Systematic Review and Meta-Analysis

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Conditioned pain modulation as a biomarker of chronic pain: a systematic review of its concurrent validity

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Abstract

Conditioned pain modulation (CPM) is a promising psychophysical biomarker of central pain mechanisms because it significantly discriminates patients with chronic pain from healthy controls. Nevertheless, it is unclear in what extent CPM assessed experimentally is correlated with clinical manifestations of pain. To assess the concurrent validity of CPM, we performed a systematic review of the literature reporting correlations between CPM responses and pain intensity, disability, duration, and area in patients with different chronic pain conditions. We included 32 studies that altogether encompassed data from 1958 patients and provided 62 correlations. The majority of the results (69%) reported nonsignificant correlations between CPM efficiency and clinical manifestations of pain, whereas the remaining results showed a correlation between CPM reduction and worse clinical symptoms of pain. The modality of stimulation, the type of pain, and the stimulation site appear to be critical variables that influenced the pattern of results. Given that most of the studies were conducted with highly heterogeneous methodologies and unclear risk of bias, the findings highlight the need for future studies using standardized measures of clinical and experimental pain before considering CPM as a valid biomarker of pain. We discuss some guidelines to overcome the constraints in this promising line of research.

Keywords: CPM, Chronic pain, Clinical manifestations of pain, QST, Pain inhibition

1. Introduction

Conditioned pain modulation (CPM) is a quantitative sensory test commonly used to assess the functionality of endogenous pain inhibition in the central nervous system. During this paradigm, a nociceptive (test) stimulus is administered in the absence and after/during the application of a second painful (conditioning) stimulus, which is applied in a remote region of the body. The evaluation of pain provoked by the test stimulus can be done either at the same time (parallel paradigm) or after the conditioning stimulus (CS) has been withdrawn (sequential paradigm).[29] In most participants with a healthy nociceptive system, the amount of pain experienced with the test stimulus will decrease during or after the application of the CS, reflecting the efficacy of the endogenous pain inhibitory pathway. However, pain inhibition is not a universal phenomenon; it is dependent on intersubject variability, and in some cases, increased intensity of pain is observed during this paradigm.[29]

In patients with chronic pain, this neurophysiological mechanism seems to be defective, as shown by a meta-analysis performed by Lewis et al.[35] According to this study, approximately 70% of the comparisons between healthy controls and patients with chronic pain revealed a significant reduction in the CPM of the patients, showing a large size effect (d = 0.78). Such magnitude suggests that CPM is a clinically significant measure of endogenous pain inhibition, which may assist the diagnostic process as well as the development and decision for efficient therapeutic strategies, sparing patients from the long "trial and error" process in treatment choice.[23] Moreover, a comprehensive review also suggests that the pattern of CPM inefficiency is most overtly expressed in patients with idiopathic pain syndromes, such as irritable bowel syndrome, temporomandibular disorders, fibromyalgia, and tension-type headache.[66] Such evidence led to the assertion that low CPM efficiency, reflecting decreased pain inhibitory capacity, may be a pathogenetic factor in the development of the idiopathic pain syndromes.[66]

Although there is solid evidence on deficits in pain modulation in several chronic pain diseases,[35,42] it is unclear whether the CPM can be considered a good predictor of pain manifestations and, thus, a valid biomarker of clinical pain. This issue is of extreme importance considering that chronic pain remains a significant clinical problem, with few effective therapies.[13] Thereby, the identification of pain biomarkers is warranted to individualize pain medicine and to improve clinical management of pain.[64] Protocols including CPM for the assessment of pain inhibition have been promising in predicting future pain status,[61,62] but the literature in this field is highly contradictory.[11,17]

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To the best of our knowledge, there is no aggregate analysis of the literature regarding the concurrent validity of CPM responses in relation to clinical pain. Therefore, and considering the previous inconsistent results, the main goal of the current study was to conduct a systematic review of studies that correlated CPM and several clinical manifestations of pain (pain intensity, duration, disability due to pain, and number of painful areas). The final goal is to explore the validity of CPM as a biomarker of pain, later guiding diagnosis, individualized pain medicine, and management of pain, which may allow for a better understanding of the pathophysiology of chronic pain disorders.

2. Methods

2.1. Systematic search

The current systematic review was preregistered in International Prospective Register of Ongoing Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=97328; number: CRD42018097328),[5] and it was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[40] The systematic search was conducted in PubMed, Web of Knowledge, and EBSCOhost (including the Academic Search Complete, Psychology and Behavioral Sciences Collection, CINAHL Plus with Full Text, Fonte Acadêmica, MedicLatina, PsycARTICLES, PsycBOOKS, and PsycINFO databases) in February 2018 and actualized in January 2019. The search expression was "("Conditioned pain modulation" or CPM or "endogenous pain modulation" or DNIC or "diffuse noxious inhibitory control" or "Quantitative Sensory Testing" or "temporal summation") AND (phenotyp* or subgroup* or "clinical pain" or "pain intensity" or "pain duration" or "chronic pain" or prediction or biomarker or "treatment response" or "treatment outcome")." The search was limited to studies with humans. In addition, we screened the reference lists of reviews in this field and of all included studies.

2.2. Selection criteria

We included observational case–control, cross-sectional, and cohort studies, as well as randomized controlled trials (RCTs) and non-RCTs that have assessed CPM in patients with chronic pain (presence of pain for 3 months or more), written in English, Portuguese, or Spanish. We excluded studies without a group of adults with chronic pain (criteria 1: wrong population); studies that did not assess CPM (criteria 2: wrong measure); studies without information about the correlation between CPM and clinical manifestations of pain (criteria 3: lack of data); and reviews, letters, commentaries, abstracts, case series, methods, or corrigendum (criteria 4: wrong publication type). Articles with duplicated data were also excluded (criteria 5: duplicated data).

2.3. Screening and selection of records

The first author (C.F.) performed the literature search and compiled the results in EndNote, where duplicates were removed. The remaining titles were transferred to Rayyan, a web application that facilitates exploring and filtering the search results.[45] On this platform, 2 researchers (C.F. and M.P-M.) blindly screened the titles and abstracts, excluded the articles out of topic, and retained the reaming studies. When this task was completed, the screening was unblinded, and disagreements were solved by consensus. A third researcher (N.S-V.) screened the reference list of the included reviews and selected titles in the topic that did not appear in the systematic search. Two researchers (C.F. and M.P-M.) read all the retained studies and, independently, decided to include or exclude them. Disagreements were solved by consensus and by the decision of the third researcher (N.S-V.).

