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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

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Abstract

. Studies have suggested that quantitative sensory testing (QST) might hold a predictive value for development of chronic postoperative pain and the response to pharmacological interventions. This review systematically summarizes the current evidence on the predictive value of QST for chronic postoperative pain and the effect of pharmacological interventions. The main outcome measures were posttreatment pain intensity, pain relief, presence of moderate-to-severe postoperative pain, responders of 30% and 50% pain relief or validated questionnaires of pain and disability.

A systematic search of MEDLINE and EMBASE yielded 25 studies on surgical interventions and 11 on pharmacological interventions. Seventeen surgical and 11 pharmacological studies reported an association between preoperative or pre-treatment QST and chronic postoperative pain or analgesic effect. The most commonly assessed QST modalities were pressure stimuli (17 studies), temporal summation of pain (TSP, 14 studies) and conditioned pain modulation (CPM, 16 studies). Of those, the dynamic QST parameters TSP (50%) and CPM (44%) were most frequently associated with chronic postoperative pain and analgesic effects. A large heterogeneity in methods for assessing TSP (n=4) and CPM (n=7) was found. Overall, most studies demonstrated low-to-moderate levels of risk of bias in study design, attrition, prognostic factors, outcome, and statistical analyses.

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This systematic review demonstrates that TSP and CPM show the most consistent predictive values for chronic postoperative pain and analgesic effect, but the heterogeneous methodologies reduce the generalizability and hence call for methodological guidelines.

Keywords: Quantitative sensory testing, chronic pain, chronic postoperative pain, analgesic effect

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Introduction

Chronic pain is a major problem in the adult population [18] and treatment is difficult due to the limited amount of available, efficient drugs and the undesired side effects. It is evident that chronic postoperative pain is present in 10-50% of patients following different surgical treatments [49,89] and the effect of available pharmacological treatments remains low [29,88]. Identifying patients responding to standard pain treatments is warranted as a start to implement individualized pain treatment.

Quantitative sensory testing (QST) can be combined using different sensory stimuli, and multiple QST protocols have been developed to probe the activity in specific nerve fibre populations and as proxies for spinal and pain modulatory functions [11,84]. Most QST protocols allow the assessment of thermal, electrical, tactile, or pressure pain modalities [12,23,35,84,104]. Reduced pain thresholds or increased sensory intensity ratings assessed at a local painful site mainly reflect modality-specific peripheral hyperalgesia whereas assessments distant to a painful site may reflect widespread hyperalgesia as a surrogate measure of central hypersensitivity [10,34]. Studies have found reduced pressure pain thresholds at distal sites to the knee in patients with knee osteoarthritis [8,37], increased sensitivity to thermal and mechanical stimuli in a subgroup of patients with neuropathies [83,101], and reduced electrical pain thresholds at the dorsal pancreatic referred dermatomes and at distant dermatomes in patients with chronic pancreatitis [55] compared with

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pain-free subjects. These studies indicate that chronic pain patients of different aetiologies show generalised widespread hyperalgesia [7].

Dynamic QST protocols have been developed to explore the central wind-up process using the proxy temporal summation of pain (TSP) [34]. Facilitated TSP has been reported across multiple chronic pain disorders such as osteoarthritis [10], fibromyalgia [36], irritable bowel syndrome [7], and in subgroups of patients with neuropathic pain [62]. Aspects of descending pain inhibitory control can most likely be mechanistically evaluated using the human proxies of conditioned pain modulation (CPM) [109], exercise-induced hypoalgesia [71], or offset analgesia [44] protocols. Impaired CPM has been reported in several chronic painful conditions when compared with pain-free subjects [7,109]. Exercise-induced hypoalgesia seems functional in asymptomatic subjects [95–98] and impaired in different pain populations [28,57,68,94]; although the current literature is inconclusive [19,28,94]. Similarly, offset analgesia seems functional in asymptomatic subjects [44] and impaired in patients with chronic pain [92].

Studies have suggested a possible association between preoperative QST parameters and chronic postoperative pain [47,56,75] and that pretreatment QST may predict the analgesic effect of pharmacological interventions [76,112]. Previous systematic reviews [2,38,46,86,103] have investigated the predictive value of QST on postoperative pain, the most recent in 2017 [86], and the predictive value of QST on the analgesic effect, the most recent in 2013 [38]. The most recent review from 2017 on surgical studies [85] indicated that preoperative QST mainly predicts chronic postoperative pain but not acute postoperative pain. As multiple studies have been published since 2017, this review systematically summarizes the current literature on the possible predictive role of QST on 1) chronic postoperative pain and 2) the analgesic effect of pharmacological interventions in patients with chronic pain.

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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 chronic postoperative pain and the analgesic effect of pharmacological interventions in patients with chronic pain. The systematic review has been registered on the Open Science Framework website (OSF.IO, registration citation: [58], link to protocol: DOI: 10.17605/OSF.IO/HSVYK).

Outcomes

The primary outcomes for chronic postoperative pain were postoperative pain intensity, postoperative pain relief, presence of moderate-to-severe postoperative pain, or validated questionnaires on pain and disability. The primary outcomes of pharmacological studies were pre- and posttreatment changes in pain scores, classification of responders to 30% or 50% pain relief, end of treatment pain intensity, or validated questionnaires on pain and disability.

Search strategy and selection of studies

A literature search was conducted in April 2020 in the databases PubMed and EMBASE. The search was limited to literature published in the last 20 years (April 2000-April 2020). Only peer-reviewed studies published in English and with available full-text articles were considered eligible for the systematic review. Two searches were conducted to identify (1) the predictive value of QST for chronic postoperative pain outcomes and (2) the predictive value of QST on analgesic effect outcomes of pharmacological interventions. The MeSH terms and/or text word combinations are shown in Table 1.

All citations were exported to EndNote X4 (Thomson Reuters, Philadelphia, PA, USA) and duplicates were removed. Due to the large number of potential studies, the initial screening was conducted on title and abstract to remove citations that did not meet the scope of the systematic review. The screening process was independently performed by two reviewers (KKP and DBL)

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after the initial systematic database search. Disagreements in relevancy were solved by consensus. In case consensus was not reached, a third reviewer (HBV) was consulted who made the final decision. After the screening, all full-text articles were obtained. Cross-referencing the included studies and the authors' own article collection was conducted for additional relevant literature. The inclusion and exclusion of relevant literature is shown in Figure 1 (PRISMA flowchart).

Eligibility criteria

The studies included had to report the predictive model of a postoperative or post-pharmacological outcome of at least one QST modality including electrical, thermal, mechanical or pressure, pain, tolerance and suprathreshold stimuli, TSP, allodynia, exercise-induced hypoalgesia, offset analgesia, CPM, or the full German Research Network on Neuropathic Pain (DFNS) protocol. Studies were included if they reported associations between QST and pain-related outcome after surgery or pharmacological intervention using correlations (Spearman or Pearson correlations), regression models, or other predictive models such as support vector machine or reduction in numbers needed to treat. Studies on animals and healthy subjects were excluded. Surgical studies were included if they assessed follow-up pain at least 3 months after surgery. Acute postoperative pain and studies in the subacute phase were not considered. Pharmacological studies were included if they studied the long-term effect (weeks of treatment) of pharmacological interventions. Therefore, studies investigating the acute effect (minutes or hours after administration) were excluded. All studies were required to have a detailed description of the utilized QST paradigm.

