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Determinants of responsiveness to multidisciplinary chronic pain management interventions: protocol for a systematic review and meta-analysis

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Keywords: multidisciplinary, chronic pain, pain management

Abstract

AIM To present a protocol for a systematic review and meta-analysis of the evidence regarding the determinants of responsiveness to multidisciplinary management of persistent pain, with pain intensity, pain-related interference, physical functioning, and health-related quality of life as the main outcomes, with consideration to multiple secondary outcomes.

METHODS To identify relevant studies, the Ovid MEDLINE, Pubmed, Ovid PsycINFO, EBSCO CINAHL and Scopus databases will be searched for all studies exploring factors associated with responsiveness to multidisciplinary pain management from study inception to the present. This protocol is being developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines. Cohorts, case-control studies, and randomized controlled trials will be included. Independent screening for eligible studies will be completed by a total of four researchers using defined criteria. Data extraction will be executed by two researchers. Study heterogeneity will be estimated using the I^2 index. A meta-analysis will be performed using random effects models. Publication bias will be evaluated by means of funnel plots and Egger's test.

DISCUSSION This systematic review will help to identify patients who most likely will or will not benefit from a multidisciplinary management of persistent pain, which may help to plan timely treatment with adequate content for each individual.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO registration number CRD42021236424.

Article Summary

Strengths and limitations of this study

- The current systematic review will provide a comprehensive outline of studies examining factors predicting responsiveness to multidisciplinary persistent pain management.
- The protocol has been designed in accordance to good practice and PRISMA-P guidelines.
- A four-member team, all with clinical and/or scientific expertise in chronic pain, will contribute to the study selection process and quality assessment to minimize the probability of personal bias.
- Only studies published in English will be included.

Background

A multidisciplinary approach has long been regarded as superior to narrower chronic pain treatment modalities in terms of improvements in pain, physical functioning, psychological factors, working ability, and well-being (1-4). Although multidisciplinary pain management is difficult to measure due to the diverse economic effects of pain on individuals and society (5), the cost-effectiveness of the approach has been supported (6).

To execute a comprehensive systematic review of the effectiveness of multidisciplinary management of persistent pain is far from easy due to the heterogeneity of studies (7). The studies available in the literature vary in terms of, for instance, patient selection, outcome variables, pain sites / type of pain examined, and the definition of interdisciplinary management. Yet, assembled reviews are needed in order to explore the diverse data regarding this topic.

The importance of patient selection has been highlighted, as not all patients benefit from multidisciplinary pain management (8). Identifying factors that may predict whether patients benefit from a multimodal approach would provide remarkable assistance in clinical decision-making. Identifying these factors would help clinicians to customize the treatment more efficiently to meet individual needs.

It is, thus, essential to systematically consider all previously studied factors that may predict the responsiveness to multidisciplinary management of chronic pain. The aim of the study presented herein is to identify and systematically analyze previously published data regarding this topic.

Methods

The current study protocol describes a systematic review and meta-analysis exploring the determinants of responsiveness to multidisciplinary chronic pain management interventions in adults.

Study design

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist will be adhered in protocol development (Table 1) (9). The review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on March 3rd, 2021 (registration number CRD42021236424).

Inclusion criteria

The included articles are required to be 1) original research articles, 2) published in full-text, 3) published in a peer-reviewed journal, and 4) published in English, and to 5) have a longitudinal (baseline–outcome) setting and 6) report empirical data (cohort, case-control or randomized controlled trial [RCT]; observational studies are also included). Inclusion criteria, defined according to population, intervention, comparison, and outcomes (PICO), are listed below in separate sections.

Population

The participants included need to be adult (over 16 years of age, no maximum age limit) chronic pain patients who have been treated by a multidisciplinary pain management team comprising a minimum of three separate professional groups (e.g., physician, physical therapist, psychologist, and psychiatric nurse; consultation may be performed routinely or on demand). Pain will be defined as chronic when the duration of pain exceeds 3 months. Articles with a patient population

comprising palliative care patients or postoperative pain patients with a normal trend of healing will be excluded. In the case of incoherence, the whole study group will discuss each of these individually.

Intervention/Prognostic factor

All independent baseline variables that were examined as potential determinants of responsiveness to multidisciplinary pain management are included. These may include, for example, sociodemographic, symptom-related, physical well-being–related, and psychological factors.

Comparison/Comparator

All alternative exposures within the prognostic factors will be taken into account.

Outcome

All articles with 1) pain (pain intensity or pain interference) or 2) health-related quality of life (HRQoL) as one primary outcome will be considered eligible. In addition to these, other relevant outcomes will be considered (e.g., psychological factors, depression)—however, articles comprising these as a primary outcome with no evaluation of any of the two determined main outcomes will be excluded. The primary focus will be on the situation immediately after a multidisciplinary treatment intervention, but studies with long-term follow-up data will also be considered. Any outcome measurements will be included (e.g., patient-reported [PROMs], evaluation by professional, objective measures).

Search methods, information sources, study selection, and data management

A comprehensive electronic search of the medical and rehabilitation literature using medical subject headings (MeSH) and text related to responsiveness to multidisciplinary chronic pain management will be performed.

The search strategy has been developed to adhere the PICO descriptors. Based on this, four domains will be set: chronic pain, responsiveness/predictor, multidisciplinary intervention (divided into two domains for searches), and outcome. These domains will be joined with operator 'AND'. Regarding each domain, encompassing terms determined based on a comprehensive consideration of literature will be used in the searches. A content expert (MM) has developed the search strategy in consultation with a senior information specialist. The comprehensiveness of the search strategy has been peer-reviewed by an informatician at the Terkko faculty library of the Helsinki University Faculty of Medicine.

Ovid MEDLINE, Pubmed, Ovid PsycINFO, EBSCO CINAHL and Scopus will be used to execute electronic searches from inception to the present. The search strategy for MEDLINE is presented in Table 2.

