A Systematic Review and Meta-Analysis Regarding the Modulation of Offset Analgesia

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This master’s thesis was written as a part of the master’s degree program in Biomedical Engineering and Informatics at Aalborg University in the spring of 2020. The thesis has been divided into two parts: “Part 1: Article” and “Part 2: Worksheets”. The first part includes a systematic review and meta-analysis regarding the modulation of offset analgesia, while the second part includes worksheets, which provide relevant background information on pain pathophysiology and basic biochemistry of the interventions mentioned in part 1. The reference list and citations followed the IEEE format, and acronyms used more than once were added to the “Acronyms” section of the thesis. The first time an acronym is mentioned, the full description will be included.

Finally, I would like to express my gratitude to my supervisor, Kristian Kjær Petersen, who has provided helpful guidance throughout this project.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>QST</td>
<td>Quantitative Sensory Testing</td>
</tr>
<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>PICO</td>
<td>Population-Intervention-Comparison-Outcome</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
</tr>
<tr>
<td>QUIPS</td>
<td>Quality In Prognosis Studies</td>
</tr>
<tr>
<td>OA</td>
<td>Offset Analgesia</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin and Noradrenalin Reuptake Inhibitors</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-Methyl-D-Aspartate</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
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<td>PTT</td>
<td>Pain Tolerance Threshold</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>PNS</td>
<td>Peripheral Nervous System</td>
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<td>PSNS</td>
<td>Parasympathetic Nervous System</td>
</tr>
<tr>
<td>RVM</td>
<td>Rostral Ventromedial Medulla</td>
</tr>
<tr>
<td>PAG</td>
<td>Periaqueductal Grey</td>
</tr>
<tr>
<td>DNIC</td>
<td>Diffuse Noxious Inhibitory Controls</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactive Disorder</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
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</tbody>
</table>
Contents

Article ........................................................................................................................................... 5

I. Introduction ................................................................................................................................. 1

II. Methods ..................................................................................................................................... 2
    Search Strategy ......................................................................................................................... 2
    PICO .......................................................................................................................................... 2
    Databases ................................................................................................................................ 2
    Study Selection and Eligibility Criteria .................................................................................... 3
    Data Extraction ......................................................................................................................... 3
    Meta-Analysis ............................................................................................................................ 3
    Risk of Bias ............................................................................................................................... 3

III. Results ..................................................................................................................................... 3
    Study Selection ......................................................................................................................... 3
    Study Characteristics ................................................................................................................ 3
    Offset Analgesia and Control Paradigms .................................................................................. 4
    Calculation of Offset Analgesia Effect ..................................................................................... 6
    Results ....................................................................................................................................... 6
    Meta-Analysis .......................................................................................................................... 6
    Risk of Bias ............................................................................................................................... 6

IV. Discussion ............................................................................................................................... 7
    Offset Analgesia Paradigms ...................................................................................................... 7
    Control Paradigms .................................................................................................................... 7
    Confounders ............................................................................................................................. 7
    Outcome Measurements ............................................................................................................ 9

V. Conclusion ............................................................................................................................... 10

Worksheets ................................................................................................................................... 11

1. Pain Pathophysiology .............................................................................................................. 12
    Peripheral Nociceptive Pathway .............................................................................................. 12
    Central Nociceptive Pathway .................................................................................................. 13
    Descending Pain Modulatory Pathway ................................................................................... 14

2. Quantitative Sensory Testing and Human Experimental Models ............................................. 15

3. Interventions ........................................................................................................................... 16
    Adrenergic Interventions ........................................................................................................ 16
    Serotonin Norepinephrine Reuptake Inhibitors ..................................................................... 16
    NSAID and Acetaminophen .................................................................................................... 16
    N-Methyl-D-Aspartate ............................................................................................................ 17
    Opioids .................................................................................................................................... 17
    Isometric Exercise ................................................................................................................... 17

References ..................................................................................................................................... 18
Part I

Article
A Systematic Review and Meta-Analysis
Regarding the Modulation of Offset Analgesia

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June 2, 2020

Abstract

Introduction: Chronic pain constitutes a large socio-economic problem and affects the patient’s quality of life. As the current knowledge of the underlying mechanisms of pain is still incomplete, different methods have been used to investigate these. Offset analgesia is an experimental paradigm, which examines the descending pain modulatory pathway, and may be used to identify central changes. This systematic review and meta-analysis provides an overview of previous studies investigating the modulation of offset analgesia in both healthy participants and patients.