2.4. Recorded variables, data collection, and analysis

The data of each included article were added to an extraction sheet developed for this review and refined when necessary. When present, the following variables were extracted from each article: type of the study, country of the main laboratory, chronic pain condition, number of patients (number of women), age, clinical pain ratings, duration of disease, medication (discontinued or not before performing CPM), characteristics of test and conditioning stimuli (intensity, location, and paradigm type), involved body parts, presence of a healthy control group, and correlations between CPM responses and clinical manifestations of pain.

This process was independently performed by 2 researchers. The first author (C.F.) extracted the information of all articles, and each of the 3 coauthors (M.P-M., N.S-V., and M.C-P.) extracted the information of part of the articles equally divided between them. Once completed, the 2 extraction sheets were compared to create a consensual version.

To the analysis of the results, the articles were separated into different clinical measures of pain (pain intensity, disability due to pain, pain duration, and number of areas with pain).

2.5. Risk of bias assessment

The risk of bias was assessed using the scale described by Lewis et al.[35] for observational studies. This scale assesses the following 4 categories of bias: (1) blindness of the assessors to the group to which the participants belong; (2) representativeness of the population, (3) comparability of patients and controls, and (4) controlled risk of know confounders. Potential confounders included medication and caffeine intake before testing, presence of pain on the test day, time of the day testing was undertaken, phase of the menstrual cycle, and screening for conditions known to influence pain thresholds. For each category, studies were assessed as low risk (0), moderate risk (1), or high risk (2) based on set criteria.[35] A total bias score was determined for each study by summing the 4 individual risk assessments, providing a total risk of bias from 0 (low risk) to 8 (high risk). The risk of bias was assessed independently by 2 authors (C.F. and M.P-M.), and discrepant opinions were solved by consensus.

3. Results

3.1. Study selection

The systematic search provided 7134 titles, and the search in the reference lists provided 24 additional studies. After excluding duplicates, 2438 studies remained and were screened based on titles and abstracts. From these studies, 248 articles were selected to the full-text assessment of eligibility, and the remaining articles were excluded for being off-topic. From the full texts assessed, 32 articles fulfilled the inclusion criteria and were retained for the systematic review. The entire selection process is represented in the flowchart of **Figure 1**.

The interrater agreement Cohen's kappa was used to compare agreement between the researchers, regarding the decision to

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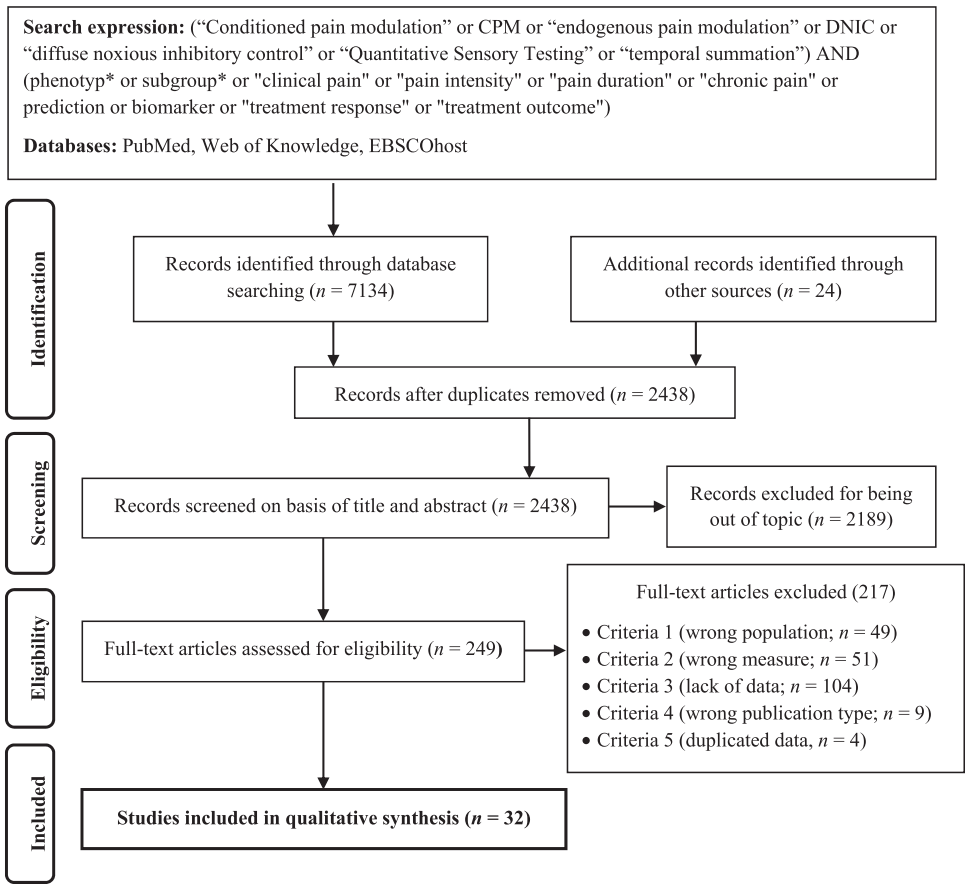

Figure 1. Flow diagram illustrating the systematic search, results, and the selection of the studies included in this systematic review.

include or exclude the eligible studies. This analysis revealed a substantial agreement (k = 0.66). **Table 1** summarizes the main features of the included articles.

3.2. Study characteristics

Two studies (6%) were RCTs, 18 (56%) were case–control studies, and the remaining (38%) were cross-sectional studies that compared subgroups of patients. The first study was published almost 15 years ago (2005), whereas the majority (75%) of the included reports were published in the past 5 years.

The reviewed articles included 1958 patients with chronic pain (1161 women), with a mean age of 50.1 years. The majority (88%) of the studies included both samples of men and women, and the most common chronic pain conditions were knee osteoarthritis (25%) and chronic back pain (low or widespread; 22%). Other conditions studied were fibromyalgia, pelvic pain syndrome, irritable bowel syndrome, and Achilles tendinopathy, among others (**Table 1**).

