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Efficacy of treatments and pain management for trapeziometacarpal (thumb base) osteoarthritis: protocol for a systematic review

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Title page

Title of the article: Efficacy of treatments and pain management for trapeziometacarpal (thumb base) osteoarthritis: protocol for a systematic review

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ABSTRACT

Introduction: The thumb is essential for daily activities. Unfortunately, this digit is commonly affected by trapeziometacarpal osteoarthritis (TMO), handicapping a large number of individuals. TMO constitutes an increasing human and economic burden for our society whose population is ageing. Limited access to adequate treatment is among the most important obstacles to optimal TMO management. Poor understanding of TMO characteristics, lack of knowledge about evidence-based treatments, simplistic pain management plans based solely on the patient's physical condition, absence of inter-professional communication and poor coordination from the primary to tertiary sectors of care also contribute to inadequate TMO management. Our research project aims to improve the quality of care and services offered to TMO patients by establishing a patient-centered, evidence-based multidisciplinary management clinical pathway coordinated across the healthcare system. This proposed systematic review is a prerequisite to ensuring our evidence-based practice, aiming to document the efficacy of all the existing modalities for TMO management.

Methods and analysis: The protocol of the systematic review is registered with PROSPERO (Registration number CRD42015015623) and will be conducted using the guidelines for systematic review of the *Cochrane Handbook* and *Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols*. We will identify studies in English and French concerning TMO treatments through searches in Cochrane Central, EMBASE, MEDLINE, PsychINFO, CINHAL, PubMed, OT Seekers, PEDRO, and the grey literature. Two reviewers will independently screen study eligibility, extract data and appraise studies using published

assessment tools. Meta-analyses will be undertaken where feasible; otherwise, narrative syntheses will be carried out. The robustness of evidence will be assessed using the GRADE system.

Ethics and dissemination: Ethics approval is not required for this study. An integrated knowledge transfer (KT) approach and end-of-project KT plan will be incorporated to effectively disseminate this review's findings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review is the first to carry out an extensive and comprehensive systematic review of all the existing treatments specific to TMO including pharmacological, non-pharmacological and surgical, not limited to any one discipline. Subsequently, the findings will allow us to better elaborate multidisciplinary TMO management clinical pathway usable from the primary to tertiary care.
- As dissemination strategies, extensive knowledge transfer (KT) strategies incorporating an integrated KT approach and an end-of-project KT plan are proposed. An integrated KT approach, entailing a collaborative partnership between researchers and end-users, will contribute to more effective dissemination.
- What limits this protocol is the language restriction to English and French for the literature search; thus language bias is possible.

INTRODUCTION

Trapeziometarcarpal osteoarthritis: an understudied but important health problem.

The most prevalent cause of chronic pain in the world is osteoarthritis (OA).[1 2] Its prevalence is increasing in an alarming manner with the ageing of the population, and it is estimated it will double before the year 2020.[3] This anticipated increase is somewhat frightening considering that OA is associated with numerous adverse consequences for affected individuals as well as increasing economic costs for our society.[3-6] Based on the meta-analysis of Pereira et al. (2011) on OA prevalence, hand OA is more prevalent than knee/hip OA, yet the former has been much less studied.[7] Despite the fact that the thumb accounts for approximately 50% of overall hand function and is essential in our daily activities,[8 9] relatively few studies have documented the prevalence of trapeziometacarpal osteoarthritis (TMO). Most of our knowledge comes from American and European studies which are based solely on radiographic findings: the prevalence rates of TMO ≥ Grade 2 (on 4- or 5-point severity scale) are highly variable ranging from 11.5% and 50.5%.[10-14] TMO was found to be more prevalent in women than men, but the prevalence steadily increases with age in both genders. Only four studies have examined the prevalence of symptomatic TMO (as defined by the presence of both radiographic findings and clinical symptoms) and the rates vary between 2.9% and 15.9%.[15-17] Some studies have revealed that only a weak to modest association between TMO radiographic findings and clinical symptoms (pain and/or functional disability) exists[11 15] —i.e., patients may exhibit important structural changes, yet report little or no pain; or patients may experience severe pain with little radiological evidence of TMO. Botha-Scheepers et al. (2009)[18] followed a group of hand OA patients over a 2-year period and found that the progression of pain intensity and physical functioning was unrelated to X-ray findings.[18]

Based on the extensive clinical experience of three of the co-authors (PH, NB, TH) of this article, the above rates of symptomatic TMO are most likely to be underestimated because healthcare professionals commonly have insufficient knowledge of TMO and misdiagnose the origin of the pain (e.g., tendinopathy vs TMO). As a result, these patients are referred to a hand specialist long after TMO pain first appears.

The chief complaint of patients with TMO is persistent pain and stiffness at the thumb base,[19-21] which limit their hand functions,[21-23] reducing both thumb mobility[24] and hand strength,[25-27] thereby affecting their daily activities (e.g., holding objects, preparing meals, writing).[22 25 28] However, only a few studies have either quantified the severity of TMO pain and/or its impact on various aspects of daily living other than physical functioning.[18 28] The same is true for the economic costs of TMO in terms of work absenteeism/presenteeism and use of healthcare resources (e.g., type and number of healthcare professionals consulted).

Why TMO and pain-related symptoms are not adequately managed?

Despite decades of research on pain assessment and management, it is clearly documented that chronic painful disorders of various origins continue to be commonly under-treated, mistreated or untreated, with a large number of patients going from one doctor to another seeking pain relief.[29] One of the major barriers to optimal management of persistent pain disorders including OA is the limited access to adequate healthcare services, having difficulty gaining *timely* access to *appropriate* pain care.[30-32] 55 to 90% of the patients with knee OA who were referred to an orthopaedic surgeon should have rather been managed by another type of healthcare professional specialised in conservative treatment of knee OA.[33-35] This type of inappropriate patient orientation in the healthcare system coupled to the lack of timely adequate and effective

management can lead to a premature and increased deterioration of the patients' physical functioning, psychological well-being, and health-related quality of life while waiting for treatment. Rapid access is essential but access to appropriate care is as important if not more important. The structure of the healthcare delivery system with silos between the primary, secondary and tertiary sectors of care does not help in this matter especially when taking into account that few healthcare professionals (and particularly at the primary care level) have sufficient knowledge or training on pain management.[36 37]

TMO management involves various modalities including pharmacological therapy,[19 38 39] corticosteroid/hyaluronic acid injections,[19 21 39] hand exercises,[39-41] orthoses,[21 38 39 41 42] joint protection education,[38] assistive devices,[38 41] physical agent modality[38 39 42] and surgery.[39 41 43] These modalities are provided by different healthcare professionals such as primary care physicians, rheumatologists, physiatrists, orthopedic surgeons, plastic surgeons, radiologists, pharmacists, physical therapists, and occupational therapists. However, not knowing which healthcare professionals provide which therapeutic modalities to TMO patients, primary care physicians may not know to whom they should refer their patients. There are clinical guidelines for osteoarthritis published by the *American College of Rheumatology* (ACR), the *European Union League Against Rheumatism* (EULAR), and the *National Institute for Health and Care Excellence* (NICE). Yet, none of guidelines are specific to the thumb based arthritis.