Methods and Material: The PICO framework was used to construct the structured literature search, which included the databases: PubMed, Embase, Web of Science, and the Cochrane Library. The PRISMA guidelines were followed throughout the study selection process, while the QUIPS tool was used to assess the risk of bias within each individual study. Furthermore, a summary, including key information from each study, was created. Three forest plots divided into categories of: all studies, studies including healthy participants and studies including patients, were calculated for the meta-analysis.

Results: Nine studies were included in this systematic review, of which eight were included in the meta-analysis. The studies investigated the α-adrenergic, β-adrenergic, opioidergic, noradrenergic, and serotonergic pathways along with NMDA receptor antagonists, NSAIDs in combination with acetaminophen and isometric exercise. No studies found a statistically significant difference.

Conclusion: The findings in this systematic review indicate that a method of modulating offset analgesia has yet to be found at the current time.

I. INTRODUCTION

Pain is a complicated phenomenon, partly due to its high variability between individuals and that it is influenced by various factors, including sleep deprivation and psychological disorders. When an injury occurs, part of the human body’s initial response is acute pain. The purpose of this is to alert us of situations, which could be potentially harmful, and prevent further damage. This process makes acute pain an essential part of our survival. However, if the pain does not subside after the injury has healed, it no longer serves this purpose, and might become chronic. [1] [2] [3] [4] The definition of chronic pain is continuously being debated, and recently the World Health Organisation (WHO) and the International Association for the Study of Pain (IASP) collaborated to provide an updated classification hereof in the 11th edition of the International Classification of Diseases (ICD). [5] The new definition states: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Chronic pain is pain that persists or recurs for longer than 3 months.” [6].

A study by Breivik et al. revealed that 19% of the adult European population suffers from moderate to severe chronic pain, and even though there are various analgesic or non-drug treatments available for chronic pain disorders, 40% reported that these failed to provide pain relief. [7] This inadequacy of treatment not only constitutes a large socio-economic burden, but also has consequences for the patient’s ability to work, socialise and perform other daily activities, thus affecting the quality of life. [7] [4] [3]. To overcome this, preventive strategies or optimisation of treatment is necessary. However, as the current knowledge of the underlying mechanisms of pain, and its transition from acute to chronic, is still incomplete, further investigation is necessary. [1] [2] [3]
To this end, different methods to assess various aspects of the peripheral and Central Nervous System (CNS) exist. One of the commonly used methods allows researchers to evaluate the excitability of nociceptive pathways by applying stimuli of different modalities as a part of a battery of psychophysiological tests. This method is called Quantitative Sensory Testing (QST), [8] [9] and the use hereof has brought about many important discoveries. An example is the finding that a dysfunction or attenuation of the descending pain modulatory pathway might be related to the development and maintenance of chronic pain. [10] [11] [8] In humans, one test paradigm for this is Conditioning Pain Modulation (CPM), which is the concept of “pain inhibits pain”. Here, one noxious stimulus at a specific body site is inhibited by another noxious stimulus at another site. [12] [8]

Another, more recently discovered, test paradigm is Offset Analgesia (OA), which is defined as a disproportionately large drop in pain ratings following a small decrease in noxious stimulus. [13] In this paradigm, all noxious stimuli are applied at the same body site, in a train of three temperatures. A noxious temperature is applied (T1), followed by an increase in temperature (T2) before returning to the first temperature (T3). In healthy participants, a significant reduction in the perception of pain is present in the first following seconds of the T3 period [14] [13] [12]. However, studies indicate that patients with chronic pain disorders have an impaired OA response [15] [16] [17], which suggests that a method of modulation hereof might be advantageous. Consequently, the purpose of this systematic review and meta-analysis is to provide an overview of the current knowledge regarding the modulation of OA.

II. METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18].

Search Strategy

PICO

To perform a structured literature search, the Population-Intervention-Comparison-Outcome (PICO) framework was used to formulate research questions. The following PICO questions were formed:

- "Which methods have been used to measure offset analgesia in studies regarding the modulation hereof in humans?"
- “Can offset analgesia be modulated in humans?”