From the selected articles, 38% did not include a control group. From the remaining studies, 70% found significant differences in CPM efficacy between patients with chronic pain and healthy controls, 10% found a significant reduction in CPM for one experimental group but not for other, and 20% of the studies did not find significant differences between patients and controls (**Table 2**).

3.3. Synthesis of the conditioned pain modulation results

Table 2 shows a summary of the main results, along with detailed information about the CPM protocols. From the 32 included articles, we extracted 62 correlations between CPM response and clinical manifestations of pain, specifically pain intensity (and severity),[1–3,6,12,14–17,19,21,24–26,28,31,37–39,41,44,46,48,49,52–54,56,58,59] disability (and interference) due to pain,[1,11,14,19,26,38,41,46,58] duration,[2,3,12,15,16,24,26,38,39,44,52,53] and number of areas with pain.[3,19,25,36,49] Considering the aim of this systematic review, the results will be aggregated by clinical features of pain.

The most common CS was cold or iced water, with temperatures ranging from 0 to 12°C (50%), and the contralateral hand was the region most frequently selected (31%). Nine studies (28%) used tourniquets around the arm, leg, and thumb, and the remaining used thermodes (13%) or hot water (9%).

Regarding the test stimulus, the most common was pressure delivered by algometry, used in 59% of the studies, and the forearm (31%) was the region most frequently selected, followed by the trapezius (22%). The remaining test stimuli were thermal (19%), mechanical (tourniquet, 13%; brush and von Frey filaments, 6%), or electrical (6%). The test stimulus was applied in the painful areas in 34% of the studies and in nonpainful areas in 44% of them. The remaining studies (22%) applied the test stimulus in both painful and nonpainful areas. When we analyzed the pattern of correlations according to this variable, we found that 73% of the correlations were nonsignificant when test stimuli were applied in nonpainful areas, a percentage that increases to 85% when test stimuli were applied in both painful and nonpainful areas. Stimulating painful areas decreased this percentage to 59%.

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Table 1

General characteristics of the studies reviewed.

Reference	Country	Study type	Chronic pain condition	n (fem)	M_{age} (SD)	Risk of bias
[1]	USA	RCT	Knee osteoarthritis	40 (21)	60.0 (9.2)	4
[3]	Denmark	CC	Knee osteoarthritis	217 (115)	63.8 (8.0)	5
[2]	Denmark	CC	Knee osteoarthritis	48 (24)	62.6 (1.6)	3
[6]	Netherlands	CC	Pancreatitis	48 (13)	49 (mdn)	4
[11]	Belgium	CC	Idiopathic neck pain and whiplash-associated disorders	67 (67)	35.8 (10.8)	5
[12]	Brazil	CC	Low back pain	30 (18)	51.0 (8.7)	4
[14]	USA	CS	Knee osteoarthritis	267 (169)	56.8 (7.3)	6
[15]	Israel	CC	Posttraumatic headache after mild traumatic brain injury	16 (3)	36.5 (11.8)	4
[17]	USA	CS	Discogenic back pain	31 (21)	51.6 (10.6)	7
[16]	USA	CS	Temporomandibular joint disorder	53 (41)	34	4
[19]	Ireland	RCT	Knee osteoarthritis	40 (18)	63.7 (9.95)	4
[21]	Germany	CC	Local back pain, widespread back pain, and fibromyalgia	177 (129)	56.8 (9.97)	6
[24]	Israel	CC	Pelvic pain syndrome and painful bladder syndrome	39 (39)	40.4 (11.4)	4
[25]	Israel	CC	Spinal cord injury with central neuropathic pain	27 (4)	48.4 (14.3)	7
[26]	Spain	CS	Neck/shoulder pain	20 (20)	46.8 (1.3)	5
[28]	USA	CC	Irritable bowel syndrome	20 (20)	27.4 (6.6)	5
[31]	Belgium	CC	Shoulder pain	25 (13)	31.4 (10.97)	3
[36]	Spain	CS	Knee osteoarthritis	53 (34)	70.2 (7.4)	4
[38]	USA	CS	Back/neck pain	190 (82)	49.5 (10.9)	7
[37]	USA	CS	Back pain	55 (35)	49.3 (9.5)	7
[39]	Switzerland	CC	Low back pain	34 (17)	50.8 (14.0)	6
[43]	USA	CS	Knee osteoarthritis	129 (68)	64.1 (8.65)	7
[44]	Japan	CC	Temporomandibular joint disorder	16 (14)	43.0 (4.0)	5
[46]	USA	CC	Low back pain	25 (14)	57.6 (10.8)	4
[48]	France	CC	Postherpetic neuralgia	9 (5)	67.0 (4.0)	4
[49]	Germany	CC	Tension-type headache	29 (13)	37.1 (13.5)	3
[52]	Denmark	CS	Knee osteoarthritis	24 (14)	61.5 (1.8)	7
[53]	Netherlands	CC	Achilles tendinopathy	20 (4)	42.9 (13.5)	7
[54]	Sweden	CC	Central poststroke pain	10 (4)	60.2 (11.9)	4
[59]	Denmark	CS	Spinal pain	108 (58)	45.7 (11.6)	7
[56]	Denmark	CS	Mixed chronic pain conditions	61 (42)	45.4 (11.2)	6
[58]	Denmark	CS	Low back pain/neck pain	70 (43)	48.0 (12.9)	8

CC, case–control studies; CS, cross-sectional studies; RCT, randomized controlled trials.

In the majority of studies (59%), the test stimuli were applied at threshold levels (ie, the moment when participants start to feel pain), whereas in 22% of them, the test stimuli were applied at suprathreshold levels (ie, some magnitude on the subjective threshold). One study (3%) did not specify the intensity of the test stimuli, and the remaining studies (19%) used fixed ratings on Numeric Rating Scales or Visual Analogue Scales (**Table 2**).

3.4. Correlations between conditioned pain modulation responses and clinical manifestations of pain

Pain intensity was the clinical feature most frequently correlated with the CPM responses (34 correlations; 55%). The majority of the studies assessed pain intensity through Numeric Rating Scales (47%),[8] followed by Visual Analogue Scales (24%)[20] and the Brief Pain Inventory (BPI; 15%).[9] Besides these, 2 studies (6%) analyzed correlations between CPM and the scores of the Graded Chronic Pain Scale,[10] 1 study (3%) assessed pain intensity with a customized questionnaire, and 2 studies (6%) did not specify the scale used. With regard to the time period, 7 studies (21%) assessed the average pain intensity during the past 24 hours, 5 (15%) assessed the average pain intensity during the past week, 1 study (3%) during the past 4 weeks, and 2 studies (6%) assessed the intensity of current pain. However, 19 studies (56%) did not specify the period at which the assessment of pain intensity was referred (**Table 2**).

