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Effect of pain induction or pain reduction on conditioned pain modulation in adults :
a systematic review

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Abstract: Pain facilitation as well as pain inhibition might be present in chronic pain patients. A decreased efficacy of pain inhibition can be measured by conditioned pain modulation (CPM). The use of the CPM paradigm in scientific research has boosted over the last few years and is recognized for its high clinical relevance in chronic pain patients. It is however unclear whether the presence of pain and possible modulations of pain influences the efficacy of endogenous pain inhibition, measured by CPM. This systematic literature study aimed to provide an overview of the effects of clinical pain and experimental pain induction or pain reduction on CPM in adults. A systematic literature search was conducted in the databases "Pubmed" and "Web of Science". Only full texts of original studies regarding the effect of clinical pain and experimentally induced pain and pain reduction on CPM in adults were included. The included articles were scored on methodological quality and through a CPM-paradigm. Twelve articles of good to moderate quality were included in this review. Some pain inhibitory medication and oral contraceptives inhibit the CPM mechanism. Removing chronic pain by surgery results in an improved CPM response. This effect is not observed when removing acute pain. The present study shows that analgesic medication and oral contraceptives might inhibit the CPM response whereas there is limited evidence that pain relieving surgery improves CPM in chronic pain patients. However the results merely suggest that decreased CPM values (as in chronic pain patients) can improve after elimination of pain.

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Ghent, 1 feb 2014

To the editors of PAIN®

To the Editorial Board of PAIN®

Please find enclosed our manuscript "Effect of Pain Induction and Pain reduction on Conditioned Pain Modulation (CPM) in Adults: a systematic review" by Goubert D, Danneels L, Cagnie B, Van Oosterwijck J, Kolba K, Noyez H, Meeus M, which we would like to submit for publication as a systematic review in PAIN®. This manuscript contains 19 pages, 3 tables and 1 figure. Goubert D was the principal writer of the manuscript. Kolba K and Noyez H participated in the search strategy, information extraction and methodological quality. Both were hereby counseled and supervised by Meeus M and Goubert D. Meeus M, Danneels L and Cagnie B were the initiators of the review and Van Oosterwijck J developed the CPM checklist. Finally, Danneels L, Cagnie B, Van Oosterwijck J and also Meeus M contributed by reading and completing this manuscript.

To our knowledge, this is the first systematic review concerning the effect of pain on endogenous pain modulation systems. We intended to evaluate whether pain induction or pain inhibition change the efficacy of the CPM mechanism in adults by determining the influence of clinical (acute/chronic) and experimental pain induction or pain reduction on CPM. This study puts forward that some analgesic medications might inhibit the CPM response. On the other hand, removal of the peripheral pain source through surgery might restore the lowered CPM response in chronic osteoarthritis patients. Since the literature is scarce about the effect of pain induction or pain reduction on the CPM response, we think this systematic review might be an important contribution to the restricted knowledge on this topic. Moreover, this review might reach some interesting topics for future qualitative research. The review is reported following the PRISMA statement and will serve as an important reference manuscript for further CPM investigations.

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All authors have approved the manuscript and agree with its submission to PAIN®. We confirm that this manuscript has not been published elsewhere and is not under consideration for publication by any other online or print journal. The results of this systematic review has been presented on the 8th congress of the European Federation Of IASP® Chapters in Florence (October 9-12,2013) in the form of a poster presentation. No financial or other relationships might lead to a conflict of interest.

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Thank you for receiving our manuscript and considering it for review. We look forward to hearing from you.

Yours sincerely

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Summary

Pain inhibiting medications might cause an inhibition of the CPM response whereas it can improve by removing the peripheral cause of chronic pain through surgery.

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Effect of Pain Induction or Pain Reduction on
Conditioned Pain Modulation in Adults:
a Systematic Review

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1. INTRODUCTION

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or is described in terms of such damage (www.iasp-pain.org). Acute pain is a body's warning when there is actual tissue damage that ensures people to pay attention to the injury so further damage can be prevented. Chronic pain however is often less functional since patients still experiences pain although the original source of tissue damage has usually been resolved. In these patients transmission of pain signals from the periphery to the spinal cord persists and might produce changes in the central nervous system, a phenomenon is called central sensitization [27]. Recent research shows that augmented pain facilitation as well as reduced pain inhibition might occur in chronic pain patients, like whiplash disorders [25], chronic fatigue syndrome [22], rheumatoid arthritis [18], fibromyalgia [32] and chronic low back pain [10]. The capacity of pain inhibition can be measured by the Conditioned Pain Modulation (CPM) paradigm [32] previously termed as Diffuse Noxious Inhibitory Control (DNIC) or Heterotopic Noxious Conditioning Stimulation (HNCS). Basically, CPM works through the "pain-inhibits-pain" principle in which an additional painful (conditioned) stimulus can suppress the initial experienced pain through the descending and inhibiting pathways. It is then quantified by calculating the amount of pain reduction in the test stimulus (TS) before/during/after the administration of a painful conditioning stimulus. Pain perception during/after this conditioning stimulus (CS) should be lower than before, since the conditioning stimulus activates the endogenous pain inhibitory system (i.e. CPM) [38]. This analgesic CPM effect can persist for a few seconds or even several minutes after the removal of the conditioned stimulus [6,28,33]. The CPM response is suggested to work through a spino-bulbo-spinal loop, with an ascending pathway in the ventrolateral funiculi involving the subnucleus reticularis dorsalis in the medulla oblongata and a descending pathway in the dorsolateral funiculi [4]. The mechanism behind CPM is however complex and not yet fully understood.