The resulting keywords and Medical Subject Headings (MeSH) terms for each PICO search block are represented in Table 1. As it appears from the table, the optional element "C" (comparison) in the PICO framework was not included in this search strategy, as most research regarding OA remains exploratory.

Table 1: The three squares: P (Population), I (Intervention) and O (Outcome) illustrate the PICO search blocks and their respective keywords, used in the structured literature review.

<table>
<thead>
<tr>
<th>P</th>
<th>I</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>“Offset Analgesia”</td>
<td>Method*</td>
</tr>
<tr>
<td>Healthy</td>
<td>Technique* (MeSH)</td>
<td>Mechanism*</td>
</tr>
<tr>
<td></td>
<td>Modulat*</td>
<td>Analges*</td>
</tr>
<tr>
<td></td>
<td>Inhibit*</td>
<td>Pain*</td>
</tr>
<tr>
<td></td>
<td>“Pain Perception” (MeSH)</td>
<td>“Pain Measurement” (MeSH)</td>
</tr>
<tr>
<td></td>
<td>“Pain Threshold” (MeSH)</td>
<td>Nocicept* (MeSH)</td>
</tr>
</tbody>
</table>

Databases

As a part of the search strategy, four different databases were included in this review to increase the likelihood that all relevant papers were identified: PubMed, Embase, Web of Science and the Cochrane Library. The search took place at the beginning of April 2020 and consisted of the keywords from the PICO search blocks, connected by Boolean operators. The quotation-mark operator (“”) was used when searching for an exact match of a combination of two or more words. The three PICO blocks were connected by the “OR” operator, and each keyword within was combined by the "AND" operator. An example of the search string used for the PubMed database is provided below:

(Patients OR Healthy) AND (“Offset Analgesia”) AND (Method* OR Technique* OR Design OR Mechanism* OR Analges* OR Inhibit* OR Nocicept* OR Pain* OR “Pain Perception” OR “Pain Measurement” OR “Pain Threshold”)
### Study Selection and Eligibility Criteria

For this systematic review, the PRISMA flow diagram for study selection was completed. First, records were identified through the chosen databases and possibly other sources, after which duplicates were removed. Subsequently, an initial screening of titles and abstracts was performed to remove records based on the inclusion and exclusion criteria described below.

Studies were excluded if they were related to animal research or written in languages other than English. Inclusion criteria specified that studies had to include patients or healthy participants, and only peer-reviewed full-text articles were included. Finally, studies including a pharmacological or otherwise modulatory intervention on OA were included.

### Data Extraction

For every article included in the qualitative synthesis, information providing an overview of the participants, study design and results were extracted and summarised. Information regarding participants involved population (healthy or diagnosis), while information concerning the study design included the type of intervention(s) and details regarding the OA paradigm. 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 or individual temperatures were present. If individual temperatures were used, this was specified in the summary according to the description in the article. The summary of the results reported whether any modulation of OA was present.

### Meta-Analysis

For the meta-analysis, the mean, standard deviation (SD) and number of participants was specified for each group (after intervention and baseline/placebo) within each study. If a study included more than one outcome measurement, each subgroup was added as a separate entry. Based on the mean and SD, the respective standardised mean differences and confidence intervals were calculated. Some articles did not represent the results as mean and/or SD, but rather as a confidence interval, SE or p-values, and in these cases, the desired data was obtained by converting this information. The meta-analysis was produced as a random-effects model with the DerSimonian and Laird method [19], including the pooled standardised mean difference and the pooled 95% confidence interval. Furthermore, the meta-analysis included a calculation of heterogeneity, reported as I²-values.

### Risk of Bias

The chosen method for the risk of bias assessment was the Quality In Prognosis Studies (QUIPS) tool, developed by Hayden et al. [20], which is also recommended by the Cochrane Methods Prognosis group [21]. This 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 articles in this systematic review do not involve a prognostic factor, this was defined as the intervention (e.g. Ketamine), 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 on each included article.

### III. 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 9 peer-reviewed full-text articles were included in the systematic review, and 8 were included in the meta-analysis. The article which was not included in the meta-analysis was excluded due to missing data needed to perform the data analysis.