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Table 2

Conditioned pain modulation (CPM) results.

Reference	n	Test stimulus, test, intensity, location	Conditioning stimulus, intensity, location, paradigm type	CG	Clinical manifestation	Finding pattern	Main results
[1]	40 KOA	Mechanical (algometer), PPT, threshold, trapezius, nonpainful area	Thermal (cold water), 60 s, contralateral hand up to the wrist, nonpainful area, sequential paradigm	No	Pain intensity (NRS) and disability (WOMAC)	Negative	Nonsignificant correlations between CPM and both measures
[3]	217 KOA	Mechanical (algometer), PPT, threshold, painful knee	Mechanical (tourniquet), 60/100, contralateral arm, nonpainful area, parallel paradigm	Yes*	Pain intensity (VAS, maximal, past 24 h), pain duration, and area	Mixed	Significant negative correlation between CPM and pain intensity and duration. Nonsignificant correlation between CPM and pain area
[2]	48 KOA	Mechanical (algometer), PPT, threshold, peripatellar region, painful area	Mechanical (tourniquet), 4/10, left arm, nonpainful area, parallel paradigm	Yes*	Pain intensity (VAS, maximal, past 24 h) and pain duration	Negative	Nonsignificant correlation between CPM and pain intensity and duration
[6]	48 CP	Electrical (self-adhesive electrodes), ePTT, threshold, nondominant knee, nonpainful area	Thermal (cold water), 120 s, dominant hand, sequential paradigm	Yes*	Pain intensity (VAS)	Positive	Significant negative correlation between CPM and pain intensity
[11]	67 INP and WAD	Mechanical (algometer), PPT, threshold, trapezius (painful area) and quadriceps (nonpainful area)	Thermal (cold water), 120 s, contralateral hand up to the wrist, parallel paradigm	Yes†	Pain-related disability (NDI)	Negative	Nonsignificant correlations between CPM and pain-related disability
[12]	30 LBP	Mechanical (algometer), PPT, threshold, lumbar region, painful area	Thermal (cold water), 120 s, leg ipsilateral to the most painful side, parallel paradigm	Yes†	Pain intensity (NRS, past week) and duration	Negative	Nonsignificant correlation between CPM and pain intensity and duration
[14]	267 KOA	Thermal (thermode), 40-60/100, left ventral forearm, nonpainful area	Thermal (cold water), 40-60/100, right hand, sequential paradigm	No	Pain disability (WOMAC) and intensity (GCPS)	Mixed	AA: Decreased CPM predicted greater pain-related disability and intensity. NHW: Decreased CPM predicted greater pain intensity, but not pain-related disability
[15]	16 PTHA-TBI	Mechanical (algometer), PPT, threshold, nondominant forearm, nonpainful area	Thermal (thermode), 2°C above threshold, shin, parallel paradigm	Yes*	Pain intensity (VAS) and duration	Mixed	Significant negative correlation between CPM and pain intensity. Nonsignificant correlation between CPM and pain duration
[17]	31 DBP	Mechanical (algometer), PPT, threshold, contralateral trapezius, painful area	Thermal (cold water), 30 s, right hand, parallel paradigm	No	Pain intensity (VAS)	Negative	Nonsignificant correlations between CPM and pain intensity after opioid treatment
[16]	53 TMD	Mechanical (algometer), PPT, right brachioradialis and trapezius, nonpainful area	Thermal (cold water), 20 s, contralateral hand up to the wrist, parallel paradigm	No	Pain duration and intensity (BPI)	Negative	Nonsignificant correlations between CPM and pain duration and intensity
[19]	40 KOA	Mechanical (algometer), PPT, threshold, average of the medial joint line of the index knee (painful area) and forearm (nonpainful area)	Thermal (cold water), 60 s, contralateral hand, sequential paradigm	Yes*	Pain area (unilateral vs bilateral), intensity (NRS), and disability (WOMAC)	Negative	Nonsignificant differences between abnormal and normal CPM groups for pain area, intensity, and disability
[21]	177 LBP, WBP, and FM	Mechanical (algometer), PPT, threshold, paraspinal muscles, painful area	Thermal (thermode), 120 s, hand, sequential paradigm	No	Pain intensity in the past 4 wk (NRS)	Positive	Significant negative correlation between CPM and pain intensity
[24]	39 PPS and PBS	Thermal (thermode), 60 s, 50/100, dominant forearm, nonpainful area	Thermal (hot water), 80 s, nondominant hand, parallel paradigm	Yes*	Pain intensity on trigger points (NRS, 24 h), duration, severity, and interference (BPI)	Mixed	Significant negative correlation between CPM and pain intensity on trigger points. Nonsignificant correlation between CPM and pain severity and duration

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Table 2 (*continued*)