A four-member team, all with clinical and/or scientific expertise in chronic pain, contribute to the study selection process. The selection decisions will be based on inclusion criteria. First, articles that meet the search terms will be screened by title by one researcher (MM). Secondly, remaining articles will be screened by abstract by two researchers separately (MM, MH). Thirdly, remaining articles will be screened by full text in terms of PICO eligibility and study objective relevance by three researchers separately (MM, MP, MH). Fourthly, one researcher (PV) will finally review all of the articles in order to ensure the relevance regarding the study objective and eligibility criteria.

All conflicts will be discussed with the full review team. Original study authors will be contacted if eligibility criteria remain elusive following a review by the full review team.

The final study inclusion, accompanied with reasons for exclusion, will be presented in a PRISMA-P flow diagram (9). EndNote reference software will be used to record and deduplicate search results. Search strategy results will be uploaded to Covidence (Veritas Health Innovation, Melbourne, Australia), an online platform for systematic reviews.

Data synthesis and meta-analysis estimation

The following study information will be included: article data (author, publication year); study population (number of patients treated and analyzed, age, pain-related information [duration, localization, diagnosis], eligibility criteria); study design and intervention (duration, setting, professions included); predictive variables; outcomes (type of measurement, all follow-up time points, outcome variables [e.g., pain intensity, pain interference, HRQoL, physical functioning, psychological factors, depression]); research and statistical information (blinding method in RCTs, imputation method, withdrawals of data).

A coding sheet will be developed in order to be able to transform the described data into categorical data. The data extraction sheet will be pilot-tested in the first five studies. Two reviewers (MM, MP) will independently extract data from all included studies and cross-compare them at review completion. In the case of discrepancies, a third experienced researcher will be consulted (PO).

Narrative synthesis

All included articles will be considered in a narrative synthesis. Predictive variables will be evaluated in association with outcomes as follows: positive association, negative association, no association.

Quantitative synthesis

A minimum of two studies need to provide data on the same predictor group in order for these variables to be included in a quantitative analysis. All studies with incomplete data for standardization will be considered in the narrative synthesis. Outcome data will be processed as effect sizes and odds ratios (OR) with 95% confidence intervals (CI).

The RevMan Review Manager software version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata MP version 16 (StataCorp, Texas, USA) will be used to pool the results of the individual studies. The threshold for statistical significance will be set at $P = 0.05$. Heterogeneity between studies will be estimated using the I^2 index. In the case of substantial heterogeneity ($I^2 > 50\%$), the subsequent meta-analysis will be omitted, and data will be synthesized only qualitatively (10). Meta-analysis will be performed using random effects models, weighting individual studies by sample size. Synthesized effect sizes will be reported as pooled ORs with 95% CIs. Publication bias will be evaluated by means of funnel plots and Egger's test.

Quality assessment and confidence in evidence

The search for eligible studies, the critical appraisal of the risk of bias, and quality evaluation will be completed by several experienced independent researchers. The quality of the evidence will be summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (11). Based on the GRADE evaluation, the quality of evidence will be regarded as high, moderate, low, or very low (11). Several GRADE domains (e.g., risk of bias, imprecision,

inconsistency, publication bias, effect size) will be considered, and based on these, evidence may be downgraded or upgraded. The whole review group will contribute to the quality of evidence consideration. A summary of findings table will be presented.

Patient and Public Involvement

No patient involved.

Discussion

A multidisciplinary approach is essential in effective chronic pain management (7). The current systematic review project will center upon providing updated evidence regarding factors that may predict responsiveness to multidisciplinary chronic pain management interventions. The review will use robust methodology and examine a wide range of predictive variables, also taking into account several secondary outcomes—in addition to improvement in the pain situation, physical functioning, and HRQoL as primary outcomes.

The major strengths of the present systematic review are that it 1) aims for a meta-analysis, 2) includes prospective cohorts, case-control studies, and RCTs, 3) searches through a vast diversity of journals and databases, and 4) aims to investigate diverse predictive variables and several chronic pain situations. Also, the current review will investigate a wide array of primary (pain intensity and pain interference, physical functioning, heath-related quality of life) and secondary outcomes. In chronic pain management, an interdisciplinary management approach may lead to improvements in other outcomes besides pain, which may markedly improve individuals' HRQoL. Therefore, it is essential to consider multiple outcome domains when evaluating treatment responsiveness.

A multidisciplinary approach is a gold standard in chronic pain management; however, several factors may pose challenges in regard of responsiveness. Treatment needs to be provided in a timely fashion, and potential comorbidities (e.g., psychiatric diseases and symptoms) need to be recognized and treated. The current review aims to identify potential challenges—and, on the other hand, protective factors—regarding responsiveness, which may be beneficial in planning timely treatment with adequate content for chronic pain.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for the current study.

Authors' contributions

MM, MH and MP designed the study. PO and PV contributed to the statistical designing. MM and PO prepared the manuscript. All authors read and approved the final manuscript.

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Table 1

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

Section and topic	*Item No*	*Checklist item*	*Page No*
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
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	10
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4,5
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	4,5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study	6,7

		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	Table 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6,7
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)	6,7
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	7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	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)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8,9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8,9

Table 2

The review search strategy for MEDLINE.

Search term #1
(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)
Search term #2
(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)
Search term #3
(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)
Search term #4
(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)
Search term #5
(outcome* OR response* OR improvement* OR progress* OR effect*)
#1 AND #2 AND #3 AND #4 AND #5

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia, Rehabilitation medicine
Keywords:	Pain management < ANAESTHETICS, Rehabilitation medicine < INTERNAL MEDICINE, GENERAL MEDICINE (see Internal Medicine)

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Keywords: multidisciplinary, chronic pain, pain management

Abstract

INTRODUCTION The current manuscript presents a protocol for a systematic review and meta-analysis of the evidence regarding the determinants of responsiveness to multidisciplinary management of chronic pain, with pain intensity, pain-related interference, physical functioning, and health-related quality of life as the main outcomes, with consideration to multiple secondary outcomes.

METHODS AND ANALYSIS To identify relevant studies, the Ovid MEDLINE, Pubmed, Ovid PsycINFO, EBSCO CINAHL and Scopus databases will be searched for all studies exploring factors associated with responsiveness to multidisciplinary pain management from study inception to the present. Cohorts, case-control studies, and randomized controlled trials will be included. Independent screening for eligible studies will be completed by a total of four researchers using defined criteria. Data extraction will be executed by two researchers. Study heterogeneity will be estimated using the I^2 index. A meta-analysis will be performed using random effects models. Publication bias will be evaluated by means of funnel plots and Egger's test.