#### Study Characteristics

A summary of the study characteristics is shown in Table 2. Six studies recruited healthy participants. One of these assessed the effect of antihypertensives (Clonidine: n=40, once, parallel [22]), which was tested against a placebo. Two studies investigated the effect of opioid agonists (Oxycodone: n=20, 4 days, crossover [23]),
REMIFENTANIL: n=19, once, crossover [24]), in which Oxycodone was tested against a placebo, and Remifentanil was tested against a control group. Furthermore, the effect of β-blockers (Propranolol: n=25, once, crossover [25]), Serotonin and Noradrenalin Reuptake Inhibitors (SNRI) (Venlafaxine: n=20, 4 days, crossover [23]) and N-Methyl-D-Aspartate (NMDA) receptor antagonists (Ketamine: n=10, once, crossover [26]) were investigated and tested against a placebo. Additionally, two studies investigated the effect of isometric exercise (n=36, once [27]) and opioid antagonists (Naloxone: n=19, once, crossover [24]). Isometric exercise was tested alone, while Naloxone was tested against a control group.

Finally, three studies recruited patients. These investigated the effect of opioid agonists ((Diabetic polyneuropathy, Tapentadol: n=24, 4 weeks, parallel [28]), (Chronic lumbosacral radicular neuropathic pain, Hydromorphone: n=30, 4 weeks [29]) and Non-Steroidal Anti-Inflammatory Drug (NSAID) in combination with acetaminophen (Knee osteoarthritis, Ibuprofen + acetaminophen: n=42, 3 weeks [30]). Tapentadol was tested against placebo while Hydromorphone and NSAID + acetaminophen were tested alone.

Sample sizes ranged between 10-40 (healthy) and 24-42 (patients). The studies included a total of 246 participants, of which 150 were healthy (99 males), and 96 were patients (54 males). Mean age (mean ± SD) ranged from 23.6 ± 6.6 to 26.8 ± 3.9 in healthy participants and from 47.5 ± 13.1 to 63.09 ± 8.60 in patients. Six of the studies were Randomised Controlled Trials (RCTs) [22] [28] [26] [23] [25] [24], two were pre-post studies [27] [30] and one was a prospective cohort study [29].

Offset Analgesia and Control Paradigms

All OA paradigms were conducted using heat, with baseline temperatures ranging between 32 and 35°C. Four studies applied fixed temperatures including 49-50-49 °C [29] [24], 48-49-48 °C [25] and
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Study Design</th>
<th>Results (OA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nahman-Averbuch et al. (2016)</td>
<td>Healthy (40)</td>
<td>Clonidine (0.15 mg.)</td>
<td>No significant effect on OA magnitude</td>
</tr>
<tr>
<td>Niesters et al. (2014)</td>
<td>Patients - diabetic polyneuropathy (24)</td>
<td>Tapentadol (individually titrated dose)</td>
<td>No significant effect on OA magnitude</td>
</tr>
<tr>
<td>Suzan et al. (2015)</td>
<td>Patients - chronic lumbosacral radicular neuropathic pain (30)</td>
<td>Hydromorphone (individually titrated dose)</td>
<td>No significant effect on OA magnitude</td>
</tr>
<tr>
<td>Petersen et al. (2018)</td>
<td>Healthy (25)</td>
<td>Propranolol (40 mg.)</td>
<td>No significant effect on OA magnitude</td>
</tr>
<tr>
<td>Petersen et al. (2019)</td>
<td>Patients - knee osteoarthritis (42)</td>
<td>Ibuprofen + acetaminophen (1.2 g. + 3 g.)</td>
<td>No significant effect on OA magnitude</td>
</tr>
<tr>
<td>Olesen et al. (2018)</td>
<td>Healthy (20)</td>
<td>Adding 1 Oxycodeine (10 mg.)</td>
<td>No significant effect on OA magnitude</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adding 2 Venlafaxine (37.5 mg.)</td>
<td></td>
</tr>
<tr>
<td>Niesters et al. (2011)</td>
<td>Healthy (10)</td>
<td>Ketamine (40 mg./70 kg.)</td>
<td>No significant effect on OA magnitude</td>
</tr>
<tr>
<td>Harris et al. (2018)</td>
<td>Healthy (36)</td>
<td>Isometric exercise (20-25% MVC - 5 mins.)</td>
<td>No significant effect of EIH on OA magnitude</td>
</tr>
<tr>
<td>Martucci et al. (2012)</td>
<td>Healthy (19)</td>
<td>Adding 1 Naloxone (0.01 mg./kg.)</td>
<td>No significant effect on OA magnitude</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adding 2 Remifentanil (individually titrated dose)</td>
<td></td>
</tr>
</tbody>
</table>
46-47-46 °C [30], while five studies individualised these based on the participant’s heat pain ratings. Three studies used pain rating 50/100 (“Heat Pain 50” [27] and “eVAS > 50mm” [28] [26]), while another study used pain rating 60/100 (“pain60”) [22] as T1. In these studies, T2 was T1+1°C, and T3 was the same as T1. The final study chose Pain Tolerance Threshold (PTT)- 1°C [23] as T1, PTT as T2, while T3 was the same temperature as T1.

