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Complete List of Authors:	O'Leary, Helen; University College Dublin, School of Public Health, Physiotherapy and Population Science Doody, Catherine; University College Dublin, School of Public Health, Physiotherapy and Population Science Smart, Keith; St. Vincent's University Hospital, Physiotherapy Department Moloney, Niamh; The University of Sydney, Faculty of Health Sciences Blake, Catherine; University College Dublin, School of Public Health, Physiotherapy and Population Science
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Pain sensitization and the risk of poor outcome following physiotherapy for knee osteoarthritis: protocol for a prospective cohort study

O'Leary H, Smart KM, Moloney NA, Blake C and Doody CM.

*Helen O'Leary, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: helen.oleary@ucdconnect.ie Telephone: 00 353 86 0665530

Keith M Smart, Physiotherapy Department, St Vincent's University Hospital, Elm Park, Dublin, Ireland.
Email: k.smart@svuh.ie

Niamh A Moloney, Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, Australia.
Email: niamh.moloney@sydney.edu.au

Catherine Blake, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: c.blake@ucd.ie

Catherine M Doody, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: c.doody@ucd.ie

*Corresponding author

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ABSTRACT

Introduction

Pain is the dominant symptom of knee osteoarthritis and recent evidence suggests factors outside of local joint pathology, such as pain sensitization, can contribute significantly to the pain experience. It is unknown how pain sensitization influences outcomes from commonly employed interventions such as physiotherapy.

The aims of this study are, firstly to identify people with knee osteoarthritis who display signs and symptoms associated with pain sensitization using clinical tools and quantitative sensory testing. Secondly, we will investigate if indications of pain sensitization at baseline are associated with poor outcome following physiotherapy.

Methods and analysis

This is a multi-centre prospective cohort study with 140 participants. Eligible patients with moderate/severe symptomatic knee osteoarthritis will be identified at outpatient clinics. A baseline assessment will provide a comprehensive description of the somatosensory characteristics of each participant; by means of clinical examination, quantitative sensory testing and validated questionnaires measuring pain and functional capacity. Participants will then undergo physiotherapy treatment. The primary end point will be on completion of physiotherapy (estimated to be at 3 months) and questionnaires will assess change in pain, disability (sub-scales of Western Ontario and McMasters University Score Osteoarthritis Index) and participants' global rating of change. These primary outcome measures will dichotomise participants into treatment 'responders' and 'non-responders' according to the Osteoarthritis Research Society International (OARSI) treatment responder criteria.

For data analysis results from pressure pain thresholds, temporal summation and conditioned pain modulation will create a composite score of pain sensitization. Logistic regression will explore the relationship between response to physiotherapy and pain sensitization while accounting for confounders.

Ethics and dissemination

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee and by the St. Vincent's Healthcare Group Ethics and Medical Research

Committee. The results will be presented at international conferences and published in a peer review journal.

Trial Registration Number ClinicalTrials.gov Identifier: NCT02310945

ARTICLE SUMMARY

Strengths and limitations of this study

To our knowledge this is the first study examining the effects of pain sensitization on physiotherapy outcomes in knee osteoarthritis.

Strengths of this study protocol include; the relatively large sample given the comprehensive assessment procedure involved, the use of a broad range of validated measures to study pain processing and the gathering of control QST data from healthy volunteers.

This study will focus on tests to identify features of pain sensitivity based on their utility and practicality in the clinical setting. However these criteria necessitate the exclusion of certain tests, such as thermal pain thresholds, that are difficult to carrying out reliably in the clinical setting in a limited assessment time.

As this is a clinically based observational study there is likely to be variation in physiotherapy intervention. The findings of this research may call for a further research examining the effects of a targeted treatment programme for pain sensitization compared to usual care.

INTRODUCTION

Knee osteoarthritis (OA) is a prevalent joint disease that causes a huge burden of pain, disability and loss of productivity worldwide.[1–3] With ageing populations and increasing obesity, the prevalence of OA is rising, thus its timely and effective management is a priority within healthcare.[3,4]

The pathophysiology of knee OA pain is complex. Altered processing of nociceptive inputs at spinal and higher brain centers may help explain discrepancies between pain severity and pathological abnormalities in OA.[5–7] Pain sensitization is defined as increased responsiveness of nociceptive neurons to their normal input and/or recruitment of a response to normally sub-threshold inputs.[8] It is proposed that these changes in central pain processing due to chronic nociceptive input into the nervous system from the arthritic can contribute to an enhanced, persistent and more widespread pain response.[9,10] Recent studies in knee OA have found the presence of increased pain sensitivity at remote sites, enhanced temporal summation (TS) and hypersensitivity to various stimuli to be associated with reports of more severe symptoms.[5,6,11] These cross-sectional studies linking features of sensitization to greater levels of pain and disability do not explore if pain sensitivity has any prognostic implications.

There is some evidence to suggest increased pain sensitivity negatively affects treatment outcomes. In painful musculoskeletal conditions such as shoulder impingement and lateral epicondylalgia widespread pressure pain sensitivity and thermal hyperalgesia, have been linked with a poorer prognosis.[12,13] Surgical outcomes for knee osteoarthritis may also be affected with the presence of increased pain sensitivity prior to total knee replacement associated with more persistent pain after surgery.[14,15]

Although joint replacement is considered an effective treatment for end-stage knee OA, the majority of patients with knee OA are managed conservatively. Physiotherapy is a widely recommended conservative treatment approach.[16] Studies of prognosis in knee OA have focused on demographic and psychological variables[17–19], few studies have focused on factors relating to abnormal pain processing. Despite recent claims that the domain of altered central pain processing makes an important contribution to the clinical pain experience in some people with knee OA[20], no longitudinal studies have explored prognostic factors relating to pain sensitization and outcome following physiotherapy. In whiplash associated disorders the presence of sensory hypersensitivity and cold hyperalgesia has been shown to reduce the likelihood of a positive response to physiotherapy treatment.[21] Thus it is conceivable, but currently unproven, that knee OA patients with evidence of pain sensitization have poorer outcomes following physiotherapy.

One obstacle to investigating the implications of pain sensitization is reliably identifying it in the clinical setting. Clinical criteria proposed for assessing central sensitization rely principally on the clinician's subjective interpretation of patient symptoms.[22] Although useful clinically, for research purposes more objective measures are preferable. Due to the complexity of the pain experience it is inadvisable to rely on any single test to reflect peripheral and central pain mechanisms.[23,24] A multi-tissue assessment using a multi-modal stimuli approach has been advocated,[25], and will be adopted in this study. Recognised features of central and peripheral sensitization previously identified in knee OA patients will be utilised in this study and these include extended areas of hyperalgesia,[26,27], enhanced TS,[6,9], and dysfunctional conditioned pain modulation (CPM).[9,27]

This study will explore clinical outcomes of knee OA (pain, function, patient's global assessment) following physiotherapy, investigating the association between key features of pain sensitization and the likelihood of a poor outcome. Distinguishing patients at risk of a poor outcome may help determine appropriate management strategies in a timely manner.

Study aims

The main aims of the study are; firstly to provide a comprehensive description of the somatosensory characteristics of people with pain associated with knee OA (by means of quantitative sensory testing (QST), and validated questionnaires measuring pain, functional capacity and quality of life) and secondly, to investigate if the presence of pain sensitization at baseline is associated with poorer response to

physiotherapy treatment. We hypothesise that the presence of pain sensitization at baseline is associated with a greater risk of poor outcome at a follow-up post physiotherapy treatment

METHODS AND ANALYSIS

Study design

A multi-centre observational cohort study with assessments at baseline, post-treatment and at six months will be conducted. Following the baseline assessment for features of pain sensitization all participants will receive usual physiotherapy care. The relationship between pain sensitization and outcomes in terms of pain and disability will be explored through regression analysis.

Setting

The study will be set in the physiotherapy outpatient departments of three large publicly funded teaching hospitals in Dublin, Ireland.

Participants

Patients with symptomatic knee OA referred for physiotherapy treatment by a hospital consultant or clinical specialist physiotherapist will be eligible for inclusion. Full details of inclusion/exclusion criteria are summarised in Table 1.

At the time of recruitment knee pain must be the participant's primary musculoskeletal complaint they are seeking treatment for, and physiotherapy must be the main treatment being undertaken over the study period. Participants recruited at musculoskeletal assessment clinics will be screened by the clinical specialist physiotherapist. Patients on the physiotherapy waiting list will be screened for suitability by the principal investigator over the telephone.

Table 1. Study inclusion and exclusion criteria

Inclusion Criteria	
Diagnosis	Knee osteoarthritis diagnosed by American College of Rheumatology clinical criteria
Age	Over 50 years
Pain duration	Knee pain for at least 6 months
Severity	Pain ≥ 5/10 on Numerical Rating Scale

Medication	Willing to abstain from simple analgesics and NSAIDs for 24 hours prior to testing
Consent	Willing and able to give full consent
Exclusion Criteria	
Pathology	Lumbar or cervical radiculopathy, systematic inflammatory disease, positive screen for diabetic neuropathy, neuropathic pain
Past medical history	Previous surgery or disease of the peripheral or central nervous system, sensory loss secondary to chemotherapy or radiotherapy, fibromyalgia, chronic fatigue syndrome
Cognitive ability	Cognitive or psychiatric disorder interfering with ability to fully consent or cooperate with assessment
Other treatment	Injection or physiotherapy treatment for knee joint within previous 3 months
Medication	Taking anti-depressant or anti-convulsant medication

Healthy controls

Healthy participants are defined as people with no current pain or chronic pain problems in the past year. Forty age and gender matched controls will be recruited from the general population, and from the staff and student population in University College Dublin. The controls will provide reference data for QST results and enable calculation of standardised *z* scores using the following formula: $z = (\text{value}_{\text{participant}} - \text{mean}_{\text{controls}}) / \text{standard deviation}_{\text{controls}}$. This allows comparison of QST results between controls and knee pain participants independent of the unit of measurement.[28]

Investigator

The principal investigator will be a senior physiotherapist with twelve years clinical experience. The same investigator will carryout all tests and is trained in using QST.

Recruitment procedure

A consecutive sample of knee osteoarthritis patients with moderate/severe knee pain will be recruited. Between June 2014 and July 2015 potentially eligible participants will be identified at musculoskeletal assessment clinics and from physiotherapy outpatient waiting lists. A feasible recruitment rate is estimated at 12 patients per month with recruitment continuing until the specified numbers are achieved. Those who agree to participate will attend for a baseline assessment prior to commencing physiotherapy treatment. Written informed consent will be obtained before enrolment in the study. Figure 1 represents the flow of participants through the study.

Physiotherapy management

Physiotherapy treatment will be in line with current clinical guidelines for the management of knee OA.[29] Treatment will typically involve between four and six physiotherapy appointments. In some cases treatment may take the format of a small group exercise intervention. A workshop led by the principal investigator will be held at each recruitment site prior to study commencement where physiotherapists will receive an update on clinical guidelines and current best evidence on management of knee OA. This will standardise treatment to some degree, but intervention will be individualised at the discretion of the treating physiotherapist and in consultation with the patient.

At each appointment the treating physiotherapist will record by means of a checklist the type and duration of treatment, patient adherence and any treatment side effects.

Assessment

Baseline assessment

A schematic view of the outcome measures recorded at baseline and follow up is presented in Table 2. Each baseline assessment will take approximately 50 minutes to complete at the physiotherapy clinic by the principal investigator. Some questionnaires will be posted and completed in advance by participants.

Follow up assessment

The primary endpoint will be at completion of physiotherapy treatment, this time point is estimated to be on average at 3 months. Physiotherapy administration staff will alert the principal investigator when a participant is discharged. Thereupon pain, disability and global rating of change will be assessed by means of a postal questionnaire. Information will also be recorded on use of co-interventions or change in medication for knee pain.

Six months after enrolment into the study participants will complete a postal questionnaire assessing pain and function. They will exit the study at this point.

Assessment procedures and minimising bias

In order to improve reliability of the assessment and minimise bias standardised assessment procedures will be followed. Studies support the reliability of QST measures where protocols are standardised and both the tester and participant are carefully instructed.[25] At each location testing will be undertaken in the same temperature controlled room by the same investigator, using a single set of testing

devices. Each session will begin by familiarising participants with standardised test procedures.[30,31] Physical testing will be performed prior to in-depth subjective assessment or without knowledge of questionnaire scores. Test order is important,[32], and a pre-determined sequence will be used beginning with non-noxious stimuli. CPM can induce a residual effect and will be the final test.[33] With bilateral symptoms the most painful knee will be selected, if both are equally symptomatic the right knee will be tested.