Data extraction, synthesis, and assessment

The data extraction was conducted by KKP. For studies on chronic postoperative pain, the data included type of surgery, patient cohort, QST parameters tested, follow-up time after surgery, the dependent outcomes of the prediction model, and preoperative predictors and their associated predictive value for the dependent variable. For the pharmacological studies, the data involved type

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of pharmacological intervention, patient cohort, QST parameters tested, treatment period, dependent variable in the prediction model, and predictive value of the QST parameters for the dependent variable. All outcomes were narratively synthesized to provide an overview of each QST paradigm assessed and presented within each domain of QST in its prediction of chronic postoperative pain or analgesic effect of pharmacological interventions. This was conducted due to the large heterogeneity in both the QST paradigms used and the clinical cohorts included in the studies, which meant that a meta-analysis would not be appropriate. The methodological and the overall quality of the included studies were assessed by two reviewers (KKP and DBL) using the Quality In Prognosis Studies (QUIPS) tool [43]. Following the guidelines, each study was assessed on methodological quality in the major categories of "Study participation", "Study attrition", "Prognostic factor measurement", "Outcome measurement", "Study confounding", and "Statistical analysis and reporting". Disagreements in the risk of bias analysis were solved by consensus, and if no consensus was reached, a third reviewer (HBV) was consulted.

Results

The literature searches identified 1811 surgical and 2689 pharmacological studies of which 25 surgical and 11 pharmacological studies were included (see figure 1). The outcome parameters of the surgical studies were postoperative pain intensity (12 studies [1,4,105,111,39,48,56,61,67,75,77,100]), postoperative pain relief (3 studies [9,79,94]), presence of moderate-to-severe postoperative pain (6 studies [16,41,70,72,82,91]), or validated questionnaires on pain and disability (3 studies [40,107,108]), table 2. The outcome parameters in the pharmacological studies were pre- and posttreatment changes in pain scores (4 studies [25,76,78,112]), migraine scores (1 study [51]), and classification of responders to 30% (3 studies [5,63,73]) or 50% (2 studies [20,21]) pain relief, and end of treatment pain intensity [24], table 3.

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Most studies (27 studies) reported using multivariate statistical models, and univariate analyses were reported in nine studies.

Quality assessment

The quality assessment is presented in table 4 (surgical) and 5 (pharmaceutical). The reviewers (KKP and DBL) initially agreed on 89% of the ratings. Consensus was reached on all ratings following discussion.

QST variables

Electrical stimuli

Electrical stimuli were reported as electrical detection threshold, electrical pain threshold, or electrical pain tolerance threshold. Electrical stimuli were reported in four studies and found predictive in two studies (2/4 = 50%) [61,73].

Electrical detection threshold

Electrical detection threshold was reported in one surgical study and no pharmacological studies. Preoperative electrical pain threshold was not found significantly associated with the chronic postoperative pain intensity after total knee arthroplasty [61].

Electrical pain threshold

Electrical pain threshold was reported in two surgical studies and one pharmacological study. Low preoperative electrical pain threshold and high pain at rest predicted the chronic postoperative pain intensity after total knee arthroplasty [61]. Electrical pain threshold was not significantly associated with persistent chronic postoperative pain or disability following segment spinal surgery of chronic low back pain patients [70].

In the pharmacological studies, using a support vector machine analysis the pre-treatment ratio between electrical pain threshold at a pancreatic referred dermatome versus a non-affected

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dermatome predicted the response to pregabalin (reduction in clinical pain score of 30% or more after three weeks of treatment compared with placebo) with a sensitivity of 87.5% and specificity of 80.0% [73].

Electrical pain tolerance threshold

EPTT was reported in one surgical study in which preoperative electrical pain tolerance threshold was not associated with the chronic postoperative pain intensity after major abdominal surgery [105]. No pharmacological studies reported electrical pain tolerance threshold.

Thermal stimuli

Thermal stimuli were reported as cold and warm detection threshold, cold and heat pain threshold, and suprathreshold heat and cold stimuli. Thermal stimuli were reported in 11 studies and found predictive in five studies (5/11 ≈ 45%) [1,25,51,64,77].

Warm detection threshold

Warm detection thresholds were reported in three surgical studies and one pharmacological study. One surgical study reported a linear regression model demonstrating that low preoperative warm detection threshold, low heat pain threshold, low degree of radiologically assessed osteoarthritis and high TSP predicted a high chronic postoperative pain intensity following total knee arthroplasty in patients with knee osteoarthritis [77]. Two surgical studies did not find an association between preoperative warm detection thresholds and chronic postoperative pain intensity (groin hernia repair surgery [1] and breast cancer surgery[4]). One pharmacological (duloxetine for treatment of diabetic peripheral neuropathy [112]) study did not find associations between preoperative warm detection threshold and analgesic effect.

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Heat pain threshold

Heat pain thresholds were reported in nine surgical and three pharmacological studies. One surgical study reported a linear regression model including low preoperative heat pain threshold, low warm detection threshold, low degree of radiologically assessed osteoarthritis, and high TSP which predicted a high chronic postoperative pain intensity following total knee arthroplasty in patients with knee osteoarthritis [77]. Eight surgical studies did not find associations between preoperative heat pain thresholds and chronic postoperative pain intensity (thoracic surgery [111], groin hernia repair surgery [1], arthroscopic surgery of the shoulder [100] and breast cancer surgery [4]), postoperative Western Ontario and McMaster Universities Osteoarthritis Index scores (total knee arthroplasty [107]), and the presence of moderate-to-severe chronic postoperative pain (total knee arthroplasty [72] and segmental spinal surgery [70]).

In the pharmacological studies, a hierarchical regression model demonstrated that low heat pain threshold was associated with a small analgesic effect of opioids in patients with postherpetic neuralgia [25]. Further, using multivariate regression models a great analgesic response to duloxetine in patients with migraine [51] and painful diabetic neuropathy [112] were not significant associated with pretreatment heat pain thresholds.

Cold detection threshold

Cold detection thresholds were reported in two surgical studies and one pharmacological study. Preoperative or pretreatment cold detection thresholds were not statistically significantly associated with the chronic postoperative pain intensity (total knee arthroplasty [77] and breast cancer surgery[4]) or the analgesic effect (duloxetine for diabetic peripheral neuropathy [112]), respectively.

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Cold pain threshold

Cold pain thresholds were reported in four surgical and no pharmacological studies. Preoperative cold pain thresholds were not significantly associated with the chronic postoperative pain intensity (total knee arthroplasty [67,77]) and the presence of moderate-to-severe chronic postoperative pain (thoracic surgery [16] and segmental spinal surgery [70]).

Suprathreshold heat and cold stimuli

Suprathreshold heat and cold stimuli were reported in three surgical and no pharmacological studies. In a logistic regression model, preoperative high pain intensities to suprathreshold heat stimuli along with lowered warm detection thresholds and pain-related impairment of activity were predictive of the presence of moderate-to-severe chronic postoperative pain following hernia repair [1]. Preoperative suprathreshold heat stimuli and suprathreshold cold stimuli were not significantly associated with postoperative pain intensity (thoracic surgery [111]) and the presence of moderate-to-severe chronic postoperative pain (thoracic surgery [16]).

