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Systematic Review

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Modulation of offset analgesia in patients with chronic pain and healthy subjects – a systematic review and meta-analysis

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Abstract

Objectives: Offset analgesia (OA) induces a brief pain inhibition and studies suggest OA impairment in patients with chronic pain when compared to healthy subjects. Conditioned pain modulation remains the most studied descending pain inhibitory control mechanism and is modulated by centrally-acting analgesics. Since OA may be mediated by similar neural substrates as conditioned pain modulation, understanding if OA is a peripheral or central proxy of pain modulation is important. The modulatory effect of centrally-acting drugs on OA in healthy and chronic pain populations has not yet been systematically reviewed and meta-analyzed, and this systematic review and meta-analysis aimed to identify studies employing interventions for modulating OA magnitude.
Methods: A systematic search of PubMed, Embase, Web of Science, and the Cochrane Library yielded 146 records of which 11 (172 healthy pain-free subjects, 106 chronic pain patients) were eligible for qualitative synthesis, and 10 for meta-analysis on overall modulatory effect of interventions on OA, and subgroup analysis of patients and healthy pain-free subjects.
Results: Risk of bias was evident for study participation and study confounding in the included studies. Several different methods for assessing and calculating OA magnitude were identified, which may affect interpretability of findings and warrants standardization. The meta-analysis showed no modulatory effects on OA overall (standardized mean difference (SMD) [95%CI]: 0.04 [−0.22, 0.30], Z=0.29, p=0.77), or in the subgroup analysis for patients (SMD [95%CI]: −0.04 [−0.63, 0.71], Z=0.13, p=0.90) or healthy pain-free subjects (SMD [95%CI]: 0.01 [−0.21, 0.24], Z=0.11, p=0.91). Moderate to substantial heterogeneity was found for the overall analysis (I^2=47%, p=0.03) and patient subgroup analysis (I^2=75%, p=0.003).
Conclusions: The current systematic review and meta-analysis conclude that centrally-acting drugs and exercise do not influence OA. Evidence on the peripheral contribution to OA response requires further investigations. Preclinical models of OA should be established to identify the neurophysiology and -biology behind OA.

Keywords: healthy subjects; modulation; offset analgesia; systematic review and meta-analysis.

Introduction

Chronic pain affects approx. 20% of the world population [1] although the underlying modulatory mechanisms for the transition from acute to chronic pain remain largely unknown. The descending pain inhibitory pathways have received growing interest and the fundamentals widely studied in animals [2]. Human experimental pain assessment of descending pain inhibitory control includes condition pain modulation (CPM) [3], exercise induced hypoalgesia [4] and offset analgesia (OA) [5, 6], where CPM traditionally has been the most studied. It is evident that CPM is impaired in several chronic pain conditions when compared with healthy subjects [7] while a recent systematic review and meta-analysis concluded that healthy populations present with a larger OA response when compared to chronic pain populations [8].

OA is assessed by administration of three consecutive painful heat pulses with the first (T1) and the last (T3) being at the same temperature whereas the second pulse (T2) is slightly more painful and OA is observed as a

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disproportional reduction in perceived pain from T2 to T3 [9]. Studies have suggested that OA and CPM are impaired in patients with neuropathic pain [10, 11] and osteoarthritis [12], which could suggest that OA and CPM may share common neural pain pathways. In contrast, earlier studies have found that different brain regions are activated during CPM and OA [13] and combining an OA paradigm with a CPM paradigm provide additional hypoalgesic effects compared to a CPM paradigm alone [14]. Nonetheless, preclinical trials have established that noradrenaline and serotonin are important neurotransmitters for descending pain inhibitory control [15–17] and a human trial suggested that patients with painful diabetic neuropathy and impaired CPM, responded better to duloxetine and restored CPM (a serotonin and noradrenalin reuptake inhibitor) [18]. In addition, studies have found that increased clinical pain intensities are associated with impairment of CPM [19, 20] and that blocking the clinical pain will normalize CPM [21, 22]. Furthermore, prolonged administration of opioids seems to negatively affect CPM [23]. Together, it seems evident that multiple pharmacological and surgical interventions can modulate CPM and that CPM is driven by central pain mechanisms and neurotransmitters such as serotonin and noradrenaline. While the difference in OA magnitude between healthy and chronic pain patients has recently been meta-analyzed [8], and systematically compared to CPM [6], the current systematic review and meta-analysis aimed to investigate the modulatory effects of interventions on OA magnitude in healthy and chronic pain populations, with a particular interest in centrally-acting drugs.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. The Population-Intervention-Comparison-Outcome (PICO) framework was used to formulate research questions. The following PICO questions were formed (1) “Which methods have been used to measure offset analgesia in studies regarding the modulation hereof in humans?” and (2) “Can offset analgesia be modulated in humans?” The resulting keywords and Medical Subject Headings (MeSH) terms for each PICO search block is represented in Table 1.