In addition to an OA paradigm, four studies used a control paradigm. One study pseudo-randomised the order of which paradigm was conducted first, and used the temperatures 49-50-35 °C with the same time intervals as the OA paradigm [24], while another study applied a constant temperature of PTT-1°C for 30 seconds, and randomised the order of paradigms [23]. Both studies used the control paradigm to assess whether the intervention had any effect on general pain ratings. The final two studies used the control paradigms to calculate the OA effect. One of these studies performed the conducting the control paradigm first, in which a constant temperature of 48°C was kept for 30 seconds [25], whereas the control paradigm of the other study was performed last and involved a constant temperature of 46°C for 30 seconds [30].

**Calculation of Offset Analgesia Effect**

The OA effect was calculated differently between the studies. Seven articles subtracted the minimum pain rating during T3 (T3_{min}) from the maximum pain rating during T2 (T2_{max}) (OA = T2_{max} – T3_{min}). Three of the articles used this calculation for the statistical analysis [22] [24] [29], while the other four normalised the data (OA_corrected = OA/T2_{max}) [27] [28] [26] [23]. The remaining two articles calculated the average pain ratings subsequent to the change in temperature from T2 to T3 (16 sec. – 20 sec.) and compared them to the same period of a control paradigm, in which participants were subjected to a constant stimulus of 48 °C for 30 seconds [25] [30].

**Results**

The articles included in this review found that the magnitude of OA cannot be significantly modulated by exercise, NSAIDs in combination with acetaminophen, NDMA receptor antagonists or the α-adrenergic, β-adrenergic, opioidergic, noradrenergic and serotonergic pathways.

**Meta-Analysis**

Three forest plots were created for the meta-analysis, describing either: all studies (Figure 2), studies including healthy participants (Figure 3) or studies, including patients (Figure 4). Two studies were divided into subgroups, as they had multiple outcome measurements. In the forest plot including all studies, heterogeneity was low (I² = 3%), while the pooled standardised mean difference and 95% confidence interval was 0.04 (-0.13, 0.20), which was not statistically significant (p = 0.67). One study in this analysis did not cross the line of no effect (-1.01 [-1.95, -0.07]). The forest plot of studies including healthy participants showed a moderate heterogeneity (I² = 32%), along with a pooled standardised mean difference and 95% confidence interval of 0.02 (-0.23, 0.28), which was also not statistically significant (p = 0.87). This sub-analysis also includes the study that did not cross the line of no effect. Finally, the forest plot of studies including only patients showed no heterogeneity (I² = 0%) with a standardised mean difference and 95% confidence interval of 0.02 (-0.26, 0.30), which was not statistically significant (p = 0.89).

**Risk of Bias**

As seen in Table 3, three articles were deemed high risk in “study participation”, as they failed to describe the population of interest, recruitment method and necessary sample size [22] [28] [24]. Three other articles were assessed as medium risk, as they also failed to describe one or more of the abovementioned elements [25] [23] [30]. The remaining three articles were rated low risk, as they provided a sufficient description of the domain [29] [26] [27]. All articles were deemed low risk concerning "study attrition", aside from one, which was rated medium risk, as it failed to describe the characteristics of participants who did not complete the study [29], while other articles 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 articles were rated as low risk, as both domains were well described, while all articles in the domain "study confounding" were rated as medium risk, due to failure from all articles to account for potential confounders. All articles were deemed low risk in the "statistical analysis and reporting domain".
Table 3: QUIPS table, illustrating the assessment of each of the six domains for every article included in this systematic review.