Cutaneous mechanical stimuli

Cutaneous mechanical stimuli were reported as mechanical detection and pain threshold. Cutaneous mechanical stimuli were reported in seven and predictive in no studies (0/7 = 0%)

Mechanical detection threshold

Mechanical detection thresholds were reported in two surgical studies and one pharmacological study. Preoperative and pretreatment mechanical detection thresholds were not statistically significantly associated with the chronic postoperative pain intensity (surgical correction of funnel chest [39] and breast cancer surgery [4]), or analgesic effect (duloxetine for treatment of diabetic peripheral neuropathy [112]).

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Mechanical pain threshold

Mechanical pain thresholds were reported in four surgical studies and one pharmacological study. Preoperative and pretreatment mechanical pain thresholds were not associated with chronic postoperative pain intensity (total knee arthroplasty [67] and breast cancer surgery[4]), presence of moderate-to-severe postoperative pain (total knee arthroplasty [72]), postoperative Oxford shoulder score (arthroscopic subacromial decompression [40]), or analgesic effect (duloxetine for treatment of diabetic peripheral neuropathy [112]).

Pressure stimuli

Pressure stimuli were studied as pressure pain and tolerance threshold as well as cuff-induced pressure pain and tolerance thresholds. Deep pressure stimuli were reported in 17 studies and were predictive in five studies (5/17 ≈ 29%) [9,56,79,107,108].

Pressure pain threshold

Pressure pain thresholds were reported in 11 surgical and three pharmacological studies. Low pressure pain thresholds assessed at the osteoarthritic affected knee [56] were associated with postoperative pain, low pressure pain thresholds at the non-affected knee [9] were associated with postoperative pain relief, and low pressure pain thresholds at the forearm [107] were associated with postoperative high Western Ontario and McMaster Universities Osteoarthritis Index scores following total knee arthroplasty. A study found that low pressure pain thresholds assessed at the forearm in patients with hip osteoarthritis were associated with high postoperative Western Ontario and McMaster Universities Osteoarthritis Index scores following total hip arthroplasty but not in patients with knee osteoarthritis following total knee arthroplasty [108]. Eight studies did not find a statistically significant association between preoperative pressure pain thresholds and chronic postoperative pain intensity (total knee arthroplasty [56], surgical correction of funnel chest [39] and breast cancer surgery[4]), postoperative pain relief (total knee arthroplasty [79,94]), or the

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presence of moderate-to-severe postoperative pain (total knee arthroplasty [72,82] and segmental spinal surgery [70]).

For the pharmacological studies, three studies found no association between pretreatment pressure pain thresholds and analgesic effect (COX-2 [5] inhibitors and NSAID gels [24] for treatment of painful knee osteoarthritis and pregabalin for treatment of painful chronic pancreatitis [73]).

Pressure tolerance threshold

Pressure tolerance thresholds were reported in two surgical and no pharmacological studies. Preoperative pressure tolerance threshold was not associated with the chronic postoperative pain intensity (major abdominal surgery [105]) and presence of persistent pain and disability (segmental spinal surgery [70]).

Cuff-induced pain detection threshold

Cuff-induced pressure pain thresholds were reported in three surgical studies and one pharmacological study. Low cuff-induced pressure pain threshold assessed at the lower leg in patients with knee osteoarthritis was associated with chronic postoperative pain relief following total knee arthroplasty [79]. Two studies did not find a significant association between preoperative cuff-induced pressure pain thresholds and the chronic postoperative pain intensity (total knee arthroplasty [56]) or postoperative pain relief (total knee arthroplasty [94]). One pharmacological study demonstrated no association between pretreatment cuff-induced pressure pain threshold and analgesic effect (oral NSAIDs and paracetamol for the treatment of pain in knee osteoarthritis [76]).

Cuff-induced pressure tolerance threshold

Cuff-induced pain tolerance thresholds were reported in three surgical studies and one pharmacological study. Three surgical studies did not find a significant association between preoperative cuff-induced pain tolerance threshold and the chronic postoperative pain intensity

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(total knee arthroplasty [56]) or postoperative pain relief (total knee arthroplasty [79,94]). The pharmacological study did not find a significant association between pretreatment cuff-induced pain tolerance threshold and analgesic effect (oral NSAIDs and paracetamol for the treatment of pain in knee osteoarthritis [76]).

Dynamic mechanical allodynia

Dynamic mechanical allodynia was reported in three surgical and no pharmacological studies and was reported predictive in one study (1/3 ≈ 33%). The presence of preoperative dynamic mechanical allodynia (yes/no) was associated with the chronic postoperative pain intensity in females undergoing gynecologic laparoscopy [48]. Two studies did not find associations between preoperative dynamic mechanical allodynia and the postoperative pain intensity (surgical correction of funnel chest [39] and total knee arthroplasty [67]).

Temporal summation of pain

Temporal summation of pain (TSP) was reported in 14 studies (9 surgical and 5 pharmacological studies) and predictive in 7 studies (7/14 = 50%) [5,56,75–77,82,91].

In the surgical studies, TSP was assessed using mechanical stimuli [56,75,77,82,91], heat stimuli [100], and cuff stimuli [56,79]. In five surgical studies, high preoperative TSP was associated with the chronic postoperative pain intensity following total knee arthroplasty [56,75,77] and the presence of moderate-to-severe chronic postoperative pain (total knee arthroplasty [82] and abdominal or laparoscopic hysterectomy [91]). Four studies reported that preoperative TSP was not associated with the chronic postoperative pain intensity (total knee arthroplasty [79] and arthroscopic shoulder surgery [100]), postoperative WOMAC (total knee arthroplasty [17]), and the presence of moderate-to-severe chronic postoperative pain (breast cancer surgery [41]).

In the pharmacological studies, TSP was assessed using mechanical stimuli [24,51,112], computer-controlled pressure stimuli [5], and manual cuff stimuli [76]. In two studies, high TSP was reported

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to be associated with poor analgesic effect after four weeks of treatment with COX-2 inhibitors [5] and three weeks of treatment with NSAIDs and paracetamol [76] in patients with knee osteoarthritis. Three studies did not find an association between pretreatment TSP and the analgesic effect of duloxetine for diabetic peripheral neuropathy [112],migraine [51], or topical NSAIDs for painful knee osteoarthritis [24].

Conditioned pain modulation

Conditioned pan modulation (CPM) was reported in 17 studies (12 surgical and 5 pharmacological studies) and predictive in seven studies (7/17 ≈ 41%) [24,78,94,105,111,112].