ETHICS AND DISSEMINATION The proposed study does not involve collection of primary data. Therefore, no ethical approval is required. The results of the systematic review and meta-analysis will be presented in a peer-reviewed journal and at conferences.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO registration number CRD42021236424.

Article Summary

Strengths and limitations of this study

- The current manuscript presents a detailed protocol for a systematic review, which aims to provide an outline of studies examining factors predicting responsiveness to multidisciplinary chronic pain management.
- The review is comprehensive as it will include search of multiple databases, and several possible prognostic factors, chronic pain conditions and outcome variables.
- During the systematic review, both data screening and collection, assessment of the risk of bias and judgement of the quality of evidence will be performed independently by at least two researchers of the five-member team, all with clinical and/or scientific expertise in chronic pain.
- The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines and good practice will be followed in data extraction and review development and reporting.
- Limiting the inclusion criteria to English papers may result in language bias.

Background

Disability related to chronic pain not only arises from somatic pathology but is always contributed by psychological and social aspects (1). Due to this biopsychosocial nature of chronic pain, a multidisciplinary approach has long been regarded as superior to narrower, unimodal chronic pain treatment modalities in terms of improvements in pain, physical functioning, psychological factors (e.g. self-management of pain, coping resources, emotional burden), working ability, and well-being (2-6). The International Association for the Study of Pain (IASP) defines multidisciplinary treatment as treatment provided by professionals from different disciplines (7). According to a meta-analysis, patient treated by multidisciplinary approach functioned 75% better than patients either untreated or treated by conventional, unimodal treatment approaches at long-term follow-up (3). Although multidisciplinary pain management is difficult to measure due to the diverse economic effects of pain on individuals and society (8), the cost-effectiveness of the approach has been supported (9).

The importance of patient selection has been highlighted, as not all patients benefit from multidisciplinary pain management (1). However, indefinitely, systematic reviews examining the current topic do not exist. To execute a comprehensive systematic review of the effectiveness of multidisciplinary management of chronic pain is far from easy due to the heterogeneity of studies (10). The studies available in the literature vary in terms of, for instance, patient selection, outcome variables, pain sites / type of pain examined, and the definition of interdisciplinary management.

Identifying factors that may predict whether patients benefit from a multimodal approach would provide remarkable assistance in clinical decision-making. Identifying these factors would help

clinicians to customize the treatment more efficiently to meet individual needs, and thus offer best possible pain treatment for each individual.

It is, thus, essential to systematically consider all previously studied factors that may predict the responsiveness to multidisciplinary management of chronic pain. The aim of the study presented herein is to identify and systematically analyze previously published data regarding this topic. Thus, the main research question of the presented systematic review is 'Which baseline factors may predict who will benefit from multidisciplinary management of chronic non-cancer pain'.

Methods

The current study protocol describes a systematic review and meta-analysis exploring the determinants of responsiveness to multidisciplinary chronic pain management interventions in adults. The review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on March 3rd, 2021 (registration number CRD42021236424).

Eligibility criteria

The included articles are required to be 1) original research articles, 2) published in full-text, 3) published in a peer-reviewed journal, and 4) published in English, and to 5) have a longitudinal (baseline–outcome) setting and 6) report empirical data (cohort, case-control or randomized controlled trial [RCT]; observational studies are also included). There will be no limitations on year of publication. Eligibility criteria, defined according to population, intervention, comparison, and outcomes (PICO), are listed below in separate sections.

Population

The participants included need to be adult (over 16 years of age, no maximum age limit) chronic pain patients who have been treated by a multidisciplinary pain management team. Pain will be defined as chronic when the duration of pain exceeds 3 months. Articles with a patient population comprising palliative care patients or postoperative pain patients with an average of an expected trend of healing will be excluded. In the case of incoherence, the whole study group will discuss each of these individually.

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To ensure adherence to IASP definition of multidisciplinary treatment (7), multidisciplinary teams included herein needed to comprise a minimum of three separate professional groups (e.g., physician, physical therapist, psychologist, and psychiatric nurse; consultation may be performed routinely or on demand).

All independent baseline variables that were examined as potential determinants of responsiveness to multidisciplinary pain management are included. These may include, for example, sociodemographic, symptom-related, physical well-being–related, and psychological factors (e.g. resilience, catastrophizing, coping, perceived stress, psychological flexibility).

Comparison/Comparator

All alternative exposures within the prognostic factors will be taken into account.

Outcome

Responsiveness will be defined as a positive effect of an intervention on the examined outcome variables.

All articles with 1) pain (pain intensity or pain interference) or 2) physical functioning or 3) health-related quality of life (HRQoL) as one primary outcome will be considered eligible. A rationale for determining HRQoL and physical functioning as primary outcomes in addition to pain is that they reflect pain-related disability well (11-14). In addition to these, other relevant outcomes will be considered (e.g., psychological factors, depression, working ability, analgesic consumption)—however, articles comprising these as a primary outcome with no evaluation of any of the three determined main outcomes as a primary outcome will be excluded. The primary focus will be on the situation immediately after a multidisciplinary treatment intervention, but studies with long-term follow-up data (e.g. outcome consideration after several years of follow-up) will also be

considered. Any outcome measurements will be included (e.g., patient-reported [PROMs], evaluation by professional, objective measures).

Search methods, information sources, study selection, and data management

A comprehensive electronic search of the medical and rehabilitation literature using medical subject headings (MeSH) and text related to responsiveness to multidisciplinary chronic pain management will be performed.

The search strategy has been developed to adhere the PICO descriptors. Based on this, four domains will be set: chronic pain, responsiveness/predictor, multidisciplinary intervention (divided into two domains for searches), and outcome. These domains will be joined with operator 'AND'. Regarding each domain, encompassing terms determined based on a comprehensive consideration of literature will be used in the searches. A content expert (MM) has developed the search strategy in consultation with a senior information specialist. The comprehensiveness of the search strategy has been peer-reviewed by an informatician at the Terkko faculty library of the Helsinki University Faculty of Medicine.