Table 2. Outcome measures and collection points

Domain	Variable	Instrument for Data Collection	Collection Points
Demographics	Age, Gender, Educational attainment, Employment status, Martial status	Baseline assessment questionnaire	Baseline
Pain	Self reported pain	WOMAC pain sub-scale	Baseline, post treatment*, 6 months
	Pain intensity	Numerical rating scale	Baseline, 6 months
	Location & quality	Knee Pain Map	Baseline
	Neuropathic pain symptoms	Modified PainDETECT	Baseline
	Characteristics of osteoarthritic pain	Intermittent and Constant Osteoarthritis Pain Instrument	Baseline
	Widespread pain	Body chart Manual tender point count	Baseline
Function	Self reported function	WOMAC function sub-scale	Baseline, post treatment, 6 months
Quality of life	Health related quality of life	EQ-5D 5L	Baseline
Central Sensitization Symptoms	Non-musculoskeletal central sensitization symptoms	Central Sensitization Inventory	Baseline
Quantatitive Sensory Testing	Light touch	Von Frey filaments	Baseline
	Vibration	Graded tuning fork	Baseline
	Pain pressure Thresholds	Pressure algometry	Baseline
	Dynamic allodynia Static allodynia	Brush stroke Von Frey Filaments	Baseline
	Thermal hyperalgesia	Thermo-rollers	Baseline
	Temporal summation	Repetitive mechanical stimuli with weighted pinprick	Baseline

	Conditioned pain modulation	Cold pressor test	Baseline
Confounding Variables	Obesity	Ratio of waist circumference to height	Baseline
	Depressive symptoms	Centre for Epidemiologic Studies Depression Scale	Baseline
	Comorbidities	Self Administered Comorbidity Questionnaire	Baseline
Management related variables	Treatment adherence	Sports Injury Rehabilitation Adherence Scale	During treatment
		Patient attendance ratio	During treatment
		Home Exercise Compliance Assessment	During treatment
	Treatment type and duration, Adverse effects	Therapist record sheet	During treatment
	Medication use and co-Interventions	Follow-up questionnaire	Post treatment, 6 months
Treatment outcome	Response to treatment	OARSI Responder Criteria; WOMAC pain and function subscales, global rating of change	Post treatment

* Post treatment assessment will be at approximately 3 months

Primary outcome measure

The main outcome is a positive response to physiotherapy treatment and this will be determined using a set of responder criteria by the Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI).[34] The criteria will be applied to the relevant data gathered at post treatment follow-up and identify 'responders' and 'non-responders' to physiotherapy. The responder criteria are summarised in Figure 2. For application of the criteria pain and function will be measured with the subscales of the Western Ontario and McMasters University Score Osteoarthritis Index (WOMAC LK 3.0). Validity and reliability of these subscales are well established, including for postal surveys.[35–37] Global rating of change will be measured with a 7-point Likert scale. This scale captures relevant change by asking the patient about any improvement or deterioration that has occurred with physiotherapy treatment.[38] Two points on the scale will represent a 20% improvement.

Secondary outcome measures

Pain assessment

The following valid and reliable measures of pain will be recorded; The Pain Intensity Numerical Rating Scale (Pain NRS) will measure participant's average pain intensity over the previous seven days.[39,40] The Knee Pain Map will be used to record more detailed information about the location and quality of knee pain.[41] Widespread pain is defined for this study according to the American College of Rheumatology classification criteria using pain drawings marked by participants on a body manikin.[42] Widespread pain is associated with more severe knee pain and functional decline.[43,44]

Pain and quality of life questionnaires

Modified PainDETECT (mPD-Q)

This questionnaire will record any neuropathic component to participants' symptoms. It has been previously used for the screening of neuropathic pain-like symptoms in knee OA in an elderly cohort.[45] Participants with more neuropathic pain-like symptoms (scores > 12/38) are more likely to have signs of central sensitisation.[46]

Intermittent and Constant Osteoarthritis Pain Instrument (ICOAP)

This validated questionnaire assesses various facets of both intermittent and constant pain for the knee, including effects on sleep and quality of life, degree of frustration and worry associated with the pain.[47] Two predictability items will be administered to capture unpredictable spontaneous pain, thought to have the greatest impact on participant well-being.[48]

Central Sensitization Inventory (CSI)

This self-report inventory has preliminary validity and reliability and assesses for symptoms not related to the musculoskeletal system but common to central sensitization syndromes.[49,50] Good sensitivity (81%) and specificity (79%) values were found with a cut-off score of 40 (out of 100) to identify patients with symptoms of central sensitization.[50]

EuroQoL EQ-5D

The EQ-5D is a frequently used generic quality of life instrument, designed by the EuroQoL group.[51] A modified form has been developed with an enlarged number of possible answers to avoid a ceiling effect.[52] The EQ-5D has acceptable reliability and validity when used in patients with knee OA.[53]

Quantitative Sensory Testing (QST)

QST is a psychophysiological measure of perception in response to external stimuli of controlled intensity.[31] This QST protocol will make reference to the well-established German Neuropathic Pain Consortium (DFNS) protocol,[31], and will utilise clinical QST methods recommended by the International Association for the Study of Pain.[30] This current study's assessment protocol aims to be more accessible using tools that are relatively inexpensive and adaptable to the clinical setting.[54]

Test sites used will be as follows; *Site 1*: On the medial or lateral knee joint line, depending where the patient indicates their greatest pain (3 cm medial to medial edge of patella or corresponding site laterally), *Site 2*: Over ipslateral tibialis anterior muscle (5 cm distal to the tibial tuberosity), *Site 3*: On the contralateral forearm (5 cm distal to lateral epicondyle of humerus on the volar aspect). Somatosensory abnormalities over the area of *Site 2* tibialis anterior are thought to provide evidence of spreading sensitisation from the symptomatic knee. Changes at *Site 3* would indicate more widespread sensitisation at a generalised level in the central nervous system.[9]

Light touch

Mechanical detection thresholds will be tested using a set of von Frey filaments (Opti-hair2-Set, Marstock, Germany). Monofilaments beginning with the smallest diameter will be applied to the skin. Light touch threshold (gm/mm^2) will be recorded as the last filament (gm/mm^2) that can be perceived. Test-retest reliability of this method for knee OA has been established.[28]

Mechanical allodynia

Dynamic mechanical allodynia will be assessed by lightly stroking the knee and forearm with a brush stroke three times (Senselab Brush No 5, Somedic). Static allodynia will be assessed using von Frey filaments. The presence of mechanical allodynia will be recorded if this non-noxious stimulation evokes a sensation of pain.[55]

Thermal hyperalgesia

Thermal rollers with predetermined temperatures of 25°C (cold) and 40°C (warm) (Senselab Rolltemp Somedic) will be used to detect thermal hyperalgesia at the forearm and knee.[54] Participants will be asked to report if the thermal sensation is perceived as painful when the rollers are passed lightly over the skin.

Vibration

Vibration detection threshold will be measured with a graded tuning fork (Rydel–Seiffer, 64 Hz) placed over 3 bony prominences (ulnar styloid, patella and medial malleolus). Vibration detection threshold is determined as a mean disappearance threshold of the vibrations on an 8/8 scale with the stimulus repeated three times.[31]

Pressure pain thresholds (PPTs)

Pressure will be applied using an electronic digital algometer with a probe size of 1 cm^2 (SomedicAB, Sweden) and an application rate of 30 kPa/s. The participant will be instructed to press an automatic cut off button when the first sensation of pressure pain is perceived. A cut-off point is set at 1000kPa. PPTs will be measured 3 times at the 3 test sites; the first measurement will be excluded and the mean of the last two measurements will be used for analysis. Test-retest reliability using this technique has been demonstrated in patients with knee OA.[56]

Mechanical temporal summation (TS)

The participant will assign a pain rating to a single stimulus by a weighted pinprick (MRC Systems 256 mN) and for a series of 10 pinprick stimuli of the same intensity (1/s applied within an area of 1 cm^2).[57] This procedure will be applied twice on a marked area the forearm and knee site. The mean pain rating of the pinprick trains minus the mean pain rating of the single stimuli will give a value for TS.[58,59]

Conditioned pain modulation (CPM)

The cold presser test is recommended for assessment of CPM in the clinical setting.[60,61] The test stimulus will be PPT; the conditioning stimulus will be cold immersion. PPTs will be recorded as outlined above. With the participant seated comfortably, the opposite arm to that used for PPT testing will be immersed in a bath of icy water (4°C monitored by thermometer) up to the elbow for 60 seconds. Participants unable to tolerate the water bath will rate their pain before withdrawing the arm (aim for at least 5 on NRS).[33] Re-testing of PPTs on the contralateral forearm will take place immediately after immersion. The PPT values after the CPT will be divided by PPTs recorded before the test. A value > 1 reflects an analgesic effect due to CPM.

Manual tender point examination

Tender points are typically identified according to the American College of Rheumatology criteria for fibromyalgia.[62] Points can be reliably identified by

application of pressure with the thumb pad of the tester's dominant hand to 18 designated sites for 4 seconds until 4 kg (450kPa) of pressure is achieved. Those points where pressure causes pain are summed to give a tender point total. Detecting tender points with digital palpation has good intra-rater reliability and is considered a useful clinical measure for deep tissue hyperalgesia.[63]

Confounding variables

Potentially confounding socio-demographic parameters, including sex, age, martial status, employment status and educational level will be recorded on a standardized form.[19,64,65] Obesity will be measured by recording participants' waist circumference to height ratio.[66]

Other factors known to predict poor outcome in knee OA or influence pain and disability will be accounted for including multiple comorbidities and depressive symptoms.[17] The Centre for Epidemiologic Studies Depression Scale (CES-D) is a valid and reliable measure of depression in community dwelling elderly and a score >16 is considered indicative of depressive symptoms.[67] For each of these variables the method of assessment is detailed in Table 2.

It is inconclusive if radiographic severity has an effect on clinical outcomes and a diagnosis of knee OA can be made clinically without radiographic evidence. For these reasons x-ray results will not be included in the analysis.[68]

Patient adherence

Patient adherence to treatment is thought to be an important determinant of clinical outcome in knee OA.[16,69] The physiotherapist will calculate an attendance ratio for each patient.[70,71] Additionally The Sports Injury Rehabilitation Adherence Scale (SIRAS) will be used to measure physiotherapists' perceptions of their patient's rehabilitation adherence at each clinic appointment. In addition to its proven psychometric properties, the SIRAS has been shown to be a reliable scale for use in clinical physiotherapy.[72] The Home Exercise Compliance Assessment (HECA) is a widely used self-report method of assessment to measure adherence. At each physiotherapy appointment participants will record the extent to which they adhered to home exercises and physical activity advice since their previous clinic appointment.[71]

Identifying and quantifying pain sensitization

Abnormal PPTs and TS have been previously used for identifying sub-groups of patients with widespread pain hypersensitivity.[5,73] Conditioned pain modulation is reflective of the endogenous inhibitory capacity of the nociceptive system and dysfunction of CPM is associated with conditions where central sensitization is a recognised hallmark.[74,75] Hypersensitivity to stimuli assessed at the painful knee reflects peripheral sensitization while hypersensitivity at a distant site is thought to be a consequence of central sensitization.[76] In knee OA joint it can be difficult to distinguish peripheral sensitization from central sensitization as knee OA symptoms are often reported bilaterally therefore testing a local and remote site is deemed appropriate.

Pain sensitization will therefore be operationalized by the presence of decreased PPTs and enhanced TS at local (knee) and remote (arm) sites in addition to dysfunctional CPM. Standardised *z*-scores for each of these 5 components will be computed for each participant, and compared to QST results from age and gender matched healthy controls. Where PPTs are decreased, TS is enhanced or CPM is dysfunctional in relation to control data points for pain sensitization will be allocated. The cut-off point for what is abnormal or sensitized will be determined when control data has been gathered and the spread or variability of 'normal' results is seen. Points will be summed to produce a pain sensitization score where a higher score will represent greater pain sensitization. This composite score can be used in the logistic regression model. Creation of a pain sensitization index involving amalgamation of QST data has been utilised in previous musculoskeletal research.[77,78]

Data analysis plan

Data will be analysed using SPSS v 20 (SPSS Inc., Chicago, IL). Descriptive statistics will be calculated for all outcome measures at baseline, including for all continuous variables, means, standard deviations, or medians with ranges of scores; and for categorical variables, frequencies and percentages.

Initial analyses will be exploratory to compare symptom profiles between people who respond to treatment and treatment non-responders. Treatment responders will be categorised by the OMERACT-OARSI responder criteria as described previously. Categorical variables will be analysed using chi-square tests. Multivariate analysis of variance (MANOVA) will be used to compare continuous normally distributed variables between responders and non-responders. The Kruskal-Wallis test will be used for comparison of variables that are not normally distributed. A *p* value of less

than 0.05 will be considered significant. In cases where data is missing a non-responder imputation will be applied (ie. baseline observation carried forwards). A sensitivity analysis will be carried out to assess if this changes the results.

A logistic regression model will be developed to predict response to physiotherapy treatment with 'treatment responder' as the dependant variable. The model will be adjusted for predetermined variables based on the previous literature (age, gender, obesity, socioeconomic status, depressive symptoms, treatment adherence, comorbidities and presence of widespread pain).[17,19,64,65] The pain sensitization score will be entered into the regression model as an independent variable.

Sample size

The sample size was calculated based on the number of explanatory variables planned for inclusion in the logistic regression model. It is intended to include 8 explanatory variables and allow 15 participants for each explanatory variable.[79] Recruiting 140 participants while allowing for a 20% loss to follow-up should ensure adequate numbers.

Dropouts

All participants will be followed up on discharge from physiotherapy. Patients who discontinued treatment will have the opportunity to provide follow-up data. Patients will be considered lost to follow-up if they do not complete the primary outcome measure post treatment.

ETHICS AND DISSEMINATION

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee (ref. no. 2013/11/Chair) and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee (ref. no. HOL/9414) and will be conducted in accordance with the Helsinki Declaration. Fully informed written consent will be obtained and patients incapable of giving full consent will not be recruited.