In the surgical studies, the test stimulus was assessed using pressure [17,39,70,75,82,94,105], cuff [56,79], heat [41,70,100,111], and electrical [70,105] stimuli with the conditioning stimuli being hot water [41,100,111], cold water [39,70,75,82,94,105], tonic cuff pressure [56,79], or pinching [17]. In four studies, preoperative impaired CPM was associated with chronic postoperative pain intensity (thoracic surgery [111], major abdominal surgery [105]), high postoperative WOMAC scores (total knee arthroplasty [17]), and a reduction in postoperative pain relief (total knee arthroplasty [94]). Eight studies did not find an association between preoperative CPM and the chronic postoperative pain intensity (total knee arthroplasty [56,75,79,82], surgical correction of funnel chest [39], and arthroscopic shoulder surgery [100]), postoperative pain relief (total knee arthroplasty [79]), and the presence of moderate-to-severe chronic postoperative pain (total knee arthroplasty [82], breast cancer surgery [41], and segmental spinal surgery [70]).

In the pharmacological studies, the test stimulus was assessed using pressure [5,24], cuff [78], and heat [51,112] stimuli with the conditioning stimuli hot water [112], cold water [51], or tonic cuff pressure [5,24,78]. Impaired CPM was associated with a great analgesic effect of duloxetine in patients with diabetic neuropathy [112]. This was also the case with topical NSAIDs [24] or NSAIDs and paracetamol [78] in patients with knee osteoarthritis. Pretreatment CPM was not

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associated with the analgesic effect of COX-2 inhibitors in patients with knee osteoarthritis [5] or duloxetine in patients with migraine [51]. Of note, Kisler et al., 2019 [51] found that the pretreatment test stimulus and the conditioned test stimulus in the CPM paradigm predicted the analgesic effect of duloxetine in patients with migraine but not the calculated CPM effect itself.

Offset analgesia

Offset analgesia was reported in one pharmacological study in which the pretreatment offset analgesia showed no association with the analgesic effect of NSAID and paracetamol for patients with knee osteoarthritis [78].

Exercise induced hypoalgesia

Exercise induced hypoalgesia was reported in one surgical study in which low preoperatively exercise induced hypoalgesia was associated with low postoperative pain relief following total knee arthroplasty [94].

Hypoesthesia area

One study assessed the preoperative size of the hypoesthesia area using warm (40^0C) and cold (25^0C) rolls and found an association between the size of the hypoesthesia and the chronic postoperative pain intensity following breast cancer surgery [4].

The German Research Network on Neuropathic Pain (DFNS) protocol

The German Research Network on Neuropathic Pain (DFNS) protocol consists of a wide range of QST modalities including allodynia, thermal detection and pain thresholds, paradoxical heat sensations, mechanical detection, pain thresholds, mechanical suprathreshold, TSP (wind-up), vibration detection threshold, and pressure pain threshold. The DFNS protocol was assessed in three pharmacological studies. In two pharmacological studies, the DFNS protocol was utilized to define the irritable nociceptor (IN) or non-irritable nociceptor (NIN) in patients with peripheral

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neuropathic pain. One study found that that the number needed to treat (NNT) for 50% pain relief of oxcarbazepine was 3.9 for IN and 13 for NIN [21]. A study found that that the NNT for 50% pain relief of lidocaine 5% patch was 7.5 for IN and not definable for the NIN due to recruitment issues. Finally, the DFNS protocol was used to predict the responders (+30% pain alleviation) and non-responders to capsaicin patch treatment in patients with peripheral neuropathy and found a sensitivity of 70% and a specificity of 100% for patients with cold pain thresholds and mechanical pain thresholds > 0.8 compared with z-values from DFNS [64].

Prediction of specific surgical procedures

In this review, 16 studies addressed joint-related surgeries, 3 studies thoracic-related surgeries, 4 studies abdominal and gynecology-related surgeries, and 2 studies addressed breast cancer surgeries. A significant preoperative prediction was demonstrated for 11 studies (69%) in the joint-related surgeries, 1 study (33%) in the thoracic-related surgeries, 4 studies (100%) in the abdominal and gynecology-related surgeries, and 1 study (50%) related to breast cancer surgery.

Discussion

The current systematic review describes the predictive role of QST on pain after surgical and pharmacological interventions. Twenty-five surgical (10 new studies since the latest review [85]) and 11 pharmacological (8 studies since the latest review [38]) studies published since 2000 were identified. Seventeen studies demonstrated an association between preoperative QST and chronic postoperative pain and 11 studies demonstrated an association between pre-treatment QST and the analgesic effect of pharmacological interventions but with a large heterogeneity in the QST paradigms used. Significant preoperative predictions were most often presented for joint-related surgeries and abdominal and gynecology-related surgeries. TSP, CPM and different variations of pressure thresholds were the most frequently reported methods, and TSP and CPM were most frequently found as predictors of the chronic postoperative pain intensity, the presence of moderate-

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to-severe chronic postoperative pain, postoperative pain relief and the analgesic effect to pharmacological interventions.

The predictive value of quantitative sensory testing

This review suggests a possible association between the selected QST parameters and chronic postoperative pain and the analgesic response to pharmacological interventions, but the results are not consistent. Overall, the most utilized QST paradigms were mechanical and pressure stimuli, TSP, and CPM, which were also most frequently associated with chronic postoperative pain or analgesic effect. In addition, the strength of the predictive value of QST varied with R^2 values ranging from 0.13 to 0.673, which further underlines that variance explanation remains suboptimal at best. Finally, it is important to acknowledge that the literature on the predictive role of QST for chronic postoperative pain and analgesic response to pharmacological interventions is conflicting, and therefore QST might not be appropriate as clinical guiding tool yet.

Decades of research has focused on the difference in QST parameters comparing pain-free subjects and patients with chronic pain; yet the differences have not been established to be specific for the pain diagnosis [7,34,83,101,106]. It is evident that some patients with chronic pain are generally more pain sensitive than others [6,93,101], but the underlying factors driving the increased pain sensitivity are still largely unclear. Studies have suggested that the pain sensitivity can be increased in patients with chronic pain due to, e.g., sleep impairment [90], increased pain catastrophizing [69], or comorbidities such as diabetes [27]. These factors are often observed in patients in chronic pain populations and warrant consideration when addressing the predictive value of QST in future studies.

A previous review [85] suggested a link between different QST modalities and certain pain disorders. To exemplify this, cutaneous stimuli have been found to activate cutaneous fibres [3] and

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pressure stimuli using algometers have been found to target muscles [30] or fascia [65]. This could indicate that, e.g., cutaneous activation would be suited for dermatological disorders and pressure stimuli would be suited for patients with muscle or joint pain. The most studied population of the current review was patients with osteoarthritis, and the hypothesis that pressure stimuli should adhere better to these patients is not supported by the current review since pressure stimuli were rarely (approx. 29%) predictive of chronic postoperative pain or analgesic effect. In addition, joint-related surgeries and abdominal and gynaecology-related surgeries were most often studied, and preoperative QSTs were most often associated with chronic postoperative pain, which could indicate that preoperative QSTs are more frequently predictive of certain surgical procedures. Future studies should pursue this hypothesis to clarify if there is an interaction between certain QST modalities and certain pain disorders.