PubMed, Embase, Web of Science and the Cochrane Library were systematically searched. The search was performed in April 2020 and consisted of the keywords from the PICO search blocks, connected by Boolean operators. Only peer-reviewed studies published in English and with available full-text articles were considered eligible for the systematic review. The systematic review has been registered on the Open Science Framework website (OSF.IO, link to protocol: DOI: 10.17605/OSF.IO/D78EV).

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

P	I	O
Patients Healthy	“Offset analgesia”	Method* Technique* (MeSH) Mechanism* Modulat* Analges* Inhibit* Pain* “Pain perception” (MeSH) “Pain measurement” (MeSH) “Pain threshold” (MeSH) Nocicept* (MeSH)

Study selection and eligibility criteria

For this systematic review, the PRISMA flow diagram for study selection was completed (Figure 1). First, all records were exported to EndNote X4 (Thomson Reuters, Philadelphia, PA, USA), and duplicates were removed. Subsequently, an initial screening of titles and abstracts was performed to remove records based on the inclusion and exclusion criteria. Peer-reviewed full text articles were included if they (1) investigated offset analgesia before and after an intervention or between placebo and active intervention; and (2) included patients or healthy participants. Non-English [25] and animal studies were excluded. The screening process was independently performed by two reviewers (XJU and DBL) after the initial systematic database search. Disagreements in relevancy were solved by consensus. In case consensus was not reached, a third reviewer (KKP) was consulted who made the final decision. Cross-referencing the included studies and the authors’ own article collection was performed for additional relevant literature, if appropriate.

Data extraction for the qualitative synthesis

Information on participants (healthy or patient populations), study design (type of intervention and OA paradigm used), and results (modulation of OA) were extracted and summarised for the qualitative synthesis. If more than one type of intervention was used in an article, this was indicated by separating them into different numbers ((1) or (2)). In these cases, the given number was coupled to the specific intervention for the remainder of the summary of that article. Methods using both fixed and individual temperatures were present. If individual temperatures were used, this was specified in the summary according to the description in the article.

Data extraction for meta-analysis

The primary outcome OA at baseline and post-intervention was extracted from the included articles by one reviewer (XJU) and checked for consistency by another (DBL). Data were entered into Excel for data overview and then imported to RevMan (Review Manager v5.4, The Nordic Cochrane Centre, Copenhagen, Denmark).

