



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Quantitative sensory testing as an assessment tool to predict the response to standard pain treatment in knee osteoarthritis

a systematic review and meta-analysis

Petersen, Kristian Kjær-Staal; Kilic, Kübra; Hertel, Emma; Sejersgaard-Jacobsen, Trine Hyttel; Jørgensen, Marlene Kanstrup; Troelsen, Anders; Arendt-Nielsen, Lars; Boye Larsen, Dennis

Published in:
Pain Reports

DOI (link to publication from Publisher):
[10.1097/pr9.0000000000001079](https://doi.org/10.1097/pr9.0000000000001079)

Creative Commons License
CC BY 4.0

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):

Petersen, K. K-S., Kilic, K., Hertel, E., Sejersgaard-Jacobsen, T. H., Jørgensen, M. K., Troelsen, A., Arendt-Nielsen, L., & Boye Larsen, D. (2023). Quantitative sensory testing as an assessment tool to predict the response to standard pain treatment in knee osteoarthritis: a systematic review and meta-analysis. *Pain Reports*, 8(4), [e1079]. <https://doi.org/10.1097/pr9.0000000000001079>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -



Quantitative sensory testing as an assessment tool to predict the response to standard pain treatment in knee osteoarthritis: a systematic review and meta-analysis

Kristian Kjær-Staal Petersen^{a,b,*}, Kübra Kilic^a, Emma Hertel^{a,b}, Trine Hyttel Sejersgaard-Jacobsen^{c,d}, Marlene Kanstrup Jørgensen^{c,d}, Anders Troelsen^e, Lars Arendt-Nielsen^{a,b,f}, Dennis Boye Larsen^a

Abstract

Emerging evidence suggest that quantitative sensory testing (QST) may predict the treatment response to pain-relieving therapies. This systematic review and meta-analysis focus on the predictive value of QST for pain management of knee osteoarthritis (OA). MEDLINE and EMBASE were systematically searched for all studies from year 2000 to 2023 on pretreatment QST and treatment of OA including surgical, pharmaceutical, and nonsurgical and nonpharmaceutical therapies. Preclinical studies and reviews were excluded. The systematic review followed the PRISMA guidelines and was pre-registered on the Open Science Framework website (link: <https://osf.io/4FETK/>, Identifier: DOI 10.17605/OSF.IO/4FETK). Meta-analysis were conducted to demonstrate the strength of the pre-treatment QST predictions on pain outcomes after OA treatments. Sixteen surgical (all on total knee arthroplasty [TKA], N = 1967), 5 pharmaceutical (4 on non-steroidal anti-inflammatory drugs [NSAIDs], N = 271), and 4 exercise-based therapy studies (N = 232) were identified. Pretreatment QST parameters predicted pain-relieving treatment outcomes in 81% of surgical, 100% of pharmaceutical, and 50% of exercise-based therapy studies. Meta-analyses found pretreatment QST profiles to predicted pain outcomes after TKA (random effects: 0.309, 95% confidence interval [CI]: 0.206–0.405, $P < 0.001$), NSAIDs (random effects: 0.323, 95% CI: 0.194–0.441, $P < 0.001$), and exercise-based therapies (random effects: 0.417, 95% CI: 0.138–0.635, $P = 0.004$). The overall risk of bias for the included studies was low to moderate. This systematic review and meta-analysis demonstrate weak-to-moderate associations between pretreatment QST and pain outcomes after standard OA pain treatments. Based on this work, it is hypothesized that a subset of specific pain sensitive patients with OA exist and that these patients do not respond adequately to standard OA pain treatments.

Keywords: Osteoarthritis, Quantitative sensory testing, Total knee arthroplasty, Nonsteroidal anti-inflammatory drugs, Exercise-based therapies

1. Introduction

Osteoarthritis (OA) is a major clinical problem with an estimated prevalence of 3754 per 100,000,⁵³ and the prevalence is

expected to increase in the future.^{11,13,22} Osteoarthritis Research Society International (OARSI) provides recommendations for the treatment of pain in OA^{9,66} with (1) surgical, (2) pharmaceutical

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

K. K.-S. Petersen, K. Kilic contributed equally to this manuscript.

^a Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark, ^b Center for Mathematical Modeling of Knee Osteoarthritis (MathKOA), Department of Material and Production, Faculty of Engineering and Science, Aalborg University, Aalborg, Denmark, ^c Department of Anesthesia, Aalborg University Hospital, Thisted, Denmark, ^d Department of Orthopedic Anesthesia, Aalborg University Hospital, Aalborg, Denmark, ^e Department of Orthopedic Surgery, Copenhagen University Hospital, Hvidovre, Denmark, ^f Department of Medical Gastroenterology, Mech-Sense, Aalborg University Hospital, Aalborg, Denmark

*Corresponding author. Address: Department of Health Science and Technology, School of Medicine, Aalborg University, Fredrik Bajers Vej 7 D3, DK-9220 Aalborg, Denmark. Tel.: +45 9940 7529; fax: +45 9815 4008. E-mail address: kkp@hst.aau.dk (K.K.-S. Petersen).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painreports.com).

Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The International Association for the Study of Pain. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

PR9 8 (2023) e1079

<http://dx.doi.org/10.1097/PR9.0000000000001079>

therapy, and (3) exercise-based therapy in combination with patient education being the most common. In addition, total knee arthroplasty (TKA), topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs), and exercise-based therapy in combination with patient education is considered the standard pain therapies for the treatment of pain in OA, and more recently, duloxetine have been conditionally recommended as a treatment option for a subset of patients with OA pain.¹⁰ It is well described that these treatments provide patients with pain relief but that a subpopulation of patients does not obtain substantial effects of the treatments.^{12,17,57} Methods to identify patients in risk of a poor response before these treatments could improve health care and potentially lead to personalized pain medicine.

Quantitative sensory testing (QST) has been suggested as surrogate measure for peripheral and central pain mechanisms.⁷ In particular, pressure pain thresholds (PPT), temporal summation of pain (TSP), and conditioned pain modulation (CPM) are often used to profile patients with OA.² Lower PPTs assessed over a painful area (eg, a painful OA knee) mainly reflect localized hyperalgesia, whereas lower PPTs assessed outside of a painful area reflect widespread pressure hyperalgesia, which, based on animal studies, is considered a sign of central pain sensitization.¹ Temporal summation of pain is considered a proxy for the phenomenon of wind-up in dorsal horn neurons where the same stimulus is applied several times at fixed intervals and intensities yielding increased pain perception.²⁵ Conditioned pain modulation is assumed to be the human surrogate model for diffuse noxious inhibitory controls assessed in animals,³⁶ reflecting the balance of descending pain inhibitory and facilitatory mechanisms.⁶² In general, patients with severe OA exhibit lower PPTs (locally and widespread), facilitated TSP, and impaired CPM when compared with healthy asymptomatic subjects,⁴ and emerging evidence suggest that QST might be a predictive tool for standard pain treatments.⁴⁹ Studies indicate that some patients are more pain sensitive than others,^{3,23,31} and the new pain descriptor “nociplastic” may apply to these pain sensitive patients.³³

Parades et al.⁴² reviewed the literature on the predictive role of QST on acute and chronic pain after TKA and identified 9 studies in which preoperative QST predicted chronic postoperative pain, but the field has grown since the Parades et al.⁴² review, and it is currently unknown if these predictions can be applied to other standard pain therapies for OA as recommended by the OARSI.⁹ The current paper aims to provide an up-to-date systematic review and meta-analysis on the possible role of specific QST parameters to predict outcome after surgical, pharmacological, and exercise-based therapies in OA.

2. Methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, this systematic review investigated the predictive role of QST on standard pain therapies for knee OA. The systematic review followed the PRISMA guidelines and was registered on the Open Science Framework website (OSF.IO, registration link: <https://osf.io/4FETK/>, study identifier: DOI: 10.17605/OSF.IO/4FETK). Studies from year 2000 to 2022 were included.

2.1. Search strategy and selection of studies

A systematic literature search was performed in February 2023 in the databases MEDLINE and EMBASE by 2 reviewers (K.K.P. and D.B.L.).

An example of the MeSH terms and text words used in each database is provided in Supplementary table 1 and 2 (available at <http://links.lww.com/PR9/A194>). The reference manager Mendeley was used to export the citations, and all the duplicates were excluded.

2.2. Eligibility criteria

Studies were included if they investigated one or more preoperative QST measures, including thermal, pressure, electrical, mechanical pain detection, tolerance, and suprathreshold stimuli, TSP, CPM, or exercise-induced hypoalgesia before standard pain treatment for OA. Furthermore, studies had to investigate associations between preoperative QST measures and the pain-related outcome after surgery, pharmaceutical therapies, or nonsurgical and nonpharmaceutical therapies by means of correlations (Spearman and Pearson correlations), regression models, or other predictive models.

A minimum of 6 months postoperative follow-up was chosen for surgical studies to assess chronic pain, as earlier research has reported the largest pain improvement 3 to 6 months after, eg, total knee arthroplasty surgery.⁶¹ Pharmacological and exercise-based studies were included if they investigated long-term effects of therapy (weeks/months), whereas studies focused on the acute effects of pharmacological or exercise-based therapies were excluded. In addition, the exclusion criteria consisted of languages other than English, conference abstracts, and animal studies.

Pain outcomes were reported through pain intensity, postoperative pain relief, presence of moderate-to-severe postoperative pain, or validated questionnaires on pain and disability including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Visual Analogue Scale (VAS), and Numerical Rating Scale (NRS).

2.3. Data extraction and synthesis of included literature

The title of publications identified in the databases was reviewed by 2 reviewers (K.K.P. and D.B.L.) in a blinded fashion before meeting. After removing duplicates, abstracts of the articles were screened for potential eligibility and posterior full-read text by the same 2 reviewers (K.K.P. and D.B.L.) independently. The data were independently extracted by 2 investigators (K.K.P. and D.B.L.). For each study, the recorded data were on the total number of subjects, the pretreatment predictors (including QST paradigms), the follow-up time, the dependent outcome of the predictive model, and type of the predictive model. In case of discrepancies in data extraction and synthesis, a third investigator (LAN) was available to make the final decisions.