This review investigated the predictive role of QST for chronic postoperative pain and analgesic response to pharmacological interventions although these two outcomes are different. In a pain mechanistic context, surgical procedures aim to remove the peripheral pain driver, and it has been demonstrated that a pain-free recovery after removal of such peripheral drives by, e.g. total knee [37] or hip arthroplasty [54] does normalize the responses to CPM and TSP when comparing pre- and six months postoperative assessments. The advantage of certain pharmacological interventions is the possibility to target central pain mechanisms. As an example, preclinical trials have established that serotonin and noradrenalin are important for descending pain inhibition [13,14,60], and human administration of duloxetine (a serotonin and noradrenaline reuptake inhibitor) does improve CPM in patients with painful diabetic neuropathy [112]. Likewise, the N-methyl-D-aspartate (NMDA) receptors are important for dorsal horn neuron excitability, and human administration of ketamine (a NMDA antagonist) reduces TSP in patients with fibromyalgia [36].

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Therefore, specific QST modalities might be better predictors for a certain treatment if the pain mechanistic profile is matched with the intervention.

The most consistent predictive QST paradigms were TSP and CPM, but these studies utilized multiple different protocols (assessment parameters and modalities). The reliability of CPM has been questioned [50] and studies comparing CPM protocols have highlighted that different test and conditioning stimuli combinations will yield different reliability results [45,99]. Some CPM protocols operate under the premise that the conditioning stimulus should be painful (VAS > 3) and that the CPM effect increases with increased conditioning stimulus intensity [35]. Conversely, other protocols are based on the notion that the intensity of the conditioning stimulus is independent of the CPM effect [33]. The 2015 recommendation for CPM [110] called for standardization of CPM testing across laboratories, which would greatly increase the generalizability of CPM in future studies. However, the current review highlights that the variability in different QST modalities has the potential to be utilized as predictor of pain after surgery and pharmacological interventions. It is well-known that dynamic QST modalities such as TSP and CPM are influenced by multiple factors such as sleep deprivation [26,59], use of opioids [66], or high clinical pain intensities [10]. Therefore, standardized protocols based on pain-free subjects might not represent the clinical use of QST.

Quality assessment

In this systematic review, the included studies overall demonstrated a low-to-moderate bias distributed among the four categories for bias assessment. For study participation, missing information on sampling frame and recruitment and place for assessment were the main causes for bias. For study attrition, lack of description of loss to follow-up and differences in participants completing and not completing the study were the main reasons for bias. In the category prognostic factor measurement, validity and reliability of the used methods together with the uncertainty with

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respect to the cut-offs chosen were the main reasons for bias. Confounding was another category that revealed substantial bias, in that confounders in either study design or analysis were rarely accounted for and that multivariate analyses were not carried out consistently.

Future directions

The current review highlights inconsistencies in QST as predictors of outcomes after surgical treatments and pharmacological interventions. The most consistent findings include studies assessing central pain mechanisms, and therefore future studies are encouraged to include parameters such as TSP or CPM and to understand the variability in the assessment of TSP and CPM. Fjeld et al., 2020 [31] studied patients with acute admission due to sciatica and found that the assessment of CPM six weeks after discharge did not predict pain at 12 months follow-up, which does highlight that the timing of assessment might be crucial. In addition, other non-QST parameters such as pain catastrophizing or epigenetic markers have been associated with chronic postoperative pain [15,22,32,80,81] and analgesic effects [39]. Including these parameters will likely increase the strength of the predictive models in future studies. Finally, due to the large heterogeneity in choice of QST parameters, standardization is needed and assessment of both painful and non-painful anatomic regions should be considered since this could influence the predictive value of QST [107,108].

In 2016, a task force appointed by The International Association for the Study of Pain [53] suggested “nociplastic” as a new pain descriptor to describe a state in which the nociceptive functions are changed. Several studies have now identified that specific subgroups of patients with chronic pain exist [6,93] and that these patients respond poorly to standard care treatments [42,74–76]. Understanding if modulation of specific central pain pathways prior to standard care treatments does increase the likelihood of positive analgesic responses would move this field forward. In this

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regard, acknowledging that a large variety of sensitization manifestations may represent a large variety of natural or acquired sensorimotor function modalities might be important.

Studies have found that, e.g., duloxetine can improve CPM [112] and ketamine can reduce TSP [36]. A recent study [52] on patients scheduled for total knee arthroplasty recruited "pain sensitive" patients using the central sensitization inventory questionnaire and found that preoperative and six weeks postoperative administration of duloxetine reduced the postoperative pain intensity at 2-12 weeks follow-up compared with placebo. Studies combining preoperative predictors with pharmacological interventions targeting these predictions might pave the way for the future of personalized pain medicine.

Limitations

The current review is limited to studies assessing chronic postoperative pain defined as pain reported at least three months after surgery. Several studies on the predictive role of QST for acute postoperative pain have been conducted (see review from 2017 [85]). Of note, studies such as Lunn et al., 2013 and Izumi et al., 2017 studied the postoperative period from 30 days to 6 weeks after surgery and these studies are not included in the current review.

Further, the current review is limited by not addressing studies using QST to predict the acute effect of pharmacological interventions such as Wasner et al., 2008 [102] and Schliessbach et al., 2018 [87].

Conclusion

This systematic review identified 17 surgical and 11 pharmacological studies reporting a predictive role of QST modalities for chronic postoperative pain or analgesic effect of pharmacological interventions. The strengths of the predictive models vary and no consistency was found for a single QST parameter. Pressure stimuli and dynamic QST parameters such as TSP and CPM were the

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most frequently assessed, and thermal stimuli, TSP, and CPM were most frequently associated with chronic postoperative pain or analgesic effects.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Figure legend

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram.

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Tables

Table 1: Search strategy. The MeSH and textword (tw) strings were permuted dependent on database.

		Focus	**Example keywords (PubMed search)**
1		Analgesic effect	(“Analgesia”[tw] OR “Drugs”[tw] OR “Drug therapy”[tw])
2		Postoperative pain	(“Postoperative pain”[MeSH] or “Postsurgical pain”[tw])
3		Quantitative sensory testing	((“Quantitative sensory testing”[tw] OR “QST”[tw]) OR (“Conditioned pain modulation”[tw] OR “CPM”[tw]) OR (“Temporal summation”[tw] OR “TSP”[tw]))
4		Surgery	(“Surgery”[tw])
5		Limits	“2000/01/01”[PDat], “English”[lang]

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Table 2: Surgical studies assessing quantitative sensory testing (QST) as predictors of chronic postoperative pain. QST modalities: ***ALL****: Dynamic mechanical allodynia,* ***CDT****: Cold Detection Threshold,* ***CPT****: Cold Pain Threshold,* ***cPPT****: Cuff-induced Pressure Pain Threshold,* ***cPTT****: Cuff-induced Pressure Tolerance Threshold,* ***CPM****: Conditioning Pain Modulation (c: cuff pressure test and condition stimuli, e: electrical test stimulus, heat: heat test stimulus, p: pressure test stimulus, *: hot water condition stimulus, # cold pressor tests as condition stimulus, ‡: pinching conditioning stimulus),* ***EDT****: Electrical Detection Threshold,* ***EIH****: Exercise-Induced Hypoalgesia,* ***EPT****: Electrical Pain Threshold,* ***EPTT****: Electrical Pain Tolerance Threshold,* ***HPT****: Heat Pain Threshold,* ***MDT****: Mechanical Detection Threshold,* ***MPT****: Mechanical Pain Threshold,* ***PPT****: Pressure Pain Threshold,* ***PTT****: Pressure Tolerance Threshold,* ***STCS****: Suprathreshold Cold Stimulus,* ***STHS****: Suprathreshold Heat Stimulus,* ***TSP****: Temporal Summation of Pain (c: using cuff stimuli, e: using electrical stimuli, h: using heat stimuli, m: using mechanical pinprick stimuli),* ***WDT****: Warm Detection Threshold. Other abbreviations:* ***ANOVA****: Analysis of Variance* ***N****: Number of patients participating in the study,* ***OR****: Odds Ratio,* ***R****: Coefficient of determination,* ***wks****: Weeks,* ***MO****: Months,* ***WOMAC****: Western Ontario and McMaster Universities Osteoarthritis Index (assesses pain, stiffness and function of the knee and hip),* ***KOOS****: Knee injury and Osteoarthritis Outcome Score (assesses pain, stiffness and function and daily living of patients with knee osteoarthritis).* ***(U)*** *indicates univariate analysis and* ***(M)*** *indicates multivariate analysis.* ***§****: calculated for this review only and not presented in the original paper.*