Other obstacles to optimal TMO management include 1) poor awareness and understanding of the characteristics of TMO, 2) lack of knowledge about evidence-based effective treatments, 3) simplistic pain management plans based solely on a patient's physical condition which do not necessarily meet all their needs, and/or 4) the absence of inter-professional communication. There is thus clearly a need to improve the quality of care and services provided

to TMO patients and to minimize the impact of this disorder on their daily functioning and health-related quality of life. For example, patients who undergo TMO surgery have to manage their daily activities with the unaffected hand completely on their own for several weeks after the surgery. This neglect of TMO should be more systematically recognized and efficiently dealt with throughout our healthcare system.

TMO management: Need for a multidisciplinary approach.

It is well known that certain types of chronic pain disorders other than TMO (including knee and hip OA) commonly have significant adverse consequences in various domains of a patient's life [22] [44] which should be addressed in the management plan. It is also widely recognized that a global and integrated biopsychosocial approach is needed to assess and manage chronic pain disorders in order to capture the critical and unique dimensions of a patient's experience. According to Gatchel's *Biopsychosocial Model of Chronic Pain* [45], the most widely accepted model for assessing and managing chronic pain, the pain experience is unique for each individual because it is modulated by reciprocal interactions among biological (e.g., genetics, neural processes across the neuraxis), psychological (e.g., cognitions, emotions, past learning) and social factors (e.g., education, culture). Multidisciplinary management addressing both the biological/physical and psychosocial dimensions of chronic pain is not only a key feature but is recognized by both pain scientists and clinicians such as the EULAR, ACR and NICE: more concretely, OA management has to be tailored to each patient and take into account various factors including pain intensity, limitation of activities (including employment and social activities), quality of life, comorbidity, patients' expectations, and support network[38 39 44], and the risk factors (e.g., age,[15 46] sex,[13 46-49] joint laxity,[50-52] obesity,[10 13 53-56] heredity,[57-60] and repetitive movements[8 10 61-63]).

Objectives

Our ultimate aim is to improve the quality of care and delivery of services for TMO patients by developing a patient-centered, evidence-based TMO management clinical pathway[64] coupled to most optimal treatments which are evidence-based. As a prerequisite, through a systematic review of the literature, we need to document the efficacy of the existing pharmacological, non-pharmacological and surgical modalities to relieve pain and improve function in TMO patients. This paper aims to present the protocol for this systematic review of the literature.

METHODS AND ANALYSIS

The guidelines for systematic review of the literature *Cochrane Handbook for Systematic Reviews of Interventions*[65] and *Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols* (PRISMA-P)[66 67] are referred to. The review will involve five steps (See figure 1).

Research team

The team combines relevant and complementary disciplines with members: pain psychology (MC), pharmacy (LL), plastic surgery (PH), radiology (NB), physiotherapy (NG), occupational therapy (TH) and a librarian-informationist (DZ). The team also brings solid expertise both in participatory and quantitative research (MC, LL, NB, NG) as well as in epidemiology and biostatistics (MC, LL). MC's research expertise is in the field of pain assessment/management and knowledge translation. LL focuses on the of knowledge transfer on primary care clinical practices in the cardiovascular field. PH, plastic surgeon and administrator, operates and takes care of yearly about 50 TMO patients. NB, radiologist and researcher, routinely performs image-guided steroid and hyaluronic acid injections. NG has research expertise in systematic reviews of the

literature, lower limb osteoarthritis, and technology assessment. TH, a PhD student and an occupational therapist, has treated TMO patients for over 13 years. DZ has collaborated on a series of systematic reviews.

Step 1. Identification of potential eligible studies

Our academic librarian-informationist (DZ) will search through bibliographic electronic databases CINAHL, EMB Review, EMBASE, MEDLINE, OTseeker, PEDro, PsychINFO, PubMed, and the grey literature. The first search will combine words and expressions for three conceptual groups: trapeziometacarpal joint, osteoarthritis, and treatment. To ensure that psychotherapeutic modalities for TMO will be picked up, the following keywords will be added: *cognitive therapy, cognitive behavior therapy, relaxation, biofeedback, supportive psychotherapy, group therapy* and *counseling*. For the second search, the first two conceptual groups will be the same while the third group will focus on "pain". For each database, we will use words and expressions from controlled vocabulary (MESH, EMTREE and others) and free text searching. The searches will be restricted to articles published in English and French. Handsearching will also be used to identify other references (TH, MC). A pilot search through the CINAHL, EMB Review, EMBASE, MEDLINE, OTseeker, PEDro, PsychINFO and PubMed have identified approximately 2000 references, demonstrating the study's feasibility.

Step 2. Applying eligibility criteria

Once the results from multiple searches will be merged by the librarian (DZ) using the reference management software EndNote, duplicate records will be removed (DZ, TH). Titles and abstracts of studies will be screened independently by two reviewers for eligibility (MC, TH). Agreement

between the two reviewers will be established using kappa statistic.[65] Full text copies of potentially relevant reports will be retrieved (TH). They will be analyzed against eligibility criteria and the results will be recorded in Part 1 (General Information) and Part 2 (Eligibility) of the *Cochrane Effective Practice and Organisation of Care Group (EPOC) Data Abstraction Form* [65] by the two screeners. In the cases where no consensus is reached by the two reviewers, a third reviewer (PH) will determine the eligibility of the study. Part 1 of the EPOC form includes study identification (surname of first author and year of first full report of study), date form completed, name of person extracting data, report title, publication type, study funding source and possible conflicts of interest. Part 2 consists of study characteristics (type of study, participants, types of intervention/outcome measure).

Criteria for considering studies for this review

i. Types of studies

Meta-analyses, systematic reviews of the literature, randomized controlled trials (RCT) will be included. If there are no RCT, non-randomized controlled trials, controlled before-after studies, interrupted time series and repeated measures studies will be considered as well as observational studies (cohort, case-control).[39 68] Case series, review articles, editorials and commentaries will be excluded. The studies with higher evidence will be prioritized to determine the efficacy of therapeutic modalities. Results of most recent systematic reviews and those of reviews including more studies will be prioritized if there are more than one systematic review on a given intervention.

ii. Types of participants

Studies conducted among TMO adults who had received treatment to decrease pain and/or improve function will be included. Studies on diseases other than primary TMO (e.g., traumatic osteoarthritis, rheumatoid arthritis), on osteoarthritis other than the trapeziometacarpal joint, or on animals will be excluded. Studies including osteoarthritis of different joints will be included if the data of TMO are separately presented.

iii. Types of interventions

All the existing therapeutic modalities for TMO treatments (e.g., pharmacological, non-pharmacological, surgical) to reduce pain and improve function will be included. The possible interventions are "drug therapy", "surgery", "manual therapy", "psychotherapy", "orthoses", "acupuncture", "hand exercises", "assistive devices", "education", "joint injections", "joint protection", "laser therapy" and "thermotherapy". The comparators are another intervention or a non-exposed control group.

iv. *Type of outcomes*

Primary outcomes are pain and function, considered core outcomes for osteoarthritis clinical trials according to the international consensus group OMERACT (*Outcome measures in Rheumatology*).[44 69] Secondary outcomes are patients' psychological well-being, health-related quality of life and treatment satisfaction.