Reference	n	Test stimulus, test, intensity, location	Conditioning stimulus, intensity, location, paradigm type	CG	Clinical manifestation	Finding pattern	Main results
[25]	27 SCI-NP	Thermal (thermode), 5 s, 5-6/10, arm, nonpainful area	Thermal (hot water), 30 s, contralateral hand to the wrist, parallel paradigm	Yes*	Pain intensity and area	Mixed	Significant negative correlation between CPM and pain area. Nonsignificant correlation between CPM and pain intensity
[26]	19 N/SP	Mechanical (algometer), PPT, suprathreshold, leg of the painful side	Mechanical (tourniquet), 5-6/10, contralateral leg, nonpainful area, parallel paradigm	Yes	Pain duration, intensity (NRS, past week, and 24 h), arm (DASH) and neck disability (NDI)	Mixed	Significant negative correlation between CPM and arm pain disability. Nonsignificant correlation between CPM and pain duration, both measures of pain intensity and neck pain disability
[28]	20 IBS	Thermal (thermode), 6/10, 30 seconds, arm, nonpainful area	Thermal (cold water), 60 s, nondominant hand up to wrist, nonpainful area, parallel paradigm	Yes*	Severity of daily gastrointestinal symptoms (past 24 h)	Negative	Nonsignificant correlation between CPM and abdominal pain (after excluded one outlier)
[31]	25 SP	Mechanical (algometer), PPT, threshold, bilaterally trapezius (painful area), nondominant middle finger, right leg calf muscle (nonpainful areas)	Thermal (thermode), 0°C, dominant hand, nonpainful area, parallel paradigm	Yes	Pain intensity (NRS)	Positive	Significant negative correlation between CPM and pain intensity
[36]	53 KOA	Mechanical (algometer), PPT, threshold, peripatellar region and ipsilateral extensor carpi radialis longus muscle, painful area	Mechanical (tourniquet), PPT, threshold, arm contralateral to the affected knee, nonpainful area, parallel paradigm	No	Pain area	Negative	Nonsignificant correlation between CPM and pain area
[38]	190 B/NP	Mechanical (algometer), PPT, threshold, right upper trapezius, painful area	Thermal (cold water), 30 s, contralateral hand up to the wrist, nonpainful area, parallel paradigm	No	Pain duration, intensity (NRS, 24 h), severity, and interference (BPI)	Negative	Nonsignificant correlations between CPM and pain duration, intensity, severity, and interference
[37]	55 BP	Mechanical (algometer), PPT, threshold, right upper trapezius, painful area	Thermal (cold water), 30 s, contralateral hand up to the wrist, parallel paradigm	No	Pain intensity (BPI)	Negative	Nonsignificant correlation between CPM and pain intensity
[39]	34 LBP	Mechanical (algometer), PPT, suprathreshold, 2nd toe, nonpainful area	Thermal (cold water), 120 s, contralateral hand up to the wrist, sequential paradigm	Yes	Pain duration and intensity (VAS)	Mixed	Significant negative correlation between CPM and pain duration. Nonsignificant correlation between CPM and pain intensity
[43]	129 KOA	Mechanical (tourniquet), PPT, 30-50/100, dominant thumb, nonpainful area	Mechanical (tourniquet), PPT, 30-50/100, nondominant thumb, nonpainful area, parallel paradigm	No	Pain intensity (BPI) and disability (WOMAC)	Negative	Nonsignificant correlations between CPM and pain intensity and disability (correlations adjusted for age)
[44]	16 TMD	Mechanical (von Frey filament and algometer), PPT, threshold, forearm (nonpainful area), masseter and TMJ (painful areas)	Mechanical (cranial compression device), PPT, suprathreshold, over the vertex around the skull, parallel paradigm, parallel and sequential paradigm	Yes*	Pain intensity (NRS) and duration	Negative	Nonsignificant correlation between CPM and pain intensity and duration
[46]	25 BP	Mechanical (algometer), PPT, threshold, dorsal forearm (nonpainful area) or ipsilateral trapezius (painful area)	Thermal (cold water), 40-60/100 according threshold, 60 s, hand up to the wrist, parallel paradigm	Yes	Pain intensity (NRS, past week) and disability (ODI)	Negative	Nonsignificant correlation between CPM and pain intensity and disability
[48]	9 PHN	Thermal (thermode), threshold, dominant forearm, nonpainful area	Thermal (cold water), 120 s, contralateral hand, sequential paradigm	Yes*	Pain intensity (NRS, past week)	Positive	Significant negative correlation between CPM and pain intensity
[49]	29 TTH	Electrical (electrostimulator), ePPT, suprathreshold, forearm (nonpainful) or temple (painful area)	Thermal (thermode), suprathreshold, thigh, nonpainful area, parallel paradigm	Yes*	Pain intensity and area (customized questionnaire)	Negative	Nonsignificant correlation between CPM and headache pain area and intensity

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Table 2 (*continued*)

Reference	n	Test stimulus, test, intensity, location	Conditioning stimulus, intensity, location, paradigm type	CG	Clinical manifestation	Finding pattern	Main results
[52]	24 KOA	Mechanical (algometer), PPT, suprathreshold, knee and leg (painful areas) and forearm (nonpainful area)	Mechanical (tourniquet), PPT, 4/10, forearm, nonpainful area, parallel paradigm	Yes*	Current pain intensity (VAS) and pain duration	Mixed	Significant negative correlation between CPM and pain intensity. Nonsignificant correlation with pain duration
[53]	20 AT	Mechanical (algometer), PPT, threshold, affected Achilles tendon (painful area)	Thermal (cold water), 4-5/10, contralateral hand up to the wrist, nonpainful area, parallel paradigm	Yes*	Pain intensity (NRS, past week) and duration	Negative	Nonsignificant correlation between CPM and pain intensity and duration
[54]	10 CPSP	Mechanical (brush), suprathreshold, area with maximum mechanical allodynia	Mechanical (tourniquet), PPT, suprathreshold, contralateral leg, sequential paradigm	Yes*	Spontaneous pain (VAS)	Positive	Significant negative correlation between CPM and spontaneous pain
[59]	108 SP	Mechanical (tourniquet), PPT, threshold, left lower leg, nonpainful area	Mechanical (tourniquet), PPT, threshold, right lower leg, nonpainful area, parallel paradigm	No	Pain intensity (NRS, 24 h)	Negative	Nonsignificant correlation between CPM and pain intensity
[56]	61 MCPC	Mechanical (tourniquet), PPT, suprathreshold, nondominant lower leg, painful area	Thermal (cold water), 120 s, dominant foot, nonpainful area, sequential paradigm	No	Pain intensity (NRS)	Positive	Significant negative correlation between CPM and pain intensity
[58]	70 BP and NP	Mechanical (tourniquet), PPT, suprathreshold, left lower leg, nonpainful area	Mechanical (tourniquet), right lower leg, nonpainful area, parallel paradigm	No	Pain intensity (NRS, 24 h) and disability (PDI)	Positive	Significant negative correlation between CPM and pain intensity and disability

AA, African Americans; AT, Achilles tendinopathy; B/NP, back/neck pain; BP, back pain; BPI, Brief Pain Inventory; CG, control group; CP, chronic pancreatitis; CPSP, central poststroke pain; DASH, Disabilities of the Arm, Shoulder, and Hand Questionnaire; DBP, discogenic back pain; ePTT, electrical pain tolerance threshold; FM, fibromyalgia; GCPS, Graded Chronic Pain Scale; IBS, irritable bowel syndrome; INP, idiopathic neck pain; IPQ-R, Illness Perceptions Questionnaire–Revised; KOA, knee osteoarthritis; LBP, low back pain; MCPC, mixed chronic pain conditions; N/SP, neck/shoulder pain; NDI, Neck Disability Index; NHW, non-Hispanic whites; NP, neck pain; NRS, Numerical Rating Scale; ODI, Oswestry Disability Index; PBS, painful bladder syndrome; PDI, Pain Disability Index; PHN, postherpetic neuralgia; PPS, pelvic pain syndrome; PPT, pressure pain threshold; PTHA-TBI, posttraumatic headache after mild traumatic brain injury; SCI-NP, spinal cord injury with central neuropathic pain; SP, shoulder pain; SP, spinal pain; TMD, temporomandibular joint disorder; TMJ, temporomandibular joint; TTH, tension-type headache; VAS, Visual Analogue Scale; WAD, whiplash-associated disorder; WBP, widespread back pain; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

* Significant difference between patients with chronic pain and healthy controls.