The study findings will be presented at national and international conferences and will be published in peer-reviewed journals.

DISCUSSION

To our knowledge this is the first study to examine the effects of pain sensitization on clinical outcomes in response to physiotherapy in patients with knee OA. The research is exploratory in nature and some limitations are outlined below.
For the purposes of this clinical research the term pain sensitization will be utilised however the lack of a widely accepted definition and criteria for identifying pain sensitization is acknowledged as a limitation.

The QST protocols originally developed for assessing neuropathic pain are lengthy.[31] However if somatosensory testing is to be incorporated into routine clinical practice it must be both time and cost-efficient.[32,86] This study will focus on tests to identify features of pain sensitivity based on their utility and practicality in the clinical setting. However these criteria necessitate the exclusion of certain tests, such as thermal pain thresholds, that are difficult to carrying out reliably in the clinical setting in a limited time frame.

The central concern of this study relates to alterations in pain processing and any potential relationship with poorer prognosis in knee OA. A range of clinical, psychological and socio-demographic predictors of poor outcome have been identified.[81–83] Incorporating all these variables is not feasible and would make for an unacceptably long participant assessment and complex analytical model. Nonetheless the most important predictor variables will be accounted for in the analysis.

This clinically based observational study does not aim to investigate the effects of specific physiotherapy treatments. It will observe people undergoing usual physiotherapy and variation in the intervention is to be expected. Nonetheless an attempt to standardise care to some degree will be made by using current evidence based guidelines and keeping a record of the physiotherapy intervention and adherence for each participant.

Recruiting the participant sample from the secondary care setting will limit the generalizability of study findings to patient populations in primary care. However including only patients from this subgroup is necessary in order to recruit a sufficient number of participants with moderate/severe symptoms.

The analyses reported in this study will be exploratory and generate rather than confirm hypotheses about pain sensitization and physiotherapy for knee OA. It is acknowledged that widespread pain hypersensitivity and somatosensory abnormalities can arise from a host of complex and interacting neurophysiological,

psychological and immunological processes.[20]

Given its relatively short follow-up period we cannot infer causality directly from our data with regard to pain sensitization and physiotherapy outcomes. Nonetheless it may point to a relationship worthy of further investigation in order to better understand pain mechanisms in knee OA and optimise physiotherapy outcomes in the future.

Footnotes

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Competing Interests The authors declare that they have no competing interests.

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Authors' Contributions HOL, CD, KS and NM assisted with the protocol design. CD, KS, NM and HOL procured the project funding. CB provided statistical advice. All authors provided feedback on drafts of the paper and approved the final manuscript.

Data Sharing Statement This is a study protocol submission.

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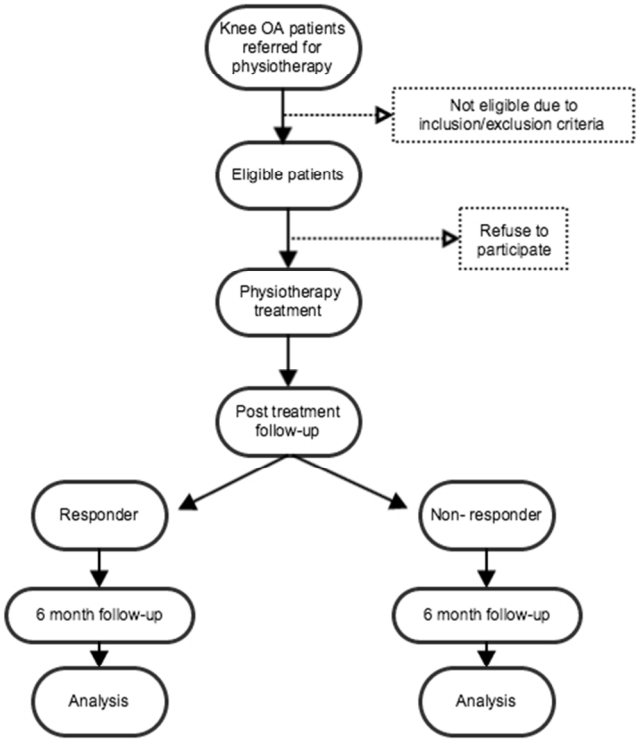
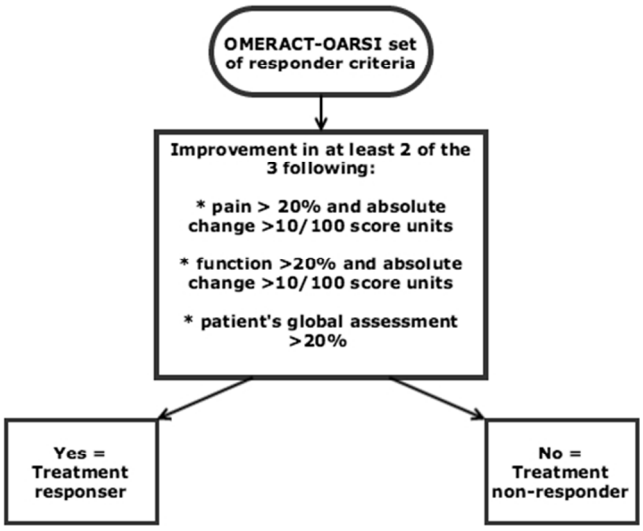
Figure Legends

Figure 1 Flow of participants through the study

Figure 2 Set of responder criteria [34]



"Flow of participants through the study"
264x208mm (72 x 72 DPI)



"Set of treatment responder criteria "
257x149mm (72 x 72 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 & 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6 & 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10, 11, 12, 13, 14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 2, 10, 11, 12, 13, 14
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15, 16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	15, 16
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	16
		(*d*) If applicable, explain how loss to follow-up was addressed	17
		(*e*) Describe any sensitivity analyses	17
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations			17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pain sensitization and the risk of poor outcome following physiotherapy for knee osteoarthritis: protocol for a prospective cohort study

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Pain sensitization and the risk of poor outcome following physiotherapy for knee osteoarthritis: protocol for a prospective cohort study

O'Leary H, Smart KM, Moloney NA, Blake C and Doody CM.

*Helen O'Leary, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: helen.oleary@ucdconnect.ie Telephone: 00 353 86 0665530

Keith M Smart, Physiotherapy Department, St Vincent's University Hospital, Elm Park, Dublin, Ireland.
Email: k.smart@svuh.ie

Niamh A Moloney, Discipline of Physiotherapy, Dept of Health Sciences, Macquarie University, NSW 2113, Australia.
Email: niamh.moloney@mq.edu.au

Catherine Blake, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: c.blake@ucd.ie

Catherine M Doody, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: c.doody@ucd.ie

*Corresponding author

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ABSTRACT

Introduction

Pain is the dominant symptom of knee osteoarthritis and recent evidence suggests factors outside of local joint pathology, such as pain sensitization, can contribute significantly to the pain experience. It is unknown how pain sensitization influences outcomes from commonly employed interventions such as physiotherapy.

The aims of this study are firstly to provide a comprehensive description of the somatosensory characteristics of people with pain associated with knee OA. Secondly, we will investigate if indicators of pain sensitization in patients with knee osteoarthritis are predictive of non-response to physiotherapy.

Methods and analysis

This is a multi-centre prospective cohort study with 140 participants. Eligible patients with moderate to severe symptomatic knee osteoarthritis will be identified at outpatient orthopaedic and rheumatology clinics. A baseline assessment will provide a comprehensive description of the somatosensory characteristics of each participant; by means of clinical examination, quantitative sensory testing and validated questionnaires measuring pain and functional capacity. Participants will then undergo physiotherapy treatment. The primary outcome will be non-response to physiotherapy on completion of the physiotherapy treatment programme as defined by the Osteoarthritis Research Society International (OARSI) treatment responder criteria.

Measures of pressure pain thresholds, temporal summation and conditioned pain modulation will be used to create a composite score of pain sensitization. Regression analyses will explore the relationship between responder status and pain sensitization while accounting for confounders.

Ethics and dissemination

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee. The results will be presented at international conferences and published in a peer review journal.

ARTICLE SUMMARY

Strengths and limitations of this study

To our knowledge this is the first study prospectively examining the effects of pain sensitization on physiotherapy outcomes.

Strengths of this proposed study include the relatively large sample for the comprehensive assessment procedure involved, the use of a broad range of validated measures to study pain processing and the gathering of our own reference QST data from healthy volunteers.

This study will focus on tests to identify features of pain sensitivity based on their utility and practicality in the clinical setting. However these criteria necessitate the exclusion of certain tests, such as thermal pain thresholds, that are difficult to carrying out reliably in the clinical setting in a limited time frame.

As this is a clinically based observational study there is likely to be variation in the duration and type of physiotherapy interventions. The findings of this research may identify clinical and psychophysiological variables predictive of a poor response to physiotherapy that might usefully inform subsequent studies aimed at targeting such variables in an attempt to optimise patients' outcomes.

INTRODUCTION

Knee osteoarthritis (OA) is a prevalent joint disease that causes a huge burden of pain, disability and loss of productivity worldwide.[1–3] With ageing populations and increasing obesity, the prevalence of OA is rising, thus its timely and effective management is a priority within healthcare.[3,4]

The pathophysiology of knee OA pain is complex. Altered processing of nociceptive inputs at peripheral, spinal and higher brain centers may help explain discrepancies between pain severity and the degree of structural and pathological abnormalities in OA.[5–7] Central sensitization is described as an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input,[8] and can manifest clinically as general pain hypersensitivity.[9] Furthermore, peripheral pro-inflammatory mediators and neuropeptides in knee OA can sensitize nociceptors in the affected knee, lowering their threshold for activation.[10] This increased responsiveness of nociceptive neurons is referred to as peripheral sensitization.[8]

Both peripheral and central sensitization, clinically referred to as pain sensitization, can contribute to painful knee OA. Pain sensitization may be useful as a clinical construct to alert clinicians to patients with a potentially upregulated nociceptive state and is proposed to contribute to an enhanced, persistent and more widespread pain response.[11] Recent studies in knee OA have found the presence of increased pain sensitivity at remote sites, enhanced temporal summation (TS) and hypersensitivity to various stimuli to be associated with reports of more severe symptoms.[5,6,12] However these cross-sectional studies linking features of sensitization to greater levels of pain and disability do not explore if pain sensitivity has any prognostic implications.

There is also some evidence to suggest increased pain sensitivity negatively affects treatment outcomes. In painful musculoskeletal conditions such as shoulder impingement and lateral epicondylalgia widespread pressure pain sensitivity and thermal hyperalgesia, have been linked with a poorer prognosis.[13,14] Surgical outcomes for knee osteoarthritis may also be affected, with the presence of increased pain sensitivity prior to total knee replacement associated with more persistent pain after surgery.[15,16]

Although joint replacement is considered an effective treatment for end-stage knee OA, the majority of patients are managed conservatively. Physiotherapy is the widely recommended conservative treatment approach for knee OA.[17] Existing studies of prognosis in knee OA have focused on demographic and psychological variables.[18–20] Whilst it has been suggested that central pain processing may contribute significantly to the clinical pain experience in some people with knee OA[21], no longitudinal studies have explored the potentially negative prognostic impact of pain sensitization on outcomes in response to physiotherapy. In whiplash associated disorders the presence of sensory hypersensitivity and cold hyperalgesia has been shown to reduce the likelihood of a positive response to physiotherapy treatment.[22] Thus it is conceivable, but currently unproven, that knee OA patients with evidence of pain sensitization have poorer outcomes following physiotherapy.

One obstacle to investigating the implications of pain sensitization is reliably identifying it in the clinical setting. Due to the complexity of pain mechanisms it is inadvisable to rely on any single test to reflect peripheral and central pain mechanisms.[23,24] A multi-tissue assessment using a multi-modal stimuli approach has been advocated,[25], and will be adopted in this study. Three constructs will be combined into a single score encompassing key features of pain sensitization previously identified in knee OA patients. [6,11,26] Composite pain sensitivity scores have recently been used to investigate its association with clinical characteristics. Our study will be the first to prospectively explore the effect of pain sensitization on clinical outcomes.

This study will investigate the extent to which (a composite measure of) pain sensitization predicts non-response to physiotherapy in patients with knee OA. Identifying clinical and psychophysical features of pain sensitization in knee OA predictive of a poor response to physiotherapy might help inform the management of such patients. It may invite clinicians to consider additional or alternative interventions aimed at reducing such pain sensitization and optimise outcomes.

Study aims

The main aims of the study are; firstly to provide a comprehensive description of the somatosensory characteristics of people with pain associated with knee OA (by means of quantitative sensory testing (QST), and validated questionnaires measuring pain, functional capacity and quality of life) and secondly, to investigate if the presence of pain sensitization at baseline is predictive of non-response to physiotherapy treatment as defined by treatment responder criteria.

We hypothesise that the presence of pain sensitization will predict a non-response to physiotherapy treatment compared to patients without evidence of pain sensitization.

METHODS AND ANALYSIS

Study design

A multi-centre observational cohort study with assessments at baseline, post-treatment and at six months will be conducted. Following the baseline assessment for features of pain sensitization all participants will receive usual physiotherapy care. The relationship between pain sensitization and outcomes in terms of pain and disability will be explored through regression analysis.

Setting

The study will be undertaken in the physiotherapy outpatient departments of three large publicly funded university teaching hospitals in Dublin, Ireland.