2.4. Quality assessment

Quality In Prognostic Studies (QUIPS) tool was independently used by 2 authors (K.K.P. and D.B.L.) to assess the quality and the methods of the included articles, more specifically to assess the overall risk of bias in each study focusing on 6 bias domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. If consensus was not reached, a third independent reviewer (LAN) was consulted for the final decision.

2.5. Meta-analysis

The studies identified for the systematic review displayed a large degree of heterogeneity in the reporting outcomes, which

complicated a traditional meta-analysis. To overcome this, studies reporting only compound R^2 values (predictive models) or odds ratios were transformed to Pearson correlation coefficients (r) for the meta-analysis. This was performed to ensure the same association statistic was used for an overall correlation coefficient, at the expense of limiting the ability to infer whether the correlation is mainly driven by the QST measure or other preintervention factors in the case of compound statistics. Where possible, single correlations between preoperative QST measures and pain outcome(s) were preferred and included in the overall meta-analysis instead of compound correlations. Here, it is important to delineate the extent to which pain sensitive QST profiles were considered with respect to pain outcome. The meta-analysis was performed to investigate if signs of pain sensitization, as reflected by QST proxies, were associated with treatment outcomes. The reverse sign correlation was used for PPT and CPM data^{34,35,41} so that a positive correlation indicated a pain sensitive profile. Correlations based on compound predictive models would be expected to have positive correlations (as the R^2 cannot be negative). Forest plots were generated to exhibit the correlational strengths between preoperative QST measures and treatment outcomes and further highlight if studies reported correlations based on compound models or singular association statistics. A higher value on the forest plot indicates a stronger association between a pretreatment QST, whereas positive values indicate that pain sensitive (pronociceptive) subjects are more likely for a poor pain-relieving outcome after therapy, and a negative value indicate that a less pain sensitive (antinociceptive) subject is more likely for a poor pain-relieving outcome after therapy.

The meta-analysis was conducted using MedCalc (v. 20.103; MedCalc Software Ltd, Ostend, Belgium), applying the Fisher z transformation of correlation coefficients and Hedges–Olin method for weighted summary correlation coefficients under a fixed effect model. As the meta-analysis is conducted on the Fisher z transformed values, data were pooled independent if correlations were based on relative^{6,45,58} or absolute^{14,16,21,34,35,38,44,46,50,52,59} pain outcomes. Studies with multiple QST outcomes with an eligible correlation to treatment outcome^{6,34,41,58} were still included with both QST parameters, but halved in population per the Cochrane guidelines, to avoid double counting.²⁹ Since heterogeneity is assumed for the included studies due to, eg, methodological differences, the summed correlation coefficient between the QST measures and pain outcome after surgery, analgesic treatment, or exercise, was estimated and plotted by both the fixed-effects and the random-effects model. Heterogeneity was assessed using the χ^2 test and I^2 statistics, where a χ^2 test $P < 0.1$ suggests significant heterogeneity with $I^2 > 60\%$ reflecting substantial heterogeneity.²⁹

3. Results

Two independent investigators (K.K.P. and D.B.L.) screened 1933 publications by title and abstract to exclude articles that did not meet the inclusion criteria. By consensus between D.B.L. and K.K.P., the initial included articles were decided for 90% of records. One senior investigator (L.A.N.) was consulted for final decisions on the remaining articles, and consensus was reached for all articles. The PRISMA flow diagram (Fig. 1) illustrates the search process, where 25 eligible publications were identified through the systematic literature search.

A total of 25 studies were identified where 16 studies focused on surgery (all on total knee arthroplasty, Table 1), 5 studies on pharmacological treatments (Table 2), and 4 studies investigated

exercise-based therapy or exercise-based therapy in combination with patient education (Table 2). Sample sizes ranged from 14 to 288 with a total of 2238 patients (1967 patients in the surgical studies, 271 patients in the pharmacological studies, and 232 patients in the nonsurgical and nonpharmacological studies).

3.1. Quantitative sensory testing modalities utilized used in the studies

A total of 25 eligible publications were identified through the systematic literature search with 16 surgical, 5 pharmacological therapy, and 4 exercise-based therapy studies.

3.2. Surgical studies

3.2.1. Electrical stimuli

Electrical stimuli were reported 1/15 studies (6%)³⁸ as electrical detection and electrical pain thresholds (EPTs). Lundblad et al.³⁸ demonstrated that lower preoperative EPTs in combination with higher preoperative pain intensity were predictive of the 18-month postoperative pain intensity.

3.2.2. Pressure stimuli

Pressure stimuli were reported in 11/16 studies (69%),^{6,21,34,35,40,44,45,52,58–60} as assessed by pressure pain thresholds using cuff algometry (cPPT),^{21,34,35,45,58} hand-held algometer (PPT),^{6,21,34,40,44,52,58–60} and pain tolerance thresholds using cuff algometry (cPTT).^{34,35,45,58} Pressure stimuli were predictive in 4/11 (36%) studies using cPDT,⁴⁵ PPT,^{6,59} and cPTT.³⁴

Wylde et al., 201⁵⁹ found that preoperative lower PPTs assessed at the forearm were associated with the 1-year postoperative WOMAC score. Petersen et al.,⁴⁵ found that lower preoperative cPPTs assessed at the lower leg were associated with lower levels of 12 months postoperative pain relief. Arendt-Nielsen et al.,⁶ found that lower preoperative PPTs assessed at the affected and nonaffected limb was associated with pain intensity after walking change from baseline to 12 months. Kurien et al., 2018 found that lower preoperative cPTT was associated with postoperative pain intensity at 6 months.

3.2.3. Thermal stimuli

Thermal stimuli were reported in 4/16 studies (25%)^{40,46,59} and found predictive of chronic postoperative pain in one study (25%).⁴⁶ Cold detection threshold (CDT),⁴⁶ and warm detection threshold (WDT)⁴⁶ were assessed in one study, cold pain threshold (CPT)^{21,39,46} were assessed in 3 studies, whereas heat pain threshold (HPT) was assessed in 3 studies.^{40,46,59} Petersen et al.,⁴⁶ found that lower HPT and lower WDT in combination with higher TSP and lower Kellgren and Lawrence scores were predictive for chronic postoperative pain intensity.

3.2.4. Temporal summation of pain

Temporal summation of pain was reported as the QST parameter in 8/16 (50%) studies^{14,16,21,34,44–46,52} as assessed using cuff algometry (TSP_{cuff})^{34,45} or monofilaments (mTSP).^{14,16,21,34,44,46,52} TSP was predictive in 6/8 (75%) studies.^{16,21,34,44,46,52}

Petersen et al.,⁴⁴ demonstrated that high levels of preoperative mTSP assessed in combination with preoperative pain intensity were predictive of 12 months postoperative pain intensity (assessed as the

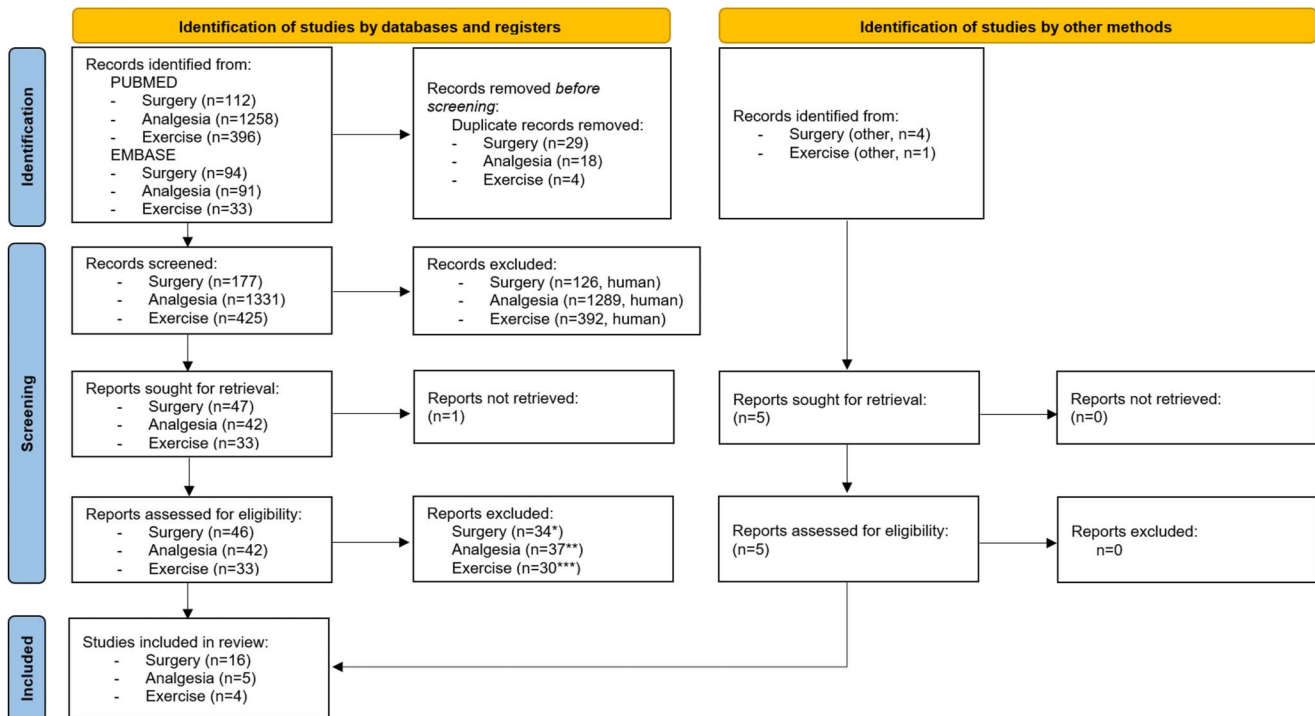


Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Reason(s) for exclusion: *Not postoperative period/pain (n = 9), not total knee arthroplasty (n = 1), no QST measure (n = 4), no prediction for postoperative pain (n = 2), abstract (n = 2), review or commentary (n = 7), protocol (n = 2), and duplicate not caught by automated duplicate procedure (n = 1); **Not postoperative period/pain (n = 3), not osteoarthritis population (n = 3), no QST measure (n = 2), no prediction for analgesic effect (n = 14), abstract (n = 2), review or commentary (n = 8), protocol (n = 2), duplicate not caught by automated duplicate procedure (n = 1), and not standard treatment (n = 1); ***no pain sensory profiling measure (n = 15), no prediction for exercise effect on pain (n = 5), abstract (n = 3), review or commentary (n = 2), protocol (n = 1), only acute effects (n = 1), no prediction for postexercise pain (n = 2), and secondary analysis of data already included (n = 1). QST, quantitative sensory testing.