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articles will be screened by full text in terms of PICO eligibility and study objective relevance by three researchers separately (MM, MP, MH). Fourthly, one researcher (PV) will finally review all of the articles in order to ensure the relevance regarding the study objective and eligibility criteria. All conflicts will be discussed with the full review team. Original study authors will be contacted if eligibility criteria remain elusive following a review by the full review team.

The final study inclusion, accompanied with reasons for exclusion, will be presented in a PRISMA-P flow diagram (15). EndNote reference software will be used to record and deduplicate search results.

Data collection process and data items

The following study information will be included: article data (author, publication year); study population (number of patients treated and analyzed, age, pain-related information [duration, localization, diagnosis], eligibility criteria); study design and intervention (duration, setting, professions included); predictive variables; outcomes (type of measurement, all follow-up time points, outcome variables [e.g., pain intensity, pain interference, HRQoL, physical functioning, psychological factors, depression]); research and statistical information (blinding method in RCTs, imputation method, withdrawals of data).

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Publication bias will be evaluated by means of funnel plots and Egger's test.

Data synthesis and meta-analysis estimation

All included articles will be considered in a narrative synthesis. Outcome data will be comprehensively collected from the individual studies. All outcomes presented will be considered in the data synthesis. Predictive variables will be evaluated in association with outcomes as follows: positive association, negative association, no association.

A minimum of two studies need to provide data on the same predictor group in order for these variables to be included in a quantitative analysis. Outcome data will be processed in an outcome-

and statistic-specific manner as effect sizes (e.g., risk ratios (RR), odds ratios (OR), mean differences, beta coefficients (B), correlation coefficients) with 95% confidence intervals (CI). Odds ratios will be converted to risk ratios where possible.

The RevMan Review Manager software version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata MP version 16 (StataCorp, Texas, USA) will be used to pool the results of the individual studies. The threshold for statistical significance will be set at P = 0.05. Heterogeneity between studies will be estimated using the I^2 index. In the case of substantial heterogeneity ($I^2 > 50\%$), the subsequent meta-analysis will be omitted, and data will be synthesized only qualitatively (19). Meta-analysis will be performed using random effects models, weighting individual studies by sample size. Synthesized effect sizes will be reported as pooled ORs with 95% CIs. Sensitivity analyses to explore sources of heterogeneity will be considered; they will be primarily performed by restricting the analysis to subsets of studies.

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No patient involved.

Discussion

A multidisciplinary approach is essential in effective chronic pain management (1). It is known, however, that not all patients benefit from multidisciplinary chronic pain management (10). The importance lies in identifying who may benefit and who may not. The current systematic review project will center upon providing updated evidence regarding factors that may associate with responsiveness to multidisciplinary chronic pain management interventions. The review will use robust methodology and examine a wide range of prognostic variables, also taking into account several secondary outcomes—in addition to improvement in the pain situation, physical functioning, and HRQoL as primary outcomes.

The major strengths of the present systematic review are that it 1) aims for a meta-analysis, 2) includes prospective cohorts, case-control studies, and RCTs, 3) searches through a vast diversity of journals and databases, and 4) aims to investigate diverse predictive variables and several chronic pain situations. Also, the current review will investigate a wide array of primary (pain intensity and pain interference, physical functioning, heath-related quality of life) and secondary outcomes. In chronic pain management, a multidisciplinary management approach may lead to improvements in other outcomes besides pain (e.g. improvements in psychological well-being), which may markedly improve individuals' HRQoL (10). Therefore, it is essential to consider multiple outcome domains when evaluating treatment responsiveness. Limiting the inclusion criteria to English papers may result in language bias, which therefore needs to be considered a limitation.

A multidisciplinary approach is a gold standard in chronic pain management (4); however, several factors may pose challenges in regard of responsiveness. Treatment needs to be provided in a timely fashion, and potential comorbidities (e.g., psychiatric diseases and symptoms) need to be

recognized and treated. The current review aims to identify potential challenges—and, on the other hand, protective factors—regarding responsiveness, which may be beneficial in planning timely treatment with adequate content for chronic pain.

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Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for the current study.

Authors' contributions

MM, MH and MP designed the study. PO and PV contributed to the statistical designing. MM and PO prepared the manuscript. All authors read and approved the final manuscript.

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Table 1

The review search strategy for MEDLINE.

Search term #1
(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)
Search term #2
(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)
Search term #3
(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)
Search term #4
(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)
Search term #5
(outcome* OR response* OR improvement* OR progress* OR effect*)
#1 AND #2 AND #3 AND #4 AND #5

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

Section and topic	*Item No*	*Checklist item*	*Page No*
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
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	10
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4,5
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	4,5

		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	6,7
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	Table 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6,7
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)	6,7
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	7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	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)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8,9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8,9

BMJ Open

Determinants of responsiveness to multidisciplinary chronic pain management interventions: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
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Keywords:	Pain management < ANAESTHETICS, Rehabilitation medicine < INTERNAL MEDICINE, GENERAL MEDICINE (see Internal Medicine)

Determinants of responsiveness to multidisciplinary chronic pain management interventions: protocol for a systematic review and meta-analysis

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Keywords: multidisciplinary, chronic pain, pain management

Abstract

INTRODUCTION The current manuscript presents a protocol for a systematic review and meta-analysis of the evidence regarding the determinants of responsiveness to multidisciplinary management of chronic pain, with pain intensity, pain-related interference, physical functioning, and health-related quality of life as the main outcomes, with consideration to multiple secondary outcomes.

METHODS AND ANALYSIS To identify relevant studies, the Ovid MEDLINE, Pubmed, Ovid PsycINFO, EBSCO CINAHL and Scopus databases will be searched for all studies exploring factors associated with responsiveness to multidisciplinary pain management from study inception to the present. Cohorts, case-control studies, and randomized controlled trials will be included. Independent screening for eligible studies will be completed by a total of four researchers using defined criteria. Data extraction will be executed by two researchers. Study heterogeneity will be estimated using the I^2 index. A meta-analysis will be performed using random effects models. Publication bias will be evaluated by means of funnel plots and Egger's test.