Participants

Patients with symptomatic knee OA,[27], referred for physiotherapy treatment by a hospital consultant or clinical specialist physiotherapist will be eligible for inclusion. Full details of inclusion/exclusion criteria are summarised in Table 1.

At the time of recruitment knee pain must be the participant's primary musculoskeletal complaint for which they are seeking treatment, and physiotherapy must be the main treatment being undertaken over the study period. Participants recruited at physiotherapy led musculoskeletal assessment clinics will be screened for eligibility by the clinical specialist physiotherapist. The principal investigator will screen patients on the physiotherapy waiting list over the telephone.

Table 1. Study inclusion and exclusion criteria

Inclusion Criteria	
Diagnosis	Knee osteoarthritis based on American College of Rheumatology clinical criteria [27] and confirmed by radiographic findings
Age	Over 50 years
Pain duration	Knee pain for at least 6 months
Severity	Pain ≥ 5/10 on Numerical Rating Scale
Medication	Willing to abstain from simple analgesics and NSAIDs for 24 hours prior to testing

Consent	Willing and able to give full consent
Exclusion Criteria	
Pathology	Lumbar or cervical radiculopathy, systematic inflammatory disease, positive screen for diabetic neuropathy, neuropathic pain
Past medical history	Previous surgery or disease of the peripheral or central nervous system, sensory loss secondary to chemotherapy or radiotherapy, fibromyalgia, chronic fatigue syndrome
Cognitive ability	Cognitive or psychiatric disorder interfering with ability to fully consent or cooperate with assessment
Other treatment	Injection or physiotherapy treatment for knee joint within previous 3 months
Medication	Taking anti-depressant or anti-convulsant medication

Healthy controls

Healthy participants are defined as people with no current pain or chronic pain problems in the past year. Forty age and gender matched controls will be recruited from the general population, and from the staff and student population in University College Dublin. The controls will provide reference data for QST results.

Investigator

The principal investigator, (HOL) collecting all baseline and follow-up data, will be a senior physiotherapist with twelve years clinical experience. The same investigator will carryout all tests and is trained in using QST.

Recruitment procedure

A consecutive sample of knee OA patients with moderate/severe knee pain (defined as self-reported pain of ≥ 5 on an 11-point numerical rating scale) will be recruited. Between June 2014 and July 2015 potentially eligible participants will be identified at musculoskeletal assessment clinics and from physiotherapy outpatient waiting lists. A feasible recruitment rate is estimated at 12 patients per month with recruitment continuing until the specified numbers are achieved. Those who agree to participate will attend for an assessment prior to commencing physiotherapy treatment. Written informed consent will be obtained before enrolment in the study. Figure 1 represents the flow of participants through the study.

Physiotherapy management

Physiotherapy treatment will be in line with current clinical guidelines for the management of knee OA.[28] Treatment will typically involve between four and six physiotherapy appointments. In some cases treatment may take the format of a small group exercise intervention. A workshop led by the principal investigator will be held at each recruitment site prior to study commencement where physiotherapists will receive an update on clinical guidelines and current best evidence on management of knee OA. This will standardise treatment to some degree, but intervention will be individualised at the discretion of the treating physiotherapist and in consultation with the patient.

Assessment

Baseline assessment

A schematic view of the outcome measures recorded at baseline and follow up is presented in Table 2. Each assessment will take approximately one hour to complete. Some questionnaires will be posted and completed in advance by participants.

Follow up assessment

The primary endpoint will be at completion of physiotherapy treatment, this time point is estimated to be on average at 3 months. Physiotherapy administration staff will alert the principal investigator when a participant is discharged. Thereupon pain, disability and global rating of change will be assessed by means of a postal questionnaire. Information will also be recorded on use of co-interventions or any change in medication for knee pain. This follow-up questionnaire will be administered 1 week of discharge from physiotherapy.

Six months after enrolment into the study, participants will complete a postal questionnaire assessing pain and function. They will exit the study at this point.

Assessment procedures and minimising bias

Studies support the reliability of QST measures where protocols are standardised and both the tester and participant are carefully instructed.[25] Standardised assessment procedures will be followed in this study. At each location testing will be undertaken in the same temperature controlled room by the same investigator, using a single set of testing devices. Each session will begin by familiarising participants with standardised test procedures.[29,30] Physical testing will be performed by the investigator prior to in-depth subjective assessment or without knowledge of questionnaire scores. Test order is important,[31], and a pre-determined sequence

will be used beginning with non-noxious stimuli. CPM can induce a residual effect and will be the final test.[32] With bilateral symptoms the most painful knee will be selected, if both are equally symptomatic the right knee will be tested. Where shoulder pain is present unilaterally the opposite forearm will be used for testing.

Table 2. Outcome measures and collection points

Domain	Variable	Instrument for Data Collection	Collection Points
Demographics	Age, Gender, Educational attainment, Employment status, Martial status	Baseline assessment questionnaire	Baseline
Pain	Self reported pain	WOMAC pain sub-scale	Baseline, post treatment*, 6 months
	Pain intensity	Numerical rating scale	Baseline, 6 months
	Location & quality	Knee Pain Map	Baseline
	Neuropathic pain symptoms	Modified PainDETECT	Baseline
	Characteristics of osteoarthritic pain	Intermittent and Constant Osteoarthritis Pain Instrument	Baseline
	Widespread pain	Body chart Manual tender point count	Baseline
Function	Self reported function	WOMAC function sub-scale	Baseline, post treatment, 6 months
Quality of life	Health related quality of life	EQ-5D 5L	Baseline
Central Sensitization Symptoms	Non-musculoskeletal central sensitization symptoms	Central Sensitization Inventory	Baseline
Quantatitive Sensory Testing	Light touch	Von Frey filaments	Baseline
	Vibration	Graded tuning fork	Baseline
	Pain pressure thresholds	Pressure algometry	Baseline
	Dynamic allodynia Static allodynia	Brush stroke Von Frey Filaments	Baseline
	Thermal hyperalgesia	Thermo-rollers	Baseline
	Temporal summation	Repetitive mechanical stimuli with weighted pinprick	Baseline
	Conditioned pain modulation	Cold pressor test	Baseline
Confounding Variables	Obesity	Ratio of waist circumference to height	Baseline
	Depressive symptoms	Centre for Epidemiologic	Baseline

		Studies Depression Scale	
	Comorbidities	Self Administered Comorbidity Questionnaire	Baseline
Management related variables	Treatment adherence	Sports Injury Rehabilitation Adherence Scale	During treatment
		Patient attendance ratio	During treatment
		Home Exercise Compliance Assessment	During treatment
	Treatment type and duration, Adverse effects	Therapist record sheet	During treatment
	Medication use and co-Interventions	Follow-up questionnaire	Post treatment, 6 months
Treatment outcome	Response to treatment	OARSI Responder Criteria; WOMAC pain and function subscales, global rating of change	Post treatment

* Post treatment assessment will be at approximately 3 months

Primary outcome variable

The main outcome is response to physiotherapy treatment and this will be determined using a set of responder criteria by the Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI).[33] Non-response to physiotherapy will be the designated categorical dependent variable upon which the subsequent regression analyses will be based.

The responder criteria will be applied to the relevant data gathered at post treatment follow-up and are summarised in Figure 2. For application of these criteria pain and function will be measured with the subscales of the Western Ontario and McMasters University Score Osteoarthritis Index (WOMAC LK 3.0). Validity and reliability of these subscales are well established, including for postal surveys.[34–36] Global rating of change will be measured with a 7-point Likert scale. This scale captures relevant change by asking the patient about any improvement or deterioration that has occurred with physiotherapy treatment.[37] Two points on the scale represents a 20% improvement.

Secondary outcome variables

Pain assessment

The following valid and reliable measures of pain will be recorded; The Pain Intensity Numerical Rating Scale (Pain NRS) will measure participant's average pain intensity

over the previous seven days.[38,39] The Knee Pain Map will be used to record more detailed information about the location and quality of knee pain.[40] Widespread pain is defined for this study according to the American College of Rheumatology classification criteria using pain drawings marked by participants on a body manikin.[41] Widespread pain is associated with more severe knee pain and functional decline.[42,43]

Pain and quality of life questionnaires

Modified PainDETECT (mPD-Q)

This questionnaire will record any neuropathic component to participants' symptoms. It has been previously used for the screening of neuropathic pain-like symptoms in knee OA in an elderly cohort.[44] Participants with more neuropathic pain-like symptoms (scores > 12/38) are more likely to have signs of central sensitisation.[45]

Intermittent and Constant Osteoarthritis Pain Instrument (ICOAP)

This validated questionnaire assesses various facets of both intermittent and constant pain for the knee, including effects on sleep and quality of life, degree of frustration and worry associated with the pain.[46] Two predictability items will be administered to capture unpredictable spontaneous pain, thought to have the greatest impact on participant well-being.[47]

Central Sensitization Inventory (CSI)

This self-report inventory has preliminary validity and reliability and assesses for symptoms not related to the musculoskeletal system but common to central sensitization syndromes.[48,49] Good sensitivity (81%) and specificity (79%) values were found with a cut-off score of 40 (out of 100) to identify patients with symptoms of central sensitization.[49]

EuroQoL EQ-5D

The EQ-5D is a frequently used generic quality of life instrument, designed by the EuroQoL group.[50] A modified form has been developed with an enlarged number of possible answers to avoid a ceiling effect.[51] The EQ-5D has acceptable reliability and validity when used in patients with knee OA.[52]

Quantitative Sensory Testing (QST)

QST is a psychophysiological measure of perception in response to external stimuli of controlled intensity.[30] This QST protocol will make reference to the well-

established German Neuropathic Pain Consortium (DFNS) protocol,[30], and will utilise clinical QST methods recommended by the International Association for the Study of Pain.[29] This current study's assessment protocol aims to be more accessible using tools that are relatively inexpensive and adaptable to the clinical setting.[53] Test sites used will be as follows; *Site 1*: On the medial or lateral knee joint line, depending where the patient indicates their greatest pain (3 cm medial to medial edge of patella or corresponding site laterally), *Site 2*: Over ipslateral tibialis anterior muscle (5 cm distal to the tibial tuberosity), *Site 3*: On the contralateral forearm (5 cm distal to lateral epicondyle of humerus on the volar aspect). Somatosensory abnormalities over the area of *Site 2* tibialis anterior are thought to provide evidence of spreading sensitization from the symptomatic knee. Changes at *Site 3* could indicate more widespread sensitization at a generalised level in the central nervous system,[11], although this can not be concluded definitively as other explanations for abnormal QST results outside the knee are also possible, for example patients with knee OA frequently have multi-site pain.[42]

Light touch

Mechanical detection thresholds will be tested using a set of von Frey filaments (Opti-hair2-Set, Marstock, Germany). Monofilaments beginning with the smallest diameter will be applied to the skin. Light touch threshold (gm/mm^2) will be recorded as the last filament (gm/mm^2) that can be perceived. Test-retest reliability of this method for knee OA has been established.[54]

Mechanical allodynia

Dynamic mechanical allodynia will be assessed by lightly stroking the knee and forearm with a brush stroke three times (Senselab Brush No 5, Somedic). Static allodynia will be assessed using von Frey filaments. The presence of mechanical allodynia will be recorded if this non-noxious stimulation evokes a sensation of pain.[55]

Thermal hyperalgesia

Thermal rollers with predetermined temperatures of 25°C (cold) and 40°C (warm) (Senselab Rolltemp Somedic) will be used to detect thermal hyperalgesia at the forearm and knee.[53] Participants will be asked to report if the thermal sensation is perceived as painful when the rollers are passed lightly over the skin.

Vibration

Vibration detection threshold will be measured with a graded tuning fork (Rydel–Seiffer, 64 Hz) placed over 3 bony prominences (ulnar styloid, patella and medial malleolus). Vibration detection threshold is determined as a mean disappearance threshold of the vibrations on an 8/8 scale with the stimulus repeated three times.[30]

Pressure pain thresholds (PPTs)

Pressure will be applied using an electronic digital algometer with a probe size of 1 cm^2 (SomedicAB, Sweden) and an application rate of 30 kPa/s. The participant will be instructed to press an automatic cut off button when the first sensation of pressure pain is perceived. A cut-off point is set at 1000kPa. PPTs will be measured 3 times at the 3 test sites; the first measurement will be excluded and the mean of the last two measurements will be used for analysis. Test-retest reliability using this technique has been demonstrated in patients with knee OA.[56]

Mechanical temporal summation (TS)

The participant will assign a pain rating to a single stimulus by a weighted pinprick (MRC Systems 256 mN) and for a series of 10 pinprick stimuli of the same intensity (1/s applied within an area of 1 cm^2).[57] This procedure will be applied twice on a marked area the forearm and knee site. The mean pain rating of the pinprick trains minus the mean pain rating of the single stimuli will give a value for TS.[58,59]

Conditioned pain modulation (CPM)

The cold presser test is recommended for assessment of CPM in the clinical setting.[60,61] The test stimulus will be PPT, while the conditioning stimulus will be cold immersion. PPTs will be recorded as outlined above. With the participant seated comfortably, the opposite arm to that used for PPT testing will be immersed in a bath of icy water (4°C monitored by thermometer) up to the elbow for 60 seconds. Participants unable to tolerate the water bath will rate their pain before withdrawing the arm (aim for at least 5 on NRS).[32] Re-testing of PPTs on the contralateral forearm will take place immediately after immersion. The PPT values after the cold pressor test will be divided by PPTs recorded before the test. A value of < 1 will be taken to reflect pain facilitation due to an inefficient CPM response.