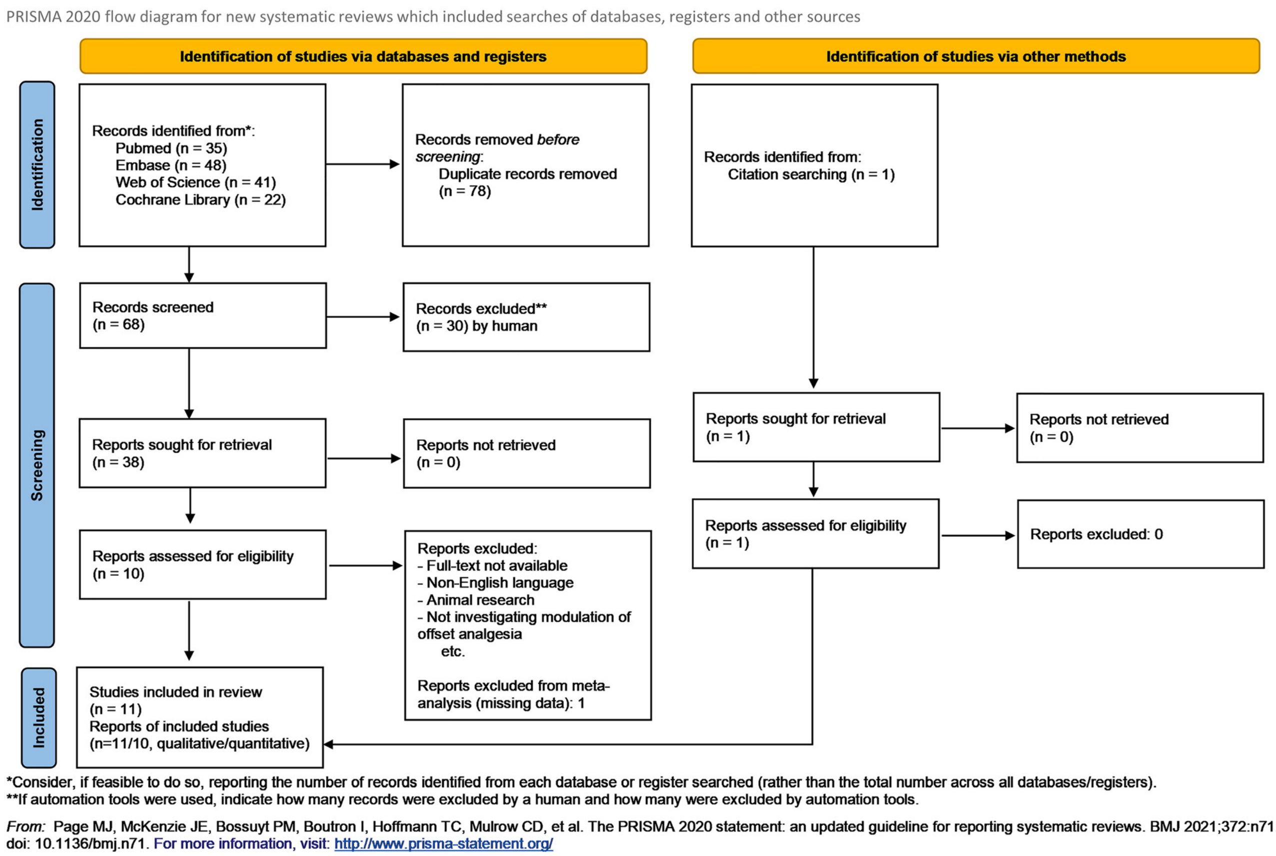

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

To provide an overview of the current literature and effects of interventions on OA, a combined meta-analysis was first performed for all included studies, using an inverse variance random-effects model to estimate the overall effect size (Z statistics; expressed as standardized mean difference, SMD) for placebo/baseline vs. intervention/after intervention (regardless of study type), respectively, on OA magnitude ($\Delta eVAS_{corrected}$ or $\Delta eVAS$). This approach was deemed appropriate since the different types of study designs (randomized controlled trials, parallel and crossover, and pre-post designs) estimated the same outcome measure (i.e. effect on OA magnitude) [26]. However, including both randomized controlled trials (five crossover) and pre-post studies may pose a challenge due to same-data dependence, but was overcome by dividing the sample size (n divided by number of treatment arms) where appropriate, to avoid double-counting participants/patients as has previously been done in other research areas (see e.g. [27]). This approach ignores the cross-over design and is, at best, conservative in its estimation of effect size because the within-participant correlations are unaccounted for [26]. A subanalysis was carried out to investigate the effects of interventions on OA magnitude in patient and healthy cohorts, separately.

Heterogeneity between the included studies was assessed by between-study variance (χ^2) and inconsistency (I^2). If the χ^2 test was <0.1, statistically significant heterogeneity was considered present, and an I^2 value >60% indicated substantial heterogeneity [28].

Risk of bias assessment

The Quality In Prognosis Studies (QUIPS) tool [29], as recommended by the Cochrane Methods Prognosis group [28], was utilized to assess risk of bias for the current review. The tool is comprised of six domains: "Study Participation", "Study Attrition", "Prognostic Factor Measurement", "Outcome Measure", "Study Confounding" and "Statistical Analysis and Reporting", in which potential issues are addressed. QUIPS is originally aimed at prognostic studies, but as the studies in this systematic review do not involve a prognostic factor, this was defined as the intervention, while the outcome measurement was defined as the OA paradigm. Based on the findings within the domains, each domain was graded either "low risk", "medium risk" or "high risk". This assessment was performed by two reviewers (XJU and DBL) on each included study. Disagreements were solved by consensus and in case consensus was not reached, a third reviewer (KKP) was consulted for the final decision.

GRADE quality rating

To rate the current quality of evidence available, the GRADE approach was used. Randomised controlled trials were rated as "High quality" whereas observational studies were rated as "Low quality". We included the domains "Study limitations" [30], "Inconsistency" [31], "Indirectedness" [32], "Imprecision" [33], and "Reporting bias" [34]. The overall quality of each study was then assessed based on their initial rating (study design) considering these subdomains in the final assessment.

Results

Study selection

The study selection process, shown in Figure 1, yielded a total of 146 records. These were identified through the database search of which 11 peer-reviewed full-text articles were included in the systematic review, and 10 were included in the meta-analysis. Two corresponding authors were contacted [12, 35] to obtain means and SD of pre- and post-intervention of which both responded [10–12, 35, 36], whereas data from one article was not retrieved after contact to the corresponding author due to technical difficulties receiving the data [37].

Study characteristics

A summary of the study characteristics is shown in Table 2. Seven studies recruited healthy participants and four studies recruited patients with chronic pain [11, 40], osteoarthritis [12] and neuropathic pain [36]. The interventions included treatment with an antihypertensive drug (Clonidine [38]), a beta-blocker (Propranolol [35]), opioids (Oxycodone [41], Remifentanil [37], Morphine [36], Tapentadol [11] and Hydromorphone [40]), an opioid antagonist (Naloxone [37]), a serotonin-noradrenalin reuptake inhibitor (Venlafaxine [41]), an N-Methyl-D-Aspartate (NMDA) receptor antagonist (Ketamine [15, 40]), a non-steroidal anti-inflammatory drug (Ibuprofen) in combination with acetaminophen [12],acute isometric exercise [42], and spinal anaesthesia [43]. Eight studies were randomized controlled trials [10, 11, 35–38, 41, 43], whereas three were exploratory trials without controls [12, 40, 42]. Sample sizes ranged between 10 and 40 (healthy) and 10–42 (patients) participants.

Table 2: Studies using pharmacological or exercise interventions to modulate OA magnitude in healthy subjects or pain patients.