Step 3. Data extraction/management

Data will be independently extracted by two persons (MC, TH) using Part 3 of the EPOC data abstract form[65] (Population and Setting) which explores population description, setting, inclusion

criteria, exclusion criteria, and methods of recruitment. Part 4 (Methods) looks at aims of study, design, unit of allocation, start date, end date, and duration of participation. Part 5 (Risk of bias) will be used at Step 4. Part 6 (Participants) considers total number of participants, withdrawals and exclusion, severity of illness, co-morbidities, other treatment, relevant sociodemographics, and subgroups. Part 7 (Intervention group) takes into account description of intervention, duration of treatment period, and others. Part 8 (Outcomes) records outcome name, time points measured/reported, outcome definition, person measuring/reporting, unit of measurement, scales, and others. Part 9 (Results) varies according to study design and nature of outcome (dichotomous/continuous). It mainly concerns comparison, outcome, subgroup, results, baseline data, number of missing participants, statistical methods and appropriateness of these methods, and others. Part 10 (Applicability) questions if important populations have been excluded from the study, if the intervention is likely to be aimed at disadvantaged groups, and if the study directly addresses the review question. Part 11 (Other information) includes key conclusions, references to other relevant studies, correspondence required for further study information, and others. In cases where data are missing, study authors will be contacted.

Step 4. Critical appraisal

Risk of bias in individual studies will be separately assessed by two reviewers (MC, TH). In the cases of disagreement, discussion will take place to achieve consensus. If necessary, the third one (PH) will appraise the study. Different assessment tools will be used depending on study design: *Assessment of Multiple Systematic Reviews* (AMSTAR) for systematic reviews of the literature,[70] EPOC *Risk of Bias Tool* for controlled studies and for interrupted time series (ITS) studies,[71]

Effective Public Health Practice Project (EPHPP) *Quality Assessment Tool for Quantitative studies* for cohort studies or case-control study).[72]

i. AMSTAR[70]

The questionnaire is composed of 11 items. It examines the clarity of a systematic review methodology: a double review, exhaustive research strategy, heterogenic analysis and publication bias. It scores each criterion on 4 scales "yes", "no", "can't answer" and "not applicable" and total score on 7 scales. Its inter-rater reliability for each item is moderate to perfect (0.51< kappa <1.00) and excellent for the global score (kappa=0.84, 95% confidence intervals (CI) 0.67-1.00). Its construct validity (Pearson coefficient) is 0.72 (95%CI 0.53-0.84). The minimal detectable difference is 0.64.[73]

ii. EPOC *Risk of Bias Tool for studies with a separate control group*[71]

This tool includes the five domains of bias determined by the *Cochrane Risk of Bias Tool*[74] - selection (random sequence generation and allocation concealment), performance, attrition (method addressing incomplete outcome), detection and reporting (selective outcome reporting) - and two other criteria regarding "similarity of baseline outcome measurements between experimental and control groups" and "similarity of baseline characteristics between experimental and control groups". Each item is scored "yes" for high risk, "no" for low risk and "unclear" if not specified in the paper.

iii. EPOC *Risk of Bias Tool for ITS studies*[71]

This tool examines four domains of risks of bias determined by the *Cochrane Risk of Bias Tool* [74] (performance, attrition, detection and reporting bias) and three risks of bias associated with the ITS study design; "was the intervention independent of other changes?", "was the shape of the intervention effect pre-specified?" and "was the intervention unlikely to affect data collection?"

iv. EPHPP *Quality Assessment Tool for Quantitative studies*[72]

This tool will be used to assess cohort and case-control studies. It includes the items defined by the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) *Statement.*[75] It includes 21 items from 8 categories (selection, study design, confounders, blinding, data collection methods, withdrawals and drop-outs, intervention integrity and analyses). This tool is considered one of the best tools for systematic review.[76] Content validity and construct validity, and inter-rater and intra-rater reliability have been demonstrated (kappa=0.74, intraclass correlation coefficient=0.77).[72 77] Administration time is 10 to 15 minutes and its ease of use has been reported.[72 76]

Step 5. Data analysis/synthesis

i. Characteristics of included studies

Descriptive statistics will present features of included studies in terms of study design, clinical and sociodemographic characteristics of participants, studied TMO treatments and their results.

ii. Efficacy analysis of each therapeutic modality

Meta-analyses will be undertaken using the Cochrane Group's Review Manager software (RevMan 5.1)[78] unless heterogeneity among studies is demonstrated by the I^2 statistic, i.e., $I^2 \geq$

50%.[79] For continuous outcomes, mean differences and standardized mean differences will be used for meta-analysis. For dichotomous outcomes, odd ratios, risk ratios, absolute risk reduction, and number needed to treat will be computed. For longitudinal studies, risk ratios or hazard ratios will be calculated; for case-control studies, odd ratios will be computed. In the presence of substantial variation among studies, narrative syntheses will be favored studies will be classified in logical categories.[80] In cases where data are missing, study authors will be contacted; otherwise, participant attrition will be treated by intention-to-treat analysis.[65] Missing statistics (e.g., standard deviation) will be calculated from available data (e.g., standard error will be reported from p-values or 95% confidence intervals).[65]

iii. Reporting biases assessment and sensitivity analyses

Reporting biases across studies will be analyzed by funnel plots when feasible—i.e., at least 10 studies are included in the meta-analysis to ensure the power of the tests.[65] Sensitivity analyses will be undertaken in case the eligibility of some studies in the meta-analysis is doubtful (e.g., low quality studies).[65]

iv. Confidence in cumulative evidence

The robustness of evidence will be assessed by using the GRADE classification[81-94] and its software GRADEpro.[95] Two tables will be dressed for each therapeutic modality. "Clinical Evidence Profile" Tables present quality of evidence for each outcome while "Clinical Evidence Summary of Findings" Tables will provide end users (administrators, healthcare professionals, patients) with key information helping them with decision making in choosing the right treatments.[81]

ETHIC AND DISSEMINATION

Ethics approval is not required for this study. As dissemination strategies, we will incorporate both an integrated knowledge transfer (KT) approach and end-of-project KT plan.[96] At the core of an integrated KT approach is a collaborative partnership among researchers, healthcare professionals of various disciplines and patients. Once completed, the systematic review findings will be presented to a group of the stakeholders during a one-day workshop where we will work together to elaborate a TMO management clinical pathway. This partnership between researchers and end-users will contribute to effective knowledge transfer.[97] With regard to our end-of-project KT plan, we will draw upon three key principles: 1) developing communication vehicles adapted to the target audience; 2) presenting concise messages; and 3) creating settings for exchange and discussion.[98] We consider the target audiences to be the: 1) scientific community, 2) healthcare professionals, 3) general public including TMO patients or those afflicted with other types of osteoarthritis or chronic pain disorders, and 4) administrators. In addition to traditional vehicles (e.g., scientific meetings, publications), we will also create a module tab on the website of the Quebec Pain Research Network and on the *Centre hospitalier de l'Université de Montréal* (CHUM) website where our project will be made accessible to the different targeted audiences. The final product (TMO management clinical pathway) will be made available in the form of a two-fold pamphlet, one will be specifically for healthcare professionals, while the other for TMO patients (i.e., patient decision aids), elaborated by following the recommendations of the *International Patient Decision Aids Standards Collaboration*.[99 100] They will be duly delivered and subsequently presented to different institutions from the primary to tertiary sectors.