† Significant difference between one subgroup of patients with chronic pain and healthy controls.

Regarding the correlation results, there is a strong tendency to be nonsignificant. That is, 21 results (62%) revealed nonsignificant correlations between CPM responses and pain intensity, whereas 13 results (38%) found significant negative correlations. In the later studies, a higher intensity of pain was associated with less efficient CPM responses. Of note, one study found significant negative correlations between CPM and pain intensity when assessed on trigger points but did not find significant correlations between CPM and pain intensity when assessed through the BPI.[24]

Pain duration was the second clinical manifestation most frequently correlated with CPM responses (12 correlations, 19%). The results obtained for this symptom were more consistent than those for the previous one, showing 10 (83%) nonsignificant correlations and 2 (17%) significant and negative correlations. The significant correlations showed that longer duration of chronic pain was associated with less efficient CPM responses.

Disability (and interference) due to pain was correlated with the CPM responses in 11 studies (18%), showing consistent results. In fact, 8 results (73%) revealed nonsignificant correlations between CPM responses and disability due to pain, whereas only 3 studies (27%) found significant negative correlations. Of note, one study found significant correlations between CPM responses and arm pain disability but nonsignificant correlations between CPM responses and neck pain disability,[26] whereas other study found that CPM responses predicted greater pain-related disability in a sample of African Americans, but not in a sample of non-Hispanic White Americans.[14] The majority of the studies assessed pain disability through the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; 45%),[10] followed by the Neck Disability Index (18%).[32] Besides these, one correlation (9%) was between CPM and the scores of Disabilities of the Arm, Shoulder, and Hand questionnaire,[27] and the final 3 studies used the interference subscale of the BPI, the Oswestry Disability Index,[18] and the Pain Disability Index.[50]

Conditioned pain modulation responses were correlated with a number of painful areas in 5 studies (8%), with 4 of them (80%) showing nonsignificant correlations between CPM and number of areas with pain and 1 (20%) showing significant negative correlations. This later study assessed pain areas in terms of unilateral or bilateral pain, whereas in the remaining studies, the number of painful areas was directly reported by the patients, extracted from their drawings, or referred to specific conditions such as walking.

As referred above, the majority of the studies that included a healthy control group showed that CPM efficacy was significantly reduced in patients than in controls. However, significant negative correlations between CPM efficacy and clinical manifestations of pain were found in both studies that showed significant and non-significant differences between patients and controls (33% and 30%, respectively).

To understand whether the procedure used to assess CPM could influence the pattern of results, we analyzed the data according to the CPM protocol. The majority of the correlations were obtained from procedures that used mechanical test

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stimuli and thermal conditioning stimuli (47%). Among these studies, 81% found nonsignificant correlations between CPM responses and clinical features of pain. The second most common paradigm (31%) used mechanical test and mechanical conditioning stimuli, and also, the majority of the correlations obtained (67%) were nonsignificant. The paradigm using electrical test stimuli and thermal conditioning stimuli was selected in 6% of the studies and throws a similar pattern of nonsignificant correlations (67%). This pattern was inverted in paradigms that used thermal test and thermal conditioning stimuli (15% of the studies), where 55% of the correlations between CPM and clinical manifestations of pain were significant and negative. The type of the CPM procedure (parallel or sequential) did not affect the pattern of results, considering that 73% and 77% of the procedures, respectively, found nonsignificant correlations between CPM and clinical pain.

We also analyzed the data considering the sample size. To this purpose, we split-half the studies according to the median of the sample size (median n = 40), and we found the same pattern of results obtained for the total number of studies. That is, both studies with less and more than 40 participants had a strong tendency to find nonsignificant correlations between CPM efficacy and clinical manifestations of pain (76% and 68%, respectively).

Finally, although the limits among the categories of chronic pain are not well established,[30] we analyzed the results in relation to the type of clinical pain syndrome. In neuropathic pain (16% of the studies), we included posttraumatic headache after mild traumatic brain injury,[15] spinal cord injury with central neuropathic pain,[25] postherpetic neuralgia,[48] central poststroke pain,[54] and spinal pain.[59] In nociceptive pain (69% of the studies), we included knee osteoarthritis,[1–3,14,19,36,41,52] back, shoulder, and neck pain,[12,17,26,31,37–39,46,58] temporomandibular joint disorder,[16,44] pancreatitis,[6] Achilles tendinopathy,[53] pelvic pain syndrome, and painful bladder syndrome.[24] In idiopathic pain (9% of the studies), we included studies of idiopathic neck pain and whiplash-associated disorders,[11] tension-type headache,[49] and irritable bowel syndrome.[28] Two studies were excluded from this analysis for including mixed pain conditions.[21,56] The results of this analysis revealed that 100% of the studies of idiopathic pain and 73% of the studies with nociceptive pain found nonsignificant correlations between CPM and clinical manifestations of pain. For neuropathic pain, on the contrary, the majority of the correlations (57%) were significant and negative.

3.5. Risk of bias

Table 1 shows the total score of the risk of bias for each study (the scores given by the category are presented in Table 1 of the supplementary material, available at http://links.lww.com/PAIN/A851). Total bias scores ranged from 3 to 8 (maximal risk), with a mean of 5. The majority of the studies scored 4 (34%) and 7 (22%) in the risk of bias scale.