CPM has been identified as an advanced measurement with high clinical relevance [29]. First of all, changes in the individual CPM response can predict the risk of developing postoperative chronic pain [40] as it has been hypothesized that a low CPM efficacy can be associated with higher pain morbidity [41]. Besides this, CPM might indicate whether a certain treatment actually reduces pain or not and can also be used as a pain inhibiting treatment modality on its own [42].

This CPM mechanism has been investigated in several populations with deviating methodologies. In patients with chronic pain CPM seems to fail most of the time [1,9,12,14,17,34] while results in acute patients or patients in which central sensitization is not assumed are more obscure [41]. It is therefore not clear whether the presence of the pain itself plays an important role in the CPM response. Possibly CPM fails when an additional conditioning pain stimulus is administered, in the presence of 2 already existing pain stimuli (clinical pain and test stimulus). Briefly, this review tries to assess efficacy of endogenous pain inhibition by evaluating the influence of a conditioning pain stimulus on test pain, if patients are already in pain. The literature is scarce about the effect of changing pain status (induction or reduction) on CPM response. Therefore this systematic review is intended to evaluate whether pain induction or pain inhibition changes the efficacy of the CPM mechanism in adults by determining the influence of clinical (acute/chronic) and experimentally induced pain or pain reduction on CPM. The present study systematically reviews the scientific literature according to the PRISMA guidelines.

2. METHODS

2.1. Research question

According to the PRISMA-guidelines, a PICO approach was applied to formulate the research question. This leads to the following question: "What is the influence of clinical (acute/chronic) and experimentally induced pain or pain reduction (I) on Conditioned Pain Modulation (O) in adults (P)? Studies were included if they examined the influence of clinical (acute/chronic) or experimentally induced pain or relief on CPM in human populations (≥ 18).

2.2. Search Strategy

The search strategy was conducted by 2 researchers (KK & HN) trained by DG & MM during October and November of 2012. DG is a PhD candidate and MM obtained the degree of PhD and is experienced in writing and training researchers in writing systematic reviews. The electronic databases PubMed and Web

of Science (WOS) were screened. Twelve key words were used in multiple combinations: conditioned pain modulation, diffuse noxious inhibitory control, heterotopic nociceptive conditioning physiology, heterotopic nociceptive conditioning stimulus, heterotopic nociceptive conditioning stimuli, heterotopic nociceptive conditioning stimulation, counterirritation, counterstimulation, heterotopic noxious conditioning physiology, heterotopic noxious conditioning stimulus, heterotopic noxious conditioning stimuli and heterotopic noxious conditioning stimulation. These 12 synonyms were combined with the following 4 key words: clinical pain, acute pain, induced pain and experimental pain. Reference lists of the included articles were screened in order to make the search as complete as possible. The complete search strategy is presented in Table1.

2.3. Selection Criteria and Data-extraction

After de-duplication the remaining articles were screened for title and abstract. In a final phase the remaining articles were filtered by a second screening based on full text. Both researchers evaluated all articles independently. When in doubt a consensus meeting was held with DG and MM. An article was only included if everyone agreed. To be included articles had to fulfill the following criteria: 1) The study population consisted of adult men and women who were 18 years or older. Articles concerning populations with neurological or psychological disorders were excluded, due to possible changes in the nervous system. 2) Only case-controls, cohorts, cross-over studies, cross-sectional studies and randomized controlled trials (RCT) were included. Expert opinions, reviews and congress proceedings were excluded. 3) The study needed to discuss the effect of a change in pain (induction or reduction) on CPM. Studies were excluded if they only examined the pain efficacy CPM. Studies focusing on the influence of attention on the CPM response were also excluded. 4) Articles in English, Dutch, French and German were included in this systematic review. Articles in other languages were excluded.

Information was extracted from each included article: type of intervention, characteristics of participants, study objective, results of intervention on CPM, used test- and conditioning stimulus, involved body sites and CPM outcome measure (Table 2). Two reviewers extracted the information (KK & HN) and two other reviewers checked the extracted information (DG & MM).

2.4. Risk of Bias

Checklists of the EBRO platform (Evidence-based guideline development in the Netherlands, presented on the website of the Dutch Cochrane Centre (<http://dcc.cochrane.org/>)) were used to assess methodological quality. The appropriate checklist was used related to the study design of the evaluated study. Because no specific checklist is available to evaluate cross-sectional studies the case-control checklist was used (with exception of the criteria regarding the control group and blinding).

Secondly the methodological quality of the used CPM paradigm was assessed (CPM score). Six 'yes or no' questions were composed: 1) Is it clearly mentioned in the article which is the test stimulus and which is the conditioning stimulus? 2) Are the administered stimuli and the device used for the application of these stimuli clearly described? 3) Is it clearly described at which body site the test and conditioning stimuli are administered? 4) Is the sequence and timing of administration of the stimulus clearly described? 5) Is the duration of the stimulus applications clearly described? 6) Is the CPM outcome measure clearly described?

The scores were converted into percentage to compare the methodological quality among studies with different maximum score.

Methodological quality was assessed by 2 independent, blinded researchers (KK & HN). The results were compared and differences were discussed in order to obtain a consensus. When consensus could not be reached a third opinion was provided by the last author (MM). Afterwards a level of evidence (LOE) was assigned to each article using the guidelines of the EBRO platform and a level of conclusion (LOC) was determined for each topic.