ETHICS AND DISSEMINATION The proposed study does not involve collection of primary data. Therefore, no ethical approval is required. The results of the systematic review and meta-analysis will be presented in a peer-reviewed journal and at conferences.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO registration number CRD42021236424.

Article Summary

Strengths and limitations of this study

- The current manuscript presents a detailed protocol for a systematic review, which aims to provide an outline of studies examining factors predicting responsiveness to multidisciplinary chronic pain management.
- The review is comprehensive as it will include search of multiple databases, and several possible prognostic factors, chronic pain conditions and outcome variables.
- During the systematic review, both data screening and collection, assessment of the risk of bias and judgement of the quality of evidence will be performed independently by at least two researchers of the five-member team, all with clinical and/or scientific expertise in chronic pain.
- The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines and good practice will be followed in data extraction and review development and reporting.
- Limiting the inclusion criteria to English papers may result in language bias.

Background

Disability related to chronic pain not only arises from somatic pathology but is always contributed by psychological and social aspects (1). Due to this biopsychosocial nature of chronic pain, a multidisciplinary approach has long been regarded as superior to narrower, unimodal chronic pain treatment modalities in terms of improvements in pain, physical functioning, psychological factors (e.g. self-management of pain, coping resources, emotional burden), working ability, and well-being (2-6). The International Association for the Study of Pain (IASP) defines multimodal treatment as treatment provided by professionals from different disciplines (7). According to a meta-analysis, patient treated by multidisciplinary approach functioned 75% better than patients either untreated or treated by conventional, unimodal treatment approaches at long-term follow-up (3). Although multidisciplinary pain management is difficult to measure due to the diverse economic effects of pain on individuals and society (8), the cost-effectiveness of the approach has been supported (9).

The importance of patient selection has been highlighted, as not all patients benefit from multidisciplinary pain management (1). However, indefinitely, systematic reviews examining the current topic do not exist. To execute a comprehensive systematic review of the effectiveness of multidisciplinary management of chronic pain is far from easy due to the heterogeneity of studies (10). The studies available in the literature vary in terms of, for instance, patient selection, outcome variables, pain sites / type of pain examined, and the definition of interdisciplinary management.

Identifying factors that may predict whether patients benefit from a multimodal approach would provide remarkable assistance in clinical decision-making. Identifying these factors would help

clinicians to customize the treatment more efficiently to meet individual needs, and thus offer best possible pain treatment for each individual.

It is, thus, essential to systematically consider all previously studied factors that may predict the responsiveness to multidisciplinary management of chronic pain. The aim of the study presented herein is to identify and systematically analyze previously published data regarding this topic. Thus, the main research question of the presented systematic review is 'Which baseline factors may predict who will benefit from multidisciplinary management of chronic non-cancer pain'.

Methods

The current study protocol describes a systematic review and meta-analysis exploring the determinants of responsiveness to multidisciplinary chronic pain management interventions in adults. The review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on March 3rd, 2021 (registration number CRD42021236424).

The planned start date of the study will be September 1st, 2022. The planned end date of the study will be February 15th, 2023. Current study status: review protocol has been developed.

Eligibility criteria

The included articles are required to be 1) original research articles, 2) published in full-text, 3) published in a peer-reviewed journal, and 4) published in English, and to 5) have a longitudinal (baseline–outcome) setting and 6) report empirical data (cohort, case-control or randomized controlled trial [RCT]; observational studies are also included). There will be no limitations on year of publication. Eligibility criteria, defined according to population, intervention, comparison, and outcomes (PICO), are listed below in separate sections.

Population

The participants included need to be adult (over 16 years of age, no maximum age limit) chronic pain patients who have been treated by a multidisciplinary pain management team. Pain will be defined as chronic when the duration of pain exceeds 3 months. Articles with a patient population comprising palliative care patients or postoperative pain patients with an average of an expected trend of healing will be excluded. In the case of incoherence, the whole study group will discuss each of these individually.

Intervention/Prognostic factor

To ensure adherence to IASP definition of multidisciplinary treatment (7), multidisciplinary teams included herein needed to comprise a minimum of three separate professional groups (e.g., physician, physical therapist, psychologist, and psychiatric nurse; consultation may be performed routinely or on demand).

All independent baseline variables that were examined as potential determinants of responsiveness to multidisciplinary pain management are included. These may include, for example, sociodemographic, symptom-related, physical well-being–related, and psychological factors (e.g. resilience, catastrophizing, coping, perceived stress, psychological flexibility).

Comparison/Comparator

All alternative exposures within the prognostic factors will be taken into account.

Outcome

Responsiveness will be defined as a positive effect of an intervention on the examined outcome variables.

All articles with 1) pain (pain intensity or pain interference) or 2) physical functioning or 3) health-related quality of life (HRQoL) as one primary outcome will be considered eligible. A rationale for determining HRQoL and physical functioning as primary outcomes in addition to pain is that they reflect pain-related disability well (11-14). In addition to these, other relevant outcomes will be considered (e.g., psychological factors, depression, working ability, analgesic consumption)—however, articles comprising these as a primary outcome with no evaluation of any of the three determined main outcomes as a primary outcome will be excluded. The primary focus will be on

the situation immediately after a multidisciplinary treatment intervention, but studies with long-term follow-up data (e.g. outcome consideration after several years of follow-up) will also be considered. Any outcome measurements will be included (e.g., patient-reported [PROMs], evaluation by professional, objective measures).

Search methods, information sources, study selection, and data management

A comprehensive electronic search of the medical and rehabilitation literature using medical subject headings (MeSH) and text related to responsiveness to multidisciplinary chronic pain management will be performed.

The search strategy has been developed to adhere the PICO descriptors. Based on this, four domains will be set: chronic pain, responsiveness/predictor, multidisciplinary intervention (divided into two domains for searches), and outcome. These domains will be joined with operator 'AND'. Regarding each domain, encompassing terms determined based on a comprehensive consideration of literature will be used in the searches. A content expert (MM) has developed the search strategy in consultation with a senior information specialist. The comprehensiveness of the search strategy has been peer-reviewed by an informatician at the Terkko faculty library of the Helsinki University Faculty of Medicine.