DISCUSSION

TMO is a chronic and degenerative disease which can seriously handicap patients, hence affecting their quality of life. However, TMO management is far from optimal due to the limited to adequate healthcare services and other obstacles. Developing a patient-centered, evidence-based multidisciplinary TMO management clinical pathway coordinated across the healthcare system is paramount to improve the quality of care. It will help guide the decision–making process of healthcare professionals and TMO patients in choosing the most suitable therapeutic modalities most suitable. To do so, a systematic review is a prerequisite to developing an evidence-based clinical pathway. To our knowledge, this review is the first to carry out an extensive and comprehensive systematic review of all the existing treatments specific to TMO including pharmacological, non-pharmacological and surgical, not limited to any one discipline. Subsequently, the findings will allow us to better elaborate multidisciplinary TMO management clinical pathway usable from the primary to tertiary care. What limits this protocol is the language restriction to English and French for the literature search; thus language bias is possible.

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Authors' contributions

TH conceived the study and drafted the manuscript under MC's supervision. DZ developed the search strategies and made substantial contribution to the information sources and literature search

section. All authors read and approved the systematic review protocol and the final version of the manuscript.

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Competing interests

None.

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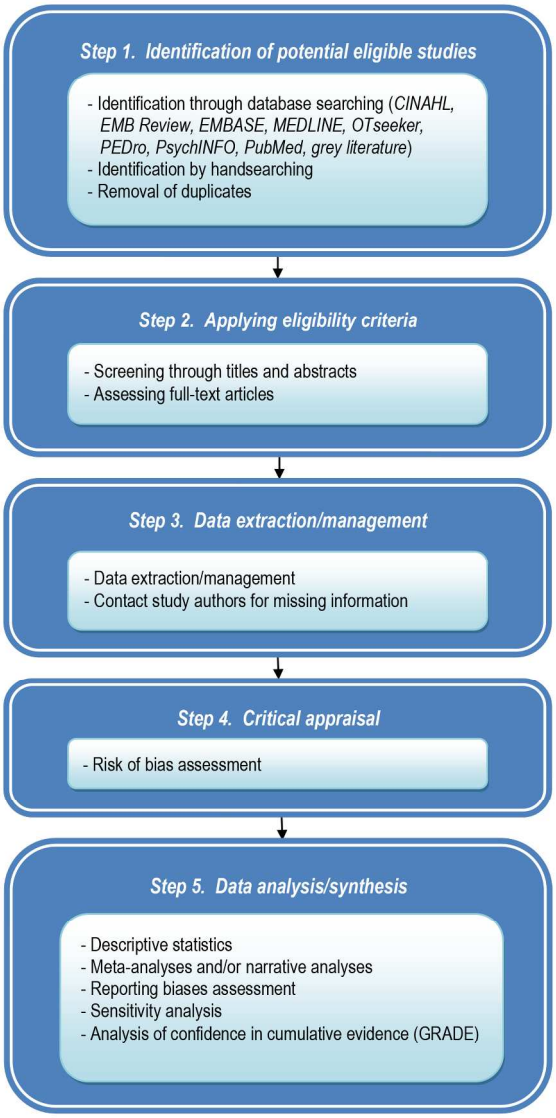

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Efficacy of treatments and pain management for trapeziometacarpal (thumb base) osteoarthritis: protocol for a systematic review

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Mr. Richard Sands
Managing Editor, *BMJ Open*
London, United Kingdom

Cover letter

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Manuscript title: Efficacy of treatments and pain management for trapeziometacarpal (thumb base) osteoarthritis: protocol of a systematic review

Dear Mr. Sands,

Thank you for your e-mail dated August 20, 2015. We are grateful to learn that you and the reviewers – Drs Norelee Kennedy and Jennifer Wolf – have recommended our manuscript for publication in *BMJ Open* with some minor revisions brought to it.

We truly appreciate the positive comments provided about our manuscript:

- "*This is a well presented paper on an important clinical topic area. The methodology is appropriate and well described. The lack of definitive evidence on prevalence of TMO, which seems to indicate low prevalence rates, does not however suggest that this is not an important area that warrants further investigation*." (Dr Kennedy)
- *"The authors propose a comprehensive review of the treatment strategies for TM OA, a problem that they accurately note is both under-diagnosed and inadequately studied and treated."* (Dr Wolf)

The reviewers' comments/suggestions were constructive and helpful, and we revised our manuscript accordingly. We also made some additional modifications based on relevant co-authors' suggestions which we believe improve our manuscript. We used the track changes mode in Microsoft Word to highlight the modifications we've made to the manuscript. A clean version of the manuscript is also provided. Based on the instructions provided in your e-mail, we uploaded the files of the revised manuscript, our responses to reviewers' comments, as well as a duly completed PRISMA-P checklist on the journal's website. At the end of the manuscript, an annex was provided as an example of search strategy for MEDLINE database, required by the PRISMA-P checklist.

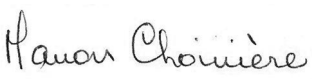
All co-authors have read and agreed upon the content of the revised manuscript.

We would like to take this opportunity to express our sincerest thanks both to you and the reviewers for your time and for allowing us to resubmit our revised manuscript.

We are looking forward to hearing from you soon.

Sincerely yours,

Manon Choinière on behalf of the authors.



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Title page

Title of the article: Efficacy of treatments and pain management for trapeziometacarpal (thumb base) osteoarthritis: protocol for a systematic review

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ABSTRACT

Introduction: The thumb is essential for daily activities. Unfortunately, this digit is commonly affected by trapeziometacarpal osteoarthritis (TMO), handicapping a large number of individuals. TMO constitutes an increasing human and economic burden for our society whose population is ageing. Limited access to adequate treatment is among the most important obstacles to optimal TMO management. Poor understanding of TMO characteristics, lack of knowledge about evidence-based treatments, simplistic pain management plans based solely on the patient's physical condition, absence of inter-professional communication, and lack of multidisciplinary treatment guidelines contribute to inadequate TMO management. On the long term, our research project aims at improving the quality of care and services offered to TMO patients by developing a patient-centered, evidence-based multidisciplinary management clinical pathway coordinated across the healthcare system. This proposed systematic review is a prerequisite to ensuring evidence-based practices and aims to document the efficacy of all the existing modalities for TMO management.

Methods and analysis: The protocol of the systematic review is registered with PROSPERO (Registration number CRD42015015623) and will be conducted using the guidelines *Cochrane Handbook for Systematic Reviews of Interventions.* We will identify studies in English and French concerning TMO treatments through searches in Cochrane Central, EMBASE, MEDLINE, PsychINFO, CINHAL, PubMed, OT Seekers, PEDRO, and the grey literature. Two reviewers will independently screen study eligibility, extract data, and appraise studies using published assessment tools. Meta-analyses will be undertaken where feasible; otherwise, narrative syntheses will be carried out. The robustness of evidence will be assessed using the GRADE system.