3. RESULTS

3.1. Study Selection

The search strategy resulted in 202 articles. After de-duplication 170 articles remained. Two articles were additionally found: one article was mentioned in the reference list in one of the included articles while other was published after the research strategy was performed. Twenty seven articles were included after

1 screening for title and abstract. Studies were excluded based on study population, study design or
2 intervention type. After screening for full text another 15 studies were excluded based on intervention
3 (research about genetics, sleep architecture or different ways to measure CPM) and study design (articles
4 not investigating the change in CPM response or a lacking protocol). After the complete screening, 12
5 studies were included in this systematic review. The entire selection process is presented in the flowchart
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15 3.2. Study Characteristics 16 17 18

19 Twelve articles were included, of which 3 were cohort studies, 2 cross-sectional studies, 4 cross-over
20 studies, 2 case-control studies and 1 RCT. The characteristics of each study were extracted and presented
21 in the evidence table (Table 2). Based on topic, articles were divided into 3 groups. Eight studies
22 investigated the effect of medication on CPM on healthy subjects [3,5,21,32]. Another 4 investigated
23 several patient populations, like chronic pancreatitis [7], cervical facet pain [8], chronic low back pain [20]
24 and general chronic pain [31]. Two studies [11,15] examined the effect of surgery on CPM in patients with
25 chronic osteoarthritis (OA). Two studies examined the influence of acute pain or experimental pain on
26 CPM: the first study [39] investigated the effect of (sub)acute shoulder pain in patients experimental
27 shoulder pain in healthy controls. The second study [25] investigated the effect of electrical induced pain in
28 the temporomandibular joint.
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40 Most frequently, mechanical (pressure) or thermal (heat) stimuli were used as the test stimulus. Electrical,
41 tactile or cold stimuli were also used. The sites of administration of these test stimuli were very different
42 among studies. The Cold Pressor Test (CPT) was the most frequently used conditioning stimulus. Seven
43 studies used this type of painful stimulation: 6 studies [7,8,20,31,32,39] immersed the hand (and wrist) in
44 ice cold water and 1 study [21] immersed the foot and leg in ice water. The duration of the CPT was
45 generally about 120 seconds. A hot water bath, pressure stimuli, CO₂ laser stimulation and a Tourniquet
46 Test (a painful ischemic compression provoked by a cuff around the upper arm) were also used as
47 conditioning stimuli. All stimuli are presented in Table 2.
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3.3. Risk of Bias

After the assessment of the methodological quality, 11 articles had a score of 50% or more. One article [25] had a CBO score of less than 50%. There was too little information concerning the blinding of the research and the degree of execution of the protocol. Besides that, not all subjects received an equal treatment, apart from the intervention. Those who were afraid of needles received an altered procedure. Before the consensus meeting, an agreement of 89.29% and 87.50% between both assessors was reached for methodological quality and quality of the CPM paradigm respectively. Four articles [3,7,20,21] obtained a LOE A2. Six articles [15,39] got a LOE B and two studies [5,8] were classified as LOE C. A complete summary of the quality assessment is given in table 3.

3.4. Synthesis of Results

3.4.1. Medication

The following medications were examined: Pregabalin [7], Tropisetron [20], Dexmedetomidine [3], Lidocaine and Bupivacaine [8], Ketamine [21], Opioids [31] and Oral Contraceptives [32], Morphine and Naloxone [5]. Some had no effect, some had a negative effect and some had a positive effect on the CPM response.

No effect on CPM response

Pregabalin is a medical drug with analgesic effects which acts upon the descending pain processes through the GABA receptors. It also binds to $\alpha_2\delta$ sites in the central nervous system and acts upon the central pain processes by decreasing neurotransmitters like Substance-P or Glutamate [7]. Bouwense et al. (2012) examined the effect of Pregabalin versus a placebo treatment on CPM response in patients with chronic pancreatitis. No difference in CPM response was seen in pancreatitis patients who received a treatment with Pregabalin in comparison to a placebo treatment ($p>0.05$).

1 Neziri et al. (2012) evaluated the effect of Tropisetron (a 5-HT₃ receptor antagonist with analgesic effect)
2 on CPM in patients with chronic low back pain. This study was conducted using an intravenous injection of
3 Tropisetron at 2 different doses, in a randomized, double-blind, placebo-controlled, crossover manner.
4 Both in Tropisetron and placebo condition a significant difference in CPM response was found after
5 treatment in comparison with baseline measurements (p=0.021). But no differences could be found
6 between the Tropisetron and placebo group (p=0.617) indicating that Tropisetron has no effect on the
7 CPM mechanism in patients.
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10 **Negative effect on CPM response**