Ovid MEDLINE, Pubmed, Ovid PsycINFO, EBSCO CINAHL and Scopus will be used to execute electronic searches from inception to the present. The supplementary Appendix A presents search strategies for all searched databases.

A four-member team, all with clinical and/or scientific expertise in chronic pain, contribute to the study selection process. The selection decisions will be based on inclusion criteria. First, articles

that meet the search terms will be screened by title by one researcher (MM). Secondly, remaining articles will be screened by abstract by two researchers separately (MM, MH). Thirdly, remaining articles will be screened by full text in terms of PICO eligibility and study objective relevance by three researchers separately (MM, MP, MH). Fourthly, one researcher (PV) will finally review all of the articles in order to ensure the relevance regarding the study objective and eligibility criteria. All conflicts will be discussed with the full review team. Original study authors will be contacted if eligibility criteria remain elusive following a review by the full review team.

The final study inclusion, accompanied with reasons for exclusion, will be presented in a PRISMA-P flow diagram (15). EndNote reference software will be used to record and deduplicate search results.

Data collection process and data items

The following study information will be included: article data (author, publication year); study population (number of patients treated and analyzed, age, pain-related information [duration, localization, diagnosis], eligibility criteria); study design and intervention (e.g. duration, setting, professions included); predictive variables; outcomes (type of measurement, all follow-up time points, outcome variables [e.g., pain intensity, pain interference, HRQoL, physical functioning, psychological factors, depression]); research and statistical information (blinding method in RCTs, imputation method, withdrawals of data).

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Authors' contributions

MM, MH and MP designed the study. PO and PV contributed to the statistical designing. MM and PO prepared the manuscript. All authors read and approved the final manuscript.

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Determinants of responsiveness to multidisciplinary chronic pain management interventions: protocol for a systematic review and meta-analysis

Appendix A. Search Strategy

Ovid MEDLINE

Fields: Title, Abstract, Subject heading word, Keyword heading word

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

AND

(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)

AND

(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)

AND

(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)

AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

Pubmed

Fields: Title/Abstract, MeSH Terms

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

AND

(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)

AND

(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)

AND

(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)

AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

Ovid PsycINFO

Fields: Title, Abstract, Heading word, MeSH word

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

AND

(predictor* OR prognostic* OR determinant* OR responsivity OR responsive* OR forecasting OR probability OR protective factor* OR moderator*)

AND

(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)

AND

(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)

AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

Ebsco CINAHL

Fields: Title, Abstract

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

AND

(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)

AND

(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)

AND

(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)

AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

Scopus

Fields: Title/Abstract/Keyword

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

AND

(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)

AND

(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)

AND

(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)

AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

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

Section and topic	*Item No*	*Checklist item*	*Page No*
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
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	10
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4,5
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	4,5

		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	6,7
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	Table 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6,7
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)	6,7
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	7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	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)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8,9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8,9

BMJ Open

Determinants of responsiveness to multidisciplinary chronic pain management interventions: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
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Determinants of responsiveness to multidisciplinary chronic pain management interventions: protocol for a systematic review and meta-analysis

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Keywords: multidisciplinary, chronic pain, pain management

Abstract

INTRODUCTION The current manuscript presents a protocol for a systematic review and meta-analysis of the evidence regarding the determinants of responsiveness to multidisciplinary management of chronic pain, with pain intensity, pain-related interference, physical functioning, and health-related quality of life as the main outcomes, with consideration to multiple secondary outcomes.

METHODS AND ANALYSIS To identify relevant studies, the Ovid MEDLINE, Pubmed, Ovid PsycINFO, EBSCO CINAHL and Scopus databases will be searched for all studies exploring factors associated with responsiveness to multidisciplinary pain management from study inception to the present. Cohorts, case-control studies, and randomized controlled trials will be included. Independent screening for eligible studies will be completed by a total of four researchers using defined criteria. Data extraction will be executed by two researchers. Study heterogeneity will be estimated using the I^2 index. A meta-analysis will be performed using random effects models. Publication bias will be evaluated by means of funnel plots and Egger's test.

ETHICS AND DISSEMINATION The proposed study does not involve collection of primary data. Therefore, no ethical approval is required. The results of the systematic review and meta-analysis will be presented in a peer-reviewed journal and at conferences.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO registration number CRD42021236424.

Article Summary

Strengths and limitations of this study

- The current manuscript presents a detailed protocol for a systematic review, which aims to provide an outline of studies examining factors predicting responsiveness to multidisciplinary chronic pain management.
- The review is comprehensive as it will include search of multiple databases, and several possible prognostic factors, chronic pain conditions and outcome variables.
- During the systematic review, both data screening and collection, assessment of the risk of bias and judgement of the quality of evidence will be performed independently by at least two researchers of the five-member team, all with clinical and/or scientific expertise in chronic pain.
- The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) guidelines and good practice will be followed in data extraction and review development and reporting.
- Limiting the inclusion criteria to English papers may result in language bias.

Introduction

Disability related to chronic pain not only arises from somatic pathology but is always contributed by psychological and social aspects (1). Due to this biopsychosocial nature of chronic pain, a multidisciplinary approach has long been regarded as superior to narrower, unimodal chronic pain treatment modalities in terms of improvements in pain, physical functioning, psychological factors (e.g. self-management of pain, coping resources, emotional burden), working ability, and well-being (2-6). The International Association for the Study of Pain (IASP) defines multimodal treatment as treatment provided by professionals from different disciplines (7). According to a meta-analysis, patient treated by multidisciplinary approach functioned 75% better than patients either untreated or treated by conventional, unimodal treatment approaches at long-term follow-up (3). Although multidisciplinary pain management is difficult to measure due to the diverse economic effects of pain on individuals and society (8), the cost-effectiveness of the approach has been supported (9).

The importance of patient selection has been highlighted, as not all patients benefit from multidisciplinary pain management (1). However, indefinitely, systematic reviews examining the current topic do not exist. To execute a comprehensive systematic review of the effectiveness of multidisciplinary management of chronic pain is far from easy due to the heterogeneity of studies (10). The studies available in the literature vary in terms of, for instance, patient selection, outcome variables, pain sites / type of pain examined, and the definition of interdisciplinary management.