Ethics and dissemination: Ethics approval is not required for this study. A comprehensive knowledge exchange and transfer (KET) plan incorporating effective strategies will be used to disseminate the findings of this review and utilize them to optimize TMO management.

STRENGTHS AND LIMITATIONS OF THIS REVIEW

- This review is the first to carry out an extensive and comprehensive systematic review of all the existing treatments specific to TMO including pharmacological, non-pharmacological and surgical ones, not limited to any one discipline. Subsequently, the findings will allow us to develop and design an evidence-based multidisciplinary TMO management pathway usable for clinicians of various disciplines across the healthcare continuum.
- An extensive knowledge exchange and transfer (KET) plan incorporating effective strategies to disseminate and share the results with end-users is proposed. The findings will be used in a future study aimed at developing an active collaborative partnership between researchers and end-users to optimize care for TMO patients.
- Language restriction to English and French for the literature search is a limitation of the proposed protocol such that language bias is possible.

INTRODUCTION

Trapeziometarcarpal osteoarthritis: an understudied but important health problem.

The most prevalent cause of chronic pain in the world is osteoarthritis (OA).[1 2] Its prevalence is increasing in an alarming manner with the ageing of the population, and it is estimated it will double before the year 2020.[3] This anticipated increase is somewhat frightening considering that OA is associated with numerous adverse consequences for affected individuals as well as increasing economic costs for our society.[3-6] Based on the meta-analysis of Pereira et al. (2011) on OA prevalence, hand OA is more prevalent than knee/hip OA, yet hand OA has been much less studied.[7] Despite the fact that the thumb accounts for approximately 50% of overall hand function and is essential in our daily activities,[8] relatively few studies have documented the prevalence of trapeziometacarpal osteoarthritis (TMO). Most of our knowledge comes from American and European studies which are based solely on radiographic findings: the prevalence rates of TMO ≥ Grade 2 (on 4- or 5-point severity scale) are highly variable ranging from 11.5% and 50.5%.[9-13] TMO was found to be more prevalent in women than men, but the prevalence steadily increases with age in both genders. The prevalence of symptomatic TMO (as defined by the presence of clinical symptoms with or without radiographic findings) and the rates vary between 1.0% and 15.9%.[14-21] Some studies have revealed that only a weak to modest association between TMO radiographic findings and clinical symptoms (pain and/or functional disability) exists[10 15] —i.e., patients may exhibit important structural changes, yet report little or no pain; or patients may experience severe pain with little radiological evidence of TMO. Botha-Scheepers et al. (2009)[22] followed a group of hand OA patients over a 2-year period and found that the progression of pain intensity and physical functioning was unrelated to X-ray findings.[22] Based on the extensive

clinical experience of three of the co-authors (PH, NB, TH) of this article, the above rates of symptomatic TMO are most likely to be underestimated because healthcare professionals commonly have insufficient knowledge of TMO characteristics and misdiagnose the origin of the pain (e.g., tendinopathy vs TMO). As a result, these patients are referred to a hand specialist long after TMO first appears.

The chief complaint of patients with TMO is persistent pain at the thumb base[23-25] which limits their hand functions,[25-27] reducing both thumb mobility[28] and hand strength,[29-31] thereby affecting their daily activities (e.g., holding objects, preparing meals, writing).[26 29 32] However, only a few studies have either quantified the severity of TMO pain and/or its impact on various aspects of daily living other than physical functioning.[22 32]

Management of TMO and pain-related symptoms

Despite decades of research on pain assessment and management, it is well documented that chronic pain disorders of various origins continue to be commonly under-treated, mistreated or untreated, with a large number of patients going from one doctor to another seeking pain relief.[33] One of the major barriers to optimal management of persistent pain disorders including OA is the limited access to adequate healthcare services. Patients commonly have difficulty gaining *timely* access to *appropriate* pain care[34-36] leading to a premature or an increased deterioration of their physical functioning, psychological well-being, and health-related quality of life while waiting for treatment. Management of TMO and pain-related symptoms can be provided by different healthcare professionals including primary care physicians, rheumatologists, physiatrists, orthopedic surgeons, plastic surgeons, radiologists, pharmacists, physical therapists, and/or occupational therapists. However, these clinicians (including hand specialists) often work in silos

and manage TMO patients based on their own clinical experience rather than on well-documented scientific evidence. Other obstacles to adequate TMO management include 1) poor awareness and understanding of the characteristics of TMO (and especially in the primary sector of care), 2) lack of knowledge about evidence-based effective treatments, and 3) simplistic pain management plans based solely on patients' physical condition which do not necessarily meet all their needs. Finally, the fact that healthcare professionals commonly have insufficient knowledge and training for managing chronic pain disorders should not be neglected.[37 38]

Management of TMO involves various modalities including pharmacological therapy,[23 39 40] corticosteroid/hyaluronic acid injections,[23 25 40] hand exercises,[40-42] orthoses,[25 39 40 42 43] joint protection education,[39] assistive devices,[39 42] physical agent modality[39 40 43] and surgery.[40 42 44] However, the relative efficacy of these modalities remains poorly documented, some of them recommended for the treatment of hand OA in general while others are specifically for TMO. Furthermore, earlier systematic reviews examining the efficacy of TMO treatment have focused solely on one type of modality (e.g., surgery, orthoses).[45 46] Chronic pain disorders commonly have significant adverse consequences in various domains of a patient's life,[26 39] and it is widely acknowledged that a multidisciplinary approach which takes into account the biopsychosocial components of the pain experience constitutes the "gold standard" for managing this type of disorder.[47 48] Therefore, there is a need to conduct a systematic review from a multidisciplinary perspective which integrates all the existing therapeutic modalities for TMO in order to 1) document their relative efficacy, and 2) examine the modalities whose efficacy for TMO is supported by scientific evidence and those which are not, without creating confusion between effective modalities with absence of documented evidence and ineffective modalities supported by evidence.

Objectives

Our ultimate aim is to improve the quality of care and delivery of services for TMO patients by developing a patient-centered, evidence-based TMO management clinical pathway[49] coupled to most optimal treatments which are evidence-based. As a prerequisite, a systematic review of the literature is needed to document the efficacy of the existing pharmacological, non-pharmacological and surgical modalities to relieve pain and improve function in TMO patients. This paper aims at presenting the protocol for this systematic review of the literature.

METHODS AND ANALYSIS

The guidelines for systematic review of the literature *Cochrane Handbook for Systematic Reviews of Interventions*[50] are referred to. The review will involve five steps (See figure 1).

Research team

The team combines relevant and complementary disciplines with members in pain psychology and pharmacology (MC), epidemiology and biostatistics (LL), plastic surgery (PH), radiology (NB), physiotherapy (NG), occupational therapy (TH) and library information science (DZ). The research expertise of MC is in the field of pain assessment/management and knowledge translation. The second author's research expertise (LL) focuses on knowledge transfer on primary care clinical practices in the cardiovascular and pain fields. The third author (PH) runs the largest hand clinic in the province of Quebec (Canada) and follows about 50 TMO patients yearly. The fourth author (NB), a radiologist and a researcher, routinely performs image-guided steroid

injections. The fifth author (NG) has research expertise in systematic reviews of the literature, lower limb osteoarthritis, and technology assessment. The sixth author (DZ) has collaborated on a series of systematic reviews. Finally, TH, a PhD student and occupational therapist, has treated TMO patients for over 13 years.

