous process.	GRADE methodology[17] was used to grade evidence and develop recommendations.	GDG was multidisciplinary (rheumatologists, internists, physical and occupational therapists, patients). GDG comprised of 4 teams: core leadership team, a voting panel, literature review team, and expert panel Recommendations were developed by voting and consensus. Recommendations required a 70% level of agreement.	Externally reviewed; published in a peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
	electrical stimulation, exercise, patient education)					
Moisset et al., 2020,[11] France						
Intended Users: Not explicitly specified but appears to be for health professionals involved in the management of neuropathic pain **Target Population:** Patients of any age with neuropathic pain	Capsaicin (relevant for this report) This guideline had a broad objective and included several therapeutic options (medical [capsaicin and other], psychological, and surgical) for neuropathic pain	Pain, adverse effects	A systematic literature review was undertaken, based on PRISMA reporting guidelines. Multiple database were searched up to January 2018.	The GRADE[17] system was used to assess the quality of evidence and to propose recommendations.	The GDG comprised a steering group 15 members) and a reading group (32 members). Members were healthcare professionals (such as neurologist, neuro-surgeon, pain physician, general practitioner, clinical pharmacologist, psychologist, psychiatrist, anesthesiologist, rheumatologist, and nurse). The reading group also had a patient member. The reading group provided comments. Comments were taken into account, and the recommendations were finalized. Voting using a scoring system was used to finalize recommendations (scored on a scale of 1 to 9, with 1 = total disagreement agreement, and 9 = total agreement). Median score ≥ 7 were considered as agreement. The recommendations were validated by the steering group.	Externally reviewed; published in a peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
SIGN, 2019,[15] UK						
Intended Users: Healthcare professionals involved with the assessment and management of chronic pain **Target Population:** Patients with chronic pain	Pharmacological treatments (such as capsaicin, NSAIDs, antidepressants, opioids); physical therapy (such as exercise, traction); psychological interventions (such as behavioral therapies, unidisciplinary education); and complimentary therapies (acupuncture, herbal medicines)	Pain, functional capability, quality of life, and adverse events	A systematic literature review was undertaken. Multiple databases were searched between 2007 and 2018 Methodology used was that of SIGN guideline development process[19] which is a rigorous process. SIGN conforms to AGREE II method.	Recommendations were graded according to the SIGN methodology.[15]	GDG was multidisciplinary individuals (such as consultant in pain management, consultant in anesthesia, general practitioner, clinical psychiatrist, physiotherapist, occupational therapist, nurse, and patient representative) Recommendations were made by informal consensus, facilitated by the program manager, details of the procedure were not presented.	Externally reviewed
Finnerup et al., 2015,[12] France						
Intended Users: Healthcare professional involved in the pharmacological management of neuropathic pain. **Target Population:** Patients with neuropathic pain	Pharmacological agents (such as capsaicin, tricyclic antidepressants, other antidepressants, serotonin norepinephrine reuptake inhibitors, opioids, botulinum toxin A, and lidocaine)	Pain, adverse effects	A systematic literature review was undertaken, based on PRISMA reporting guidelines. Multiple databases were searched between 1966 and April 2013). The authors mentioned that the AGREE II guideline development	The methodological quality of the included studies was assessed using the five-point Oxford quality scale. Recommendations were graded using GRADE	GDG was multidisciplinary (neurologists, anesthesiologists, psychologist, pharmacists, primary care physicians, and neuroscientists with expertise in neuropathic pain and systematic reviews) Recommendations were discussed and consensus was obtained; then evaluated by four external reviewers; based on feedback appropriate changes were made; final	Externally reviewed; published in a peer-reviewed journal.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
			method was followed.		recommendations were circulated by e-mail and consensus was obtained from the group. Details of the procedure for achieving consensus were not presented.	