Manual tender point examination

Tender points are typically identified according to the American College of Rheumatology criteria for fibromyalgia.[62] Points can be reliably identified by application of pressure with the thumb pad of the tester's dominant hand to 18

designated sites for 4 seconds until 4 kg (450kPa) of pressure is achieved. Those points where pressure causes pain are summed to give a tender point total. Detecting tender points with digital palpation has good intra-rater reliability and is considered a useful clinical measure for deep tissue hyperalgesia.[63]

Patient adherence

Patient adherence to treatment is thought to be an important determinant of clinical outcome in knee OA.[17,64] The physiotherapist will calculate an attendance ratio for each patient.[65,66] Additionally The Sports Injury Rehabilitation Adherence Scale (SIRAS) will be used to measure physiotherapists' perceptions of their patient's rehabilitation adherence at each clinic appointment. In addition to its proven psychometric properties, the SIRAS has been shown to be a reliable scale for use in clinical physiotherapy.[67] The Home Exercise Compliance Assessment (HECA) is a widely used self-report method of assessment to measure adherence. At each physiotherapy appointment participants will record the extent to which they adhered to home exercises and physical activity advice since their previous clinic appointment.[66]

Confounding variables

Potentially confounding socio-demographic parameters, including age, gender, martial status, employment status and educational level will be recorded on a standardized form.[20,68,69] Obesity will be measured by recording participants' waist circumference to height ratio.[70]

Other factors known to predict poor outcome in knee OA or influence pain and disability will be accounted for including multiple comorbidities and depressive symptoms.[18] The Centre for Epidemiologic Studies Depression Scale (CES-D) is a valid and reliable measure of depression in community dwelling elderly and a score >16 is considered indicative of depressive symptoms.[71] For each of these variables the method of assessment is detailed in Table 2.

The presence of widespread pain is another potential confounder,[42] however it could also be a mediator between pain sensitization and QST measures such as lowered PPTs remotely. For this reason the regression model will not be adjusted for this variable.

Radiographic severity of knee OA is poorly correlated with self-reported pain and pain sensitization. [5,6] For these reasons x-ray results will not be included in the analysis.[72]

Defining pain sensitization

In order to describe the somatosensory characteristics z-scores will be calculated for individual OA patients. The control group will provide reference data for QST results and enable calculation of a standardised *z*-score using the following formula: $z = (value_{participant} - mean_{controls}) / standard\ deviation_{controls}$. [30] Calculating the z-score for each QST modality and body site facilitates the comparison of QST results with healthy control subjects independent of the unit of measure. Any z-score outside the 10^{th} and 90^{th} percentile (or 1.28 standard deviations of the mean) is classified as abnormal.

Abnormal PPTs and TS have been previously used for identifying sub-groups of patients with widespread pain hypersensitivity.[5,73] Conditioned pain modulation is reflective of the endogenous inhibitory capacity of the nociceptive system and dysfunction of CPM is associated with conditions where central sensitization is a recognised hallmark.[74,75] Pain sensitization will therefore be operationalized using five QST results; PPTs (forearm and knee), TS (forearm and knee) and CPM. Abnormally decreased PPTs will be determined by the cut-off point described above. For an individual to be classified as having enhanced TS their absolute score needs to be > 1. For CPM a facilitatory response (where the calculated ratio is < 1) will be classified as an 'abnormal' or dysfunctional. Where PPTs are abnormally decreased, TS is enhanced or CPM is dysfunctional a single data point for each component will be allocated. The points from these 5 components will be summed to produce a pain sensitization score, where a higher score (maximum of 5) will represent greater pain sensitization. This composite score will be used in the logistic regression model. Creation of a pain sensitization score involving amalgamation of QST data has been utilised in previous musculoskeletal research.[76,77]

Data Analysis Plan

To address the first aim descriptive statistics will be calculated for all outcome measures at baseline, including for all continuous variables, means, standard deviations, or medians with ranges of scores; and for categorical variables, frequencies and percentages. In summarising descriptive QST data, z-score calculations and cut-off points will determine the prevalence of somatosensory

abnormalities in pressure pain thresholds, mechanical detection threshold, and vibration threshold. Somatosensory abnormalities such as allodynia or thermal hyperalgesia will be classified as either present or absent.

Initial analyses for the second aim will be exploratory to compare symptom profiles between people who respond to treatment and treatment non-responders. These will be categorised by the OMERACT-OARSI responder criteria as described previously. Categorical variables will be analysed using chi-square tests. Multivariate analysis of variance (MANOVA) will be used to compare continuous normally distributed variables between responders and non-responders, and from this variables associated with responder status will be identified. The Mann Whitney test will be used for comparison of variables that are not normally distributed. In cases where data is missing multiple imputations will be applied. A sensitivity analysis will be carried out to assess if this changes the results. A logistic regression model will be developed to predict non-response to physiotherapy treatment with 'treatment non-responder' (yes/no) as the dependant variable. Variables will be chosen for inclusion in the first model iteration if they are found to be associated with non-responder status in uni-variate analysis with a threshold of $p<0.05$, or if their inclusion is supported by previous literature. The model will be adjusted for predetermined variables such as age, gender, obesity, socioeconomic status, depressive symptoms, treatment adherence and comorbidities.[18,20,68,69] The pain sensitization score will be entered into the regression model as an independent variable. It is anticipated that the regression model will accommodate a maximum of 7 variables with statistical significance accepted if $p<0.05$. The best fitting and most parsimonious model will be selected as the final iteration and cross validation of the predictive model will be performed.[78] A secondary sub-analysis will explore the ability of some individual QST modalities to predict non-response to physiotherapy if entered into the regression model as single variables.

Data will be analysed using SPSS v 20 (SPSS Inc., Chicago, IL) and R v 3.0.2.

Sample size

The sample size is calculated based on the number of anticipated explanatory variables planned for inclusion in the logistic regression model. It is expected that a maximum of 7 explanatory variables will be included and 10 cases i.e. non-responders will be allowed for each explanatory variable.[79] It is estimated that 60% of patients will be classified as non-responders to physiotherapy by the OMERACT-

OARSI criteria.[80] Recruiting 140 participants while allowing for a 15% loss to follow-up should ensure adequate numbers.

Dropouts

All participants will be followed up on discharge from physiotherapy. Patients who discontinued treatment will have the opportunity to provide follow-up data. Patients will be considered lost to follow-up if they do not complete the primary outcome measure post treatment.

ETHICS AND DISSEMINATION

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee (ref. no. 2013/11/Chair) and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee (ref. no. HOL/9414) and will be conducted in accordance with the Helsinki Declaration. Fully informed written consent will be obtained and patients incapable of giving full consent will not be recruited.
The study findings will be presented at national and international conferences and will be published in peer-reviewed journals.

DISCUSSION

To our knowledge this is the first study to examine the effects of pain sensitization on clinical outcomes in response to physiotherapy in patients with knee OA. The research is exploratory in nature and some limitations are outlined below. For the purposes of this clinical research the term pain sensitization will be utilised however the lack of a widely accepted definition and criteria for identifying pain sensitization is acknowledged as a limitation.

This study will use TS and CPM responses as indicators of pain sensitization, however it is recognised that enhanced TS and dysfunctional CPM also occur in healthy populations,[59,61] and due to the natural variability in responses there is a likelihood of capturing false positives. To account for this only those falling outside the 10^{th} and 90^{th} percentile will be categorised as 'abnormal' and no individual QST modality will be used as a stand-alone measure of pain sensitization.

The QST protocols originally developed for assessing neuropathic pain are lengthy.[30] However if somatosensory testing is to be incorporated into routine clinical practice it must be both time and cost-efficient.[81] This study will focus on tests to identify features of pain sensitivity based on their utility and practicality in the

clinical setting. However these criteria necessitate the exclusion of certain tests, such as thermal pain thresholds, that are difficult to carrying out reliably in the clinical setting in a limited time frame.

The central concern of this study relates to alterations in pain processing and any potential relationship with poorer prognosis in knee OA. A range of clinical, psychological and socio-demographic predictors of poor outcome have been identified.[82–84] Incorporating all these variables is not feasible and would make for an unacceptably long participant assessment and complex analytical model. Nonetheless the most important predictor variables will be accounted for in the analysis.

This clinically based observational study does not aim to investigate the effects of specific physiotherapy treatments. It will observe people undergoing usual physiotherapy and variation in the intervention is to be expected. Nonetheless an attempt to standardise care to some degree will be made by using current evidence based guidelines and keeping a record of the physiotherapy intervention and adherence for each participant.

Recruiting the participant sample from the secondary care setting will limit the generalizability of study findings to patient populations in primary care. However including only patients from this subgroup is necessary in order to recruit a sufficient number of participants with moderate/severe symptoms.

The analyses reported in this study will be exploratory and generate rather than confirm hypotheses about pain sensitization and physiotherapy for knee OA. It is acknowledged that widespread pain hypersensitivity and somatosensory abnormalities can arise from a host of complex and interacting neurophysiological, psychological and immunological processes.[21]

Given its relatively short follow-up period we cannot infer causality directly from our data with regard to pain sensitization and physiotherapy outcomes. Nonetheless it may point to a relationship worthy of further investigation in order to better understand pain mechanisms in knee OA and optimise physiotherapy outcomes in the future.

FOOTNOTES

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Data sharing statement It is the intention of the study group, that once the study is completed, and the research articles arising from the study have been published, any data that is fully anonymised and not sensitive would be made open access. However because this intention was not declared in the original ethical applications this action would be subject to approval by the relevant research ethics committees.

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Figure Legends

Figure 1 Flow of participants through the study

Figure 2 Set of responder criteria [33]