worst pain within the past 24 hours). Petersen et al.,⁴⁶ demonstrated that high levels of mTSP assessed in combination with lower levels of HPT, WDT, and lower Kellgren and Lawrence scores were predictive of 12 months postoperative pain scores (assessed as the worst pain within the past 24 hours). Rice et al.,⁵² reported that preoperative pain intensity, mTSP, trait anxiety, and expected pain predicted 6 months postoperative WOMAC with a specificity of 64% and a sensitivity of 72%. Of note, the Rice et al., study⁵² did not find any significant preoperative predictors for 12 months postoperative WOMAC scores. Kurien et al.,³⁴ assessed preoperative TSP_{cuff} and mTSP and found that higher levels of mTSP was associated with the 6-month postoperative pain intensity. Bruehl et al.,¹⁶ demonstrated that high levels of preoperative mTSP were correlated with higher 6-month postoperative complex regional pain syndrome severity scores (CSS). Edwards et al.,²¹ demonstrated that higher preoperative mTSP, in combination with agreeableness, was predictive of higher 6-month postoperative brief pain inventory (BPI) and WOMAC scores.

3.2.5. Conditioned pain modulation

Conditioned pain modulation was reported as a QST parameter in 9/16 studies (56%).^{14, 18, 21, 34, 35, 44, 45, 52, 58}

A wide variety of different test and conditioning protocols was identified, including the use of PPT as the test stimulus with cold water immersion being the conditioning stimulus (CPM_{PPT + cold}),^{21, 44, 52} PPT and cuff algometry as the test stimulus and cold water immersion as the conditioning stimulus (CPM_{cuff + cold}),⁵⁸ PPT and interdigital pinching as test and conditioning stimulus, respectively (CPM_{PPT + i.dig.pincing}),¹⁴ cuff algometry as test and

conditioning stimulus (CPM_{cuff + cuff}),^{15, 34, 45} and contact heat as test stimulus with conditioning stimulus hot water (CPM_{heat + hot water}).¹⁸ Conditioned pain modulation predicted postoperative pain in 3/9 (33%) studies.^{18, 35, 58}

Vaegter et al.,⁵⁸ assessed preoperative CPM_{PPT + cold} and found that an impaired CPM-effect was associated with 6-month postoperative pain intensities. Larsen et al.,³⁵ assessed preoperative CPM_{cuff + cuff} and found that impaired CPM was associated with 12 months postoperative pain scores. Dürstler et al., 2021 assessed preoperative CPM_{heat + hot water} and found that lower preoperative impaired CPM predicted the presence of 6 months postoperative pain.

3.2.6. Exercise-induced hypoalgesia

Exercise-induced hypoalgesia (EIH) was reported in 1/16 studies (6%),⁵⁸ and an impaired EIH-effect was associated with 6 months postoperative pain relief.

3.3. Pharmacological therapy studies

3.3.1. Pressure stimuli

Pressure stimuli were reported in 4/5 studies (80%),^{5, 20, 47, 50} and one study (25%)⁵⁰ found pressure stimuli to be predictive for an analgesic response. Two studies reported on handheld pressure algometry,^{5, 20} and one study reported on cuff pressure pain and tolerance thresholds.⁴⁷

Petersen et al.,⁵⁰ found that lower pretreatment PTTs were predictive of a higher analgesic effect of 18-week oral duloxetine treatment.

Table 1

Studies assessing preoperative quantitative sensory testing (QST) as a predictor for chronic postoperative pain 3 months or longer in patients undergoing total knee arthroplasty.

| Reference | Year | Patients (N) | QST | Follow-up (mo) | POP outcome | Preoperative findings |
|------------------------------------|------|--------------|------------------------------|----------------|--|---|
| Lundblad et al. ³⁸ | 2008 | 69 | EDT and EPT | 18 | VAS | Regression (M): Preop pain (OR) = 6.48 EPT (OR) = 9.19 |
| Wylde et al. ⁵⁹ | 2013 | 51 | PPT and HPT | 12 | WOMAC | PPT; correlation (U) $r = 0.37$, ($R^2 = 0.1369$) |
| Noiseux et al. ⁴⁰ | 2014 | 193 | MPT, HPT, and PPT | 6 | Moderate-to-severe postoperative pain (NRS) | Regression (M): No predictive value |
| Petersen et al. ⁴⁴ | 2015 | 78 | PPTs and TSP CPM | 12 | VAS | Regression (M): TSP and preop VAS: $R^2 = 0.13^*$ |
| Wylde et al. ⁶⁰ | 2015 | 239 | PPT | 12 | WOMAC | No predictive value |
| Petersen et al. ⁴⁵ | 2016 | 103 | PPT, PTT, TSP, and CPM | 12 | VAS | Regression (M): $R^2 = 0.379$, using PPT and VAS* Combined facilitated TSP/impaired CPM associated with less pain relief |
| Vaegter et al. ⁵⁸ | 2017 | 14 | PPTs, PTT, CPM, and EIH | 6 | NRS | Correlations (U): CPM $r = 0.57$ ($R^2 = 0.3249$) EIH correlation $r = 0.53$ ($R^2 = 0.2809$) |
| Bossmann et al. ¹⁴ | 2017 | 47 | TSP and CPM | 6 | WOMAC | Regression (M): No predictive value |
| Arendt-Nielsen et al. ⁶ | 2018 | 70 | PPT | 12 | No pain (VAS 0–4 mm) | Correlation (U): PPT affected limb ($R^2 = 0.110$), PPT contralateral limb ($R^2 = 0.09$) |
| Petersen et al. ⁴⁶ | 2018 | 130 | HPT, WDT, CDT, CPT, and TSP | 12 | VAS | Regression (M): Preop mTSP, WDT, HPT, and KL: $R^2 = 0.119^*$ |
| Rice et al. ⁵² | 2018 | 288 | TSP, PPT, and CPM | 6 and 12 | WOMAC | Regression (M): TSP: OR = 1.06, WOMAC: OR = 1.01 AUC: 0.70, specificity: 0.64, sensitivity: 0.72 65.67% correctly classified at 6 mo. No prediction at 12 mo |
| Kurien et al. ³⁴ | 2018 | 50 | PPTs, TSP, PTT, TSP, and CPM | 6 | VAS | Correlation (U): PTT $r = -0.262$, ($R^2 = 0.0686$); TSP $r = 0.343$ ($R^2 = 0.1176$) |
| Larsen et al. ³⁵ | 2021 | 131 | PTT, PPT, and CPM | 12 | VAS | Correlation (U): CPM: $r = -0.18$ ($R^2 = 0.0324$) CPM: MB-lin-reg-ana, $\beta = -0.124$, $P = 0.122$ contributed to the variance explanation but was not an independent factor |
| Dürsteler et al. ¹⁸ | 2021 | 146 | CPM | 6 | The presence of postoperative pain (NRS > 3 at 6 mo postoperative follow-up) | CPM; correlation $P = 0.004$ Strength of correlation not reported |
| Bruehl et al. ¹⁶ | 2022 | 110 | TSP | 6 | CRPS CSS | Correlation (U): TSP $r = 0.22$ |
| Edwards et al. ²¹ | 2022 | 248 | PPTs, TSP, and CPM | 6 | WOMAC BPI | Regression (M): TSP $r = 0.316$ ($R^2 = 0.10$) |

* Not reported in the original paper but calculated for this review.

ALL, allodynia; AUC, area under the receiver operating characteristic curve; CDT, cold detection threshold; CPM, conditioned pain modulation; CPT, cold pain threshold; CRPS, complex regional pain syndrome; CSS, CRPS severity score; EDT, electrical detection threshold; EIH, exercise-induced hypoalgesia; EPT, electrical pain threshold; HPT, heat pain threshold; lin-reg, linear regression; M, multivariate analysis; MB-lin-reg ana, multiple backward linear regression analysis; MPT, mechanical pain threshold; NRS, numeric rating scale; OR, odds ratio; P , probability value; POP, postoperative pain; PPT, pressure pain threshold; PTT, pain tolerance threshold; r , correlation coefficient; TSP, temporal summation of pain; U, univariate analysis; VAS, Visual Analog Scale; WDT, warm detection threshold; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

3.3.2. Temporal summation of pain

Temporal summation of pain was reported in 4/5 studies (80%)^{5,20,47,50} and found predictive of the analgesic effect in 3/4 studies (75%). Arendt-Nielsen et al.,⁵ found that high TSP predicted the nonresponse of 4 weeks of oral COX-2 treatment. Petersen et al.,⁴⁷ found that higher TSP_{cuff} predicted a

nonresponse to 3 weeks of oral nonselective NSAIDs and paracetamol. Edwards et al.,²⁰ reported that mTSP did not predict the analgesic response of 4 weeks of topical NSAID treatment. Petersen et al.,⁵⁰ demonstrated that higher pre-treatment TSP_{cuff} predicted a higher analgesic effect of 18 weeks of oral duloxetine treatment.