Study	Participants Population, N	Intervention	Study design OA paradigm	Results Results (OA)
Nahman-Averbuch et al. [38]	Healthy (40)	Clonidine (0.15 mg)	T1 (PAIN60) T2 (T1 + 1 °C) T3 (T1)	No significant effect on OA magnitude
Niesters et al. [11, 39]	Patients – diabetic polyneuropathy (24)	Tapentadol *(individually titrated dose)*	T1 (eVAS > 50 mm) T2 (T1 + 1 °C) T3 (T1)	No significant effect on OA magnitude
Suzan et al. [40]	Patients – chronic lumbosacral radicular neuropathic pain (30)	Hydromorphone *(individually titrated dose)*	T1 (49 °C) T2 (50 °C) T3 (T1)	No significant effect on OA magnitude
Petersen et al. [35]	Healthy (25)	Propranolol (40 mg).	T1 (48 °C) T2 (49 °C) T3 (T1)	No significant effect on OA magnitude
Petersen et al. [12]	Patients – knee osteoarthritis (42)	Ibuprofen + acetaminophen (1.2 g + 3 g).	T1 (46 °C) T2 (47 °C) T3 (T1)	No significant effect on OA magnitude
Olesen et al. [41]	Healthy (20)	o;1 Oxycodone (10 mg). o;2 Venlafaxine (37.5 mg).	T1 (pain tolerance threshold – 1 °C) T2 (pain tolerance threshold) T3 (T1)	No significant effect on OA magnitude
Niesters et al. [10]	Healthy (10)	Ketamine (40 mg./70 kg).	T1 (eVAS > 50 mm) T2 (T1 + 1 °C) T3 (T1)	No significant effect on OA magnitude
Harris et al. [42]	Healthy (36)	Isometric exercise (20–25% MVC – 5 min).	T1 (heat pain 50/100) T2 (T1 + 1 °C) T3 (T1)	No significant effect on OA magnitude
Martucci et al. [37]	Healthy (19)	o;1 Naloxone (0.01 mg/kg). o;2 Remifentanil *(individually titrated dose)*	T1 (49 °C) T2 (50 °C) T3 (T1)	No significant effect on OA magnitude
Niesters et al. [36]	Patients – neuropathic pain (10)	o;1 ketamine (0.57 mg/kg). o;2 morphine (0.05 mg/kg)	T1 (eVAS > 50 mm) T2 (T1 + 1 °C) T3 (T1)	No significant effect on OA magnitude
Sitsen et al. [43]	Healthy (22)	Spinal anesthesia (3 mL *Bupivacaine*.)	T1 (eVAS > 50 mm) T2 (T1 + 1 °C) T3 (T1)	Significant reduction in OA during active treatment with spinal anaesthesia

OA, Offset analgesia; T1, First painful heat pulse; T2, Second painful heat pulse slightly higher than T1; T3, Third painful heat pulse at the same temperature as T1; eVAS, Electronic VAS.

Assessment of offset analgesia

All OA paradigms were conducted using heat, with baseline temperatures ranging between 32 °C and 35 °C. Four studies applied fixed temperatures including 49-50-49 °C [37, 40], 48-49-48 °C [35] and 46-47-46 °C [12], while seven studies individualised these based on the participant's heat pain ratings. Of the latter, five studies used an increasing painful heat stimulus to identify a temperature equal to a pain rating of 50/100 [10, 11, 36, 42, 43] while another study used pain rating 60/100 ("pain60") [38] as T1. In these studies, T2 was T1 + 1 °C, and T3 was the same as T1. The final study chose the pain tolerance threshold (PTT) – 1 °C as T1, PTT as T2, while T3 was the same temperature as T1 [41].

In addition to an OA paradigm, four studies used a control paradigm [12, 35, 37, 41]. One of the studies pseudo-randomised the order of which paradigm was conducted first, and used the temperatures 49-50-35 °C for the control paradigm, with the same time intervals as the OA paradigm [37]. Another study applied a constant temperature of PTT-1 °C for 30 s and randomised the order of the paradigms [41]. Finally, two studies [12, 35] used the control paradigms, in which a constant temperature, matching that of T1, was kept for 30 s, to calculate the OA effect.

Calculation of offset analgesia effect

Eight studies calculated the OA effect as the absolute difference in the minimum pain rating in T3 compared to the maximum pain rating in T2. While three of these studies used this definition for the calculation of the OA effect [37, 38, 40], six studies further corrected for the value of the maximum pain rating in T2 [10, 11, 36, 41–43]. The remaining two studies calculated the average pain ratings subsequent to the change in temperature from T2 to T3 (16–20 s) and compared them to the same period of a control paradigm, in which participants were subjected to a constant stimulus of a temperature equalling T1 for 30 s [12, 35].