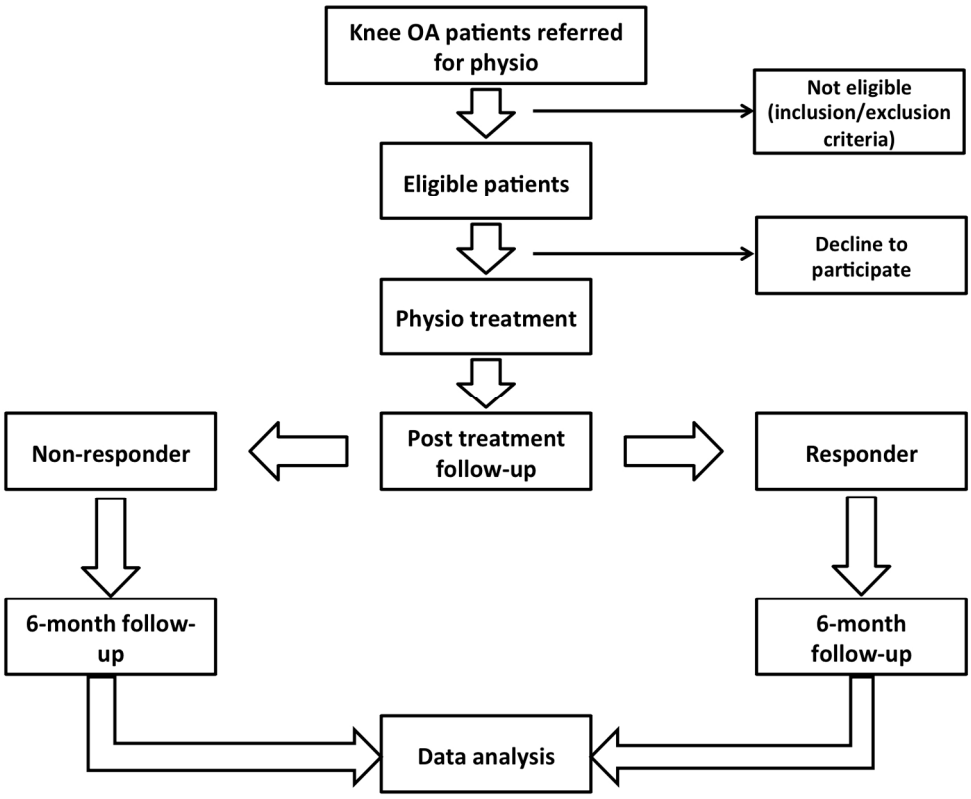

Figure 1 Flow of participants through the study

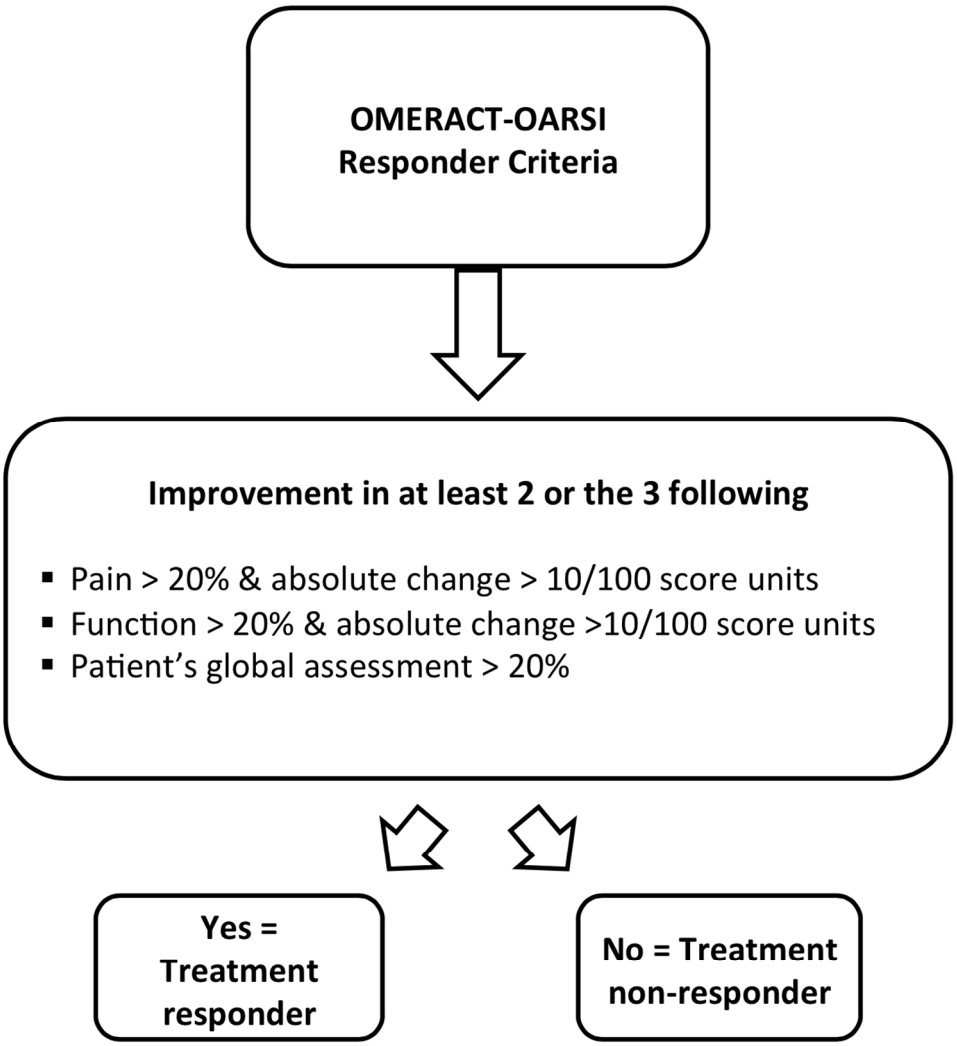

Figure 2 Set of treatment responder criteria [33]

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 & 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6 & 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10, 11, 12, 13, 14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 2, 10, 11, 12, 13, 14
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15, 16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	15, 16
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	16
		(*d*) If applicable, explain how loss to follow-up was addressed	17
		(*e*) Describe any sensitivity analyses	17
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations			17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pain sensitization and the risk of poor outcome following physiotherapy for patients with moderate to severe knee osteoarthritis: protocol for a prospective cohort study

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Pain sensitization and the risk of poor outcome following physiotherapy for patients with moderate to severe knee osteoarthritis: protocol for a prospective cohort study

O'Leary H, Smart KM, Moloney NA, Blake C and Doody CM.

*Helen O'Leary, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: helen.oleary@ucdconnect.ie Telephone: 00 353 86 0665530

Keith M Smart, Physiotherapy Department, St Vincent's University Hospital, Elm Park, Dublin, Ireland.
Email: k.smart@svuh.ie

Niamh A Moloney, Discipline of Physiotherapy, Dept of Health Sciences, Macquarie University, NSW 2113, Australia.
Email: niamh.moloney@mq.edu.au

Catherine Blake, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: c.blake@ucd.ie

Catherine M Doody, School of Public Health, Physiotherapy and Population Science, University College Dublin, Dublin, Ireland.
Email: c.doody@ucd.ie

*Corresponding author

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ABSTRACT

Introduction

Pain is the dominant symptom of knee osteoarthritis and recent evidence suggests factors outside of local joint pathology, such as pain sensitization, can contribute significantly to the pain experience. It is unknown how pain sensitization influences outcomes from commonly employed interventions such as physiotherapy.

The aims of this study are firstly to provide a comprehensive description of the somatosensory characteristics of people with pain associated with knee OA. Secondly, we will investigate if indicators of pain sensitization in patients with knee osteoarthritis are predictive of non-response to physiotherapy.

Methods and analysis

This is a multi-centre prospective cohort study with 140 participants. Eligible patients with moderate to severe symptomatic knee osteoarthritis will be identified at outpatient orthopaedic and rheumatology clinics. A baseline assessment will provide a comprehensive description of the somatosensory characteristics of each participant; by means of clinical examination, quantitative sensory testing and validated questionnaires measuring pain and functional capacity. Participants will then undergo physiotherapy treatment. The primary outcome will be non-response to physiotherapy on completion of the physiotherapy treatment programme as defined by the Osteoarthritis Research Society International (OARSI) treatment responder criteria.

A principal component analysis will identify measures related to pain sensitization to include in the predictive model. Regression analyses will explore the relationship between responder status and pain sensitization while accounting for confounders.

Ethics and dissemination

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee. The results will be presented at international conferences and published in a peer review journal.

ARTICLE SUMMARY

Strengths and limitations of this study

To our knowledge this is the first study prospectively examining the effects of pain sensitization on physiotherapy outcomes.

Strengths of this proposed study include the relatively large sample for the comprehensive assessment procedure involved, the use of a broad range of validated measures to study pain processing and the gathering of our own reference QST data from healthy volunteers.

This study will focus on tests to identify features of pain sensitivity based on their utility and practicality in the clinical setting. However these criteria necessitate the exclusion of certain tests, such as thermal pain thresholds, that are difficult to carrying out reliably in the clinical setting in a limited time frame.

As this is a clinically based observational study there is likely to be variation in the duration and type of physiotherapy interventions. The findings of this research may identify clinical and psychophysiological variables predictive of a poor response to physiotherapy that might usefully inform subsequent studies aimed at targeting such variables in an attempt to optimise patients' outcomes.

INTRODUCTION

Knee osteoarthritis (OA) is a prevalent joint disease that causes a huge burden of pain, disability and loss of productivity worldwide.[1–3] With ageing populations and increasing obesity, the prevalence of OA is rising, thus its timely and effective management is a priority within healthcare.[3,4]

The pathophysiology of knee OA pain is complex. Altered processing of nociceptive inputs at peripheral, spinal and higher brain centers may help explain discrepancies between pain severity and the degree of structural and pathological abnormalities in OA.[5–7] Central sensitization is described as an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.[8] It can have widespread effects such general pain hypersensitivity while other regional manifestations of central sensitization include spread of pain sensitivity to normal tissue, an exaggerated response to a noxious stimulus and pain after the end of a stimulus. [9] Furthermore, peripheral pro-inflammatory mediators and neuropeptides in knee OA can sensitize nociceptors in the affected knee, lowering their threshold for activation.[10] This increased responsiveness of nociceptive neurons is referred to as peripheral sensitization.[8]

Both peripheral and central sensitization, clinically referred to as pain sensitization, can contribute to painful knee OA. Pain sensitization may be useful as a clinical construct to alert clinicians to patients with a potentially upregulated nociceptive state and is proposed to contribute to an enhanced, persistent and more widespread pain response.[11] Recent studies in knee OA have found the presence of increased pain sensitivity at remote sites, enhanced temporal summation (TS) and hypersensitivity to various stimuli to be associated with reports of more severe symptoms.[5,6,12] However these cross-sectional studies linking features of sensitization to greater levels of pain and disability do not explore if pain sensitivity has any prognostic implications.

There is also some evidence to suggest increased pain sensitivity negatively affects treatment outcomes. In painful musculoskeletal conditions such as shoulder impingement and lateral epicondylalgia widespread pressure pain sensitivity and thermal hyperalgesia, have been linked with a poorer prognosis.[13,14] Surgical outcomes for knee osteoarthritis may also be affected, with the presence of increased pain sensitivity prior to total knee replacement associated with more persistent pain after surgery.[15,16]

Although joint replacement is considered an effective treatment for end-stage knee OA, the majority of patients are managed conservatively. Physiotherapy is the widely recommended conservative treatment approach for knee OA.[17] Existing studies of prognosis in knee OA have focused on demographic and psychological variables.[18–20] Whilst it has been suggested that central pain processing may contribute significantly to the clinical pain experience in some people with knee OA[21], no longitudinal studies have explored the potentially negative prognostic impact of pain sensitization on outcomes in response to physiotherapy. In whiplash associated disorders the presence of sensory hypersensitivity and cold hyperalgesia has been shown to reduce the likelihood of a positive response to physiotherapy treatment.[22] Thus it is conceivable, but currently unproven, that knee OA patients with evidence of pain sensitization have poorer outcomes following physiotherapy.

One obstacle to investigating the implications of pain sensitization is reliably identifying it in the clinical setting. Due to the complexity of pain mechanisms it is inadvisable to rely on any single test to reflect peripheral and central pain mechanisms.[23,24] A multi-tissue assessment using a multi-modal stimuli approach has been advocated,[25], and will be adopted in this study. The association between key features of pain sensitization and clinical characteristics in knee OA have been previously investigated. Our study will be the first to prospectively explore the effect of key features of pain sensitization on physiotherapy outcomes in knee OA.

This study will investigate the extent to which pain sensitization predicts non-response to physiotherapy in patients with knee OA. Identifying clinical and psychophysical features of pain sensitization in knee OA predictive of a poor response to physiotherapy might help inform the management of such patients. It may encourage clinicians to consider additional or alternative interventions aimed at reducing such pain sensitization and optimise outcomes.

Study aims

The main aims of the study are; firstly to provide a comprehensive description of the somatosensory characteristics of people with pain associated with knee OA (by means of quantitative sensory testing (QST), and validated questionnaires measuring pain, functional capacity and quality of life) and secondly, to investigate if the presence of pain sensitization at baseline is predictive of non-response to physiotherapy treatment as defined by treatment responder criteria.

We hypothesise that the presence of pain sensitization will predict a non-response to physiotherapy treatment compared to patients without evidence of pain sensitization.

METHODS AND ANALYSIS

Study design

A multi-centre observational cohort study with assessments at baseline, post-treatment and at six months will be conducted. Following the baseline assessment for features of pain sensitization all participants will receive usual physiotherapy care. The relationship between pain sensitization and outcomes in terms of pain and disability will be explored through regression analysis.

Setting

The study will be undertaken in the physiotherapy outpatient departments of three large publicly funded university teaching hospitals in Dublin, Ireland.

Participants

Patients with symptomatic knee OA referred for physiotherapy treatment by a hospital consultant or clinical specialist physiotherapist will be eligible for inclusion. Full details of inclusion/exclusion criteria are summarised in Table 1.

At the time of recruitment knee pain must be the participant's primary musculoskeletal complaint for which they are seeking treatment, and physiotherapy must be the main treatment being undertaken over the study period. Participants recruited at physiotherapy led musculoskeletal assessment clinics will be screened for eligibility by the clinical specialist physiotherapist. The principal investigator will screen patients on the physiotherapy waiting list over the telephone.

Table 1. Study inclusion and exclusion criteria

Inclusion Criteria	
Diagnosis	Knee osteoarthritis based on American College of Rheumatology clinical criteria [26] and confirmed by radiographic findings
Age	Over 50 years
Pain duration	Knee pain for at least 6 months
Severity	Average pain over past week rated as moderate or severe by the patient
Medication	Willing to abstain from simple analgesics, NSAIDs, weak opioids or

	medications that combine these, for 24 hours prior to testing
Consent	Willing and able to give full consent
Exclusion Criteria	
Pathology	Lumbar or cervical radiculopathy, systematic inflammatory disease, positive screen for diabetic neuropathy, neuropathic pain
Past medical history	Previous surgery or disease of the peripheral or central nervous system, sensory loss secondary to chemotherapy or radiotherapy, fibromyalgia, chronic fatigue syndrome
Cognitive ability	Cognitive or psychiatric disorder interfering with ability to fully consent or cooperate with assessment
Other treatment	Injection or physiotherapy treatment for knee joint within previous 3 months
Medication	Taking anti-depressant or anti-convulsant medication, strong opioids

Healthy controls

Healthy participants are defined as people with no current pain or chronic pain problems in the past year. Forty age and gender matched controls will be recruited. Controls aged 50 to 65 years will be recruited mainly from the staff and student population of University College Dublin while pain-free controls aged 65 to 80+ years will be recruited from the general population. Recruitment will be purposive in order to fill the quotas in terms of age and gender. The controls will provide reference data for QST results.

Investigator

The principal investigator, (HOL) collecting all baseline and follow-up data, will be a senior physiotherapist with twelve years clinical experience. The same investigator will carryout all tests and is trained in using QST.

Recruitment procedure

A consecutive sample of knee OA patients with moderate/severe knee pain will be recruited. Between October 2014 and September 2015 potentially eligible participants will be identified at musculoskeletal assessment clinics and from physiotherapy outpatient waiting lists. A feasible recruitment rate is estimated at 12 patients per month with recruitment continuing until the specified numbers are achieved. Potential participants will be screened over the telephone and asked to choose a categorical pain descriptor (mild/moderate/severe). Patients who rate their symptoms as mild (average symptoms over the past week) will be excluded. Those

who meet the other inclusion criteria will be asked to attend for an assessment prior to commencing physiotherapy treatment. Written informed consent will be obtained before enrolment in the study. Figure 1 represents the flow of participants through the study.