AAOS =American Academy of Orthopedic Surgeons; AGREE II = A MeaSurement Tool to Assess systematic Reviews II; AOSSM = American Orthopedic Society for Sports Medicine; APTA = American Physical Therapists Association; ASES = Arthritis Self Efficacy Scale; GRADE = Grading of Recommendations Assessment, Development and Evaluation; OA = osteoarthritis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; SF-36 = short form 36; SIGN = Scottish Intercollegiate Guidelines Network; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[8]

Strengths	Limitations
Guedes et al., 2018,[7] Portugal	
• The objective was clearly stated • Multiple databases (such as Medline, TRIP, guideline producing organizations) were searched between January 2004 and January 2016 • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done by two reviewers • Data extraction was done by one reviewer and checked by another reviewer. • Recommendations graded based on SORT[20] or if based on a different grading scale, an explanation for the grade was provided. • Characteristics of the included studies were presented • It was mentioned that the authors had no conflicts of interest	• A list of excluded studies was not provided • Publication bias does not appear to have been explored • Quality assessment of the included guidelines was not conducted
Meng and Huang, 2018,[10] China	
• The objective was clearly stated • Multiple databases (PubMed, Embase and the Cochrane library) were searched up to January 20 but lacked16. Reference list of relevant articles were also searched. • The included studies were mentioned but the number of studies included were not clearly stated • The authors mentioned that there were no competing financial interests	• Study selection was not described • A list of excluded studies was not provided • Method for article selection was not described • Method for data extraction was not described • Details of the study characteristics were not described • Quality assessment of the included guidelines was not conducted • Publication bias does not appear to have been explored

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; SORT = Strength of Recommendation Taxonomy.

Table 5: Strengths and Limitations of Guidelines Using AGREE II[9]

Item	Guideline				
	AAOS,[13] 2020, USA	Kolasinski et al., 2020,[14] USA	Moisset et al., 2020,[11] France	SIGN,[15] 2019, UK	Finnerup et al., 2015,[12] France
Domain 1: Scope and Purpose					
1. The overall objective(s) of the guideline is (are) specifically described.	yes	yes	yes	yes	yes
2. The health question(s) covered by the guideline is (are) specifically described.	yes	yes	yes	yes	yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	yes	yes	yes	yes	yes

Item	Guideline				
	AAOS,[13] 2020, USA	Kolasinski et al., 2020,[14] USA	Moisset et al., 2020,[11] France	SIGN,[15] 2019, UK	Finnerup et al., 2015,[12] France
Domain 2: Stakeholder Involvement					
4. The guideline development group includes individuals from all relevant professional groups.	yes	yes	yes	yes	yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	unclear	yes	yes	yes	unclear
6. The target users of the guideline are clearly defined.	yes	yes	Not explicitly specified but appeared to be for healthcare professionals involved in the management of neuropathic pain	yes	yes
Domain 3: Rigour of Development					
7. Systematic methods were used to search for evidence.	yes	yes	yes	yes	yes
8. The criteria for selecting the evidence are clearly described.	yes	yes	yes	yes	yes
9. The strengths and limitations of the body of evidence are clearly described.	yes	yes	yes	yes	yes
10. The methods for formulating the recommendations are clearly described.	yes	yes	yes.	yes, but details of the method of achieving consensus was not presented.	yes, but details of the method of achieving consensus was not presented.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	yes	yes	unclear	yes	yes
12. There is an explicit link between the recommendations and the supporting evidence.	yes	yes	yes	yes	yes
13. The guideline has been externally reviewed by experts prior to its publication.	yes	yes	yes	yes	yes
14. A procedure for updating the guideline is provided.	yes	Updates to be made but procedure was not presented	Not mentioned	yes	yes

Item	Guideline				
	AAOS,[13] 2020, USA	Kolasinski et al., 2020,[14] USA	Moisset et al., 2020,[11] France	SIGN,[15] 2019, UK	Finnerup et al., 2015,[12] France
Domain 4: Clarity of Presentation					
15. The recommendations are specific and unambiguous.	yes	yes	yes	yes	yes
16. The different options for management of the condition or health issue are clearly presented.	yes	yes	yes	yes	yes
17. Key recommendations are easily identifiable.	yes	yes	yes	yes	yes
Domain 5: Applicability					
18. The guideline describes facilitators and barriers to its application.	no	no	no	no	no
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	no	no	no	yes, treatment pathways were presented	no
20. The potential resource implications of applying the recommendations have been considered.	no	no	no	Mentioned but details not presented	yes
21. The guideline presents monitoring and/or auditing criteria.	no	no	no	yes	It was mentioned that implementation and monitoring strategies were discussed, however details were not presented
Domain 6: Editorial Independence					
22. The views of the funding body have not influenced the content of the guideline.	Unclear. Funded by AAOS who received no funding from external commercial sources for preparation of this guideline	Funding source not mentioned	Unclear (supported by grant from SFN)	Unclear. Funding: Healthcare Improvement Scotland	Unclear (Funding: NeuPSIG of the IASP)