Lack of blinding was the most critical issue. Only 16% of the studies indicated that the researchers who assessed CPM were blinded to patient and control subgrouping, and the presence of confounding factors remains a common area of risk. The majority of the studies (88%) were classified as high risk for confounders' control, and none of them reported the control of (at least) 4 confounding factors (medication, pain on the test day, time of the day testing was undertaken, and phase of the menstrual cycle). The most commonly controlled confounder was the restriction of analgesic medication on the testing day (or for a given period before testing), followed by the control of the pain ratings in that day.

Regarding the risk of bias in the representativeness of participants, 66% of the studies specify internationally recognized inclusion criteria and recruitment procedures. The matching between patients and controls was not applied to some of the studies because many of them compared subgroups of patients rather than patients with controls.

To understand whether the risk of bias could influence the pattern of results, we split-half the studies according to the median of the risk of bias (median n = 5), and we found the same pattern of results obtained for the total number of studies. According to a similar analysis, the risk of bias also did not appear to affect the results, considering that both studies with scores lower and higher than 5 found mostly nonsignificant correlations (78% and 64%, respectively).

4. Discussion

The efficiency of the CPM appears systematically reduced in several pain syndromes, such as irritable bowel syndrome, temporomandibular disorders, fibromyalgia, or tension-type headache.[66] A previous review meta-analyzed this effect and found that patients with chronic pain had a significant reduction in the CPM efficiency, a difference with a large effect size (d = 0.78).[35] This evidence led to the assumption that low CPM efficiency, which reflects a low capacity of the endogenous pain inhibitory pathway, is a pathogenetic factor in the development of pain syndromes.[66] Furthermore, there is a growing body of the literature, suggesting that CPM may also be an important biomarker of pain and a predictor of treatment response.[29] However, little attention has been given to the association between CPM responses and clinical manifestations of pain, without which the above premises cannot be fully established.

Bearing this in mind, this systematic review aimed to determine whether CPM assessed experimentally correlated with clinical manifestations of chronic pain. To this purpose, the review encompassed 32 articles that reported 62 correlations between CPM responses and pain intensity, disability due to pain, pain duration, and number of painful areas. Altogether, 31% of those correlations were significant and negative, showing that less efficient pain inhibition was associated with worse symptoms of clinical pain, which is consistent with the results of a previous comprehensive review.[66] However, the majority of these correlations were nonsignificant (69%), suggesting that CPM efficiency and clinical manifestations of pain may be relatively independent.

The analysis of the results taking into account the type of the CPM protocol showed to be a topic of major relevance. We found that the majority of the studies that used thermal test and thermal conditioning stimuli revealed more significant negative correlations between CPM responses and clinical manifestations of pain, whereas the majority of the remaining CPM protocols reached mostly nonsignificant correlations. A review of studies focused on healthy volunteers also showed that the paradigm used influenced the magnitude and stability of the CPM effect.[51] In chronic pain, despite previous results reporting that the type of test and CS was not a significant moderator of CPM,[35] a recent systematic review also showed that its reliability is dependent on stimulation type and parameters, test sites, and samples.[29] Given that previous studies have reported that thermal stimuli, at least when used as a CS, are more reliable to induce CPM,[43] our findings suggest that thermal CPM would be the protocol of choice to analyze associations with clinical pain.

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We also observed that CPM has been applied in sequential (before/after the presentation of the second heterotopic stimulus) or parallel paradigm (before/during) protocols, but this variable does not seem to have affected the results. Concerning the stimulation site, we found that the choice of a painful area vs a nonpainful area might be critical because the use of painful areas, already sensitized, may bias the results. Therefore, the lack of standardization in research paradigms, which is mandatory to investigate the CPM response as a biomarker of chronic pain, is the main drawback in this field of research.

This problem has been previously acknowledged by researchers and clinicians in the field and motivated a consensus meeting to guide the practice and research on CPM.[65] Although the panel of experts gave some recommendations about the desirable CPM protocol (concerning the characteristics and intensity of the test and conditioning stimuli, time of the CPM assessment, and calculation of the effect), most of the studies included in this review did not follow their guides. Thus, to assess successfully the validity of CPM as a biomarker of clinical pain, it is urgent to conduct a multicentric study using a consensual protocol. The present review suggests that special attention should be paid to the use of painful vs nonpainful stimulation sites, a variable that has not been acknowledged in previous recommendations published by expert panels.[63,65]

In addition, the assessment procedures for the clinical variables are largely heterogeneous. For instance, pain intensity, the clinical feature most frequently correlated with the CPM, has been evaluated by different scales and has been referred to different periods (from pain assessed at the moment of CPM to pain in the previous several weeks). Again, the heterogeneity in research protocols may explain why some studies found significant correlations, whereas others not. For instance, Grinberg et al.[24] found significant negative correlations between CPM and pain intensity when assessed on trigger points, but not when assessed through the BPI, suggesting that the subjective nature of the scales used to assess clinical pain intensity may influence the findings. In fact, the results obtained from the analysis according to pain condition seem to support the role of this variable. We found more significant correlations between CPM and clinical pain for neuropathic, followed by nociceptive, and finally by idiopathic pain disorders. In the last group, no correlation was found significant. It could be inferred that the subjective perception of pain is more affected by other confounding variables such as depression, anxiety, or uncertainty in idiopathic pain syndromes than in those with an identified cause, and this could explain the different pattern of results.

Previous studies that assessed the reliability of CPM concluded that it has moderate reliability and stability in patients with chronic pain.[7,60] Thus, it seems inaccurate to correlate CPM with changes in pain assessed at punctual periods, instead of considering stable clinical pain patterns (ie, mean pain intensity in the past month). Valencia et al.[60] reported that CPM was a more stable measure for female than male patients. From our systematic review, we could not support different patterns for men and women, but the sex of participants may be a further variable to control in the standardized CPM protocols suggested above.

Several studies have suggested that dysfunctional central pain inhibition may have a role in the transition from acute to chronic pain, and that CPM predicts future pain after a given intervention.[57] Nevertheless, the direction of the relationship between clinical pain and CPM is still under debate, being unclear whether chronic pain produces an imbalance between excitatory and inhibitory pain pathways or if this imbalance produces chronic pain. Although our results are not fully consistent, 17% of the studies reviewed showed that longer duration of chronic pain was associated with less efficient CPM responses. Thus, the findings suggest that the continued experience of pain may change the balance between pronociceptive and antinociceptive endogenous pain mechanisms.