<table>
<thead>
<tr>
<th>Study Participation</th>
<th>Study Attrition</th>
<th>Prognostic Factor Measurement</th>
<th>Outcome Measure</th>
<th>Study Confounding</th>
<th>Statistical Analysis and Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nahman-Averbuch et al. (2016)</td>
<td>High risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>Niesters et al. (2014)</td>
<td>High Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>Petersen et al. (2019)</td>
<td>Medium Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>Petersen et al. (2018)</td>
<td>Medium Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Medium Risk</td>
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<tr>
<td>Olesen et al. (2018)</td>
<td>Medium Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>Niesters et al. (2011)</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>Harris et al. (2018)</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Medium Risk</td>
</tr>
<tr>
<td>Martucci et al. (2012)</td>
<td>High Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Low Risk</td>
<td>Medium Risk</td>
</tr>
</tbody>
</table>

IV. DISCUSSION

This systematic review included a total of 9 studies, while 8 were included in the meta-analysis, as the final study did not report the results in a comparable manner. The studies did not find any statistically significant difference between interventions and baseline/placebo, indicating that a way to modulate OA is yet to be discovered. This is further supported by the meta-analysis, which reported no statistically significant overall effect for all three analyses (all studies, studies including patients, studies including healthy participants).

Offset Analgesia Paradigms

OA paradigms varied between studies in multiple ways, including the choice of temperature, as some studies used fixed temperatures [29] [24] [25] [30], while others chose to individualise these [27] [22] [28] [26] [23]. When choosing which method to use, several considerations must be taken into account. Firstly, the temperature should not be higher than necessary, as researchers must consider the safety and comfort of participants [31]. However, OA will not be induced if the chosen temperature is too low to be considered noxious. For this reason, choosing a fixed temperature that suits all participants can be a difficult task. However, when individualising temperatures, it must also be considered that psychological factors, such as fear, affect the perception of pain [1] [2] [4], which might lead the participant to rate the pain higher, in turn affecting the temperature used for the OA paradigm. To overcome this, a minimum temperature, which has been shown to induce OA, might be chosen. Another choice that must be considered is the assessment site as results might vary hereupon. This is based on preliminary results from a study by Naugle et al., which found that OA was induced when testing on the forearm but non-existent when testing on the palm. [32] Most studies included in this review used the volar or dorsal forearm, except for one [24], which chose the lower leg. However, it is still unclear whether this affects the outcome.

Control Paradigms

Some of the included articles also conducted control measurements, which were compared to those of OA, to assess potential adaptation or sensitisation. This is important, as any amount of adaptation or sensitisation should be subtracted from the OA measurements, in order to find the real OA magnitude. [33] [34] [12] If a constant trial is not included in the study, the magnitude of OA might be over-estimated [12], which further complicates comparisons to other studies.

Confounders

Pain is very complex, as it presents itself differently between individuals, and is influenced by multiple factors, including sleep deprivation and psychological disorders [35] [2]. For this reason, it is highly likely that confounders are present when conducting pain experiments, and these should, if possible, be accounted for in the analysis. However, while multiple studies have been conducted in regard to the connection between confounders and pain, not many have studied the influence of confounders on OA [12].
Figure 2: Forest plot describing the effect sizes of the difference between measurements of baseline/placebo and after the intervention for all included studies and subgroups. IV = Inverse Variance, CI = Confidence Interval. Results toward the left indicate a higher magnitude of offset analgesia in placebo/baseline measurements.

Figure 3: Forest plot describing the effect sizes of the difference between measurements of baseline/placebo and after the intervention for studies including healthy participants and subgroups within these. IV = Inverse Variance, CI = Confidence Interval. Results toward the left indicate a higher magnitude of offset analgesia in placebo/baseline measurements.
In the articles included in this systematic review, only one study included a possible confounder (gender), to which no statistically significant difference was found [27]. Furthermore, two studies included only male participants [25] [23], but as there at this time is no consensus as to whether gender affects OA, due to contradicting results between studies [22] [36] [32] [37], it is unknown whether this had any influence on the outcomes. Due to the lack of evidence on confounders in OA, further research is needed, and future studies should, if possible, include this.