Modulation of offset analgesia

As seen in Table 2, seven of the 11 included studies investigated the modulation of OA in healthy participants. Of these, six studies found no effect on the modulation of OA. Two studies used the 48-49-48 C° paradigm, investigating the effect of a single dose of Propranolol [35] and Oxycodone or Venalafaxine for 5 days [41], and one study used a 49-50-49 C° paradigm to explore the effects of Remifentanil or Naloxone [37]. Four studies used individualized temperatures, and investigated the effects of a single dose of Clonidine [38], a single dose of Ketamine [10], one round of isometric exercise [42], and active treatment with spinal anesthesia [43]. The remaining four studies investigated the effect of OA in patients and found no significant modulation of OA by different interventions. One study investigated the effect of a 3 week NSAIDs and paracetamol intervention using the 46-47-46 C° paradigm in knee osteoarthritis patients [12], whereas another used a 49-50-49 C° paradigm and tested 4 weeks of Hydromorphone treatment in chronic lumbosacral radicular neuropathic pain patients [40]. Individualised temperatures were used to test patients with diabetic polyneuropathy undergoing 4 weeks treatment with Tapentadol [11] and neuropathic pain patients after a single dose of Ketamine or Morphine [36].

Meta-analysis

Ten studies were included in the meta-analysis, with a total of 259 participants, of which 153 were healthy (51 females), and 106 were patients (50 females). In the combined analysis of all included studies, OA magnitude was not significantly altered when considering the placebo/baseline value vs. the intervention/after intervention (SMD [95%CI]: 0.04 [−0.22, 0.30], Z=0.29, p=0.77, Figure 2). Likewise, when considering the patient cohorts and the healthy participants separately, the interventions had no overall effect in the patients (SMD [95%CI]: 0.04 [−0.63, 0.71], Z=0.13, p=0.90; Figure 3, upper) or the healthy participants (SMD [95%CI]: 0.01 [−0.21, 0.24], Z=0.11, p=0.91; Figure 3, lower). No significant subgroup difference between the OA response magnitude in patients vs. healthy participants after interventions was found (χ^2 (1) = 0.05, p=0.82).

There was significant moderate heterogeneity among the studies (I^2=47%, p=0.03) in the combined analysis and substantial heterogeneity in the patient studies subgroup (I^2=75%, p=0.003). Conversely, no significant heterogeneity was found in the healthy participants subgroup analysis (I^2=0%, p=0.49).

Risk of bias

As seen in Table 3, three studies were deemed high risk in "study participation", as they did not describe the population of interest, recruitment method and necessary sample size [11, 37, 38]. Three other studies were assessed as medium risk, as they did not describe one or more of the abovementioned elements [12, 35, 41]. The remaining three studies were rated low risk, as they provided a sufficient description of the

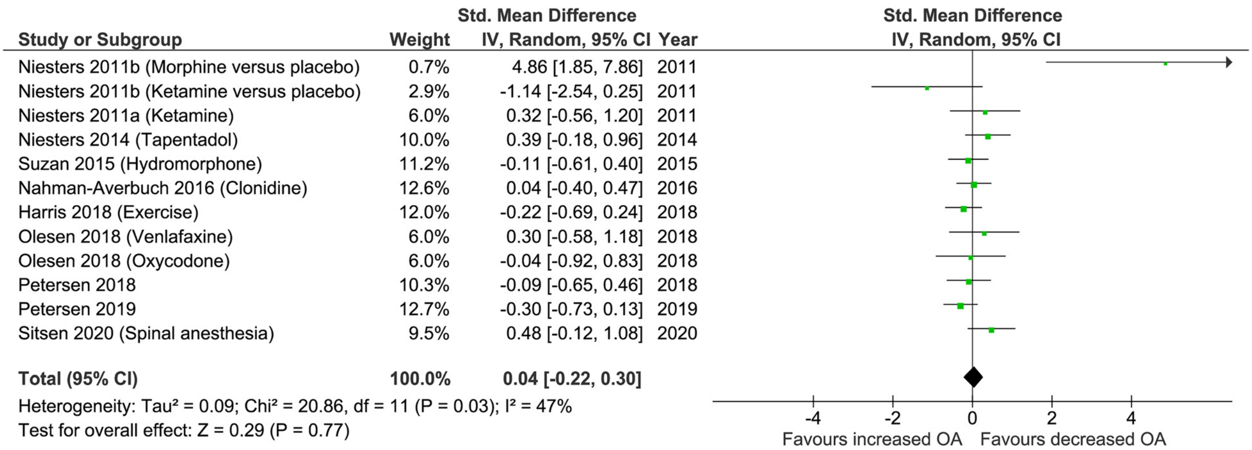

Figure 2: Effect size comparisons of the modulatory effect of different pharmacological and exercise interventions on OA magnitude. Green squares indicate standardized mean difference and error bars indicate 95% confidence intervals. OA, Offset analgesia.