11 Dexmedetomidine (DEX) is a selective α_2 -adrenergic receptor agonist with analgesic effects when given in a
12 low dosage and narcotic effects when administered intravenously in a higher, clinical dosage. One of the
13 most important target sites of DEX is located within the Locus Coeruleus in the brainstem which reduces
14 the release of noradrenalin [3]. According to the study of Baba, et al. (2012) DEX inhibits the CPM
15 paradigm in healthy adults. DEX significantly inhibits the pain reduction when administered in a low dosage
16 (VAS: p<0.05; Somatosensory evoked potentials (SEP): p<0.01) and even more in a high dosage of DEX
17 (VAS: p<0.001 en SEP: p<0.001). According to the authors of this article, DEX can be seen as a dose
18 dependent inhibitor of the CPM mechanism.
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38 Chua et al. (2011) investigated the effect of diagnostic blocks (Lidocaine and Bupivacaine) on CPM and on
39 Quantitative Sensory Testing. Both types of medications interact with sodium channels and ensure
40 analgesia and anesthesia and are often administered intra-articular to inhibit pain and reduce
41 hyperalgesia. In this study, 9 subjects with chronic cervical facet pain were tested two times: after a first
42 and a second diagnostic block (respectively DB1 and DB2). Diagnostic blocks were evaluated in the face
43 and in a pain-free reference area in the thigh. DB1 and DB2 in the thigh and DB2 in the face lowered the
44 CPM response significantly (p=0.008; p=0.021; p=0.015). DB1 in the face lowered CPM response and the
45 result approached significance (p=0.051).
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58 Ketamine, a NMDA receptor antagonist, was assumed to affect CPM in a positive way and thus contribute
59 to a long-lasting analgesic effect in patients with chronic pain [21]. However, the opposite was proven.
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After Ketamine injection, there was no CPM effect left. This drug even provoked a facilitatory pain response when a conditioning stimulus was applied in comparison when no conditioning stimulus was applied ($p<0.01$). Consequently, ketamine blocks the analgesic effect of CPM. Niesters et al. (2011) concluded that Ketamine disturbed the balance between pain inhibition and pain facilitation in preference to pain facilitation.

According to Ram et al. (2008) opioids also tend to facilitate pain during the CPM paradigm rather than enhancing pain inhibition ($p=0.003$). Men had a significant lower CPM effect when injected with opioids in comparison to non-opioids ($p=0.001$). However, this difference was not seen in the female population ($p>0.05$). Besides that, the inhibiting effect of the opioids on CPM depended on the dosage and treatment duration. The higher the opioid dosage and the longer the duration of the treatment, the lower the CPM effect in the masculine population.

In the study of Le Bars et al. (1992) the effect of Morphine (an opioid receptor agonist activating the μ -receptors) and Naloxone (an opioid receptor antagonist with high affinity for μ -receptors) CPM was measured. After a Morphine injection, there was no longer an inhibitory effect coming from the CPM mechanism ($p<0.001$).

Besides the fact that plenty of analgesic drugs inhibit the CPM paradigm, oral contraceptives (OC) also inhibit CPM. Oral contraceptives inhibit the ovulation by suppressing the release of luteinizing hormone, which in turn suppresses the estradiol peak. According to the article of Rezaii & Ernberg (2010) the endogenous pain modulation system, induced by an experimental acute pain, is less effective in women who use OC in comparison to normal menstruating women who don't take OC ($p<0.05$).

Positive effect on the CPM response

Naloxone, an opioid antagonist, is the inverse of Morphine and blocks the μ -receptors in the central nerve system. Naloxone is given when addicted to Morphine or other medications. In the study of Le Bars et al. (1992) Naloxone was administered after a Morphine dose was administered. After a Naloxone injection

the CPM response that was lowered because of the Morphine administration was normalized again (p<0.001). After a while, even a bigger CPM response was seen, compared to baseline.

In general, moderate evidence seems to suggest that medication currently used in pain management as Dexmedetomidine, Lidocaine, Bupivacaine, Morphine, Ketamine, opioids and oral contraceptives lower the CPM effect and reduce the effect of pain inhibition. Although Pregabalin and Tropicisetron had no effect on the CPM paradigm. Naloxone on the contrary, normalizes CPM effect and even increases pain inhibition again after Morphine injection.

3.4.2.Chronic Pain

Two studies examined CPM before and after a surgical intervention in patients with osteoarthritis (OA). Graven-Nielsen et al. (2012) examined patients with chronic knee OA, whereas Kosek & Ordeberg (2000) examined patients with hip OA. OA patients had a significantly decreased CPM response before surgery, in comparison to the healthy control group. Following joint replacement surgery, the CPM response was restored in chronic knee OA (p<0.0002) and in chronic hip OA (p<0.02). After surgery, the postoperative CPM response was comparable to the healthy control group.

There is moderate evidence that removing the structural cause of chronic pain through surgical interventions, improves the CPM mechanism.

3.4.3.(Sub)Acute Pain

Valencia et al. (2012) and Oono et al. (2012) investigated CPM in subjects with (sub)acute pain. The study of Valencia et al., (2012) investigated shoulder pain in healthy controls and in a patient group with (sub)acute shoulder pain because of an acute injury and requiring an arthroscopic intervention. Acute shoulder pain was provoked by exercise-induced muscle pain in the healthy control group. CPM was compared before and after this pain induction. In the patient group, CPM values were compared before and after the surgical intervention. Although there are equivocal differences in baseline measurements

1 between the patient group and the controls, the absolute difference in CPM response did not alter
2 significantly after pain induction through exercise ($p=0.778$) or after pain reduction through surgery
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4 ($p=0.186$).
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6 In the study of Oono et al., (2012) the influence of an acute stimulus in the temporomandibular joint (TMJ)
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8 on CPM was examined. This experimental pain was induced by electrical stimulation. No significant
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10 differences in CPM values were found between the subjects who received electrical stimulation and the
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12 subjects who didn't receive electrical stimulation ($p>0.05$).
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14 Based on these studies, there is moderate evidence that inducing or inhibiting (sub)acute pain does not
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16 change the CPM mechanism.
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22 4. DISCUSSION 23 24 25 26