Population

This systematic review chose to include studies using both healthy participants and patients. This was due to the low number of articles regarding the modulation of OA on patients alone. Whenever healthy participants are used in a human experimental pain model, it must be taken into consideration that the underlying psychophysiological mechanisms that are being studied might be different than those of the targeted patient group, as it is not always possible to mimic the changes that have happened to the nervous system in chronic pain [23] [38]. Thus, it cannot be excluded that any of the results in this review might have been different if the experiment had been conducted in patients. Furthermore, chronic pain may manifest itself in several different ways, and as such, the results might also differ between patient groups.

Outcome Measurements

Another factor that might impact the results is the choice of method for the outcome measures. This includes the dose, administration route and length of treatment. All the included studies followed recommendations, and most chose to err on the safe side by choosing low doses. The four studies [29] [23] [28] [24] investigating the effects of opioid agonists and antagonists, all used the recommended starting doses and continued the treatments long enough for all drugs to take peak effect [39] [40] [41] [42] [43]. One of these studies was conducted by Niesters et al. [28], who used patients with diabetic polyneuropathy, and as the study comments, it cannot be excluded that this specific population showed different results from other chronic pain groups, as they suffer from small and/or large nerve fibre damage. The outcome of these four studies indicate that OA cannot be modulated through opioidergic pathways.
One of the studies by Petersen et al. [30] investigated the effect of Ibuprofen combined with acetaminophen in patients with knee osteoarthritis and, as the study mentions, this population is mainly sensitive to mechanical stimuli, and not necessarily heat stimuli, which is involved in OA. These drugs were also taken in accordance with recommendations [44], and the results indicate that NSAIDs and acetaminophen, mediated through the cyclooxygenase (COX) pathways (and possibly others) [45][46], are not able to modulate OA.

The other study by Petersen et al. [25] assessed the function of a β adrenergic antagonist, using a low dose of propranolol, when compared with recommendations [47], and as the study points out, a higher dose might have showed an effect, but further investigation should be conducted. The study thereby indicates that OA cannot be modulated through adrenergic or serotonergic pathways, which is supported by the study from Olesen et al. [23], investigating the effects of the SNRI Venlafaxine, and partly by the study from Nahman-Averbuch et al. [22], investigating the effects of the α adrenergic agonist and antagonist Clonidine. However, Clonidine was administered orally at a low dose (0.15 mg), when compared with recommendations and other studies have shown that this drug is more effective when using intrathecal, epidural or intravenous administration [48]. Consequently, another route of administration might have resulted in a different outcome.

Finally, another included study by Niesters et al. [26], assessing the effects of the NMDA Ketamine, indicated that OA could not be modulated by blocking NMDA receptors, while the study by Harris et al. [27] indicated that OA modulation is not affected by isometric exercise. However, the latter study only included young, highly active participants, and only tested the effects of one type of exercise. Thus, the population included in this study is not very diverse, and the study questions whether aerobic or dynamic exercise might produce different results. Furthermore, the experiment was conducted over a period of only one day, so the effects of long-term exercise remain unclear.

V. CONCLUSION

The findings of this systematic review and meta-analysis suggest that OA cannot be modulated through exercise, blocking NMDA receptors or the opioidergic, COX, adrenergic, serotonergic and noradrenergic pathways. Consequently, further research is needed in order to gain a better understanding of the underlying mechanisms of OA.
Part II

Worksheets
1. Pain Pathophysiology

To understand the findings of the included articles, it is necessary to have a basic knowledge of the underlying mechanisms of the nociceptive system. For this reason, the following sections will review the physiology behind peripheral, central and descending pain mechanisms, based on previous research.

The human nervous system is responsible for many functions and can be divided into parts accordingly. The two main parts are the Central Nervous System (CNS), which is comprised of the brain and the spinal cord, and the Peripheral Nervous System (PNS), consisting of nerves going to and from the CNS. The PNS can further be divided into the Somatic Nervous System, which is in charge of voluntary movements, and the Autonomic Nervous System, which controls involuntary responses. The latter is constituted of the Sympathetic Nervous System (fight or flight) and the Parasympathetic Nervous System (PSNS) (rest or digest).