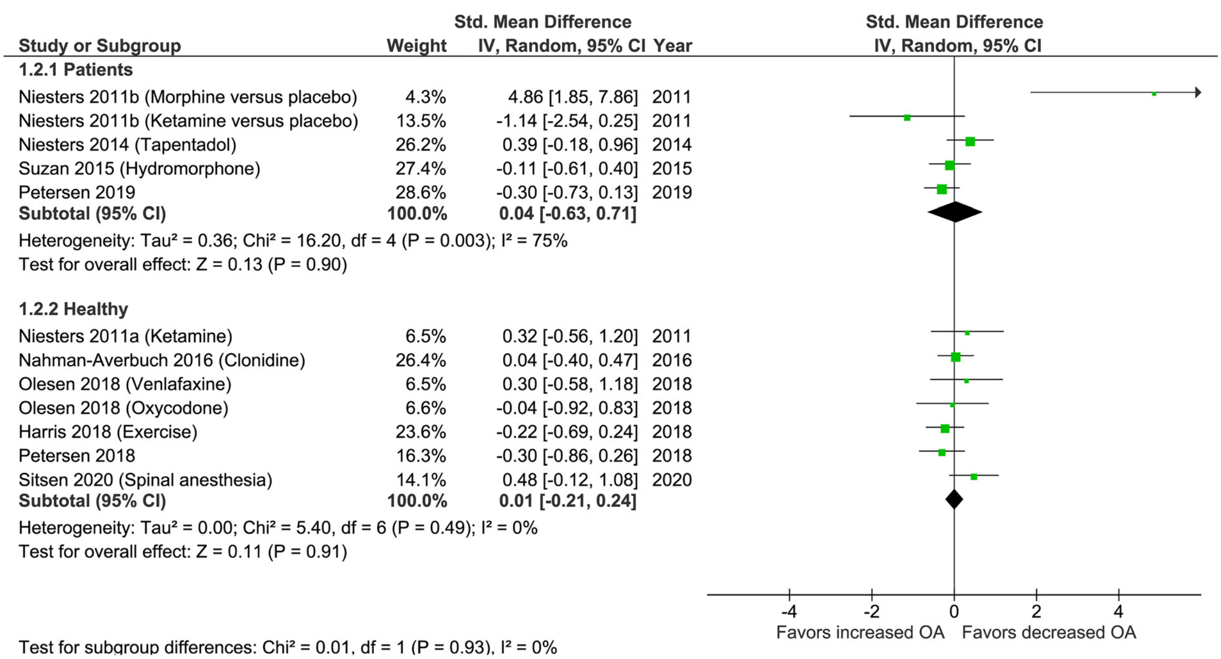

Figure 3: Effect size comparisons of the modulatory effect of different pharmacological and exercise interventions on OA magnitude in pain patients (upper frame) and healthy subjects (lower frame). Green squares indicate standardized mean difference and error bars indicate 95% confidence intervals. OA, Offset analgesia.

domain [10, 40, 42]. All studies were deemed low risk concerning "study attrition", aside from one, which was rated medium risk, as it omitted description of the characteristics of participants who did not complete the study [40], while other studies either had a 100% completion rate or provided an adequate description on the follow-up process. In the domains "prognostic factor measurement" and "outcome measure" all studies were rated as low risk, as both domains were well described, while all studies in the domain "study confounding" were rated as medium risk, due to failure to account for potential confounders. All studies were deemed low risk in the "statistical analysis and reporting domain" (Table 4).

The reviewers (XJU and DBL) initially agreed on 80.4% of the ratings. Consensus was reached on all ratings following discussion.

Table 3: Risk of Bias (RoB) for studies investigating modulation of OA in healthy and chronic pain populations. Using the Quality in Prognostic Studies (QUIPS) tool, the RoB assessment was based on study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis. In general, low-to-moderate risk of bias was observed in most studies distributed across all factors.

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Niesters et al. [10]	L	L	M	L	M	L
Niesters et al. [36]	H	L	L	L	M	L
Martucci et al. [37]	H	L	L	L	M	L
Niesters et al. [11, 39]	L	L	L	L	M	L
Suzan et al. [40]	M	M	L	L	H	L
Nahman-Averbuch et al. [38]	H	L	L	L	M	M
Olesen et al. [41]	M	L	L	L	M	L
Petersen et al. [35]	M	L	L	L	M	L
Harris et al. [42]	L	L	L	L	M	L
Petersen et al. [12]	M	M	L	L	H	L
Sitsen et al. [43]	M	L	L	L	M	L

GRADE – quality of included studies

The GRADE assessment demonstrated that while few high quality studies are available on the modulatory effects of different interventions on OA magnitude [10, 11, 35, 41, 43], much of the available literature are of low-to-moderate quality. The assessment was mainly based on issues surrounding risk of bias, inconsistency, and imprecision.

Discussion

This systematic review, for the first time, analyzed the modulatory effects of different interventions on OA response magnitude and found 11 eligible studies on modulation of offset analgesia of which 10 studies were included in the meta-analyses, demonstrating that the interventions did not modulate offset analgesia in healthy subjects, patients with chronic pain or the combined population. The current review identified several methodological differences including different temperature ranges, individualizing temperatures for each participant, the use of control paradigms, and differences in calculating offset analgesia effects which all might impact the generalizability of the results. In general, the studies demonstrated low risk of bias, with the majority of high and medium risk of bias found in the description of study participants and lack of assessing study confounding factors, which is in agreement with a recent systematic review and meta-analysis [8] and an earlier systematic review [6]. Moreover, the GRADE approach yielded overall quality assessments between low-to-high, where the major impact on quality ratings, was based on risk of bias, inconsistency, and imprecision. It is worth considering, that much of the OA research done to date, is mainly exploratory, and valid reporting bias was not estimated, which may have affected the overall quality ratings.