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Reference	Year	Type of surgery	Patients	QST parameters	Follow-up time	Postoperative dependent parameter	Models and preoperative predictors
Joint related surgeries							
Martinez et al. [67]	2007	Total knee arthroplasty	Knee osteoarthritis: N = 20	ALL, MPT, HPT, CPT	4 MO	Pain intensity	Correlations (U): No prediction
Lundblad et al. [61]	2008	Total knee arthroplasty	Knee osteoarthritis: N = 69	EDT, EPT	18 MO	Pain intensity	Regression (M): PreOP pain (OR: 6.48) and EPT (OR: 9.19)
Gwilym et al. [40]	2011	Arthroscopic subacromial decompression	Shoulder impingement syndrome: N = 17	MPT	3 MO	Oxford shoulder score	Correlation (U): No prediction
Wylde et al. [107]	2013	Total knee arthroplasty	Knee osteoarthritis: N = 51	PPTs, HPT	13 MO	WOMAC	Correlations (U): PPT: R = 0.37
Valencia et	2014	Arthroscopic	Rotator cuff	HPT, hTSP,	3 and 6	Pain intensity	Regressions (M):

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al. [100]		shoulder surgery	tendinopathy: N = 73	hCPM*	MO		No prediction
Noiseux et al. [72]	2014	Total knee arthroplasty	Knee osteoarthritis: N = 193	MPT, HPT, PPT	6 MO	Presence of moderate-to-severe postoperative pain	Regression (M): No prediction
Petersen et al. [75]	2015	Total knee arthroplasty	Knee osteoarthritis: N = 78	PPTs, mTSP, pCPM[#]	12 MO	Pain intensity	Regression (M): **§** mTSP and PreOP VAS: R^2 = 0.13
Wylde et al. [108]	2015	Total knee and hip arthroplasty	Knee osteoarthritis: N = 239, Hip osteoarthritis: N = 254	PPT	12 MO	WOMAC	Regression (M): THA: PPT: β = 0.091 (WOMAC) – 0.114 (Movement pain) TKA: no prediction
Petersen et	2016	Total knee	Knee osteoarthritis,	cPPT, cPTT,	12 MO	Pain relief	Regression (M): **§**

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al. [79]		arthroplasty	N = 103	cTSP, cCPM, PPTs			R^2 = 0.379, using cPPT and VAS
Bossmann et al.[17]	2017	Total knee arthroplasty	Knee osteoarthritis: N = 47	mTSP, pCPM‡	6 MO	WOMAC pain subscale	Regression (M): pCPM, heart rate variability and gender: R^2 = 0.09
Vaegter et al.[94]	2017	Total knee arthroplasty	Knee osteoarthritis: N = 14	cPPT, cPTT, PPT, pCPM#, EIH	6 MO	Pain relief	Correlations (U): pCPM: R = 0.57 EIH: R = 0.53
Arendt-Nielsen et al. [9]	2018	Total knee arthroplasty	Knee osteoarthritis: N = 70	PPT	12 MO	Pain relief	Regression (M): PPT: R^2 = 0.09 – 0.110
Petersen et al. [77]	2018	Total knee arthroplasty	Knee osteoarthritis: N = 130	CDT, CPT, WDT, HPT, mTSP	12 MO	Pain intensity	Regression (M): **§** PreOP mTSP, WDT, HPT and KL R^2 = 0.119
Rice et al. [82]	2018	Total knee arthroplasty	Knee osteoarthritis: N =	PPT, mTSP, pCPM#	6 and 12 MO	WOMAC pain > 30/100	Regression (M): WOMAC pain, mTSP, Trait

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			288				anxiety, expected pain: AUC: 0.70 Sensitivity: 0.72 Specificity: 0.64 Correctly classified: 65.67%
Kurien et al. [56]	2018	Total knee arthroplasty	Knee osteoarthritis: N = 50	PPTs, cPPT, cPTT, cTSP, cCPM, mTSP,		Pain intensity	Correlations (U): mTSP: R = 0.343 PPT: R = -0.262
Müller et al. [70]	2019	Segment spinal surgery	Chronic low back pain: N = 141	PPT, PTT, HPT, CPT, CPM, EPT	12 MO	Persistent pain or persistent Disability	Regression (M): No prediction
Thoracic related surgeries							
Yarnitsky et al. [111]	2008	Thoracic surgery	Posterolateral and muscle-sparing lateral	hCPM*, HPT, STHS	29 wks	Pain intensity	Regression (M): hCPM* (OR: 0.55)

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			thoracotomy: N = 62				
Grosen et al. [39]	2014	Surgical correction of funnel chest	Patients scheduled for surgical correction of funnel chest: N = 41	ALL, MDT, PPT, pCPM[#]	6 MO	Pain intensity	Regressions (M): No prediction
Bayman et al. [16]	2017	Thoracic surgery	Patients scheduled for thoracic surgery: N = 99	CPT, STHS	6 MO	Presence of postoperative pain	Regression (M): No prediction
Abdominal and gynecology related surgery							
Aasvang et al. [1]	2010	Groin hernia repair (open and laparoscopic)	Primary unilateral hernia: N = 442	WDT, HPT, STHS	6 MO	Pain intensity	Regression (M): Activity (OR: 1.16-7.37), STHS (OR: 1.34) Surgical type (OR: 0.45)

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Wilder-Smith et al. [105]	2010	Major abdominal surgery	Lower and upper gastrointestinal or genitourinary tract issues: N = 20	EPTT, PTT, eCPM#, pCPM#	6 MO	Pain intensity	Regression (M): PreOP eCPM $R^2 = 0.46$
Jarrell et al. [48]	2014	Gynecologic laparoscopy	Gynecological pain patients: N = 77	MDT, ALL	6 MO	Pain intensity	Regressions (M): The presence of preOP ALL ($R^2 = 0.590$)
Sng et al. [91]	2018	Elective abdominal or laparoscopic hysterectomy for benign conditions	Patients with benign conditions scheduled for surgery: N = 159	mTSP	6 MO	VAS > 3/10	Regression (M) mTSP: OR = 1.078 pain during sexual intercourse: OR = 5.312 Morphine consumption (24-48 h postOP): OR: 1.172
Breast cancer surgeries							
Andersen et al. [4]	2017	Breast cancer surgery	Patients with breast cancer: N = 290	MDT, MPT, WDT, CDT,	12 MO	Pain intensity	Regression (M): Size of hypoesthesia area:

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				HPT, PPT, Size of hypoesthesia area using: ALL and cold (25^0C) and warm (40^0C) rolls.			OR: 1.003 - 1.006
Habib et al. [41]	2019	Breast cancer surgery	Patients scheduled for breast cancer surgery: N = 124	mTSP, hCPM*	6 and 12 MO	VAS > 3/10 and impact of pain on daily living	Regression (M): No prediction

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Table 3: Pharmacological studies using quantitative sensory testing (QST) to predict analgesic effects. QST modalities: ***ALL****: Dynamic mechanical allodynia,* ***CDT****: Cold Detection Threshold,* ***CPT****: Cold Pain Threshold,* ***cPPT****: Cuff-induced Pressure Pain Threshold,* ***cPTT****: Cuff-induced Pressure Tolerance Threshold,* ***CPM****: Conditioning Pain Modulation (c: cuff pressure test and condition stimuli, e: electrical test stimulus, heat: heat test stimulus, p: pressure test stimulus, *: hot water condition stimulus, [#] cold pressor tests as condition stimulus),* ***EDT****: Electrical Detection Threshold,* ***EIH****: Exercise-Induced Hypoalgesia,* ***EPT****: Electrical Pain Threshold,* ***EPTT****: Electrical Pain Tolerance Threshold,* ***HPT****: Heat Pain Threshold,* ***MDT****: Mechanical Detection Threshold,* ***MPT****: Mechanical Pain Threshold,* ***s****: Offset analgesia,* ***PPT****: Pressure Pain Threshold,* ***PTT****: Pressure Tolerance Threshold,* ***STCS****: Suprathreshold Cold Stimulus,* ***STHS****: Suprathreshold Heat Stimulus,* ***TSP****: Temporal Summation of Pain (c: using cuff stimuli, e: using electrical stimuli, h: using heat stimuli, m: using mechanical pinprick stimuli, p: using pressure stimuli),* ***WDT****: Warm Detection Threshold. Other abbreviations:* ***N****: Number of patients participating in the study,* ***OR****: Odds Ratio,* ***R****: Coefficient of determination,* ***(U)*** *indicates univariate analysis and* ***(M)*** *indicates multivariate analysis.* ***§****: calculated for this review only and not presented in the original paper.*

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Reference	Year	Type of intervention(s)	Patients	QST parameters	Treatment period	Dependent parameter	Model and pretreatment predictor
Edwards et al.[25]	2006	Opioids: N = 16 TCAs: N = 14 placebo: N = 14	Postherpetic neuralgia	HPT	8 weeks	Change in pain intensity	Regression (M): Opioids: $R^2 = 0.35$ using HPT TCA: no prediction Placebo: no prediction
Yarnitsky et al. [112]	2012	Duloxetine: N = 30	Painful diabetic neuropathy	CDT, WDT, HPT, MDT, MPT, mTSP, hCPM*	5 weeks	Change in pain intensity	Regression (M): CPM: $R^2 = 0.673$
Olesen et al. [73]	2013	Pregabalin: N = 31, Placebo: N= 29	Painful chronic pancreatitis	EPT, PPT, differences in EPT and PPT in	3 weeks	Classify responders (>30% pain reduction) and non-	Support vector machine (M): EPT ratio:

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				affected and unaffected area (EPT/PPT ratio)		responders	Sensitivity: 87.5% Specificity: 80.0%
Demant et al. [21]	2014	Oxcarbazepine: N = 48 Placebo: N = 35	Peripheral neuropathic pain	ALL, WDT, CDT, HPT, CPT, PHS MDT, MPT, MPS, mTSP, VDT, PPT (DFNS protocol)	6 weeks	Patients classified into irritable nociceptor (IN) or non-irritable nociceptor (NIN). Numbers needed to treat (NNT) to obtain 50% pain relief for IN and NIN.	NNT for IN: 3.9 NNT for NIN: 13 (U)
Demant et al. [20]	2015	Lidocaine 5% patch: N = 40 Placebo: N = 40	Peripheral neuropathic pain	ALL, WDT, CDT, HPT, CPT, PHS MDT, MPT,	4 weeks	Patients classified into irritable nociceptor (IN) or non-irritable	NNT for IN: 7.5 NNT for NIN: not possible to determine due to

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				MPS, mTSP, VDT, PPT (DFNS protocol)		nociceptor (NIN). Numbers needed to treat (NNT) to obtain 50% pain relief for IN and NIN.	recruitment issues (U)
Arendt-Nielsen et al. [5]	2016	COX-2 inhibitor: N = 37, Placebo: N = 37	Knee osteoarthritis	PPT, pTSP, pCPM□	4 weeks	Change in pain intensity for non-responders (<30% and <50% reduction)	Correlation (U): pTSP predicting a non-response: R = 0.421 - 0.639
Edwards et al. [24]	2016	NSAID (topical gel), N = 35	Knee osteoarthritis	PPT, mTSP, pCPM#, pCPM□	4 weeks	Change in pain average daily pain intensity (ADP) and KOOS pain	Regressions (M): ADP: CPM R = -0.38 CPM
Mainka et al. [64]	2016	Capsaicin (topical, 8%), N = 20	Peripheral neuropathic pain	ALL, WDT, CDT, HPT, CPT, PHS	8 weeks	Classifying responders or non-responders;	Regression (M): Sensitivity: 70%, specificity: 100%

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				MDT, MPT, MPS, mTSP, VDT, PPT (DFNS protocol)		responders were defined as +30% reduction in pain or 2 points on a 0-10 NRS	for Patients with CPT and MPT > 0.8 compared with z-value from DFNS.
Petersen et al. [76]	2019	NSAID and paracetamol (oral): N = 132	Knee osteoarthritis	cPPT, cPTT, cTSP	3 weeks	Change in pain intensity	Regression (M): R^2 = 0.269 using VAS and cTSP
Petersen et al. [78]	2019	NSAID and paracetamol (oral): N = 42	Knee osteoarthritis	OA, cCPM	3 weeks	Change in pain intensity	Correlation (U): R^2 = 0.186 using cCPM and VAS
Kisler et al. [51]	2019	Duloxetine: N = 27, placebo: N = 28	Migraine	Tonic heat pain (47°C), mTSP, OA, TS_{alone}, $TS_{conditioned}$, hCPM[#]	8 weeks	Migraine improvement (pain reduction)	Regression (M): TS_{alone} (R = 0.47), $TS_{conditioned}$ (R = 0.49)