Table 2**Studies assessing pretreatment quantitative sensory testing (QST) as a predictor for pharmacological and exercise-based therapy studies.**

| Reference | Year | Patients (N) | Treatment | QST | Follow-up | Treatment outcome | Findings |
|------------------------------------|------|--|--|---|-------------------|--|---|
| Pharmacological treatments | | | | | | | |
| Arendt-Nielsen et al. ⁵ | 2016 | 37 | COX-2 inhibitor | PPT, TSP, and CPM | 4 wk | Change in pain intensity for nonresponders | Correlation (U): $r = 0.64$ for nonresponders (less than 30% pain alleviation in 16 patients) |
| Edwards et al. ²⁰ | 2016 | 35 | Topical NSAID (gel) | PPT, TSP, and CPM | 4 wk | Change in average daily pain intensity (ADP) and KOOS pain | Regressions (M): ADP: CPM: $R^2 = -0.38$ |
| Petersen et al. ⁴⁷ | 2019 | 132 | Oral NSAID and paracetamol | PPT, PTT, and TSP | 3 wk | VAS (worst pain and during activity) | Regression (M): $R^2 = 0.24-0.27$ using the VAS and TSP |
| Petersen et al. ⁴⁸ | 2019 | 42 | Oral NSAID and paracetamol | CPM, offset analgesia | 3 wk | VAS (worst pain and during activity) | Regression (M): $R^2 = 0.19$ using the VAS and CPM |
| Petersen et al. ⁵⁰ | 2022 | 25 | Duloxetine | PPT, PTT TSP, and CPM | 16 wk | Change in BPI and WOMAC | Regression (M): $R^2 = 0.46-0.76$ using TSP, PTT, BPI, WOMAC, and HADS |
| Exercise-based therapy | | | | | | | |
| Henriksen et al. ²⁸ | 2014 | RCT: Exercise group: N = 31 Control: N = 29 | 3 group based or individual session per week | PPT and TSP | 12 wk | Change in KOOS from baseline to follow-up | Correlation: No predictive value (change in PPTs from baseline to follow-up was associated with outcome: $R^2 = 0.35$) |
| O'Leary et al. ⁴¹ | 2018 | 99 | 4–6 group-based or individual sessions | PPT, TSP, CPM, MDT, VDT, and heat and cold hyperalgesia (thermal rolls) | 10.5 wk (average) | Responders and nonresponders according to the OMERACT-OARSI responder criteria | Regression (U): OR for nonresponders: TSP: OR 2.00, 95% CI 1.23–3.27 PPT: 0.48 (95% CI 0.29–0.81) |
| Arendt-Nielsen et al. ⁶ | 2018 | 49 | Education, exercise, and insoles. Weight loss and pain medicine, if needed. Two sessions per week for 8 weeks and continued for to a total of 3 mo | PPT | 12 mo | VAS after walking | Regression (M): No predictive value |
| Hansen et al. ²⁷ | 2020 | 24 | 12 sessions of neuromuscular exercises (twice weekly) | PPT, TSP, and EIH | | Responders according to the OMERACT-OARSI responder criteria | Regression (M): $R^2 = 0.468$ with PPT, EIH, and PDQ |

BPI, Brief Pain Inventory; CPM, conditioned pain modulation; EIH, exercise-induced hypoalgesia; M, multivariate analysis; MDT, mechanical detection threshold; NRS, numeric rating scale; OR, odds ratio; P , probability value; PDQ, PainDetect Questionnaire; PPT, pressure pain threshold; PTT, pain tolerance threshold; r , correlation coefficient; TSP, temporal summation of pain; U, univariate analysis; VAS, Visual Analog Scale; VDT, vibration detection threshold; WDT, warm detection threshold; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

3.3.3. Conditioned pain modulation

Conditioned pain modulation was reported in 3/5 studies (60%)^{20,48,50} and found predictive of the analgesic effect in 2/3 studies (67%). Edwards et al.,²⁰ found that an impaired $CPM_{PPT + cold}$ effect predicted poor response to 4 weeks of topical nonselective NSAIDs. Petersen et al.,⁴⁸ found that an impaired $CPM_{cuff + cuff}$ effect predicted a poor response to 3 weeks of oral nonselective NSAID and paracetamol.

3.3.4. Offset analgesia

Offset analgesia was assessed in 1/5 studies (20%),⁴⁸ and no studies found offset analgesia to be predictive of an analgesic response.

3.4. Exercise-based therapy studies

3.4.1. Thermal stimuli

Thermal stimuli were reported in 1/4 studies (25%),⁴¹ and no studies (0%) found thermal stimuli to be predictive for treatment response.

3.4.2. Pressure stimuli

Pressure stimuli were reported in 4/4 studies (100%), and 2 studies (50%) found pressure stimuli to be predictive for treatment response. O'Leary et al.,⁴¹ found that a combination of lower PPTs assessed at the knee, the tibia, and the contralateral arm predicted a nonresponse to 6 to 8 sessions of exercise-based therapy with an odds ratio (OR) of 0.48 (95% confidence interval [CI]: 0.29–0.81). Hansen et al.,²⁷ found that lower PPTs assessed at the knee in combination with lower EIH and higher PainDetect score were associated with less pain relief after 12 sessions of exercise-based therapy. Of note, Henriksen et al.,²⁸ did find that a change in cuff PPT from baseline to follow-up was associated ($R^2 = 0.35$) with a change in KOOS from baseline to follow-up.

3.4.3. Temporal summation of pain

Temporal summation of pain was assessed in 3/4 studies (75%), and one study (33%) found TSP to predict treatment outcome. O'Leary et al.,⁴¹ found that a combination of increased mTSP assessed at the knee, the tibia, and the contralateral arm was

associated with a nonresponse to 6 to 8 sessions of exercise-based therapy with a an OR of 2.00 (95% CI: 1.23–3.27).

3.4.4. Mechanical and vibration detection threshold

O'Leary et al.,⁴¹ assessed mechanical and vibration detection thresholds and did not find these associated with a nonresponse to 6 to 8 sessions of exercise-based therapy.

3.4.5. Conditioned pain modulation

O'Leary et al.,⁴¹ assessed CPM and found no association with a nonresponse to 6 to 8 sessions of exercise-based therapy.

3.4.6. Exercise-induced hypoalgesia

Hansen et al.,²⁷ assessed EIH using 2 different assessments at the m. quadriceps femoris and m. tibialis anterior and found that lower EIH assessed at the m. quadriceps femoris predicted less pain relief after 12 sessions of exercise-based therapy.

3.5. Prediction of quantitative sensory testing parameters for treatment outcomes

3.5.1. Total knee arthroplasty

The outcome parameters reported for the 16 surgical studies included 6 on the WOMAC,^{14,21,50,52,59,60} 7 on a VAS score,^{6,34,35,38,44–46} 3 using a NRS,^{18,40,58} (Table 1), 1 using complex regional pain syndrome (CRPS) severity scores (CSS),¹⁶ and 1 on the BPI.²¹ The number of measured QST tests in each study ranged from 1^{6,16,18,60} to 6.^{21,34} A total of 13/16 studies (81%) reported statistically significant associations between preoperative QST and chronic postoperative pain after total knee arthroplasty.

3.5.2. Pharmacological therapies

Five studies were identified where 3 used different VAS scores,^{5,47,48} 1 used average daily pain intensity,²⁰ and 1 study used WOMAC and BP⁵⁰ as the outcome parameters (Table 2). Two studies reported on 3 weeks of oral nonselective NSAID in combination with paracetamol,^{47,48} 1 study reported on topical nonselective NSAIDs,²⁰ 1 study reported on an oral COX-2 inhibitory NSAID,⁵ and 1 study reported on 18 weeks of oral duloxetine treatment.⁵⁰ The number of QST modalities range from 2⁴⁸ to 3.^{5,20,47} Five of 5 studies (100%) reported an association between pretreatment QST and analgesic effect to pharmacological therapies. A total of 4/4 studies (100%) reported statistically significant associations between pretreatment QST and the analgesic effect to NSAIDs, and 1/1 (100%) study reported statistically significant association between pretreatment QST and the analgesic effect of duloxetine.

3.5.3. Exercise-based therapies

Four studies were identified with 2 studies^{27,41} using the OMERACT-OARSI responder criteria, 1 study using pain after walking,⁶ and 1 study using the KOOS²⁸ as the outcome parameters (Table 2). The number of assessed QST modalities ranged from 1 (Arendt-Nielsen et al., 2018) (Arendt-Nielsen et al., 2018) to 7.⁴¹ A total of 2/4 studies (50%) reported statistical associations between pretreatment QST and pain outcomes after exercise-based therapies.

3.6. Quality assessment

Agreement was reached for 95% of the included articles, and any discrepancies were reviewed by one expert in the field (LAN). Consensus was reached on all parameters after discussion. The quality assessment of the included articles is summarized in Table 3.

3.7. Meta-analysis

For the surgical studies, a meta-analysis based on 1367 patients indicated that a pronociceptive preoperative profile was associated with higher risk of chronic postoperative pain in both a fixed ($P < 0.001$) and random-effects ($P < 0.001$) model (see Table 4 for meta-analysis and Fig. 2 for forest plot). For the pharmacological studies, a meta-analysis based on 225 patients indicated that a pronociceptive pretreatment QST profile was associated with a less beneficial analgesic response to NSAIDs in a fixed ($P < 0.001$) and random-effects ($P < 0.001$) model (see Table 5 for meta-analysis and Fig. 3 for forest plot). For the exercise-based studies, a meta-analysis based on 154 patients indicated that a pronociceptive pretreatment QST profile was associated with less pain relief after exercise-based therapy for both fixed ($P < 0.001$) and random-effects ($P = 0.004$) models (see Table 5 for meta-analysis and Fig. 3 for forest plot). A meta-analysis for duloxetine was not conducted, since only one study⁵⁰ assessed the predictive value of QST on the analgesic effect of duloxetine for OA pain.