Modulation of offset analgesia

It remains unclear if the OA mechanism is primarily peripherally or centrally mediated [6] but OA can be induced by applying varying stimuli trains in different dermatomes [5], which may indicate a central component. This is important since OA modulation has traditionally been investigated utilizing therapies that target primarily the peripheral (e.g. NSAIDs and paracetamol) and central nervous system (e.g. ketamine or serotonin-noradrenalin reuptake inhibitors).

The current review identified two studies targeting the autonomic nervous system [35, 38], where heart rate variability is often used to assess the parasympathetic activity in the autonomic nervous system. Studies have found a decrease in heart rate variability in patients with chronic pain [44] and in models of experimentally-induced pain [45]. Administration of propranolol can decrease opioid-induced hyperalgesia [46] and reduce the pain intensity after i.m. injections of serotonin [47], indicating a link between drugs targeting the autonomic nervous system and pain mechanisms. The studies reviewed in the current work

Table 4: GRADE of the included studies. Low-to-high quality evidence is available on the modulatory effects of interventions on OA magnitude in healthy volunteers and chronic pain patients. The GRADE approach identified several issues within risk of bias, inconsistency, and imprecision subdomains that all affected the overall quality assessment. Publication bias was not assessed, due to the exploratory nature of OA research at present time.

	Risk of bias	Inconsistency[f]	Indirectness[g]	Imprecision[h]	Reporting bias[i]	Quality[j]
Niesters et al. [10]	Serious limitations[a]	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Moderate
Niesters et al. [36]	Serious limitations[b]	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Low
Martucci et al. [37]	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Low
Niesters et al. [11, 39]	No serious limitations	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	High
Suzan et al. [40]	Serious limitations[c]	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Low
Nahman-Averbuch et al. [38]	Serious limitations[d]	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Moderate
Olesen et al. [41]	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	High
Petersen et al. [35]	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	High
Harris et al. [42]	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Low
Petersen et al. [12]	Serious limitations[e]	Serious inconsistency	No serious indirectness	Serious imprecision	Undetected	Low
Sitsen et al. [43]	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision	Undetected	High

[a]Limitations with respect to methods applied and settings for volunteers vs. patients, randomization/blinding/placebo included, but no confounders measured. [b]Limitations in sample frame, inclusion, period/place, and exclusion criteria; Serious limitations in confounding, i.e. no confounders accounted for, but with a strong experimental design for systematic bias. [c]Limitations in sample frame and eligibility; no accounting for confounders or systematic bias in study design. [d]Limitations in sample frame and eligibility; no accounting for confounders in study design; statistical models may not be appropriate for answering the hypotheses of the studies. [e]Limitations in eligibility (subsample of other cohort); Retention rate low and not controlling for baseline offset-analgesia between included versus excluded patients, no information on dropouts but available information on loss to follow-up; no accounting for confounders or systematic bias in study design. [f]Moderate I^2 value of 47% indicates some heterogeneity among the included studies and may be ascribed to inconsistent effect sizes. Our sub-group meta-analysis showed that the primary inconsistency was related to the OA responses in patients. Therefore, the inconsistency impact on overall study quality only affected studies in which effect size estimates were based on data from patients. [g]Studies include comparisons in populations of interest – no serious indirectness can be inferred based on the exploratory nature of OA research. [h]Imprecision based on CIs of the estimated effect sizes, suggests no major impact, however, it is worth considering that most studies included in this systematic review only obtained data from small cohorts of patients. Per GRADE6 guidelines, we opted to flag for serious imprecision, but want to highlight that most research within the modulatory effects of interventions on OA, is exploratory. [i]Due to the exploratory nature of OA research at the time this systematic review was conducted, it is unclear whether reporting bias is present. [j]Based on study design (observational versus randomized controlled trials), limitations, inconsistencies, indirectness, imprecisions, and reporting bias.

[35, 38] assessed healthy subjects and it is unclear if OA was dysregulated in these populations which may explain the lack of modulation to drugs targeting the autonomic nervous system. In fact, Nahman-Averbuch et al. [38] did demonstrate an association between changes in heart rate variability and improvements in OA effect, which supports this hypothesis.