Physiotherapy management

Physiotherapy treatment will be in line with current clinical guidelines for the management of knee OA.[27] Treatment will typically involve between four and six physiotherapy appointments. In some cases treatment may take the format of a small group exercise intervention. A workshop led by the principal investigator will be held at each recruitment site prior to study commencement where physiotherapists will receive an update on clinical guidelines and current best evidence on management of knee OA. This will standardise treatment to some degree, but intervention will be individualised at the discretion of the treating physiotherapist and in consultation with the patient.

Assessment

Baseline assessment

A schematic view of the outcome measures recorded at baseline and follow up is presented in Table 2. Each assessment will take approximately one hour to complete. Some questionnaires will be posted and completed in advance by participants.

Follow up assessment

The primary endpoint will be at completion of physiotherapy treatment, this time point is estimated to be on average at 3 months. Physiotherapy administration staff will alert the principal investigator when a participant is discharged. Thereupon pain, disability and global rating of change will be assessed by means of a postal questionnaire. Information will also be recorded on use of co-interventions or any change in medication for knee pain. This follow-up questionnaire will be administered 1 week of discharge from physiotherapy.

Six months after enrolment into the study, participants will complete a postal questionnaire assessing pain and function. They will exit the study at this point.

Assessment procedures and minimising bias

Studies support the reliability of QST measures where protocols are standardised and both the tester and participant are carefully instructed.[25] Standardised

assessment procedures will be followed in this study. At each location testing will be undertaken in the same temperature controlled room by the same investigator, using a single set of testing devices. Each session will begin by familiarising participants with standardised test procedures.[28,29] Physical testing will be performed by the investigator prior to in-depth subjective assessment or without knowledge of questionnaire scores. Test order is important,[30], and a pre-determined sequence will be used beginning with non-noxious stimuli. CPM can induce a residual effect and will be the final test.[31] With bilateral symptoms the most painful knee will be selected, if both are equally symptomatic the right knee will be tested. Where shoulder pain is present unilaterally the opposite forearm will be used for testing.

Table 2. Outcome measures and collection points

Domain	Variable	Instrument for Data Collection	Collection Points
Demographics	Age, Gender, Educational attainment, Employment status, Martial status	Baseline assessment questionnaire	Baseline
Pain	Self reported pain	WOMAC pain sub-scale	Baseline, post treatment*, 6 months
	Pain intensity	Numerical rating scale	Baseline, 6 months
	Location & quality	Knee Pain Map	Baseline
	Neuropathic pain symptoms	Modified PainDETECT	Baseline
	Characteristics of osteoarthritic pain	Intermittent and Constant Osteoarthritis Pain Instrument	Baseline
	Widespread pain	Body chart Manual tender point count	Baseline
Function	Self reported function	WOMAC function sub-scale	Baseline, post treatment, 6 months
Quality of life	Health related quality of life	EQ-5D 5L	Baseline
Central Sensitization Symptoms	Non-musculoskeletal central sensitization symptoms	Central Sensitization Inventory	Baseline
Quantatitive Sensory Testing	Light touch	Von Frey filaments	Baseline
	Vibration	Graded tuning fork	Baseline
	Pain pressure thresholds	Pressure algometry	Baseline
	Dynamic allodynia Static allodynia	Brush stroke Von Frey Filaments	Baseline

	Thermal hyperalgesia	Thermo-rollers	Baseline
	Temporal summation	Repetitive mechanical stimuli with weighted pinprick	Baseline
	Conditioned pain modulation	Cold pressor test (conditioning stimulus) and PPTs (test stimulus)	Baseline
Confounding Variables	Obesity	Ratio of waist circumference to height	Baseline
	Depressive symptoms	Centre for Epidemiologic Studies Depression Scale	Baseline
	Comorbidities	Self Administered Comorbidity Questionnaire	Baseline
Management related variables	Treatment adherence	Sports Injury Rehabilitation Adherence Scale	During treatment
		Patient attendance ratio	During treatment
		Home Exercise Compliance Assessment	During treatment
	Treatment type and duration, Adverse effects	Therapist record sheet	During treatment
	Medication use and co-Interventions	Follow-up questionnaire	Post treatment, 6 months
Treatment outcome	Response to treatment	OARSI Responder Criteria; WOMAC pain and function subscales, global rating of change	Post treatment

* Post treatment assessment will be at approximately 3 months

Primary outcome variable

The main outcome is response to physiotherapy treatment and this will be determined using a set of responder criteria by the Outcome Measures in Rheumatology - Osteoarthritis Research Society International (OMERACT-OARSI).[32] Non-response to physiotherapy will be the designated categorical dependent variable upon which the subsequent regression analyses will be based.

The responder criteria will be applied to the relevant data gathered at post treatment follow-up and are summarised in Figure 2. For application of these criteria pain and function will be measured with the subscales of the Western Ontario and McMasters University Score Osteoarthritis Index (WOMAC LK 3.0). Validity and reliability of these subscales are well established, including for postal surveys.[33–35] Global rating of change will be measured with a 7-point Likert scale. This scale captures relevant change by asking the patient about any improvement or deterioration that

has occurred with physiotherapy treatment.[36] Two points on the scale represents a 20% improvement.

Secondary outcome variables

Pain assessment

The following valid and reliable measures of pain will be recorded; The Pain Intensity Numerical Rating Scale (Pain NRS) will measure participant's average pain intensity over the previous seven days.[37,38] The Knee Pain Map will be used to record more detailed information about the location and quality of knee pain.[39] Widespread pain is defined for this study according to the American College of Rheumatology classification criteria using pain drawings marked by participants on a body manikin.[40] Widespread pain is associated with more severe knee pain and functional decline.[41,42]

Pain and quality of life questionnaires

Modified PainDETECT (mPD-Q)

This questionnaire will record any neuropathic component to participants' symptoms. It has been previously used for the screening of neuropathic pain-like symptoms in knee OA in an elderly cohort.[43] Participants with more neuropathic pain-like symptoms (scores > 12/38) are more likely to have signs of central sensitisation.[44]

Intermittent and Constant Osteoarthritis Pain Instrument (ICOAP)

This validated questionnaire assesses various facets of both intermittent and constant pain for the knee, including effects on sleep and quality of life, degree of frustration and worry associated with the pain.[45] Two predictability items will be administered to capture unpredictable spontaneous pain, thought to have the greatest impact on participant well-being.[46]

Central Sensitization Inventory (CSI)

This self-report inventory has preliminary validity and reliability and assesses for symptoms not related to the musculoskeletal system but common to central sensitization syndromes.[47,48] Good sensitivity (81%) and specificity (79%) values were found with a cut-off score of 40 (out of 100) to identify patients with symptoms of central sensitization.[48]

EuroQoL EQ-5D

The EQ-5D is a frequently used generic quality of life instrument, designed by the EuroQoL group.[49] A modified form has been developed with an enlarged number of possible answers to avoid a ceiling effect.[50] The EQ-5D has acceptable reliability and validity when used in patients with knee OA.[51]

Quantitative Sensory Testing (QST)

QST is a psychophysiological measure of perception in response to external stimuli of controlled intensity.[29] This QST protocol will make reference to the well-established German Neuropathic Pain Consortium (DFNS) protocol,[29], and will utilise clinical QST methods recommended by the International Association for the Study of Pain.[28] This current study's assessment protocol aims to be more accessible using tools that are relatively inexpensive and adaptable to the clinical setting.[52] Test sites used will be as follows; *Site 1*: On the medial or lateral knee joint line, depending where the patient indicates their greatest pain (3 cm medial to medial edge of patella or corresponding site laterally), *Site 2*: Over ipsilateral tibialis anterior muscle (5 cm distal to the tibial tuberosity), *Site 3*: On the contralateral forearm (5 cm distal to lateral epicondyle of humerus on the volar aspect). Somatosensory abnormalities over the area of *Site 2* tibialis anterior are thought to provide evidence of spreading sensitization from the symptomatic knee. Changes at *Site 3* could indicate more widespread sensitization at a generalised level in the central nervous system,[11], although this can not be concluded definitively as other explanations for abnormal QST results outside the knee are also possible, for example patients with knee OA frequently have multi-site pain.[41]

Light touch

Mechanical detection thresholds will be tested using a set of von Frey filaments (Opti-hair2-Set, Marstock, Germany). Monofilaments beginning with the smallest diameter will be applied to the skin. Light touch threshold (gm/mm^2) will be recorded as the last filament (gm/mm^2) that can be perceived. Test-retest reliability of this method for knee OA has been established.[53]

Mechanical allodynia

Dynamic mechanical allodynia will be assessed by lightly stroking the knee and forearm with a brush stroke three times (Senselab Brush No 5, Somedic). Static allodynia will be assessed using von Frey filaments. The presence of mechanical allodynia will be recorded if this non-noxious stimulation evokes a sensation of pain.[54]

Thermal hyperalgesia

Thermal rollers with predetermined temperatures of 25°C (cold) and 40°C (warm) (Senselab Rolltemp Somedic) will be used to detect thermal hyperalgesia at the forearm and knee.[52] Participants will be asked to report if the thermal sensation is perceived as painful when the rollers are passed lightly over the skin.

Vibration

Vibration detection threshold will be measured with a graded tuning fork (Rydel–Seiffer, 64 Hz) placed over 3 bony prominences (ulnar styloid, patella and medial malleolus). Vibration detection threshold is determined as a mean disappearance threshold of the vibrations on an 8/8 scale with the stimulus repeated three times.[29]

Pressure pain thresholds (PPTs)

Pressure will be applied using an electronic digital algometer with a probe size of 1 cm^2 (SomedicAB, Sweden) and an application rate of 30 kPa/s. The participant will be instructed to press an automatic cut off button when the first sensation of pressure pain is perceived. A cut-off point is set at 1000kPa. PPTs will be measured 3 times at the 3 test sites; the first measurement will be excluded and the mean of the last two measurements will be used for analysis. Test-retest reliability using this technique has been demonstrated in patients with knee OA.[55]

Mechanical temporal summation (TS)

The participant will assign a pain rating to a single stimulus by a weighted pinprick (MRC Systems 256 mN) and estimate an overall pain rating for a series of 10 pinprick stimuli of the same intensity (1/s applied within an area of 1 cm^2).[29] This procedure will be applied twice on a marked area at the forearm and knee site. To get a value for TS the mean pain rating of the two pinprick trains will be calculated minus the mean pain rating of the two single stimuli ~~will give a value for TS~~.[56]

Conditioned pain modulation (CPM)

The cold presser test is recommended for assessment of CPM in the clinical setting.[57,58] The test stimulus will be PPTs, while the conditioning stimulus will be cold immersion. PPTs will be recorded as outlined above. With the participant seated comfortably, the opposite arm to that used for PPT testing will be immersed in a bath of icy water (4°C monitored by thermometer) up to the elbow for 60 seconds. Participants unable to tolerate the water bath will rate their pain before withdrawing

the arm (aim for at least 5 on NRS).[31,57] Re-testing of PPTs on the contralateral forearm will take place immediately after immersion. The PPT values after the cold pressor test will be divided by PPTs recorded before the test. A value of ≤ 1 will be taken to reflect no CPM effect.

Manual tender point examination

Tender points are typically identified according to the American College of Rheumatology criteria for fibromyalgia.[59] Points can be reliably identified by application of pressure with the thumb pad of the tester's dominant hand to 18 designated sites for 4 seconds until 4 kg (450kPa) of pressure is achieved. Those points where pressure causes pain are summed to give a tender point total. Detecting tender points with digital palpation has good intra-rater reliability and is considered a useful clinical measure for deep tissue hyperalgesia.[60]

Patient adherence

Patient adherence to treatment is thought to be an important determinant of clinical outcome in knee OA.[17,61] The physiotherapist will calculate an attendance ratio for each patient.[62,63] Additionally The Sports Injury Rehabilitation Adherence Scale (SIRAS) will be used to measure physiotherapists' perceptions of their patient's rehabilitation adherence at each clinic appointment. In addition to its proven psychometric properties, the SIRAS has been shown to be a reliable scale for use in clinical physiotherapy.[64] The Home Exercise Compliance Assessment (HECA) is a widely used self-report method of assessment to measure adherence. At each physiotherapy appointment participants will record the extent to which they adhered to home exercises and physical activity advice since their previous clinic appointment.[63]

Confounding variables

Potentially confounding socio-demographic parameters, including age, gender, martial status, employment status and educational level will be recorded on a standardized form.[20,65,66] Obesity will be measured by recording participants' waist circumference to height ratio.[67]

Other factors known to predict poor outcome in knee OA or influence pain and disability will be accounted for including multiple comorbidities and depressive symptoms.[18] The Centre for Epidemiologic Studies Depression Scale (CES-D) is a valid and reliable measure of depression in community dwelling elderly and a score

>16 is considered indicative of depressive symptoms.[68] For each of these variables the method of assessment is detailed in Table 2.

The presence of widespread pain is another potential confounder,[41] however it could also be a mediator between pain sensitization and QST measures such as lowered PPTs remotely. For this reason the regression model will not be adjusted for this variable.

Radiographic severity of knee OA is poorly correlated with self-reported pain and pain sensitization. [5,6] For these reasons x-ray results will not be included in the analysis.[69]

Data Analysis Plan

In order to describe the somatosensory characteristics z-scores will be calculated for individual OA patients. The control group will provide reference data for QST results and enable calculation of a standardised *z*-score using the following formula: $z = (\text{value}_{\text{participant}} - \text{mean}_{\text{controls}}) / \text{standard deviation}_{\text{controls}}$. [29] Calculating the z-score for each QST modality and body site facilitates the comparison of QST results with healthy control subjects independent of the unit of measure. For data analysis where cut-off points are required z-scores outside the 10^{th} and 90^{th} percentile (or 1.28 standard deviations of the mean) will be classified as abnormal.