Step 1. Identification of potential eligible studies

Our academic librarian-informationist (DZ) will search through bibliographic electronic databases CINAHL (from 1937 onwards), EMB Review (from 1991 onwards), EMBASE (from 1974 onwards), MEDLINE (from 1946 onwards), OTseeker, PEDro, PsychINFO (from 1806 onwards), PubMed, and the grey literature (CADTH, Clinical Trials, National Guideline Clearing House, NICE, MedNar, Google Scholar, OAIster and Open Grey). The first search will combine words and expressions for three conceptual groups: trapeziometacarpal joint, osteoarthritis, and treatment. To ensure that psychotherapeutic modalities for TMO will be picked up, the following keywords will be added: *cognitive therapy, cognitive behavior therapy, relaxation, biofeedback, supportive psychotherapy, group therapy* and *counseling.* For the second search, the first two conceptual groups will be the same while the third group will focus on "pain". For each database, we will use words and expressions from controlled vocabulary (MESH, EMTREE and others) and free text searching. The searches will be restricted to articles published in English and French. Handsearching will also be used to identify other references (TH, MC). A pilot search through the CINAHL, EMB Review, EMBASE, MEDLINE, OTseeker, PEDro, PsychINFO and PubMed have identified approximately 2000 references, demonstrating the study's feasibility.

Step 2. Applying eligibility criteria

Once the results from multiple searches will be merged by the librarian (DZ) using the reference management software EndNote, duplicate records will be removed (DZ, TH). Titles and abstracts of studies will be screened independently by two reviewers for eligibility (MC, TH). Agreement between the two reviewers will be established using kappa statistic.[50] Full text copies of potentially relevant reports will be retrieved (TH). They will be analyzed against eligibility criteria and the results will be recorded in Part 1 (General Information) and Part 2 (Eligibility) of the *Cochrane Effective Practice and Organisation of Care Group (EPOC) Data Abstraction Form* [50] by the two screeners. In the cases where no consensus is reached by the two reviewers, a third reviewer (PH) will determine the eligibility of the study. Part 1 of the EPOC form includes study identification (surname of first author and year of first full report of study), date form completed, name of person extracting data, report title, publication type, study funding source and possible conflicts of interest. Part 2 consists of study characteristics (type of study, participants, types of intervention/outcome measure).

Criteria for considering studies for this review

i. Types of studies

Meta-analyses, systematic reviews of the literature, randomized controlled trials (RCT) will be included. If there are no RCT, non-randomized controlled trials, controlled before-after studies, interrupted time series and repeated measures studies will be considered as well as observational studies (cohort, case-control).[40 51] Case series, review articles, editorials and commentaries will be excluded. The studies with higher evidence will be prioritized to determine the efficacy of therapeutic modalities. Results of most recent systematic reviews and those of reviews including

more studies will be prioritized if there is more than one systematic review on a given intervention.

ii. Types of participants

Studies conducted among TMO adults who had received treatment to decrease pain and/or improve function will be included. Studies on diseases other than primary TMO (e.g., traumatic osteoarthritis, rheumatoid arthritis), on osteoarthritis other than the trapeziometacarpal joint, or on animals will be excluded. Studies including osteoarthritis of different joints will be included if the data of TMO are separately presented.

iii. Types of interventions

All the existing therapeutic modalities for TMO treatments (e.g., pharmacological, non-pharmacological, surgical) to reduce pain and improve function will be included. The possible interventions are "drug therapy", "surgery", "manual therapy", "psychotherapy", "orthoses", "acupuncture", "hand exercises", "assistive devices", "education", "joint injections", "joint protection", "laser therapy" and "thermotherapy". The comparators are another intervention or a non-exposed control group.

iv. *Type of outcomes*

Primary outcomes are pain and function, considered core outcomes for osteoarthritis clinical trials according to the international consensus group OMERACT (*Outcome measures in Rheumatology*).[52 53] Secondary outcomes are patients' psychological well-being, health-related quality of life and treatment satisfaction.

Step 3. Data extraction/management

Data will be independently extracted by two persons (MC, TH) using Part 3 of the EPOC data abstract form[50] (Population and Setting) which explores population description, setting, inclusion criteria, exclusion criteria, and methods of recruitment. Part 4 (Methods) looks at aims of study, design, unit of allocation, start date, end date, and duration of participation. Part 5 (Risk of bias) will be used at Step 4. Part 6 (Participants) considers total number of participants, withdrawals and exclusion, severity of illness, co-morbidities, other treatment, relevant sociodemographics, and subgroups. Part 7 (Intervention group) takes into account description of intervention, duration of treatment period, and others. Part 8 (Outcomes) records outcome name, time points measured/reported, outcome definition, person measuring/reporting, unit of measurement, scales, and others. Part 9 (Results) varies according to study design and nature of outcome (dichotomous/continuous). It mainly concerns comparison, outcome, subgroup, results, baseline data, number of missing participants, statistical methods and appropriateness of these methods, and others. Part 10 (Applicability) questions if important populations have been excluded from the study, if the intervention is likely to be aimed at disadvantaged groups, and if the study directly addresses the review question. Part 11 (Other information) includes key conclusions, references to other relevant studies, correspondence required for further study information, and others. In cases where data are missing, study authors will be contacted.

Step 4. Critical appraisal

Risk of bias in individual studies will be separately assessed by two reviewers (MC, TH). In the cases of disagreement, discussion will take place to achieve consensus. If necessary, the third one

(PH) will appraise the study. Different assessment tools will be used depending on study design: *Assessment of Multiple Systematic Reviews* (AMSTAR) for systematic reviews of the literature,[54] EPOC *Risk of Bias Tool* for controlled studies and for interrupted time series (ITS) studies,[55] *Effective Public Health Practice Project* (EPHPP) *Quality Assessment Tool for Quantitative studies* for cohort studies or case-control study).[56]

i. AMSTAR[54]

The questionnaire is composed of 11 items. It examines the methodological quality of a systematic review including double review, exhaustive research strategy, heterogenic analysis and publication bias. It scores each criterion on 4 scales "yes", "no", "can't answer" and "not applicable" and total score on 7 scales. Its inter-rater reliability for each item is moderate to perfect (0.51< kappa <1.00) and excellent for the global score (kappa=0.84, 95% confidence intervals (CI) 0.67-1.00). Its construct validity (Pearson coefficient) is 0.72 (95%CI 0.53-0.84). The minimal detectable difference is 0.64.[57]

ii. EPOC *Risk of Bias Tool for studies with a separate control group*[55]