Identifying factors that may predict whether patients benefit from a multimodal approach would provide remarkable assistance in clinical decision-making. Identifying these factors would help

clinicians to customize the treatment more efficiently to meet individual needs, and thus offer best possible pain treatment for each individual.

It is, thus, essential to systematically consider all previously studied factors that may predict the responsiveness to multidisciplinary management of chronic pain. The aim of the study presented herein is to identify and systematically analyze previously published data regarding this topic. Thus, the main research question of the presented systematic review is 'Which baseline factors may predict who will benefit from multidisciplinary management of chronic non-cancer pain'.

Methods and analysis

The current study protocol describes a systematic review and meta-analysis exploring the determinants of responsiveness to multidisciplinary chronic pain management interventions in adults. The review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on March 3rd, 2021 (registration number CRD42021236424).

The planned start date of the study will be September 1st, 2022. The planned end date of the study will be February 15th, 2023. Current study status: review protocol has been developed.

Eligibility criteria

The included articles are required to be 1) original research articles, 2) published in full-text, 3) published in a peer-reviewed journal, and 4) published in English, and to 5) have a longitudinal (baseline–outcome) setting and 6) report empirical data (cohort, case-control or randomized controlled trial [RCT]; observational studies are also included). There will be no limitations on year of publication. Eligibility criteria, defined according to population, intervention, comparison, and outcomes (PICO), are listed below in separate sections.

Population

The participants included need to be adult (over 16 years of age, no maximum age limit) chronic pain patients who have been treated by a multidisciplinary pain management team. Pain will be defined as chronic when the duration of pain exceeds 3 months. Articles with a patient population comprising palliative care patients or postoperative pain patients with an average of an expected trend of healing will be excluded. In the case of incoherence, the whole study group will discuss each of these individually.

Intervention/Prognostic factor

To ensure adherence to IASP definition of multidisciplinary treatment (7), multidisciplinary teams included herein needed to comprise a minimum of three separate professional groups (e.g., physician, physical therapist, psychologist, and psychiatric nurse; consultation may be performed routinely or on demand).

All independent baseline variables that were examined as potential determinants of responsiveness to multidisciplinary pain management are included. These may include, for example, sociodemographic, symptom-related, physical well-being–related, and psychological factors (e.g. resilience, catastrophizing, coping, perceived stress, psychological flexibility).

Comparison/Comparator

All alternative exposures within the prognostic factors will be taken into account.

Outcome

Responsiveness will be defined as a positive effect of an intervention on the examined outcome variables.

All articles with 1) pain (pain intensity or pain interference) or 2) physical functioning or 3) health-related quality of life (HRQoL) as one primary outcome will be considered eligible. A rationale for determining HRQoL and physical functioning as primary outcomes in addition to pain is that they reflect pain-related disability well (11-14). In addition to these, other relevant outcomes will be considered (e.g., psychological factors, depression, working ability, analgesic consumption)—however, articles comprising these as a primary outcome with no evaluation of any of the three determined main outcomes as a primary outcome will be excluded. The primary focus will be on

the situation immediately after a multidisciplinary treatment intervention, but studies with long-term follow-up data (e.g. outcome consideration after several years of follow-up) will also be considered. Any outcome measurements will be included (e.g., patient-reported [PROMs], evaluation by professional, objective measures).

Search methods, information sources, study selection, and data management

A comprehensive electronic search of the medical and rehabilitation literature using medical subject headings (MeSH) and text related to responsiveness to multidisciplinary chronic pain management will be performed.

The search strategy has been developed to adhere the PICO descriptors. Based on this, four domains will be set: chronic pain, responsiveness/predictor, multidisciplinary intervention (divided into two domains for searches), and outcome. These domains will be joined with operator 'AND'. Regarding each domain, encompassing terms determined based on a comprehensive consideration of literature will be used in the searches. A content expert (MM) has developed the search strategy in consultation with a senior information specialist. The comprehensiveness of the search strategy has been peer-reviewed by an informatician at the Terkko faculty library of the Helsinki University Faculty of Medicine.

Ovid MEDLINE, Pubmed, Ovid PsycINFO, EBSCO CINAHL and Scopus will be used to execute electronic searches from inception to the present. The supplementary Appendix A presents search strategies for all searched databases.

A four-member team, all with clinical and/or scientific expertise in chronic pain, contribute to the study selection process. The selection decisions will be based on inclusion criteria. First, articles

that meet the search terms will be screened by title by one researcher (MM). Secondly, remaining articles will be screened by abstract by two researchers separately (MM, MH). Thirdly, remaining articles will be screened by full text in terms of PICO eligibility and study objective relevance by three researchers separately (MM, MP, MH). Fourthly, one researcher (PV) will finally review all of the articles in order to ensure the relevance regarding the study objective and eligibility criteria. All conflicts will be discussed with the full review team. Original study authors will be contacted if eligibility criteria remain elusive following a review by the full review team.

The final study inclusion, accompanied with reasons for exclusion, will be presented in a PRISMA-P flow diagram (15). EndNote reference software will be used to record and deduplicate search results.

Data collection process and data items

The following study information will be included: article data (author, publication year); study population (number of patients treated and analyzed, age, pain-related information [duration, localization, diagnosis], eligibility criteria); study design and intervention (e.g. duration, setting, professions included); predictive variables; outcomes (type of measurement, all follow-up time points, outcome variables [e.g., pain intensity, pain interference, HRQoL, physical functioning, psychological factors, depression]); research and statistical information (blinding method in RCTs, imputation method, withdrawals of data).

A coding sheet will be developed in order to be able to transform the described data into categorical data. The data extraction sheet will be pilot-tested in the first five studies. Two reviewers (MM,

MP) will independently extract data from all included studies and cross-compare them at review completion. In the case of discrepancies, a third experienced researcher will be consulted (PO).