To address the first aim descriptive statistics will be calculated for all outcome measures at baseline, including for all continuous variables, means, standard deviations, or medians with ranges of scores; and for categorical variables, frequencies and percentages. In summarising descriptive QST data, z-score calculations and cut-off points will determine the prevalence of somatosensory abnormalities in pressure pain thresholds, mechanical detection threshold, and vibration threshold. Somatosensory abnormalities such as allodynia or cold hyperalgesia will be classified as either present or absent.

Initial analyses for the second aim will be exploratory to compare symptom profiles between people who respond to treatment and treatment non-responders. These will be categorised by the OMERACT-OARSI responder criteria as described previously. Categorical variables will be analysed using chi-square tests. Multivariate analysis of variance (MANOVA) will be used to compare continuous normally distributed variables between responders and non-responders, and from this variables associated with responder status will be identified. The Mann Whitney test will be

used for comparison of variables that are not normally distributed. In cases where data is missing multiple imputations will be applied. A sensitivity analysis will be carried out to assess if this changes the results.

A principal component analysis (PCA) will be used to determine which variables relating to sensitization (light touch, vibration, allodynia, cold hyperalgesia, PPT arm, PPT knee, PPT tibia, TS arm, TS knee, CPM) to include in the predictive model.[70] PCA may facilitate data reduction as some variables related to pain sensitization may be highly correlated while some sensory modalities may represent distinct individual dimensions of pain perception.[71] Prior to conducting PCA the suitability of the data for this type of analysis will need to be assessed. Components with an eigenvalue > 1.0 from PCA will be subsequently entered into the regression model investigating predictive factors for non-response to physiotherapy.

A logistic regression model will be developed to predict non-response to physiotherapy treatment with 'treatment non-responder' (yes/no) as the dependant variable. Variables will be chosen for inclusion in the first model iteration if they are found to be associated with non-responder status in uni-variate analysis with a threshold of $p<0.05$, or if their inclusion is supported by previous literature. The model will be adjusted for predetermined variables such as age, gender, socioeconomic status, depressive symptoms, treatment adherence and comorbidities.[18,20,65,66] Results of the principal component analysis will be entered into the regression model. It is anticipated that the regression model will accommodate a maximum of 7 variables with statistical significance accepted if $p<0.05$. The best fitting and most parsimonious model will be selected as the final iteration and cross validation of the predictive model will be performed.[72] A secondary sub-analysis will explore the ability of some individual QST modalities to predict non-response to physiotherapy if entered into the regression model as single variables.

Data will be analysed using SPSS v 20 (SPSS Inc., Chicago, IL) and R v 3.0.2.

Sample size

The sample size is calculated based on the number of anticipated explanatory variables planned for inclusion in the logistic regression model. It is expected that a maximum of 7 explanatory variables will be included and 10 cases i.e. non-responders will be allowed for each explanatory variable.[73] It is estimated that 60% of patients will be classified as non-responders to physiotherapy by the OMERACT-

OARSI criteria.[74] Recruiting 140 participants while allowing for a 15% loss to follow-up should ensure adequate numbers.

Dropouts

All participants will be followed up on discharge from physiotherapy. Patients who discontinued treatment will have the opportunity to provide follow-up data. Patients will be considered lost to follow-up if they do not complete the primary outcome measure post treatment.

ETHICS AND DISSEMINATION

This study has been approved by St. James's Hospital/AMNCH Research Ethics Committee (ref. no. 2013/11/Chair) and by the St. Vincent's Healthcare Group Ethics and Medical Research Committee (ref. no. HOL/9414) and will be conducted in accordance with the Helsinki Declaration. Fully informed written consent will be obtained and patients incapable of giving full consent will not be recruited.
The study findings will be presented at national and international conferences and will be published in peer-reviewed journals.

DISCUSSION

To our knowledge this is the first study to examine the effects of pain sensitization on clinical outcomes in response to physiotherapy in patients with knee OA. The research is exploratory in nature and some limitations are outlined below. For the purposes of this clinical research the term pain sensitization will be utilised however the lack of a widely accepted definition and criteria for identifying pain sensitization is acknowledged as a limitation.

It is recognised that some experimental pain modalities such as enhanced TS and facilitatory CPM are often interpreted as hallmarks of pain sensitization but these can also occur in healthy populations.[56,58] It is important to acknowledge ~~due to~~ this natural variability in responses and the likelihood of these tests capturing false positives. To account for this no individual QST modality will be used as a stand-alone measure of pain sensitization and QST results will be compared to normative data.

The QST protocols originally developed for assessing neuropathic pain are lengthy.[29] However if somatosensory testing is to be incorporated into routine clinical practice it must be both time and cost-efficient.[52,75] This study will focus on

tests to identify features of pain sensitivity based on their utility and practicality in the clinical setting. However these criteria necessitate the exclusion of certain tests, such as thermal pain thresholds, that are difficult to carrying out reliably in the clinical setting in a limited time frame.

The central concern of this study relates to alterations in pain processing and any potential relationship with poorer prognosis in knee OA. A range of clinical, psychological and socio-demographic predictors of poor outcome have been identified.[76–78] Incorporating all these variables is not feasible and would make for an unacceptably long participant assessment and complex analytical model. Nonetheless the most important predictor variables will be accounted for in the analysis.

This clinically based observational study does not aim to investigate the effects of specific physiotherapy treatments. It will observe people undergoing usual physiotherapy and variation in the intervention is to be expected. Nonetheless an attempt to standardise care to some degree will be made by using current evidence based guidelines and keeping a record of the physiotherapy intervention and adherence for each participant.

Recruiting the participant sample from the secondary care setting will limit the ability to generalise the study findings to patient populations in primary care. The generalizability is further limited by only including patients with moderate or severe knee symptoms. This limitation was deemed necessary in order to include sufficient numbers of patients likely to have features of sensitization, as we know pain sensitization is related to pain intensity.[5] Furthermore optimising management in secondary care is a priority; this is where Irish patients usually access not just physiotherapy services but more invasive treatments such as joint injection or surgery.

The analyses reported in this study will be exploratory and generate rather than confirm hypotheses about pain sensitization and physiotherapy for knee OA. It is acknowledged that widespread pain hypersensitivity and somatosensory abnormalities can arise from a host of complex and interacting neurophysiological, psychological and immunological processes.[21]

Given its relatively short follow-up period we cannot infer causality directly from our data with regard to pain sensitization and physiotherapy outcomes. Nonetheless it may point to a relationship worthy of further investigation in order to better

understand pain mechanisms in knee OA and optimise physiotherapy outcomes in the future.

FOOTNOTES

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Data sharing statement It is the intention of the study group, that once the study is completed, and the research articles arising from the study have been published, any data that is fully anonymised and not sensitive would be made open access. However because this intention was not declared in the original ethical applications this action would be subject to approval by the relevant research ethics committees.

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Figure Legends

Figure 1 Flow of participants through the study

Figure 2 Set of responder criteria [32]

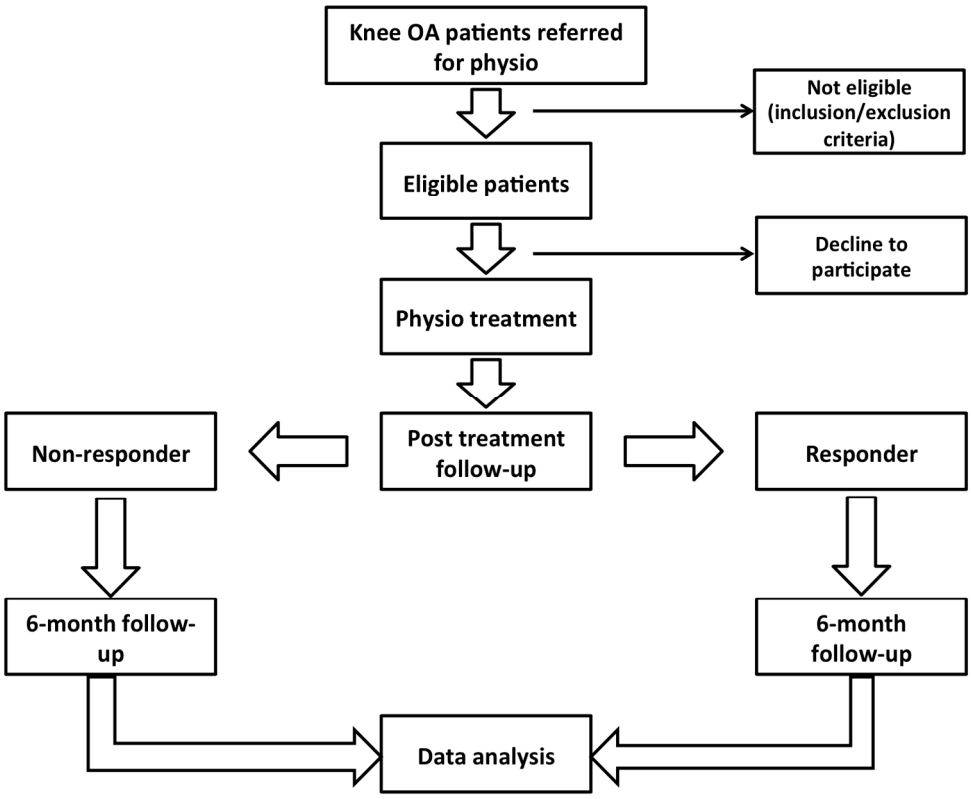

Figure 1 Flow of participants through the study

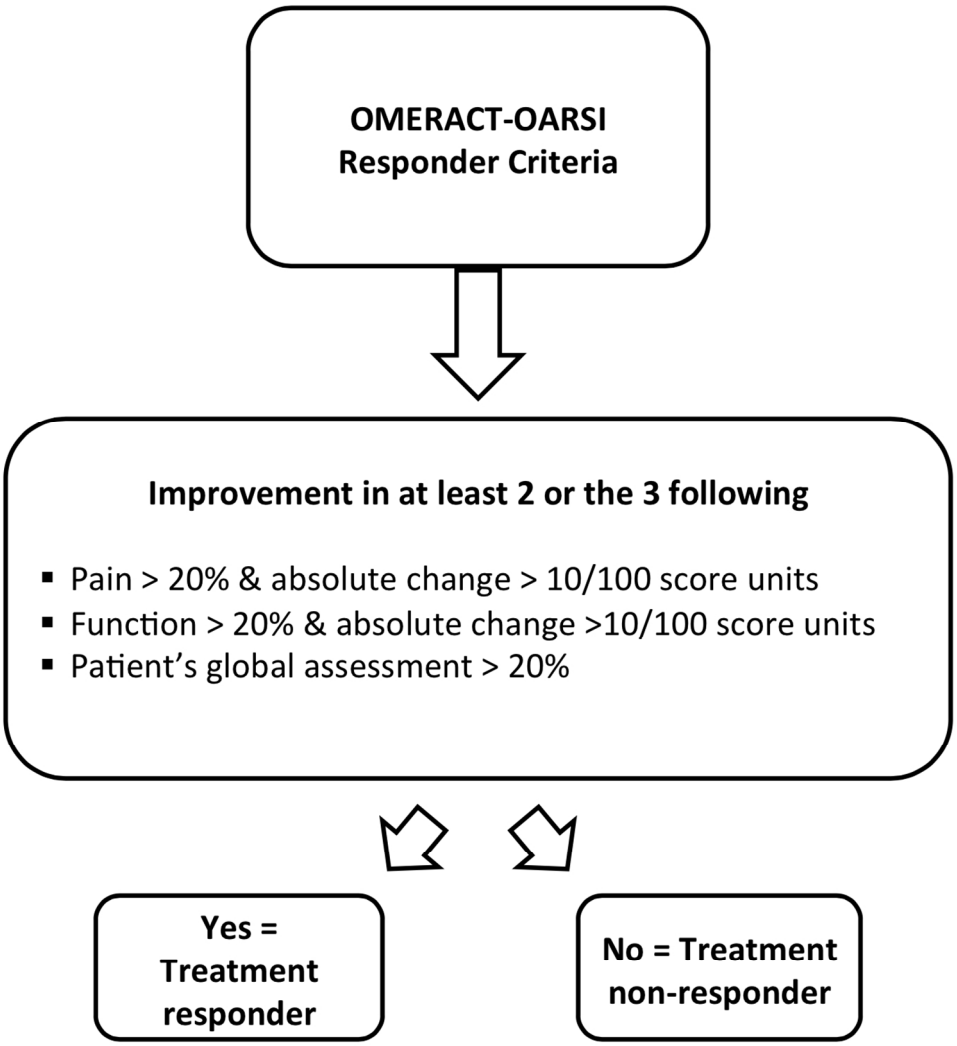

Figure 2 Set of treatment responder criteria [33]

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4 & 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6 & 7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9, 10, 11, 12, 13, 14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table 2, 10, 11, 12, 13, 14
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	15, 16
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	15, 16
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	16
		(*d*) If applicable, explain how loss to follow-up was addressed	17
		(*e*) Describe any sensitivity analyses	17
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations			17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.