Item	Guideline				
	AAOS,[13] 2020, USA	Kolasinski et al., 2020,[14] USA	Moisset et al., 2020,[11] France	SIGN,[15] 2019, UK	Finnerup et al., 2015,[12] France
23. Competing interests of guideline development group members have been recorded and addressed.	Conflicts were declared but how they were addressed were not described	It was reported that in accordance with ACR policy, the principal investigator and the Literature Review Team leader were free of conflicts, and all teams had >50% members free of conflicts	Conflicts were declared but how they were addressed were not described	All individuals involved in the guideline development process are required to declare conflicts of interest. The method for addressing conflicts was not described.	Conflicts were recorded and addressed, but details of methods used to address conflicts were not presented

AAOS = American Academy of Orthopedic Surgeons; ACR = American College of Rheumatology; AGREE II = Appraisal of Guidelines for Research and Evaluation II; IASP = International Association for the Study of Pain; NeuSPIG = Special Interest Group on Neuropathic Pain; SFN = Société française de neurorogie; SIGN = Scottish Intercollegiate Guidelines Network,

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews

Main study findings	Authors' conclusion
Guedes et al., 2018,[7] Portugal	
As the findings (i.e., recommendations) are from the systematic review of guidelines, the findings are presented in Table 7 (Summary of Recommendations in Included Guidelines)	
Meng and Huang, 2018,[10] China	
As the findings (i.e., recommendations) are from the systematic review of guidelines, the findings are presented in Table 7 (Summary of Recommendations in Included Guidelines)	

Table 7: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Systematic Review of Guidelines	
Guedes et al., 2018,[7] Portugal	
ACOEM guideline, 2011 Evidence: Not reported Recommendation: "Topical capsaicin is recommended for chronic hand OA or acute flares of OA (p. 42)"[7] --- **RACGP guideline, 2009** Evidence: One low quality RCT including 200 patients ([OA of hip [33 patients], knee [66 patients], shoulder, or hand) ; treatment duration: 6 weeks) reported that capsaicin (0.025%, four times daily) was more effective than placebo in reducing pain (assessed using VAS). Capsaicin was associated with transient local adverse events such as burning and erythema, which diminished with continued use, there were no serious adverse effects. Recommendation: "Topical capsaicin is recommended, alone or in combination with other drugs, for the short-term treatment of mild-moderate persistent symptoms of hip and knee OA, and for acute flares of symptoms (p. 42)"[7] --- **RCP guideline, 2008** Evidence: Four RCTs on OA at various sites were identified (one RCT on knee and shoulder OA; the second RCT on knee OA; the third RCT on knee, hip, shoulder, and hand; and the fourth RCT on	**ACOEM guideline, 2011** **Strength of evidence:** not reported **Strength of recommendation:** C (the intervention is recommended, although there is limited evidence regarding the benefits of this intervention) --- **RACGP guideline, 2009** **Strength of evidence:** weak **Strength of recommendation:** D (body of evidence is weak and recommendation must be applied with caution) --- **RCP guideline, 2008** **Strength of Evidence:** high **Strength of Recommendation:** B (limited-quality patient-oriented evidence)