The current systematic search found five studies investigating opioid receptor antagonists [37] or agonists [11, 36, 40, 41]. Impaired CPM has been demonstrated in long-time opioid-users compared to non-users [48], which could indicate an interaction between opioids and descending pain inhibitory control. Studies indicate that the acute effect of opioids might block the descending pain inhibitory control systems [49, 50] and that the administration of naloxone can counter this acute effect [49]. Based on this, and since OA is partly mediated by descending pain inhibitory control system [6], it would be logical that OA could be modulated by targeting the opioid receptors. The current results did not support that OA can be modulated by opioid antagonists or agonists, which may be predicated on functioning OA prior to administration or that OA is not mediated by descending pain inhibitory control systems. Similarly, preclinical studies have identified that serotonin and noradrenalin are important neurotransmitters for the function of the descending noxious inhibitory control systems [16, 17]. Human administration of duloxetine (a serotonin-noradrenalin reuptake inhibitor) can improve CPM in patients with diabetic neuropathies [18] and if OA is partly mediated by CPM, administration of e.g. venlafaxine (another serotonin-noradrenalin reuptake inhibitor) should modulate OA. Olsen et al. [41] administered venlafaxine to healthy subjects and found no modulation, which could be explained by the lack of impaired OA often observed in healthy subjects [6] or that OA is not mediated by descending pain inhibitory control systems. Of note, the morphine treatment in Niesters et al. [36] was the only treatment shown to have a modulatory effect on OA (compared to placebo; i.e. no crossing the null effect) in the meta-analysis. One possibility, as also highlighted by the authors, may be the smaller sample included in the study, that could have inflated the overall effect size in the meta-analysis.

Dorsal horn hyperexcitability can be reduced in patients with fibromyalgia by administration of ketamine (N-Methyl-D-Aspartate (NMDA) receptor antagonist) [51]. The current review identified two studies in both healthy subjects and patients with chronic pain assessing OA before and after administration of ketamine [10, 36] where both studies showed no effect of ketamine on OA magnitude, indicating that OA is not mediated by dorsal horn hyperexcitability.

Non-selective NSAIDs and paracetamol inhibits the production of prostaglandin through cyclooxygenase (COX). Studies suggest that an analgesic effect of NSAIDs and paracetamol depends on an intact serotonin system [52] and that NSAIDs and paracetamol might enhance the activity of the cannabinoid system [53]. A study on administration of COX-2 selective NSAIDs patients with knee osteoarthritis was able to modulate widespread pressure hyperalgesia and temporal summation [54], suggesting that COX-2 selective NSAIDs might act on central pain mechanisms. The current review identified one study assessing patients with knee osteoarthritis where three weeks of NSAIDs and paracetamol treatment did not modulate OA magnitude, which could indicate that non-selective NSAIDs and paracetamol do not modulate central pain mechanisms.

Exercise induced hypoalgesia is induced by applying a test stimulus before and after an acute bout of exercise [55] and the effect is believed (in part) to be due to activation of the descending pain inhibitory pathways [56, 57]. Vaegter et al. [57] assessed the effect of the cold pressor test (often used to assess CPM) and an acute bout of cycling and isometric contractions (often used to assess exercise induced hypoalgesia) on pressure pain tolerance thresholds and found similar increases after both interventions, suggesting similar mechanisms. The current review identified a single study [42], which attempted to modulate OA using an acute bout of isometric exercise but found no differences in OA suggesting that OA might not be mediated by exercise induced mechanisms or that the effect cannot add on to the already existing mechanism of OA.

Niesters et al. [39] found that short-time epidural anesthesia (segmental blocking of peripheral input to the central nervous system) can lead to cortical reorganization as reflected by functional MRI and hyperalgesia in healthy subjects. The current review identified one study [43] that reported reduced OA following epidural anesthesia suggesting that an acute deafferentation might impact OA and suggests that central pain mechanisms are partly involved in OA.

At present, few studies have investigated the peripheral component of OA. For instance, Martucci et al. [58] explored whether a peripherally-induced transient sensitization by capsaicin cream application could modulate OA magnitude in healthy subjects, but found no differences. As such, the peripheral contribution to OA responses remains elusive and may call for further exploration.

Offset analgesia methodology

The current review found large methodology differences in between studies where 36% (4/11 studies) applied fixed temperatures [12, 35, 37, 40] and 64% (7/11 studies) individualized the temperature based on the each participant [10, 11, 36, 38, 41–43]. In addition, 36% (4/11 studies) used a control paradigm [12, 35, 37, 41]. Similarly, this review reported multiple varying calculations of the OA effect, which calls for standardization. Conclusively, this review demonstrates large methodological inconsistencies, which might impair the progression of this research field which is in line with a recent systematic review and meta-analysis on OA magnitude in healthy and chronic pain populations [8]. A consensus statement on recommendations for future development, similar to that of the CPM paradigm [59], is warranted.

Limitations

The current meta-analysis was conducted on combined data from randomized controlled trials including crossover and parallel trials, and pre-post studies, imposing a limitation on the effect size estimation [26]. However, there are two primary reasons as to why this is unlikely to affect the overall conclusion since (1) proper wash-out periods between each treatment arm were included in the included cross-over trials and (2) no significant overall effect size was found for the interventions on OA magnitude.

Conclusions

The current review identified 11 papers and 10 papers were used for the meta-analyses. The meta-analysis was unable to demonstrate modulation of offset analgesia through centrally-acting drugs or an acute bout of isometric exercise, suggesting that the evidence for a central pain mechanistic component of OA is, at present, limited. In addition, evidence on the peripheral contribution to OA and its modulation is scarce, which may warrant further investigation.

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