We found that disability/interference due to pain was the variable that showed more consistently nonsignificant correlations with CPM. This is understandable taking into account that the perceived interference may be modulated by other variables not directly related to pain, such as psychological distress or negative mood, catastrophism, self-efficacy, or coping with pain strategies, among others.[34,55] Thereby, future studies that aim to investigate the correlation between this clinical manifestation of pain and CPM may control the moderating role of other cognitive and affective variables.

Regarding the number of areas with pain, although some authors had suggested that it would be interesting to study CPM in subgroups of patients attending to their pattern of localized vs generalized pain,[57] we found that CPM only correlated with the number of painful areas in 1 of 5 reports. Nevertheless, these results are worthy to be explored in future studies because they may be explained by the fact that the majority of the patients included in the present review had localized pain (eg, knee osteoarthritis and chronic back pain).

In sum, although the reviewed articles did not consistently support the concurrent validity of CPM in relation to clinical pain, there are a number of issues that may have influenced the results and prevent us to reject the null hypothesis that CPM is not a valid biomarker of chronic pain. In addition, our results support the notion that pain inhibition is not a universal phenomenon, being dependent on intersubject variability. Significant correlations between CPM and clinical pain were similar in studies that showed significant and non-significant differences between the CPM efficacy of patients and controls. Such result suggests that, even in cases of a normal inhibitory system, as revealed by a lack of differences between patients and controls, individual variability in CPM magnitude may be linked with clinical characteristics of pain.

Moreover, biomarkers of pain intensity may be multifactorial, and one single marker may not be able to predict or correlate with this or other clinical manifestations of pain. In line with this hypothesis, one study showed that the combination of CPM and temporal summation is a better predictor of pain intensity than each one individually.[3] It would be worthwhile to test this hypothesis in future studies and to investigate whether CPM is a good predictor of treatment response because this variable was not analyzed in the current review.

Regarding the risk of bias, our results were similar to those obtained by Lewis et al.[35] The assessment of CPM by technicians who were blinded to patient and control subgrouping is still a minority, and the presence of confounding factors remains a common area of risk. Moreover, the matching between patients and controls was not applied to all the studies because they compare subgroups of patients more than patients and controls. The inclusion of a control group is of extreme importance when considering CPM as a clinical tool for quantification of the pain inhibitory system. In the absence of normative CPM data, including age- and sex-matched healthy controls should be mandatory in CPM research.

The effect of medication, especially of drugs affecting the central nervous system, seems to be a major confounder. A systematic review revealed that drugs used for pain management might cause an inhibition of the CPM response in a noncontrolled

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manner; some medications work through inhibition of pain-facilitating systems, whereas others through activation of pain-inhibiting systems.[22] Thus, a lower CPM response of a patient under analgesic medication can be incorrectly interpreted as reduced endogenous modulation instead of being attributed to the intake of CPM-inhibiting drugs.[4] Although most of the studies restricted analgesic medication, they did it for a variable period before testing. Besides analgesic medication, other confounders appear to influence CPM magnitude and to be sources of between-subject variability. For instance, variables such as pain catastrophizing and negative processing of pain, menstrual phase, stress, and high-order cognitive processes, such as distraction or expectations, are potential confounders to be controlled.[22,42] In comparison with Lewis et al. results,[35] we found less risk of bias in the representativeness of participants, with more studies specifying internationally recognized inclusion criteria and recruitment procedures.

Altogether, we can conclude that most of the data were obtained from studies with unclear risk of bias, and the lack of blinding is the main drawback in this field of study. However, considering that studies with a low and high risk of bias had the same pattern of results, this variable does not appear to influence the correlation between CPM and clinical manifestations of pain.

This systematic reviewed encountered a number of limitations. First, the reviewed articles reported measures of various CPM paradigms tested in heterogeneous chronic pain populations. Therefore, although it would be desirable to metanalyze these results, the heterogeneity of data made it inappropriate. Calculating a mean heightened correlation could bridge this gap. However, the majority of the studies did not provided statistical and descriptive results when correlations were nonsignificant.

Moreover, the data that we synthesized came from secondary analyses of studies that were not designed to test the correlations between CPM and clinical pain. Thereby, to obtain stronger conclusions, future studies should be designed to test these correlations and should include standardized measures of clinical and experimental pain. The current tendency of the literature appears to be following this necessity, considering that the majority of the included reports were published in the past year. This is an interesting finding considering the extensive literature about CPM responses in chronic pain, and also considering that diffuse noxious inhibitory control (DNIC) was first described in animals about 40 years ago[33] and in humans about 30 years ago. Thereby, this finding is suggestive of a recent and growing interest regarding the correlations between CPM dysfunction and the clinical manifestations of pain.

In this review, we only included studies using CPM, which is one of the available indices to study pain modulation. It would be interesting to review the correlations between clinical pain and other dynamic psychophysical measures such as temporal summation. In fact, a previous study found that the cluster that best predicts future pain development is defined by low CPM and high temporal summation, while CPM alone was not a good predictor.[47] Thus, the joint assessment of CPM and temporal summation could improve the concurrent validity of those biomarkers of pain.

5. Conclusion

The current systematic review was conducted to determine whether CPM responses are correlated with clinical manifestations of chronic pain. Altogether, our results do not support a significant correlation between them and, thus, throw doubts on the validity of CPM as a biomarker of clinical pain. However, this conclusion has to be taken with caution, considering the high heterogeneity among the included studies (concerning samples, CPM protocols, and clinical pain assessment) and their unclear risks of bias.

Our systematic review emphasizes the need for future studies conducted with the specific goal of testing the correlation between CPM responses and clinical manifestations of pain, including standardized measures of clinical pain and CPM, and controlling for confounding factors that may affect CPM responses, such as medication intake, sex, or type of chronic pain disease. We recommend the use of thermal CPM protocols, stimulation of nonpainful areas, and stable measures of clinical pain (comprising at least the past month), taking attention to the characteristic of pain (localized vs generalized) and sex.

Conditioned pain modulation is easy to obtain and implement in clinical practice, being consistently impaired in a number of chronic pain conditions. Thus, this measure could be useful to improve clinical management of pain and individualize pain medicine.[64] Nevertheless, this promising field of research faces the following 2 major challenges: to provide normative data that would allow the use of the CPM response for diagnostic purposes and to investigate whether CPM can be a prognostic biomarker of future pain, as is already being investigated in recent studies (Yarnitzsky et al., 2008).[57,62]

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A851.

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