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Table 4. Risk of Bias (RoB) for studies investigating the prognostic value of QST parameters on chronic postoperative pain. Using the Quality in Prognostic Studies (QUIPS) tool, the RoB assessment was based on study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis. In general, low-to-moderate risk of bias was observed in most studies distributed across all factors.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Martinez et al. 2007	**M**	**L**	**M**	**L**	**M**	**L**
Lundblad et al. 2008	**M**	**H**	**M**	**M**	**H**	**L**
Yarnitsky et al. 2008	**M**	**L**	**L**	**M**	**L**	**M**
Aasvang et al. 2010	**L**	**L**	**L**	**M**	**H**	**L**
Wilder-Smith et al. 2010	**L**	**L**	**L**	**M**	**M**	**M**
Gwilym et al. 2011	**M**	**L**	**L**	**L**	**H**	**M**
Wylde et al. 2013	**M**	**L**	**L**	**L**	**M**	**M**
Grosen et al. 2014	**L**	**M**	**L**	**L**	**L**	**L**
Jarrell et al. 2014	**L**	**H**	**M**	**M**	**H**	**L**

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Valencia et al. 2014	**M**	**M**	**L**	**L**	**L**	**L**
Noiseux et al. 2014	**M**	**L**	**L**	**L**	**M**	**L**
Petersen et al. 2015	**M**	**L**	**L**	**M**	**M**	**L**
Wylde et al. 2015	**L**	**M**	**L**	**M**	**L**	**L**
Petersen et al. 2016	**L**	**M**	**L**	**M**	**M**	**L**
Bayman et al. 2017	**M**	**M**	**L**	**L**	**L**	**L**
Bossmann et al. 2017	**M**	**M**	**L**	**L**	**L**	**L**
Andersen et al. 2017	**L**	**L**	**M**	**M**	**L**	**L**
Vaegter et al. 2017	**M**	**L**	**L**	**L**	**M**	**L**
Arendt-Nielsen et al. 2018	**L**	**M**	**L**	**M**	**L**	**M**
Petersen et al. 2018	**L**	**M**	**M**	**L**	**M**	**L**
Rice et al. 2018	**L**	**L**	**L**	**L**	**M**	**L**
Sng et al. 2018	**L**	**M**	**L**	**M**	**M**	**L**
Kurien et al. 2018	**M**	**L**	**L**	**M**	**M**	**L**
Habib et al. 2019	**L**	**L**	**L**	**L**	**M**	**H**
Müller et al. 2019	**L**	**M**	**L**	**L**	**L**	**L**

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Table 5. Risk of Bias (RoB) for studies investigating the prognostic value of QST parameters on analgesic effect after non-surgical treatments. Using the Quality in Prognostic Studies (QUIPS) tool, the RoB assessment was based on study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis. In general, low-to-moderate risk of bias was observed in most studies distributed across all factors.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Edwards et al. 2006	**M**	**M**	**M**	**L**	**M**	**L**
Yarnitsky et al. 2012	**M**	**M**	**L**	**L**	**M**	**L**
Olesen et al. 2013	**L**	**L**	**L**	**L**	**M**	**M**
Demant et al. 2014	**L**	**L**	**L**	**M**	**M**	**L**
Demant et al. 2015	**L**	**L**	**M**	**L**	**M**	**L**
Arendt-Nielsen et al. 2016	**L**	**M**	**L**	**L**	**M**	**L**
Edwards et al. 2016	**M**	**M**	**L**	**L**	**M**	**L**
Mainka et al. 2016	**L**	**L**	**L**	**L**	**M**	**M**
Petersen et al. 2019	**L**	**M**	**L**	**L**	**M**	**L**
Petersen et al. 2019	**L**	**L**	**L**	**L**	**M**	**L**
Kisler et al. 2019	**M**	**M**	**L**	**M**	**M**	**L**

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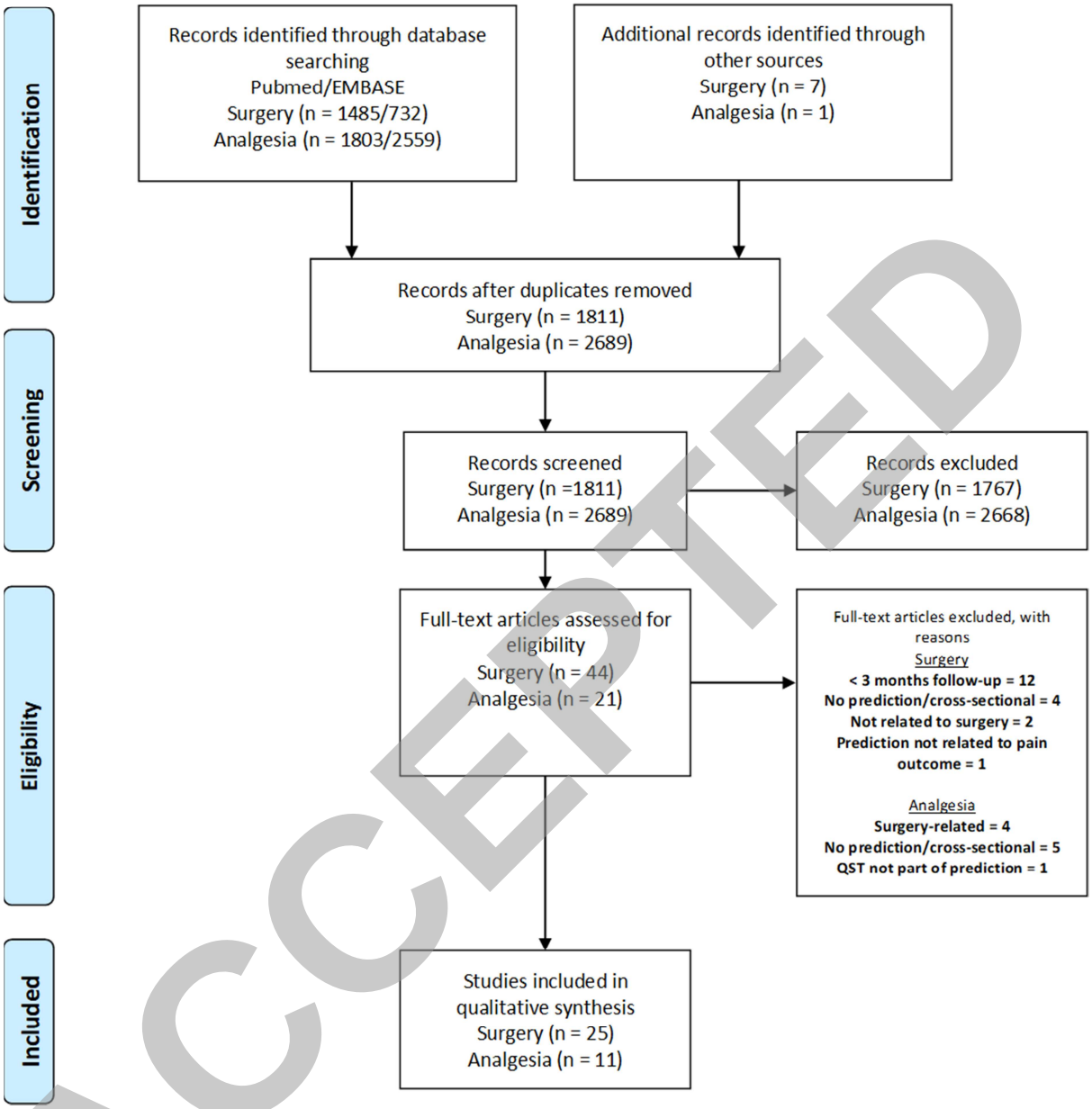

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