27 4.1. Results 28 29 30

31 The main objective of this systematic review was to determine what is known thus far about the influence
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33 of clinical (acute or chronic) and experimentally induced pain or pain reduction on the CPM response in
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35 adults.
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40 The present study revealed that several drugs used for pain management can cause an inhibition of the
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42 CPM response. Each drug however, probably creates this effect through another working mechanism.
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44 Some medications work through inhibition of pain facilitating systems, others through activation of pain
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46 inhibiting systems. Pregabalin [7] is an analgesic medication, but no effect on CPM could be found,
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48 suggesting it rather targets pain facilitating mechanisms. Tropicisetron [20] as well is supposed to influence
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50 generalized hyperalgesia, what might be the reason why the researchers didn't found any effect on CPM
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52 response.
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57 A lot of these medications have been tested on healthy controls [3,5,7,21,32] which might underline the
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59 influence of the drug itself, besides any confounding disease-related factors. Because a lot of chronic pain
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1 patients take all kinds of analgesic medication, a lower CPM response could be incorrectly interpreted as a
2 reduced CPM mechanism due to the chronic disease, but can in fact be attributed to the intake of CPM
3 inhibiting drugs [3]. Future research should take this into account when interpreting their results.
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8 Researchers point at multiple systems that might contribute to pain inhibitory systems, like personal
9 variables. King et al., (2013) detected that negative cognitive processing of pain might influence
10 endogenous analgesia. Also Nir et al., (2012) emphasized the relevance of cognitive mechanisms altering
11 CPM characteristics. Moont et al., (2010) on the other hand found that modulation of CPM is not due to
12 cognitive attention. The influence of gender is also discussable. Although the majority of studies found no
13 gender dependent differences on CPM [2,16,24,30], in the study of Ram et al. (2008) men only
14 experienced lower CPM response after opioid intake. Until now it is difficult to make firm conclusions on
15 these aspects. Future investigations might clarify these obscurities.
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27 The studies of Graven-Nielsen et al., (2012) and Kosek & Ordeberg (2000), pointed out that the CPM
28 mechanism is less effective in OA patients before surgical intervention in comparison to the CPM response
29 after surgery. According to the authors this shows that a reduced CPM mechanism is being maintained by
30 peripheral pathology. Once the peripheral pathology is surgically approached, the CPM response is
31 restored.
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38 Possibly the chronic peripheral pain itself might blur the CPM response as this acts as a third pain stimulus,
39 besides the TS and CS. So before the CS is administered, the peripheral pain might work as CS and compass
40 a pain-inhibits-pain mechanism, which will be abrogated when the real CS is administered in a CPM
41 experiment. Another plausible explanation might be found in the use of analgesic medication in chronic
42 pain patients which might affect the CPM response. A lot of patients might diminish the amount of
43 medication after removal of the peripheral pain source which can influence subsequently the restoration
44 of the CPM mechanism.
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53 Unlike in chronic diseases, removing clinical or experimental acute pain does not alter the CPM response.
54 According to Valencia et al., (2012) this is due to the fact that the pain has not become chronic yet and
55 therefore could not decrease CPM efficacy. So the CPM response needs to be decreased before it might
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improve after removal of this pain. Oono et al., (2012) concluded that CPM deficiencies in pain conditions are most likely more related to the duration of clinical pain than to the pain itself.

Based on the preceding conclusions, one can assume that there is a difference between the effect of analgesic medication and pain relieving surgery in patients with chronic pain. Whereas medication mostly inhibits CPM, surgery rather restores a reduced CPM mechanism in chronic pain patients through the removal of the peripheral pathology. These results suggest that analgesic medication has a central and inhibiting effect on CPM, whereas surgery correcting peripheral pathology has a peripheral and stimulating effect on CPM.

4.2. Limitations

There were some limitations regarding to the included articles. In the studies of Baba et al. (2012), Chua et al. (2011), Le Bars et al. (1992) and Niesters et al. (2011) a rather small population size (only 9 or 10 subjects) was used. Therefore, these studies have less statistical power and undermine the reliability of their results. Besides this, studies examining the CPM response in some specific patient populations in which impaired endogenous pain modulation is expected, are lacking, like patients with fibromyalgia, chronic fatigue syndrome, chronic whiplash associated disorders and other chronic diseases.

Two studies did not retest all patients within the same time frame after surgery. In the study of Graven-Nielsen et al. (2012) a wide postoperative time frame was used (5 to 28 weeks after surgery) to retest the patients. Also in the study of Kosek & Ordeberg, (2000) a time frame ranging from 6 to 14 months after surgery was used. The large differences in moment of retesting between various test subjects can lead to misinterpretation of the test results.