Heterogeneity for the surgical meta-analysis was substantial ($I^2 = 70.05\%$), and the Eggers test was nonsignificant ($P = 0.117$), indicating no evidence of publication bias. Low heterogeneity was observed for the pharmaceutical meta-analysis ($I^2 = 13.74\%$), and the Eggers test was significant ($P = 0.00389$), suggesting possible publication bias. Finally, heterogeneity for the exercise-based meta-analysis was substantial ($I^2 = 69.65\%$), and the Eggers test was significant ($P = 0.042$), suggesting a potential publication bias.

4. Discussion

The current systematic review and meta-analysis describe the predictive role of QST profiling for pain outcomes after total knee arthroplasty, NSAID, and duloxetine therapy and exercise-based therapy in patients with osteoarthritis. The systematic review identified that 13/16 studies (81%) reported an association between preoperative QST profiling and chronic postoperative pain, 5/5 studies (100%) reported an association between pretreatment QST profiling and analgesic effects of NSAIDs and duloxetine, and 2/4 studies (50%) reported an association between pretreatment QST profiling and response to exercise-based therapy. The meta-analyses indicated that QST parameters were associated with poor outcome after TKA surgery, and NSAID and exercise-based therapies, which suggests that patients with a pain sensitive profile are less likely to respond to these standard pain treatments for osteoarthritic pain.

4.1. The predictive value of quantitative sensory testing profiling

Other systematic reviews have reported a possible predictive value of QST for postoperative pain after different surgical interventions.^{49,54} One review included acute and chronic postoperative pain measures and concluded that QST before TKA surgery did not consistently predict pain after surgery,⁵⁴ whereas a recent review⁴⁹ found that preoperative QST was predictive in

Table 3

Risk of bias based on the quality in prognostic studies (QUIPS) tool for studies investigating the prognostic value of pain sensory profiles on poor response to standard pain therapies for patients with knee osteoarthritis.

| | Study participation | Study attrition | Prognostic factor measurement | Outcome measurement | Study confounding | Statistical analysis and reporting |
|------------------------------------|---------------------|-----------------|-------------------------------|---------------------|-------------------|------------------------------------|
| Surgical studies | | | | | | |
| Lundblad et al. ³⁸ | M | H | M | M | H | L |
| Wylde et al. ⁵⁹ | M | L | L | L | M | M |
| Noiseux et al. ⁴⁰ | M | L | L | L | M | L |
| Petersen et al. ⁴⁴ | M | L | L | M | M | L |
| Wylde et al. ⁶⁰ | L | M | L | M | L | L |
| Petersen et al. ⁴³ | L | M | L | M | M | L |
| Bossmann et al. ¹⁴ | M | M | L | L | L | L |
| Vaegter et al. ⁵⁸ | M | L | L | L | M | L |
| Arendt-Nielsen et al. ⁶ | L | M | L | M | L | M |
| Petersen et al. ⁴⁶ | L | M | M | L | M | L |
| Rice et al. ⁵² | L | L | L | L | M | L |
| Kurien et al. ³⁴ | M | L | L | M | M | L |
| Dürsteler et al. ¹⁸ | L | L | L | L | M | M |
| Larsen et al. ³⁵ | M | L | L | L | M | L |
| Bruehl et al. ¹⁶ | L | M | L | L | M | L |
| Edwards et al. ²¹ | M | H | L | L | M | M |
| Pharmacological studies | | | | | | |
| Arendt-Nielsen et al. ⁵ | L | M | L | L | M | L |
| Edwards et al. ²⁰ | M | M | L | L | M | L |
| Petersen et al. ⁴⁷ | L | M | L | L | M | L |
| Petersen et al. ⁴⁸ | L | L | L | L | M | L |
| Petersen et al. ⁵⁰ | L | L | L | L | M | L |
| Exercise-based studies | | | | | | |
| Henriksen et al. ²⁸ | L | M | L | M | M | M |
| O'Leary et al. ⁴¹ | L | L | L | L | L | L |
| Arendt-Nielsen et al. ⁶ | L | L | M | L | L | M |
| Hansen et al. ²⁷ | L | L | L | L | M | M |

H, high risk of bias; L, low risk of bias; M, medium risk of bias.

68% of cases for chronic postoperative pain after different surgical procedures. This may indicate that preoperative QST is a better or at least more consistent predictor of chronic postoperative pain than acute postoperative pain as previously suggested.⁵⁴ The current systematic review is the first to review the predictive value of QST for responses to pharmacological-based and exercise-based therapies in patients with OA.

The systematic review demonstrated that widespread pressure hyperalgesia (25%), TSP (38%), and CPM (19%) were the most frequently reported predictive QST parameters for continued pain after total knee arthroplasty, which is consistent with earlier reviews on multiple different surgical interventions.^{49,54} In addition, TSP (60%) and CPM (40%) were the most frequently reported predictive QST parameters for the pharmacological treatments. Finally, widespread pressure pain hyperalgesia (50%) was the most frequently reported predictive QST parameter for pain relief after exercise-based therapy. The results from the meta-analyses indicate that pain-sensitive pretreatment QST profiles are associated with less pain relief after total knee arthroplasty, NSAIDs, and exercise-based therapies. Conclusively, these findings suggest that knee OA patients defined as "sensitized" might not respond sufficiently to standard therapies as recommended by the OARSI guidelines.⁶⁵

4.2. Quality assessment

The risk of bias analysis identified low-to-moderate bias distributed among the 6 categories: study participation, study attrition, prognostic factor of measurement, outcome measurement, confounding, and statistical analysis/reporting. The study participation was mainly biased due to missing data on sampling frame,

recruitment, and place for assessment, whereas the study attrition often lacked information on missing data, loss to follow-up, and differences in the patients who completed the study and those who did not. The main reasons for bias in the prognostic factor of measurement and outcome categories were related to the validity or reliability of the measures (both prognostic and outcome). The confounders category revealed moderate bias due to the lack of clear definition of confounding variables and attempts to account for these in the study designs. Statistical analyses and reporting were not consistent in the included articles.

4.3. Future perspectives

The current systematic review and meta-analysis indicates that a subset of OA patients exist, who are not responding adequately to the 3 investigated standard pain treatments for OA, and it is, therefore, important to consider alternative treatment options for these patients.

Animal studies indicate that serotonin and noradrenaline are important neurotransmitters for functional descending pain inhibitory control,^{8,37} which is assessed using the CPM paradigm in humans.⁶⁴ The OARSI recommends duloxetine (a serotonin/noradrenaline reuptake inhibitor) as a pharmaceutical treatment for pain in OA when depression and widespread pain is present.⁹ Four weeks of duloxetine have been found to provide pain relief and restore impaired CPM in patients with painful diabetic neuropathies, indicating a link between modulation of serotonin and noradrenaline and QST response.⁶³ Recently, Koh et al.,³² randomized pain sensitive patients to duloxetine or placebo before and 6 weeks after total knee arthroplasty and found significant 12 weeks postoperative pain relief in the duloxetine group when

Table 4

Weighted correlations with 95% confidence interval for the correlation between preoperative quantitative sensory testing measures and postoperative pain.

| Study | Sample size | Correlation coefficient | 95% CI | z | P | Weight (%) | |
|---|-------------|-------------------------|-------------------|-------|--------|------------|--------|
| | | | | | | Fixed | Random |
| Lundblad et al. ³⁸ (EPT) | 69 | 0.522 | 0.326 to 0.675 | | | 4.91 | 7.08 |
| Wylde et al. ⁵⁹ (PPT) | 51 | 0.370 | 0.105 to 0.586 | | | 3.57 | 6.28 |
| Petersen et al. ⁴⁴ (TSP) | 78 | 0.240 | 0.0185 to 0.439 | | | 5.58 | 7.38 |
| Petersen et al. ⁴³ (PPT & VAS) | 103 | 0.616 | 0.480 to 0.723 | | | 7.44 | 8.00 |
| Bossmann et al. ¹⁴ (CPM) | 47 | 0.300 | 0.0140 to 0.541 | | | 3.27 | 6.06 |
| Vaegter et al., 2017 (CPM)* | 7 | 0.570 | -0.321 to 0.926 | | | 0.30 | 1.13 |
| Vaegter et al. ⁵⁸ (EIH)* | 7 | 0.530 | -0.371 to 0.917 | | | 0.30 | 1.13 |
| Petersen et al. ⁴⁶ (TSP) | 130 | 0.193 | 0.0215 to 0.353 | | | 9.45 | 8.46 |
| Arendt-Nielsen et al., 2018 (PPT affected leg)* | 35 | 0.330 | -0.00365 to 0.598 | | | 2.38 | 5.21 |
| Arendt-Nielsen et al. ⁶ (PPT nonaffected leg)* | 35 | 0.345 | 0.0133 to 0.608 | | | 2.38 | 5.21 |
| Rice et al. ⁵² (TSP) | 291 | 0.0160 | -0.0992 to 0.131 | | | 21.43 | 9.58 |
| Kurien et al., 2018 (PTT)*† | 25 | 0.262 | -0.149 to 0.595 | | | 1.64 | 4.22 |
| Kurien et al. ³⁴ (TSP)* | 25 | 0.343 | -0.0603 to 0.650 | | | 1.64 | 4.22 |
| Larsen et al. ³⁵ (CPM)† | 131 | 0.180 | 0.00874 to 0.341 | | | 9.52 | 8.47 |
| Bruehl et al. ¹⁶ (TSP) | 110 | 0.220 | 0.0342 to 0.391 | | | 7.96 | 8.14 |
| Edwards et al. ²¹ (TSP) | 248 | 0.316 | 0.199 to 0.424 | | | 18.23 | 9.41 |
| Total (fixed effects) | 1392 | 0.261 | 0.210 to 0.310 | 9.785 | <0.001 | 100.00 | 100.00 |
| Total (random effects) | 1392 | 0.309 | 0.206 to 0.405 | 5.670 | <0.001 | 100.00 | 100.00 |

The table demonstrates both fixed and random effects based on weighted fixed and random-effects correlation coefficients (Fisher z transformation).