This tool includes the five domains of bias determined by the *Cochrane Risk of Bias Tool*[58] - selection (random sequence generation and allocation concealment), performance, attrition (method addressing incomplete outcome), detection and reporting (selective outcome reporting) - and two other criteria regarding "similarity of baseline outcome measurements between experimental and control groups" and "similarity of baseline characteristics between experimental and control groups". Each item is scored "yes" for high risk, "no" for low risk and "unclear" if not specified in the paper.

iii. EPOC *Risk of Bias Tool for ITS studies*[55]

This tool examines four domains of risks of bias determined by the *Cochrane Risk of Bias Tool* [58] (performance, attrition, detection and reporting bias) and three risks of bias associated with the ITS study design; "was the intervention independent of other changes?", "was the shape of the intervention effect pre-specified?" and "was the intervention unlikely to affect data collection?"

iv. EPHPP *Quality Assessment Tool for Quantitative studies*[56]

This tool will be used to assess cohort and case-control studies. It includes the items defined by the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) *Statement.*[59] It includes 21 items from 8 categories (selection, study design, confounders, blinding, data collection methods, withdrawals and drop-outs, intervention integrity and analyses). This tool is considered one of the best tools for systematic review.[60] Content validity and construct validity, and inter-rater and intra-rater reliability have been demonstrated (kappa=0.74, intraclass correlation coefficient=0.77).[56 61] Administration time is 10 to 15 minutes and its ease of use has been reported.[56 60]

Step 5. Data analysis/synthesis

i. Characteristics of included studies

Descriptive statistics will present features of included studies in terms of study design, clinical and sociodemographic characteristics of participants, studied TMO treatments and their results.

ii. Efficacy analysis of each therapeutic modality

Meta-analyses will be undertaken using the Cochrane Group's Review Manager software (RevMan 5.1)[62] unless heterogeneity among studies is demonstrated by the I^2 statistic, i.e., $I^2 \geq 50\%$.[63] For continuous outcomes, mean differences and standardized mean differences will be used for meta-analysis. For dichotomous outcomes, odd ratios, risk ratios, absolute risk reduction, and number needed to treat will be computed. For longitudinal studies, risk ratios or hazard ratios will be calculated; for case-control studies, odd ratios will be computed. In the presence of substantial variation among studies, narrative syntheses will be favoured studies will be classified in logical categories.[64] In cases where data are missing, study authors will be contacted; otherwise, participant attrition will be treated by intention-to-treat analysis.[50] Missing statistics (e.g., standard deviation) will be calculated from available data (e.g., standard error will be reported from p-values or 95% confidence intervals).[50]

iii. Reporting biases assessment and sensitivity analyses

Reporting biases across studies will be analyzed by funnel plots when feasible—i.e., at least 10 studies are included in the meta-analysis to ensure the power of the tests.[50] Sensitivity analyses will be undertaken in case the eligibility of some studies in the meta-analysis is doubtful (e.g., low quality studies).[50]

iv. Confidence in cumulative evidence

The robustness of evidence will be assessed by using the GRADE classification[65-78] and its software GRADEpro.[79] Two tables will be dressed for each therapeutic modality. "Clinical Evidence Profile" Tables present quality of evidence for each outcome while "Clinical Evidence Summary of Findings" Tables will provide end users (administrators, healthcare professionals,

patients) with key information helping them with decision making in choosing the right treatments.[65]

ETHIC AND DISSEMINATION

Ethics approval is not required for this study. Once completed, the systematic review findings will be presented to a group of stakeholders during a one-day workshop where researchers, clinicians from various disciplines, managers/decision-makers and patients will work together to elaborate a TMO management clinical pathway. This partnership between researchers and end-users will contribute to effective knowledge exchange and transfer.[80] With regard to our end-of-project KT plan, we will draw upon three key principles: 1) developing communication vehicles adapted to the target audience; 2) presenting concise messages; and 3) creating settings for exchange and discussion.[81] We consider the target audiences to be the: 1) scientific community, 2) healthcare professionals, 3) general public including TMO patients or those afflicted with other types of osteoarthritis or chronic pain disorders, and 4) administrators. In addition to traditional vehicles (e.g., scientific meetings, publications), we will also create a module tab on the website of the Quebec Pain Research Network and on the *Centre hospitalier de l'Université de Montréal* (CHUM) website where the results of the project will be made accessible to the different targeted audiences. The final product (TMO management clinical pathway) will be made available in the form of a two-fold pamphlet, one will be specifically for healthcare professionals, while the other for TMO patients (i.e., patient decision aids), elaborated by following the recommendations of the *International Patient Decision Aids Standards Collaboration*.[82 83] They will be duly delivered and subsequently presented to different institutions from the primary to tertiary sectors of care.

DISCUSSION

TMO is a chronic and degenerative disease which can seriously handicap patients, hence affecting their quality of life. However, TMO management is far from optimal due to several obstacles including limited access to adequate healthcare services. Developing a patient-centered, evidence-based multidisciplinary treatment algorithm for TMO is paramount to improving the quality of care to this patient clientele. It will help guide the decision–making process of clinicians and TMO patients in choosing the most suitable therapeutic modalities. To do so, a systematic review is a prerequisite, and to our knowledge, we are the first to propose the conduct of an extensive and comprehensive literature review of all the existing treatments for TMO including pharmacological, non-pharmacological and surgical modalities, not limited to any one discipline. Language restriction to English and French for the literature search is a limitation of the proposed protocol such that language bias is possible. However the obtained findings will be crucial in developing a TMO treatment algorithm useful to all stakeholders across the healthcare continuum.

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Authors' contributions

TH conceived the protocol and drafted the manuscript under MC's supervision. DZ developed the literature search strategies and made substantial contributions to the section regarding information

sources and literature search. All authors contributed to the preparation of the manuscript, read and approved the final version of this systematic review protocol.

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Competing interests

No, there are no competing interests.

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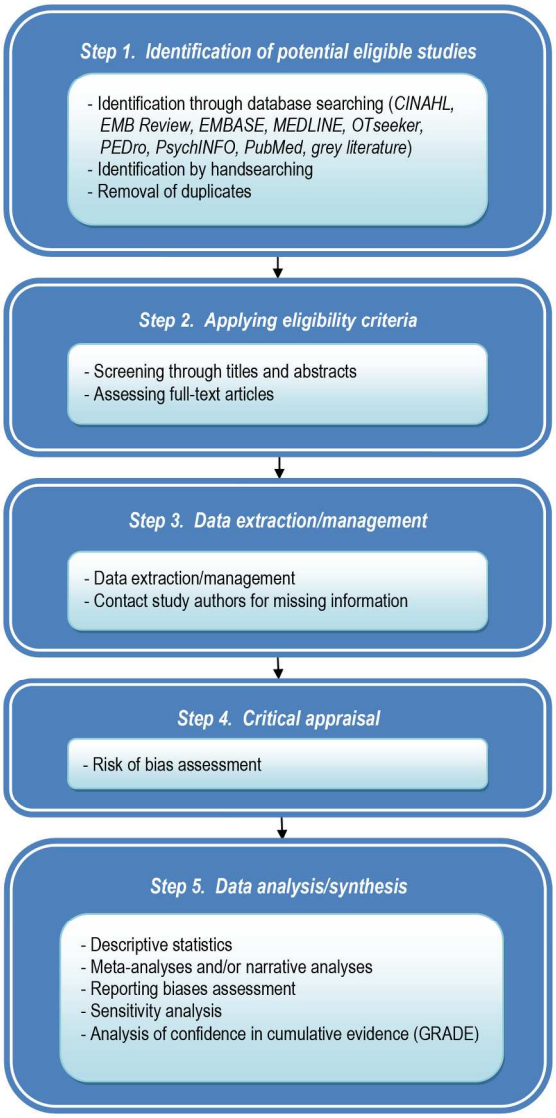