A third arguable restriction could be the intensity of the CS, which needs to be painful enough to obtain a decent CPM response [5]. After administration of certain medications, the bottom up stimulus might be suppressed and might consequently result in an inadequate CPM response. Since not all studies examined the intensity sensation of CS and TS after administration of the medication, one cannot assume all stimuli

1 were intense enough to arouse a decent CPM response, which might explain why Bouwense et al., (2012)
2 and Neziri et al., (2012) did not find any changes at all in CPM response.
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6 In addition to these limitations, a lot of articles did not take into account the several parameters that may
7 influence the CPM paradigm. Except for the article of Rezaii & Ernberg (2010), no other article mentioned
8 the menstrual cycle phase of the female subjects in their study protocol although hormonal levels might
9 influence the CPM paradigm [37]. Only 2 articles [20,32] mentioned the use of oral contraceptives during
10 testing. Also other medication use was not prohibited for all participating populations [5,7,8,15,25,39].
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12 Therefore interactions from other medication affecting the CPM mechanism cannot be excluded.
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17 Other personal factors like the psychological state of patients (anxiety, depression, emotional status,
18 attention span), factors responsible for comorbidity (smoking or obesity) and ethnic origin were usually not
19 mentioned. Kosek & Ordeberg (2000) did not even mention the sex ratio in the population or control
20 group. The possible influence of these factors therefore cannot be ruled out. Also patients' expectations
21 were not taken into account as a result of which placebo effects cannot be excluded.
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31 The fact that only a few studies examined the influence of an additional experimental stimulus (besides the
32 test stimulus and the conditioning stimulus) on CPM, can also be seen as a limitation. Only 2 articles
33 [25,39] examined the effect of introducing a third experimental and painful stimulus to the test protocol.
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41 Finally, a wide variety of test stimuli, conditioning stimuli, sites of administration, duration and intensity of
42 the stimuli were included in this systematic review. No exclusion criteria were formulated to narrow down
43 this variety. These differences in methodology can cause differences in the CPM effect [29] and can
44 therefore influence the conclusions that were made by the present study.
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5. CONCLUSION

The present study shows that analgesic medication and oral contraceptives might cause an inhibition of the CPM response. A possible explanation is that a lot of medication might have a central and inhibiting effect on the CPM mechanism by blocking the signal transition between the medulla oblongata and the periphery. Further research is needed to explain and interpret this hypothesis.

On the other hand, removing the peripheral cause of chronic pain through surgery can ameliorate the CPM response in patients with osteoarthritis. However, the removal of acute pain through surgical interventions or the removal of acute, experimental induced pain does not alter the CPM response. These results suggest that disturbance of the CPM mechanism in patients may be time dependent: first, the CPM response should be significantly decreased, like in chronic pain, before CPM can significantly improve again, after the removal of this pain.

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FIGURE CAPTATIONS

Figure 1: Flowchart of the selection process (n=number of articles)

Figure 1

Flowchart of the selection process (n=number of articles)

Table 1

Database	Search terms	Additional filters	Results	Total before de-duplication	Total after de-duplication
PubMed	(1) OR (2) OR (3) OR (4) OR (5) OR (6) OR (7) OR (8) OR (9) OR (10) OR (11) OR (12) AND (clinical pain OR acute pain OR induced pain OR experimental pain)	Language: English, French, Dutch, German	83	202	170
		Age: adult, 18+			
		Species: human			
WOS	(1) OR (2) OR (3) OR (4) OR (5) OR (6) OR (7) OR (8) OR (9) OR (10) OR (11) OR (12) AND (clinical pain OR acute pain OR induced pain OR experimental pain) AND human AND adult NOT animal NOT child	Language: English, French, Dutch, German	119		

Complete search strategy ((1)=“conditioned pain modulation”; (2)=“diffuse noxious inhibitory control”; (3)=heterotopic nociceptive conditioning physiology; (4)=heterotopic nociceptive conditioning stimulus; (5)=heterotopic nociceptive conditioning stimuli; (6)=heterotopic nociceptive conditioning stimulation; (7)counterirritation; (8)=counterstimulation; (9)=heterotopic noxious conditioning physiology; (10)=heterotopic noxious conditioning stimulus; (11)=heterotopic noxious conditioning stimuli; (12)=heterotopic noxious conditioning stimulation).

Table 2

Study	Characteristics study population (patient population; control population; age)	Intervention (patient population; control population)	Study objective	Test stimulus (type; site)	Conditioning stimulus (type; site; duration)	Outcome measure	CPM Result
Baba et al. (2012) [3]	PP: Healthy (n=10; M=5; F=5) CP: N/A A: 26-41 years [mean 29.6 ± SD 4.3 years]	PP: normal saline (0.095mL/kg/h); Dexmedetomidine (DEX) (0.38µg/kg/h & 0.75µg/kg/h) CP: N/A	Effect of low / high dosage of DEX on CPM	T: electrical S: tooth	T: CO2-laser S: hand D: 60 pulses	SEP +VAS	Low dosage of DEX: CPM response↓ (VAS p<0.05; SEP p<0.01) High dosage: CPM response ↓↓(VAS p<0.001 en SEP p<0.001)
Bouwense et al. (2012) [7]	PP: Chronic (n=64; M=40; F=24)) CP: Healthy (n=15; M=8; F=7) A (PP): IQR 45-62 years [mean 53.5 years] A (CP): IQR 35-49 years [mean 38 years]	PP: Pregabalin (75mg, 150 mg & 300mg) or Placebo CP: N/A	Effect of Pregabalin on CPM in patients with chronic pancreatitis	T: pressure S: non-dominant knee (L4)	T: CPT (1°C±3°C) S: dominant hand D: max. 120 s	pPTT	Pregabalin: no effect on CPM response (p>0.05)
Chua et al. (2011) [8]	PP: Cervical facet pain (n=9; M=7; F=2) CP: N/A A: 52-60 years [mean 58 years]	PP: Diagnostic blocks (lidocaine or bupivacaine) CP: N/A	Effect of diagnostic blocks (Lidocaine, Bupivacaine) on QST and CPM	T: electrical S: non painful side, anterior thigh + face	T: CPT (temp N/A) S: dominant hand D: max. 180 s/80 mm VAS	EPTT	Diagnostic blocks: CPM response ↓ (DB1 thigh p=0.008; DB2 thigh p=0.021; DB1 face p=0.051; DB2 face p=0.015)
Le Bars et	PP: Healthy (n=9; M=4; F=5)	PP: Morfine (0.05mg/kg, 5ml) & Naloxone	Effect of low dosage	T: electrical (RIII)	T: hot water bath	EMG RIII	Morfine: CPM response ↓,