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
hand OA). Based on these four high quality RCTs (sample sizes: 59 to 200 patients; and study durations: 4 weeks to 12 weeks), topical capsaicin was found to be more effective than placebo in reducing pain (assessed using VAS), and articular tenderness; statistically significantly different in most cases. One RCT reported more adverse events in the capsaicin group compared to the placebo group (69% versus 30%), but there were no serious adverse events with capsaicin. Recommendation: "Topical capsaicin should be considered as an adjunct to core treatment (education, exercise and weight loss) for knee and hand OA (p. 42)"[7]	
Meng and Huang, 2018,[10] China	
Evidence: Not reported for any of the included guidelines Recommendations: **NICE, 2014** "Topical capsaicin should be considered as an adjunct to core treatments. (p. 3 of 7)."[10] **OARSI, 2014** "Capsaicin: Appropriate for knee-only OA without relevant comorbidities. (p. 3 of 7)."[10] **ACR, 2012** "Conditionally recommends that healthcare providers do not use topical capsaicin. (p. 3 of 7)."[10] **AGS, 2009** "Other topical agents, including capsaicin or menthol, may be considered for regional pain syndromes. (p. 3 of 7)."[10] **ELAR, 2003** "There is (1B) evidence for the efficacy and use of topical NSAIDs and capsaicin in the management of knee OA and these treatments have a good safety record. (p. 3 of 7)."[10]	**Strength of evidence:** **NICE, 2014**: not reported. **OARSI, 2014**: not reported. **ACR, 2012**: not reported. **AGS, 2009**: moderate. **ELAR, 2003**: 1B (description not presented) **Strength of recommendations:** **NICE, 2014**: not reported. **OARSI, 2014**: not reported. **ACR, 2012**: conditional. **AGS, 2009**: weak. **ELAR, 2003:** not reported
Individual Guidelines	
AAOS, 2020,[13] USA	
Evidence: Evidence on capsaicin was not presented, but it was mentioned that credible evidence was not available. "Data regarding the use of complementary and alternative medicines (CAMs) for the management of GJO is lacking. The peer reviewed literature does not provide credible evidence that the above modalities provide benefit or harm to patients with GJO. In view of these deficiencies, we cannot support or restrict the usage of the above alternative treatment options when managing symptomatic GJO. (p. 46)."[13]	**Strength of evidence**: No reliable evidence **Strength of recommendation**: Consensus (1 star) (i.e., "There is no supporting evidence. In the absence of reliable evidence, the systematic literature review development group is making a recommendation based on their clinical opinion. [p. 19]"[13])

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Note: CAMs include acupuncture, dry needling, cannabis, CBD oil, non-prescription pain patches, capsaicin, shark cartilage, glucosamine and chondroitin, cupping. Recommendation: "In the absence of reliable evidence, the work group cannot recommend for or against the use of the following: Acupuncture Dry needling Cannabis Cannabodiol (CBD) Oil Capsaicin Shark Cartilage Glucosamine and Chondroitin Cupping Transcutaneous Electrical Nerve Stimulation (TENS) (p. 46)."[13]	
Kolasinski et al., 2020,[14] USA	
Evidence: Based on evidence from 3 RCTs involving patients with knee or hip OA and comparing capsaicin with placebo, the authors reported that there was serious imperfection with respect to the WOMAC pain and function results, and VAS pain results showed a small pain reduction that fell within the bounds of a non-clinically significant improvement (definition of non-clinically significant improvement was not presented). Based on the results of a network meta-analysis indirectly comparing capsaicin with topical NSAIDs, the authors reported that there was no significant difference between the treatments with respect to improvement in pain. They also mentioned that the average risk of bias was serious, and the quality of evidence was further downgraded considering indirect comparison and imprecision in effect size. No studies involving patients with hand OA, and comparing topical capsaicin with placebo, or NSAIDs (oral or topical) were identified. Recommendation: "Topical capsaicin is conditionally recommended for patients with knee OA and conditionally recommended against in patients with hand OA. (p. 229)."[14]	**Strength of evidence:** moderate (3 RCTs) or very low (network-meta analysis) for knee and hip OA; very low (no studies) for hand OA **Strength of recommendation:** conditional
Moisset et al., 2020,[11] France	
Evidence: *High concentration capsaicin:* Seven placebo-controlled trials on high concentration capsaicin patch were identified and of these five showed a positive effect on pain. *Low concentration capsaicin:*	*High concentration capsaicin:* **Strength of evidence**: High quality of evidence, low effect size **Strength of recommendation**: Weak. *Low concentration capsaicin:* **Strength of evidence:** Low to moderate