* Sample size halved per guidelines, to account for multiple inclusions.

† Originally a negative correlation but reversed so that a larger positive value indicates higher pain sensitization.

95% CI, 95% confidence interval; CPM, conditioned pain modulation; EIH, exercise-induced hypoalgesia; EPT, electrical pain threshold; PPT, pressure pain threshold; PTT, pressure tolerance threshold; VAS, Visual Analogue Scale.

compared with placebo. In addition, administration of ketamine (an N-methyl-D-aspartate receptor antagonist) to patients with fibromyalgia can reduce TSP,²⁶ and since facilitated TSP is associated with chronic postoperative pain after total knee arthroplasty,^{1,45,46} this may be a future target for patients undergoing surgery. Based on these findings, it may be hypothesized that pain-sensitive patients (based on TSP and CPM) before total knee arthroplasty

could benefit from preoperative pharmaceutical interventions to normalize the facilitation of pain mechanisms, and large scale studies are initiated to pursue this hypothesis.⁵⁶

It is important to acknowledge that several factors interact with the pain sensory profiles,⁴³ and multiple other preoperative risk factors are associated to poor response to standard pain therapies. Cognitive factors (such as anxiety, depression, or pain

Table 5

Weighted correlations with 95% confidence interval for the correlation between pretreatment pain sensory profiles and analgesic effect in pharmacological and exercise-based therapy studies.

| Study | Sample size | Correlation coefficient | 95% CI | z | P | Weight (%) | |
|--|-------------|-------------------------|------------------|-------|--------|------------|--------|
| | | | | | | Fixed | Random |
| Pharmacological therapies | | | | | | | |
| Arendt-Nielsen et al. ⁵ (TSP) | 16 | 0.639 | 0.210 to 0.862 | | | 6.10 | 7.71 |
| Edwards et al. ²⁰ (CPM) | 35 | 0.380 | 0.0535 to 0.633 | | | 15.02 | 17.73 |
| Petersen et al. ⁴⁷ (TSP) | 132 | 0.270 | 0.104 to 0.421 | | | 60.56 | 53.46 |
| Petersen et al. ⁴⁸ (VAS & CPM) | 42 | 0.440 | 0.157 to 0.656 | | | 18.31 | 21.10 |
| Total (fixed effects) | 225 | 0.346 | 0.222 to 0.458 | 5.260 | <0.001 | 100.00 | 100.00 |
| Total (random effects) | 225 | 0.360 | 0.219 to 0.487 | 4.733 | <0.001 | 100.00 | 100.00 |
| Exercise-based therapies | | | | | | | |
| Henriksen et al. ²⁸ (PPT) | 31 | 0.590 | 0.298 to 0.781 | | | 19.72 | 23.71 |
| O'Leary et al. ⁴¹ (TSP)* | 50 | 0.188 | -0.0953 to 0.443 | | | 33.10 | 27.59 |
| O'Leary et al. ⁴¹ (PPT)*† | 49 | 0.198 | -0.0881 to 0.454 | | | 32.39 | 27.45 |
| Hansen et al. ²⁷ (PPT, EIH & PDQ) | 24 | 0.680 | 0.381 to 0.850 | | | 14.79 | 21.25 |
| Total (fixed effects) | 154 | 0.366 | 0.216 to 0.500 | 4.578 | <0.001 | 100.00 | 100.00 |
| Total (random effects) | 154 | 0.417 | 0.138 to 0.635 | 2.849 | 0.004 | 100.00 | 100.00 |

The table demonstrates both fixed and random effects based on weighted fixed and random-effects correlation coefficients (Fisher z transformation).

* Sample size halved per guidelines, to account for multiple inclusions.

† Originally a negative correlation but reversed so that a larger positive value indicates higher pain sensitization.

95% CI, 95% confidence interval; CPM, conditioned pain modulation; EIH, exercise-induced hypoalgesia; EPT, electrical pain threshold; PPT, pressure pain threshold; PDQ, PainDetect Questionnaire; VAS, Visual Analogue Scale.

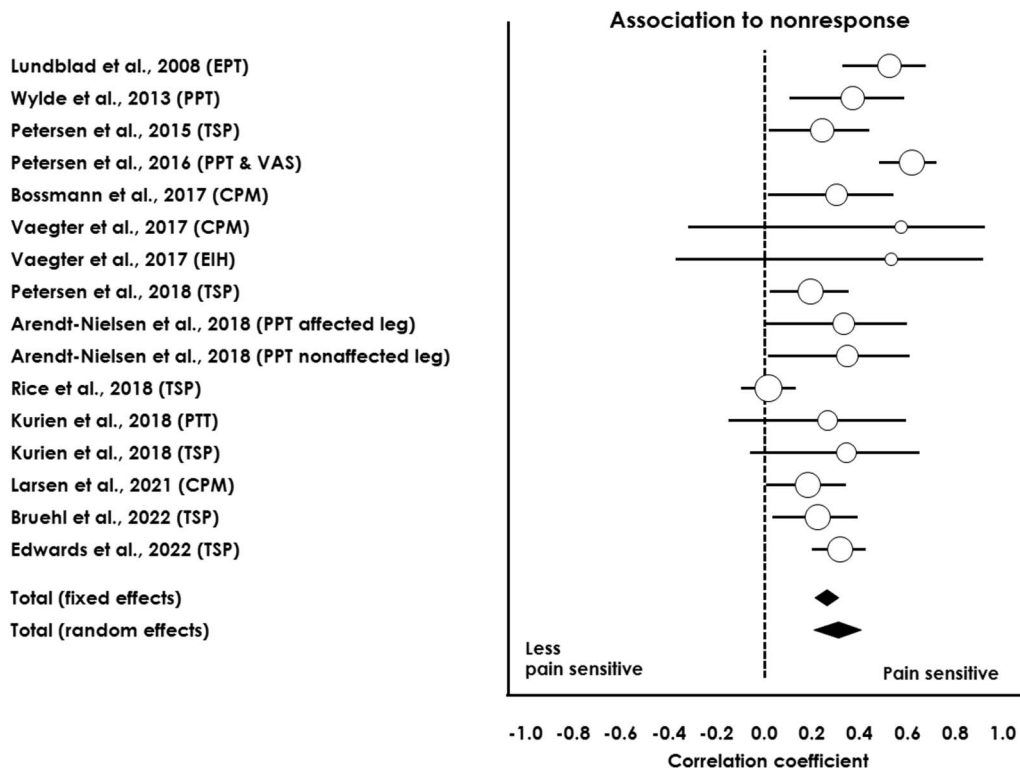


Figure 2. Forest plot from surgical studies assessing associations between preoperative pain sensory profiles and chronic postoperative pain after total knee arthroplasty. The correlation coefficient (positive values) indicates the strength of association between the preoperative QST parameter and the postoperative pain outcome. CPM, conditioned pain modulation; EIH, exercise-induced hypoalgesia; EPT, electrical pain threshold; PPT, pressure pain threshold; PTT, pressure tolerance threshold; QST, quantitative sensory testing; VAS, Visual Analogue Scale.

catastrophizing) are a well-known risk factor for chronic postoperative pain.^{19,51} A recent study demonstrated that the combination of preoperative CPM and pain catastrophizing yielded a stronger prediction model than each of the assessments alone,³⁵ which suggests that adding cognitive factors to the existing prediction models will strength the models in the future. In addition, quality of sleep is decreased in different chronic pain conditions, including OA,¹⁵ and this have been shown to further deteriorate and increase, eg, cognitive factors¹⁵ and inflammation,³⁰ respectively. Elevated levels of proinflammatory cytokines have been associated to pain after total knee arthroplasty,²⁴ and proinflammatory cytokines can sensitize peripherally and centrally pain pathways,⁵⁵ thereby potentially yielding a pronociceptive profile. It is, therefore, highly likely that a combination of QST and inflammatory mediator assessments will increase the predictive value for chronic postoperative pain after total knee arthroplasty in the future.

Likely, many complex interactions between risk factors for a poor response to standard OA pain therapies exist, and understanding these interactions in the future is likely to advance the field towards a personalized mechanistic-based treatment approach for OA.

4.4. Methodological considerations and limitations for the interpretation of the review

The search strategy was limited to 2 databases and English language, and it cannot be excluded that pertinent papers were missed. The included studies used a wide variety of different assessment methods, number of included patients, and outcome measures, which should be considered when assessing this work.

The studies included in this systematic review and meta-analysis displayed a medium-to-large degree of heterogeneity for the surgical, pharmacological, and exercise-based therapy studies, which traditionally will complicate the conduct of a meta-analysis. The current work did present a meta-analysis based on recalculations of odds ratios and R^2 values which may introduce interpretative limitations which should be considered. In addition, the number of studies included in the meta-analysis predominantly favored associations between QST and treatment outcomes, which likely leads to publication bias, and this should be considered when interpreting the results.

The pharmacological and exercise-based meta-analysis is linked underpowered for a meta-analysis. The surgical, pharmacological, and exercise-based meta-analyses did indicate a trend towards publication bias, which should be considered when interpreting the data.