al. (1992) [5]	CP: N/A A: 24-36 years [N/A]	(0.006mg/kg, 5ml) CP: N/A	of Morfine / Naloxone on CPM (measured via RIII reflex) in healthy controls	reflex) S: L N. Suralis, ankle	(46°C) S: R hand up to 5 cm above wrist D: 120 s	reflex	reflex↑ (p<0.001) Naloxone: CPM response ↑, reflex↓ (p<0.001)
Neziri et al. (2012) [20]	PP: Chronic LBP (n=30; M=15; F=15) CP: Chronic LBP A: 23-78 [mean 51 ± SD 15 years]	PP: Tropisterson (2mg & 5mg) CP: Placebo (20ml, 0.9% saline)	Effect of Tropisetron on CPM in chronic LBP	T: pressure S: plantar tip of the 2nd toe (most painful side)	T: CPT (0,1±0,7°C) S: ipsilat (most painful side) hand D: max. 120 s	PPT	Tropisetron: no effect on CPM response (p=0.016)
Niesters et al. (2011) [21]	PP: Healthy (n=10; M=4; F=6) CP: Healthy A: range N/A [mean 24.1 ±3.7 years]	PP: Ketamine (40mg per 70 kg) CP: Placebo	Effect of Ketamine on CPM and Offset Analgesia	T: heat (placebo 46.1±2.5°C; ketamine 45.9±2.9°C) S: L arm, ventral	T: CPT (placebo 10.3±3.9°C; ketamine 10.7±3.8°C) S: foot + lower leg (side N/A) D: 55 s	eVAS	Ketamine: CPM response ↓ (p<0.01) No effect on Offset Analgesia.
Ram et al. (2008) [31]	PP: Chronic pain (n=73; M=38;F=35) CP: Chronic pain (n=37; M=20;F=17) A: 19-76 years [49.5±16.5 years]	PP: Opioid (OP) - Oxycodone (n=17; 20-80mg/day) - Morphine (n=3; 10-360 mg/day) - Tramadol (n=21; 50-400mg/day) - Propoxyphene (n=18; 40-200mg/day) - Fentanyl (n=13; 25-375µg/h) - Codein (n=4; 15-45mg/day) CP: Non-Opioid (NOP)	Effect of OP / NOP on CPM and on hyperalgesia in chronic pain	T: heat (37±47°C) S: L thenar	T: CPT (12°C) S: R hand D: max. 180 s	NPS	↓CPM response in OP vs NOP (p=0.003) ↓CPM response in OP vs NOP in men (p=0.001)

		<ul style="list-style-type: none"> - Diclofenac (n=3; 50-100mg/day) - Etodolac (n=18; 400-1800mg/day) - Celecoxib (n=2; 200-600mg/day) - Ibuprofen (n=4; 400-800mg/day) - Paracetamol (n=3; 500-2000mg/day) - Dipyrrone (n=4; 500-1500mg/day) - Indometacine (n=1; 200-600mg/day) - Etoricoxib (n=7; 60-240mg/day) 					
Rezaii & Ernberg (2010) [32]	PP: Healthy (n=15; M=0; F=15) CP: Healthy (n=17; M=0; F=17) A: range N/A [mean 24.2 ± SD 3.2 years]	PP: Oral Contraceptives (OC) (different combinations of hormones, but all containing ethinyl & gestagen) CP: no OC	Influence of OC on CPM in healthy women	T: pressure S: L or R, most prominent part of m. masseter + tip of the 3rd finger	T: CPT (3°C) S: contralateral hand + wrist D: max. 300 s	NRS	↓CPM response in OC vs non OC (p<0.05)
Graven-Nielsen et al. (2012) [11]	PP: Knee osteoarthritis (OA) (n=20; M=6; F=14) CP: Healthy (n=21; M=4; F=17) A (PP): 48-86 years [mean 68 years] A (CP): 40-81 years [mean 60 years]	PP: knee replacement surgery CP: no intervention	Influence of chronic tissue damage (caused by knee OA) on the maintaining of central sensitization measured by CPM	T: pressure (cuff) S: bilat, knee: 7x peripatellar region	T: ischem ex (TT) S: L arm, lower rim of cuff 3 cm proximal to the cubital fossa D: 4 cm VAS	PPT	Preoperative: ↓CPM response in OA (p<0.03) Postoperative: ↑CPM response in OA (p<0.0002)
Kosek & Ordeberg (2000) [15]	PP: Hip OA (n=15; M=?; F=?) CP: Healthy (n=15; M=?; F=?) A (PP): 29-66 years [mean 52 years]	PP: total hip replacement (n=11); osteotomy (n=2) CP: no intervention	Influence of chronic pain (caused by hip OA) on CPM,	T: pressure/tactile/cold/ heat (temp N/A)	T: ischem ex (TT) S: ipsilateral to most painful hip, just	PPT	Preoperative: ↓CPM response in OA vs controls (p<0.02)