Risk of bias in individual studies

The search for eligible studies, the critical appraisal of the risk of bias, and quality evaluation will be completed by several experienced independent researchers. The risk of bias will be evaluated at the individual study level by means of Cochrane Collaboration's tool for assessing risk of bias in randomized trials and Newcastle-Ottawa Scale (NOS) in obsevational studies (16-17). Information regarding the risk of bias will be summarized in the narrative synthesis.

The quality of the evidence will be summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (18). Based on the GRADE evaluation, the quality of evidence will be regarded as high, moderate, low, or very low (18). Several GRADE domains (e.g., risk of bias, imprecision, inconsistency, publication bias, effect size) will be considered, and based on these, evidence may be downgraded or upgraded. The whole review group will contribute to the quality of evidence consideration. A summary of findings table will be presented.

Bias across studies

Publication bias will be evaluated by means of funnel plots and Egger's test.

Data synthesis and meta-analysis estimation

All included articles will be considered in a narrative synthesis. Outcome data will be comprehensively collected from the individual studies. All outcomes presented will be considered in the data synthesis. Predictive variables will be evaluated in association with outcomes as follows: positive association, negative association, no association.

A minimum of two studies need to provide data on the same predictor group in order for these variables to be included in a quantitative analysis. Outcome data will be processed in an outcome- and statistic-specific manner as effect sizes (e.g., risk ratios (RR), odds ratios (OR), mean differences, beta coefficients (B), correlation coefficients) with 95% confidence intervals (CI). Odds ratios will be converted to risk ratios where possible.

The RevMan Review Manager software version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata MP version 16 (StataCorp, Texas, USA) will be used to pool the results of the individual studies. The threshold for statistical significance will be set at P = 0.05. Heterogeneity between studies will be estimated using the I^2 index. In the case of substantial heterogeneity ($I^2 > 50\%$), the subsequent meta-analysis will be omitted, and data will be synthesized only qualitatively (19). Meta-analysis will be performed using random effects models, weighting individual studies by sample size. Synthesized effect sizes will be reported as pooled ORs with 95% CIs. Sensitivity analyses to explore sources of heterogeneity will be considered; they will be primarily performed by restricting the analysis to subsets of studies.

Patient and Public Involvement

No patient involved.

Discussion

A multidisciplinary approach is essential in effective chronic pain management (1). It is known, however, that not all patients benefit from multidisciplinary chronic pain management (10). The importance lies in identifying who may benefit and who may not. The current systematic review project will center upon providing updated evidence regarding factors that may associate with responsiveness to multidisciplinary chronic pain management interventions. The review will use robust methodology and examine a wide range of prognostic variables, also taking into account several secondary outcomes—in addition to improvement in the pain situation, physical functioning, and HRQoL as primary outcomes.

The major strengths of the present systematic review are that it 1) aims for a meta-analysis, 2) includes prospective cohorts, case-control studies, and RCTs, 3) searches through a vast diversity of journals and databases, and 4) aims to investigate diverse predictive variables and several chronic pain situations. Also, the current review will investigate a wide array of primary (pain intensity and pain interference, physical functioning, heath-related quality of life) and secondary outcomes. In chronic pain management, a multidisciplinary management approach may lead to improvements in other outcomes besides pain (e.g. improvements in psychological well-being), which may markedly improve individuals' HRQoL (10). Therefore, it is essential to consider multiple outcome domains when evaluating treatment responsiveness. Limiting the inclusion criteria to English papers may result in language bias, which therefore needs to be considered a limitation.

A multidisciplinary approach is a gold standard in chronic pain management (4); however, several factors may pose challenges in regard of responsiveness. Treatment needs to be provided in a timely fashion, and potential comorbidities (e.g., psychiatric diseases and symptoms) need to be

recognized and treated. The current review aims to identify potential challenges—and, on the other hand, protective factors—regarding responsiveness, which may be beneficial in planning timely treatment with adequate content for chronic pain.

Ethics and dissemination

The proposed study does not involve collection of primary data. Therefore, no ethical approval is required. The results of the systematic review and meta-analysis will be presented in a peer-reviewed journal and at conferences.

Declarations

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for the current study.

Authors' contributions

MM, MH and MP designed the study. PO and PV contributed to the statistical designing. MM and PO prepared the manuscript. All authors read and approved the final manuscript.

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10. Vartiainen P, Heiskanen T, Sintonen H, Roine RP, Kalso E. Health-related quality of life change in patients treated at a multidisciplinary pain clinic. Eur J Pain. 2019;23(7):1318-28.
11. Taylor AM, Phillips K, Patel KV, Turk DC, Dworkin RH, Beaton D, et al. Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/OMERACT recommendations. Pain. 2016;157(9):1836-1850.
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Determinants of responsiveness to multidisciplinary chronic pain management interventions: protocol for a systematic review and meta-analysis

Appendix A. Search Strategy

Ovid MEDLINE

Fields: Title, Abstract, Subject heading word, Keyword heading word

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

AND

(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)

AND

(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)

AND

(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)

AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

Pubmed

Fields: Title/Abstract, MeSH Terms

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

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AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

Ovid PsycINFO

Fields: Title, Abstract, Heading word, MeSH word

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(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)

AND

(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)

AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

Ebsco CINAHL

Fields: Title, Abstract

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

AND

(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)

AND

(multidisciplinary OR interdisciplinary OR multimodal OR interprofessional OR multiprofessional OR biopsychosocial)

AND

(program* OR care team OR treatment approach* OR treatment OR management OR rehabilitation OR intervention* OR regimen* OR therap*)

AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

Scopus

Fields: Title/Abstract/Keyword

(chronic pain OR persistent pain OR prolonged pain OR long-lasting pain OR intermittent pain OR long-term pain OR generalized pain OR widespread pain OR diffuse pain OR constant pain OR interfering pain OR intractable pain)

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(predictor* OR prognostic* OR determinant* OR responsivity or responsive* OR forecasting OR probability OR protective factor* OR moderator*)

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AND

(outcome* OR response* OR improvement* OR progress* OR effect*)

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

Section and topic	*Item No*	*Checklist item*	*Page No*
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
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	10
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4,5
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	4,5

		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	6,7
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	Table 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6,7
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)	6,7
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	7
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	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8
	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)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8,9

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8,9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8,9