181x244mm (300 x 300 DPI)

Annex 1. MEDLINE Search strategy

Search #1

1 thumb*.tw,kw. (13971)
2 pollex.tw,kw. (48)
3 Thumb/ (8064)
4 (carpal* or metacarp* or trapezio-metacarpal or trapeziometacarpal or trapezial-metacarpal or trapezialmetacarpal or (basal adj2 thumb) or (basilar adj2 thumb) or (thumb adj2 base)).tw,kw. (23424)
5 Carpal Bones/ or Trapezium Bone/ (5256)
6 trapezium.tw,kw. (791)
7 Metacarpal Bones/ (985)
8 carpo-metacarpal.tw,kw. (100)
9 carpometacarpal.tw,kw. (1239)
10 CMC.tw,kw. (6124)
11 Carpometacarpal Joints/ (438)
12 or/1-11 (46104)
13 osteoarth*.tw,kw. (48311)
14 Osteoarthritis/ (29823)
15 degenerative joint disease.tw,kw. (1800)
16 (rhizoarthrosis or rhizarthrosis).tw,kw. (56)
17 or/13-16 (60120)
18 Occupational Therapy/ or Drug Therapy/ or Physical Therapy Modalities/ or Drug Therapy, Combination/ or Physical Therapy Department, Hospital/ or Exercise Therapy/ or Occupational Therapy Department, Hospital/ (238458)
19 therap*.tw,kw. (2003741)
20 treatment*.tw,kw. (3311223)
21 Therapeutics/ (8099)
22 Psychotherapy/ (42117)
23 Splints/ (7689)
24 (surger* or (joint adj2 protection*) or (assistive adj2 device*) or (thermal adj2 modalit*)).tw,kw. (865689)
25 ((famil* adj2 support) or (social adj2 work*)).tw,kw. (20974)
26 Social Work/ (13216)
27 relaxation*.tw,kw. (96944)
28 Relaxation/ or Relaxation Therapy/ (7644)
29 cognitive therapy/ (17599)
30 (cognitive adj2 therap*).tw,kw. (12338)
31 Orthotic Devices/ (5203)
32 (orthosis or orthese*).tw,kw. (2650)
33 (orthotic adj2 device*).tw,kw. (396)
34 Biofeedback, Psychology/ (6451)
35 biofeedback.tw,kw. (5396)
36 (supportive adj2 psychotherap*).tw,kw. (574)
37 Psychotherapy, Group/ (12182)
38 (group adj2 therap*).tw,kw. (15578)
39 Directive Counseling/ or Counseling/ (30727)
40 counseling.tw,kw. (47715)
41 Self Care/ or Orthotic Devices/ or Exercise/ or Injections/ (136480)
42 (orthotic* or exercise* or injection*).tw,kw. (685837)
43 ((manual or hand) adj2 therapy).tw,kw. (2077)
44 (self adj2 management).tw,kw. (10660)
45 or/18-44 (5757132)

46 12 and 17 and 45 (1121)
47 remove duplicates from 46 (1094)
48 Animals/ not Humans/ (3989744)
49 Infant/ not Adult/ (486047)
50 47 not (48 or 49) (1009)
51 limit 50 to (english or french) (872)

Search #2

1 thumb*.tw,kw. (13971)
2 pollex.tw,kw. (48)
3 Thumb/ (8064)
4 (carpal* or metacarp* or trapezio-metacarpal or trapeziometacarpal or trapezial-metacarpal or trapezialmetacarpal or (basal adj2 thumb) or (basilar adj2 thumb) or (thumb adj2 base)).tw,kw. (23424)
5 Carpal Bones/ or Trapezium Bone/ (5256)
6 trapezium.tw,kw. (791)
7 Metacarpal Bones/ (985)
8 carpo-metacarpal.tw,kw. (100)
9 carpometacarpal.tw,kw. (1239)
10 CMC.tw,kw. (6124)
11 Carpometacarpal Joints/ (438)
12 or/1-11 (46104)
13 osteoarth*.tw,kw. (48311)
14 Osteoarthritis/ (29823)
15 degenerative joint disease.tw,kw. (1800)
16 (rhizoarthrosis or rhizarthrosis).tw,kw. (56)
17 or/13-16 (60120)
18 Acute Pain/ or Breakthrough Pain/ or Pain/ or Musculoskeletal Pain/ or Chronic Pain/ or Pain Management/ (128263)
19 pain*.tw,kw. (497011)
20 Hyperalgesia/ (8360)
21 hyperalgesia.tw,kw. (10160)
22 or/18-21 (532808)
23 12 and 17 and 22 (855)
24 remove duplicates from 23 (833)
25 Animals/ not Humans/ (3989744)
26 Infant/ not Adult/ (486047)
27 24 not (25 or 26) (819)
28 limit 27 to (english or french) (725)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (Title page, page 3)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such (not applicable)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (Abstract, page 4, line 132)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (Title page, page 3)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (Authors' contributions, page 22, line 518)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments (not applicable)
Support:		
Sources	5a	Indicate sources of financial or other support for the review (Funding statement, page 22, line 525)
Sponsor	5b	Provide name for the review funder and/or sponsor (Funding statement, page 22, line 528)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (not applicable)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (Introduction, pages 7 - 11)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (ii. Type of participants, page 15, line 353; iii. Type of interventions, page 15, line 360; iv. Type of outcomes, page 15, line 368)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (Criteria for considering studies for this review, page 14, lines 342-351)

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (Step 1. Identification of potential eligible studies, page 13, lines 311-315)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (Annex 1, page 36)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (Step 3. Data extraction/management, page 16, lines 374-391)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (Step 2. Applying eligibility criteria, page 14, lines 329-336; Step 4. Critical appraisal, page 17, lines 394-396)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (Step 3. Data extraction/management, page 16, lines 375-377 & lines 390-391)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (Step 3. Data extraction/management, page 16, lines 375-390)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (iv. Type of outcomes, pages 15-16, lines 369-372)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (Step 4. Critical appraisal, pages 17-18, lines 394-435; Step 5. Data analysis/synthesis, page 18-19, line 442-452)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (ii. Efficacy analysis of each therapeutic modality, page 19, lines 442-452)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (ii. Efficacy analysis of each therapeutic modality, page 19, lines 442-452)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (iii. Reporting biases assessment and sensitivity analyses, pages 19, lines 455-458)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (ii. Efficacy analysis of each therapeutic modality, page 19, lines 447-449)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) (iii. Reporting biases assessment and sensitivity analyses, pages 19, lines 455-456)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (iv. Confidence in cumulative evidence, pages 19-20, lines 461-466)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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