	A (CP): 30-67 years [mean 50 years]		measured before and after surgery	S: contralat to the most painful hip, Trochanter Maior Femoris/thigh/lat side of the calf	proximal to the cubital fossa D: max. 30 mm VAS		Postoperative: ↑ CPM response in OA (p<0.02)
Valencia et al. (2012) [39]	PP: Clinical shoulder pain (n=58: M=41; F=17) CP: Healthy (n=56; M=40; F=16) A (M): range N/A [mean 28.71 ± 8.44 years] A (F): range N/A [mean 32.34 ± 11.55 years]	PP: arthroscopic surgery of the shoulder CP: shoulder pain induction by exercise-induced muscle pain (by a isokinetic dynamometer)	CPM in healthy population (pain induction via ischemic exercise) vs clinical shoulder pain (pre- and postoperative)	T: heat (46,48,50°C) S: non-dominant/non-surgical thenar	T: CPT (8°C) S: dominant/surgical hand till wrist D: max. 60 s	NRS	No difference in CPM response after pain induction (p=0.778) or surgery (p=0.186)
Oono et al. (2012)	PP: Healthy (n=40; M=20; F=20) CP: Healthy A (M): 20-38 years (mean 25.4 ± SEM 0.9) A (F): 20-30 years (mean 24.9 ± SEM 0.8)	PP: TMJ pain induction by el stim (5 Hz; 0.5 ms duration) CP: without TMJ pain induction	Influence of el stim (in TMJ) on CPM + effect of gender on CPM	T: pressure S: R m. masseter + L forearm (Flexor Carpi Radialis)	T: pressure S: pericranial muscles (vertex) D: ± 7 minutes	VAS	No difference in CPM response with el stim vs without el stim (p>0.05) No sex differences

Evidence table (PP=patient population; CP=control population; A=age; n=number of patients; M=male; F=female; T=type; S=site; D=duration; N/A=not applicable; SD=standard deviation; IQR=interquartile; SEM=standard error of the mean; L=left; R=right; SEP= Somatosensory evoked potentials; (e)VAS=(electronic) visual analogue scale; NPS=numeric pain scale; NRS=numeric rating scale; pPTT=pressure pain tolerance threshold; EPTT=electrical pain tolerance threshold; EMG=electromyography; RIII reflex=nociceptive flexion reflex; PPT=pressure pain tolerance; m=musculus; CPT=cold pressure test; QST=quantitative sensory testing; LBP=low back pain; vs=versus; OA=osteoarthritis; TT=tourniquet test; ischem ex=ischemic exercise; el stim=electrical stimulation; TMJ=temporomandibular joint; temp=temperature).

Table 3

Study	Date	Study design	CBO design	CBO CPM	1	2	3	4	5	6	7	8	9	Total CBO Total CPM	LOE	LOC	TOPIC
Baba et al.	2012	CO	RCT	CBO	1	1	1	1	1	/	1	1	1	7/8	A2	3	Medication
				CPM	1	1	0	1	1	1				5/6			
Bouwense et al.	2012	RCT	RCT	CBO	1	0	1	1	1	0	1	1	1	7/9	A2		
				CPM	1	0	1	1	0	1				4/6			
Chua et al.	2011	CS	CC	CBO	1	/	1	1	/	1				4/4	C		
				CPM	1	0	1	1	1	1				5/6			
Le Bars et al.	1992	CS	CC	CBO	0	/	0	1	/	1				2/4	C		
				CPM	1	0	0	1	1	0				3/6			
Neziri et al.	2012	CO	RCT	CBO	1	1	1	1	1	1	1	1	1	8/9	A2		
				CPM	1	0	0	1	1	1				4/6			
Niesters et al.	2011	CO	RCT	CBO	1	0	1	0	0	1	1	0	1	5/9	A2		
				CPM	1	1	0	1	1	1				5/6			
Ram et al.	2008	CC	CC	CBO	1	1	1	1	0	1				5/6	B		
				CPM	1	1	1	1	1	1				6/6			
Rezaii et al.	2010	CC	CC	CBO	1	1	1	1	0	1				5/6	B		
				CPM	1	1	1	1	1	1				6/6			

Graven-Nielsen	2012	Cohort	Cohort	CBO	1	1	1	1	0	1	0	1		6/8	B	2	Chronic pain
				CPM	1	1	0	1	1	1				5/6			
Kosek et al.	2000	Cohort	Cohort	CBO	1	0	1	1	0	1	1	0		5/8	B		
				CPM	0	1	1	1	0	0				3/6			
Valencia et al.	2012	Cohort	Cohort	CBO	1	1	1	1	0	0	1	0		5/8	B	2	(Sub)acute pain
				CPM	1	0	1	1	1	1				5/6			
Oono et al. (*)	2012	CO	RCT	CBO	1	0	0	0	0	1	0	1	0	3/9	B		
				CPM	0	1	1	1	1	1				5/6			

Methodological quality (CBO, CPM), LOE, LOC (CBO=Centraal BegeleidingsOrgaan; CPM=conditioned pain modulation; LOE=level of evidence; LOC=level of conclusion; CS=cross sectional; RCT=randomised controlled trial; CC=case control; CO=cross over; 1=score fulfilled; 0= score not fulfilled; /=the answer is unclear; *empty space*=no question to be answered; (*)=CBO score < 50%).