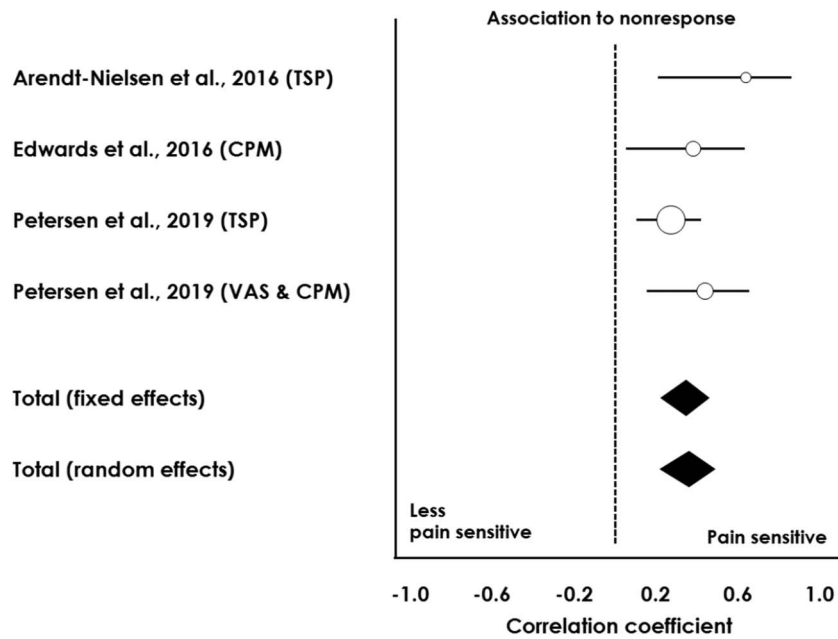
Only a single study was found exploring the predictive value of QST for the analgesic effect of duloxetine, and therefore, a meta-analysis was not conducted. An updated systematic review and meta-analysis should be completed when sufficient data are available.

The current work combined QST profiles into “pronociceptive” and “antinociceptive” profiles due to the lack of studies on individual QST methodologies. Ideally, a meta-analysis should be conducted on single parameters, and this should be considered when interpreting the results of the current work.

5. Conclusion

This systematic review and meta-analysis identified 13/16 surgical (81%), 5/5 pharmaceutical (100%), and 2/4 (50%) nonsurgical and nonpharmaceutical studies that reported a

A: Pharmacological therapies



B: Exercise-based therapies

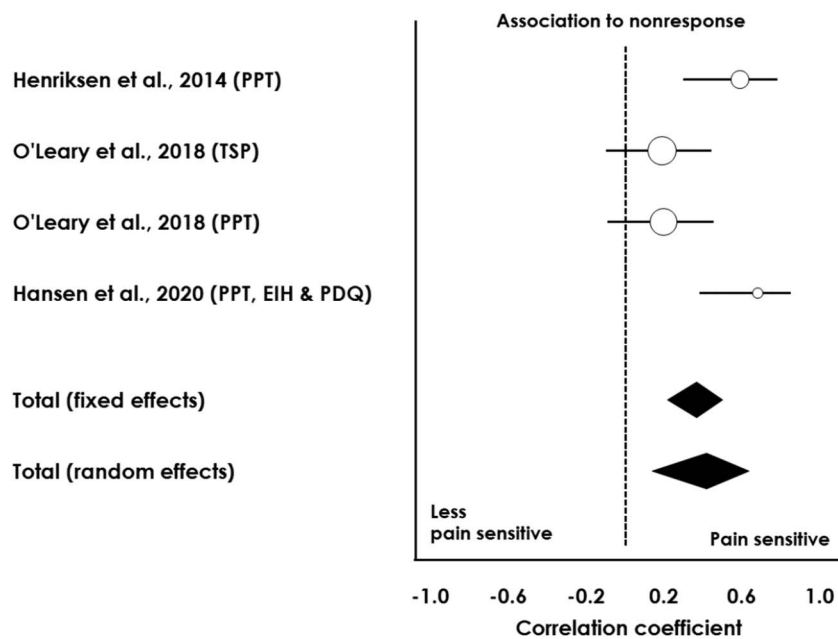


Figure 3. Forest plot from pharmacological (A) and exercise-based (B) therapy studies assessing associations between preoperative pain sensory profiles and response to therapy. The correlation coefficient (positive values) indicates the strength of association between the preoperative QST parameter and the postoperative pain outcome. CPM, conditioned pain modulation; EIH, exercise-induced hypoalgesia; EPT, electrical pain threshold; PPT, pressure pain threshold; PDQ, PainDetect Questionnaire; QST, quantitative sensory testing; VAS, Visual Analogue Scale.

statistically significant association between pretreatment QST parameters and pain responses after treatment for patients with knee osteoarthritis. Three meta-analyses demonstrated that a pretreatment QST profiling to some degree could predict poor pain-relieving response after total knee arthroplasty, NSAIDs, and exercise-based therapy. Pretreatment pressure pain thresholds, temporal summation of pain, and conditioned pain modulation

were the most frequently reported QST predictors. The studies included in the meta-analyses suffered from substantial risk of publication bias, which should be considered when interpreting the results.

Based on this work, it is hypothesized that a subset of specific pain-sensitive patients with osteoarthritis exist and that these patients do not respond adequately to standard osteoarthritic

pain treatments. Research should focus on to identify this group and offer a more comprehensive pain management program.

Disclosures

The authors have no conflict of interest to declare.

Acknowledgements

K.K.-S. Petersen acknowledge support from The Aalborg University Talent Management Programme (j.no. 771126) for providing the funding to initiate this work. Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). Center for Mathematical Modeling of Knee Osteoarthritis (MathKOA) is funded by the Novo Nordisk Foundation (grant no. NNF21OC0065373). Author contribution: K.K.-S. Petersen and D. Boye Larsen conceptualized the idea; K.K.-S. Petersen, D. Boye Larsen, K. Kilic, T.H. Sejersgaard-Jacobsen, M.K. Jørgensen, and L. Arendt-Nielsen conducted the systematic review; K.K.-S. Petersen, E. Hertel, and D. Boye Larsen conducted the meta-analysis, and K.K.-S. Petersen wrote the first draft. L. Arendt-Nielsen, K. Kilic, E. Hertel, T.H. Sejersgaard-Jacobsen, M.K. Jørgensen, A. Troelsen, and D. Boye Larsen provided an in-depth critical review of the manuscript. All author's critically revised the final manuscript and agreed to submit.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PR9/A194>.

Article history:

Received 7 October 2022

Received in revised form 27 February 2023

Accepted 9 March 2023

References

- Arendt-Nielsen L, Graven-Nielsen T. Translational musculoskeletal pain research. *Best Pract Res Clin Rheumatol* 2011;25:209–26.
- Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain* 2009;10:556–72.
- Arendt-Nielsen L, Egsgaard LL, Petersen KK, Eskehave TN, Graven-Nielsen T, Hoeck HC, Simonsen O. A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. *Eur J Pain* 2015;19:1406–17.
- Arendt-Nielsen L, Skou ST, Nielsen TA, Petersen KK. Altered central sensitization and pain modulation in the CNS in chronic joint pain. *Curr Osteoporos Rep* 2015;13:225–34.
- Arendt-Nielsen L, Egsgaard LL, Petersen KK. Evidence for a central mode of action for etoricoxib (COX-2 inhibitor) in patients with painful knee osteoarthritis. *PAIN* 2016;157:1634–44.
- Arendt-Nielsen L, Simonsen O, Laursen MB, Roos EM, Rathleff MS, Rasmussen S, Skou ST. Pain and sensitization after total knee replacement or nonsurgical treatment in patients with knee osteoarthritis: identifying potential predictors of outcome at 12 months. *Eur J Pain* 2018;22:1088–102.
- Arendt-Nielsen L. Pain sensitisation in osteoarthritis. *Clin Exp Rheumatol* 2017;35(suppl 1):68–74.
- Bannister K, Patel R, Goncalves L, Townson L, Dickenson AH. Diffuse noxious inhibitory controls and nerve injury: restoring an imbalance between descending monoamine inhibitions and facilitations. *PAIN* 2015;156:1803–11.
- Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, Blanco FJ, Espinosa R, Haugen IK, Lin J, Mandl LA, Moilanen E, Nakamura N, Snyder-Mackler L, Trojian T, Underwood M, McAlindon TE. OARS
- guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–89.
- Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, Blanco FJ, Espinosa R, Haugen IK, Lin J, Mandl LA, Moilanen E, Nakamura N, Snyder-Mackler L, Trojian T, Underwood M, McAlindon TE. OARS guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–89.
- Berenbaum F, Wallace LJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2018;14:674–81.
- Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open* 2012;2:e000435.
- Bijlsma JWW, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;377:2115–26.
- Bossmann T, Brauner T, Wearing S, Horstmann T. Predictors of chronic pain following total knee replacement in females and males: an exploratory study. *Pain Manag* 2017;7:391–403.
- Boye Larsen D, Laursen M, Simonsen O, Arendt-Nielsen L, Petersen KK. The association between sleep quality, preoperative risk factors for chronic postoperative pain and postoperative pain intensity 12 months after knee and hip arthroplasty. *Br J Pain* 2021;15:486–96.
- Bruehl S, Billings FT, Anderson S, Polkowski G, Shinar A, Schildcrout J, Shi Y, Milne G, Dematteo A, Mishra P, Harden RN. Preoperative predictors of complex regional pain syndrome outcomes in the 6 months following total knee arthroplasty. *J Pain* 2022;23:1712–23.
- Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, Aspley S, Reader S. A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. *Ann Rheum Dis* 2011;70:1534–41.
- Dürsteler C, Salazar Y, Rodriguez U, Pelfort X, Verdié LP. Conditioned pain modulation predicts persistent pain after knee replacement surgery. *Pain Rep* 2021;6:e910.
- Edwards RR, Haythornthwaite JA, Smith MT, Klick B, Katz JN. Catastrophizing and depressive symptoms as prospective predictors of outcomes following total knee replacement. *Pain Res Manag* 2009;14:307–11.
- Edwards RR, Dolman AJ, Martel MO, Finan PH, Lazaridou A, Cornelius M, Wasan AD. Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. *BMC Musculoskelet Disord* 2016;17:284–92.
- Edwards RR, Campbell C, Schreiber KL, Meints S, Lazaridou A, Martel MO, Cornelius M, Xu X, Jamison RN, Katz JN, Carriere J, Khanuja HP, Sterling RS, Smith MT, Haythornthwaite JA. Multimodal prediction of pain and functional outcomes 6 months following total knee replacement: a prospective cohort study. *BMC Musculoskelet Disord* 2022;23:302.
- Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M, McAlindon T, Spector TD, Poole AR, Yanovski SZ, Ateshian G, Sharma L, Buckwalter JA, Brandt KD, Fries JF. Osteoarthritis: new insights—part 1: the disease and its risk factors. *Ann Intern Med* 2000;133:635–46.
- Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, Campbell CM, Haythornthwaite JA, Edwards RR, Smith MT. Discordance between pain and radiographic severity in knee osteoarthritis: findings from quantitative sensory testing of central sensitization. *Arthritis Rheum* 2013;65:363–72.
- Gandhi R, Santone D, Takahashi M, Dessouki O, Mahomed NN. Inflammatory predictors of ongoing pain 2 years following knee replacement surgery. *Knee* 2013;20:316–8.
- Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. *Nat Rev Rheumatol* 2010;6:599–606.
- Graven-Nielsen T, Kendall SA, Henriksson KG, Bengtsson M, Sörensen J, Johnson A, Gerdle B, Arendt-Nielsen L, Sörensen J, Johnson A, Gerdle B, Arendt-Nielsen L. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *PAIN* 2000;85:483–91.
- Hansen S, Vaegter HB, Petersen KK. Pretreatment exercise-induced hypoalgesia is associated with change in pain and function after standardized exercise therapy in painful knee osteoarthritis. *Clin J Pain* 2020;36:16–24.
- Henriksen M, Klokke L, Graven-Nielsen T, Bartholdy C, Jørgensen TS, Bandak E, Danneskiold-Samsøe B, Christensen R, Bliddal H. Exercise therapy reduces pain sensitivity in patients with knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res (Hoboken)* 2014;66:1836–43.