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
Eleven studies on low concentration capsaicin were identified and of these seven showed a positive effect on pain (low quality evidence). One semi double-blind placebo-controlled study showed that 0.625% capsaicin was better than placebo for treatment of pain (moderate quality evidence). Two non-inferiority studies demonstrated similar effects with capsaicin cream (0.025% to 0.075%), and topical clonidine or amitriptyline for treatment of pain (moderate quality) Recommendation: *High concentration capsaicin:* "High-concentration capsaicin patches have a weak recommendation for use in peripheral neuropathic pain, including diabetic neuropathic pain. (p. 331)"[11] *Low concentration capsaicin:* "The evidence for the use of capsaicin at low concentrations, herbal preparations, nitroglycerin, clonidine and topical ketamine is inconclusive. (p. 331)"[11]	**Strength of recommendation:** Not reported
SIGN, 2019,[15] UK	
Evidence: Evidence on low dose (0.025% or 0.075%) capsaicin cream or high dose (8%) capsaicin patch was identified. One systematic review found that low dose capsaicin cream did not appear to have any benefit over placebo, in patients with neuropathic pain; evidence level: 1++. A second systematic review found that low dose capsaicin cream was better than placebo, for pain management in patients with OA; evidence level: 1+. A third systematic review found that high dose capsaicin patch was significantly better compared to placebo for treating patients with PHN or HIV neuropathy. Though beneficial, considering cost and requirement for application by specialist, it was reported that it should be used when other treatments have failed; evidence level: 1++. Recommendation: "Topical capsaicin patches (8%) should be considered in the treatment of patients with peripheral neuropathic pain when first-line pharmacological therapies have been ineffective or not tolerated. (p. 11)"[15]	**Strength of evidence:** 1++ indicates "High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. (p. 2 of 77)"[15] 1+ indicates "Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias. (p. 2 of 77)"[15] **Strength of recommendation**: A A indicates: "At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results. (p. 2 of 77)"[15]
Finnerup et al., 2015,[12] France	
Evidence: *High concentration capsaicin:* Seven studies involving patients with post-herpetic neuralgia or HIV related poly neuropathy and comparing high concentration capsaicin (8%) patch with low concentration capsaicin (0.04%) patch were identified. Of these, five studies showed sustained efficacy with single dose of capsaicin (8%) compared to	*High concentration capsaicin:* **Strength of Evidence:** High quality evidence **Strength of Recommendation:** weak

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
capsaicin (0.04%); 30 minutes application for post-herpetic neuralgia patients, and 60 minute application for HIV related poly neuropathy patients. NNT (95% CI):10.6 (7.4 to 18.8), combined value from 6 studies; NNH: not significant. *Low concentration capsaicin:* Eleven studies involving patients with painful polyneuropathy or peripheral nerve injury and comparing treatment with low concentration capsaicin (0.025% or 0.075%) with placebo were identified. NNT and NNH values were reported for some of the individual studies. Results were inconsistent, some studies showed a statistically significant NNT, whereas some studies showed a statistically significant NNH. NNT (95% CI): 8.7 (4.6 to 14), combined value from 4 studies NNH (95% CI): 8.7 (6.2 to 14), combined value from 3 studies **Recommendation:** *High concentration capsaicin:* Capsaicin 8% (daily dose: 1 to 4 patches applied to the painful area for 30 to 60 minutes every 3 months) was recommended as second-line treatment for peripheral neuropathic pain (weak recommendation). Of note, the safety regarding long term effects of repeated use of capsaicin patches is unclear, particularly with respect to degeneration of epidermal nerve fibres, which might be a cause for concern in progressive neuropathy. *Low concentration capsaicin:* The GRADE recommendation for capsaicin cream was inconclusive.	*Low concentration capsaicin:* **Strength of Evidence:** not reported **Strength of Recommendation:** inconclusive

AAOS =American Academy of Orthopedic Surgeons; ACR = American College of Rheumatology; AGS = American Geriatric Society; ACOEM = American College of Occupational and Environmental Medicine; CI = confidence interval; ELAR = European League Against Rheumatism; GJO = glenohumeral joint osteoarthritis; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HIV = human immunodeficiency virus; NNH = number needed to treat to harm; NNT = number needed to treat to benefit); NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; OARSI = Osteoarthritis Research Society International; PHN = post herpetic neuropathy; RACGP = Royal Australian College of General Practitioners; RCP = Royal College of Physicians; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.