- [29] Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions*, version 5.1. Chichester, United Kingdom: John Wiley & Sons, 2011.
- [30] Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol Psychiatry* 2016;80:40–52.
- [31] Izumi M, Hayashi Y, Saito R, Oda S, Petersen KK, Arendt-Nielsen L, Ikeuchi M. Detection of altered pain facilitatory and inhibitory mechanisms in patients with knee osteoarthritis by using a simple bedside tool kit (QuantiPain). *Pain Rep* 2022;7:e998.
- [32] Koh IJ, Kim MS, Sohn S, Song KY, Choi NY, In Y. Duloxetine reduces pain and improves quality of recovery following total knee arthroplasty in centrally sensitized patients. *J Bone Joint Surg* 2019;101:64–73.
- [33] Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice ASC, Rief W, Sluka AK. Do we need a third mechanistic descriptor for chronic pain states? *PAIN* 2016;157:1382–6.
- [34] Kurien T, Arendt-Nielsen L, Petersen KK, Graven-Nielsen T, Scammell BE. Preoperative neuropathic pain-like symptoms and central pain mechanisms in knee osteoarthritis predicts poor outcome 6 months after total knee replacement surgery. *J Pain* 2018;19:1329–41.
- [35] Larsen DB, Laursen M, Edwards RR, Simonsen O, Arendt-Nielsen L, Petersen KK. The combination of preoperative pain, conditioned pain modulation, and pain catastrophizing predicts postoperative pain 12 months after total knee arthroplasty. *Pain Med* 2021;22:1583–90.
- [36] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. *PAIN* 1979;6:305–27.
- [37] Lockwood SM, Bannister K, Dickenson AH. An investigation into the noradrenergic and serotonergic contributions of diffuse noxious inhibitory controls in a monoiodoacetate model of osteoarthritis. *J Neurophysiol* 2019;121:96–104.
- [38] Lundblad H, Kreicbergs A, Jansson K-Å. Prediction of persistent pain after total knee replacement for osteoarthritis. *J Bone Joint Surg Br Vol* 2008;90-B:166–71.
- [39] Martinez V, Fletcher D, Bouhassira D, Sessler DI, Chauvin M. The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. *Anesth Analg* 2007;105:815–21.
- [40] Noiseux NO, Callaghan JJ, Clark CR, Zimmerman MB, Sluka KA, Raket BA. Preoperative predictors of pain following total knee arthroplasty. *J Arthroplasty* 2014;29:1383–7.
- [41] O'Leary H, Smart KM, Moloney NA, Blake C, Doody CM. Pain sensitization associated with nonresponse after physiotherapy in people with knee osteoarthritis. *PAIN* 2018;159:1877–86.
- [42] Paredes AC, Pinto JM, Almeida A, Pinto PR. Predictive value of quantitative sensory testing for acute and chronic postsurgical pain after total joint arthroplasty: a systematic review. *PAIN* 2022;163:e385–400.
- [43] Petersen KK, Arendt-Nielsen L. Chronic postoperative pain after joint replacement. *Pain Clin Update* 2016;24. Available at: http://iasp.files.cms-plus.com/AM/IMAGES/PCU/PCU%2024-3_FINALFOR%20WEB.pdf
- [44] Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. *PAIN* 2015;156:55–61.
- [45] Petersen KK, Graven-Nielsen T, Simonsen O, Laursen MB, Arendt-Nielsen L. Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. *PAIN* 2016;157:1400–6.
- [46] Petersen KK, Simonsen O, Laursen MB, Arendt-Nielsen L. The role of preoperative radiologic severity, sensory testing, and temporal summation on chronic postoperative pain following total knee arthroplasty. *Clin J Pain* 2018;34:193–7.
- [47] Petersen KK, Olesen AE, Simonsen O, Arendt-Nielsen L. Mechanistic pain profiling as a tool to predict the efficacy of 3-week nonsteroidal anti-inflammatory drugs plus paracetamol in patients with painful knee osteoarthritis. *PAIN* 2019;160:486–92.
- [48] Petersen KK, Simonsen O, Olesen AE, Mørch CD, Arendt-Nielsen L. Pain inhibitory mechanisms and response to weak analgesics in patients with knee osteoarthritis. *Eur J Pain* 2019;23:1904–12.
- [49] Petersen KK, Vaegter HB, Stubhaug A, Wolff A, Scammell BE, Arendt-Nielsen L, Larsen DB. The predictive value of quantitative sensory testing: a systematic review on chronic postoperative pain and the analgesic effect of pharmacological therapies in patients with chronic pain. *PAIN* 2021;162:31–44.
- [50] Petersen KKS, Drewes AM, Olesen AE, Ammitzbøll N, Bertoli D, Brock C, Arendt-Nielsen L. The effect of duloxetine on mechanistic pain profiles, cognitive factors and clinical pain in patients with painful knee osteoarthritis—a randomized, double-blind, placebo-controlled, crossover study. *Eur J Pain* 2022;26:1650–64.
- [51] Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. *Expert Rev Neurother* 2009;9:745–58.
- [52] Rice DA, Kluger MT, McNair PJ, Lewis GN, Somogyi AA, Borotkanics R, Barratt DT, Walker M. Persistent postoperative pain after total knee arthroplasty: a prospective cohort study of potential risk factors. *Br J Anaesth* 2018;121:804–12.
- [53] Safiri S, Kolahi A-A, Smith E, Hill C, Bettampadi D, Mansournia MA, Hoy D, Ashrafi-Asgarabad A, Sepidarkish M, Almasi-Hashiani A, Collins G, Kaufman J, Qorbani M, Moradi-Lakeh M, Woolf AD, Guillemin F, March L, Cross M. Global, regional and national burden of osteoarthritis 1990–2017: a systematic analysis of the Global Burden of Disease Study 2017. *Ann Rheum Dis* 2020;79:819–28.
- [54] Sangesland A, Støren C, Vaegter HB. Are preoperative experimental pain assessments correlated with clinical pain outcomes after surgery? A systematic review. *Scand J Pain* 2017;15:44–52.
- [55] Schaible HG. Nociceptive neurons detect cytokines in arthritis. *Arthritis Res Ther* 2014;16:470.
- [56] Schug SA, Peyton P. Does perioperative ketamine have a role in the prevention of chronic postsurgical pain: the ROCKET trial. *Br J Pain* 2017; 11:166–8.
- [57] Skou ST, Roos EM. Good Life with osteoArthritis in Denmark (GLA:D™): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC Musculoskelet Disord* 2017;18:72.
- [58] Vaegter HB, Handberg G, Emmeluth C, Graven-Nielsen T. Preoperative hypoalgesia after cold pressor test and aerobic exercise is associated with pain relief 6 months after total knee replacement. *Clin J Pain* 2017; 33:475–84.
- [59] Wylde V, Palmer S, Learmonth ID, Dieppe P. The association between pre-operative pain sensitisation and chronic pain after knee replacement: an exploratory study. *Osteoarthritis Cartilage* 2013;21:1253–6.
- [60] Wylde V, Sayers A, Lenguerrand E, Gooberman-Hill R, Pyke M, Beswick AD, Dieppe P, Blom AW. Preoperative widespread pain sensitization and chronic pain after hip and knee replacement. *PAIN* 2015;156:47–54.
- [61] Wylde V, Dixon S, Miller LL, Whitehouse MR, Blom AW. 5 year outcomes and survivorship of the triathlon total knee replacement: a cohort study. *Acta Orthop Belg* 2017;83:259–67.
- [62] Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain* 2010;14:339.
- [63] Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *PAIN* 2012;153:1193–8.
- [64] Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol* 2010;23:611–5.
- [65] Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15:981–1000.
- [66] Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137–62.