When a potentially noxious stimulus is applied to a receptor in the PNS, a nociceptive signal originates with the purpose of protecting the body from further harm. The nociceptive system is depicted in Figure 5, which shows that when the receptor is activated, an action potential is created and propagated through the axon of first-order neurons to the dorsal horn, located in the spinal cord of the CNS. Here, it synapses onto second-order neurons, depending on whether it is to be converted to a reflex, in which case the response is propagated to motor neurons, or consciously processed, in which case it is further transmitted through the ascending nociceptive pathways of the ventrolateral spinthalamic tract. Signals continue along the latter pathway synapse on third-order neurons in the thalamus, where they are projected to the somatosensory cortex. The descending pathway will be further explained in another section.

Peripheral Nociceptive Pathway

The peripheral nociceptive pathway is a part of the ascending nociceptive system and contains the detectors of potentially noxious stimuli, which are specialised sensory neurons called nociceptors. Chemical, mechanical or thermal stimuli may activate these receptors, which belong to either A-δ fibres or C-fibers, depending on which type of stimulus they react to. Most C-fibers are polymodal, whereas nociceptors that respond to thermal and mechanical stimuli belong to A-δ fibres. Other C-fibers, however, are silent, which means they are only active during inflammatory processes, or selective. In addition, different types of specific nociceptors exist. Examples hereof include the Transient Receptor Potential Melastatin (TRMP8) and the Transient Receptor Potential Vanilloid (TRPV1). These receptors respond to respectively noxious cold or chemicals such as menthol, and noxious heat or chemicals such as capsaicin.

Another function of the peripheral nociceptive pathway includes initiating an inflammatory response in case of damage to the skin, with the purpose of preventing further harm and promoting healing. During this process, inflammatory mediators are released, leading to an increased response to noxious stimuli (hyperexcitability), thus enhancing the perception of pain. As a cause hereof, the innocuous stimuli may be perceived as painful, and is thus referred to as peripheral sensitisation.
Central Nociceptive Pathway

In the dorsal horn of the spinal cord, first-order neurons from the PNS synapse on second-order neurons, as seen in Figure 5. Here, neuropeptides like substance P, and neurotransmitters such as glutamate are released to facilitate the propagation of the signal [50] [52] [53]. As previously stated, an injury to the skin causes changes in the biochemical properties of receptors, due to an inflammatory process, and this might result in peripheral sensitisation. Nevertheless, this phenomenon is not restricted to the PNS, and changes might also occur centrally, in the aforementioned synapse. [53] The exact underlying mechanisms behind central sensitisation are still not fully understood, however, it has been suggested in multiple studies that continuous peripheral sensitisation might be an important factor [53] [51]. Moreover, studies have shown that removal of the peripheral stimulation may reverse central sensitisation. Once the signal has been propagated, second-order neurons in the ascending central nociceptive pathway further transmits the signal to the thalamus and the somatosensory cortex through the spinothalamic tract. Here, information regarding the intensity and location of the noxious stimuli is processed. [50] [52] [53]
Descending Pain Modulatory Pathway

The descending pathway is responsible for modulating ascending nociceptive signals at the spinal level. Once the ascending information has been interpreted by the relevant centres of the brain, it is propagated to neurons of the midbrain, more specifically the Rostral Ventromedial Medulla (RVM), the Periaqueductal Grey (PAG) and the locus coeruleus, in which modulatory processed are initialised. The PAG processes the information received from the higher centres of the brain, along with ascending nociceptive signals from the dorsal horn. Based hereupon, it regulates the synaptic activity in the synapse between first-order neurons and second-order neurons in the dorsal horn through descending signals via the RVM. This can either result in a facilitatory or inhibitory modulation. The descending pain modulation acts through pathways such as the cannabinergic, noradrenergic and opioidergic, which are highly present in the PAG and RVM pathways.

One method to estimate the function of the descending pain modulatory pathway is Offset Analgesia (OA), which is defined as a disproportional decrease in pain perception subsequent to a small decrease in noxious stimuli. In this paradigm, a train of three thermal stimuli of varying temperatures is applied. The first temperature (T1) must be noxious and is usually applied for 5 seconds. The second temperature (T2) is increased, usually by 1°C, compared to T1, while the third temperature (T3) is the same as T1. An example of an OA measurement in a healthy participant is depicted in Figure 6, from which the large decrease in pain rating between time points 10 s. and 15 s. can be seen.

![Offset Analgesia graph]

**Figure 6:** Example of an offset analgesia recording in a healthy participant. A star (*) has been inserted at each 5th second. Offset analgesia effect is evident between time point 10 s. and 15 s.
2. Quantitative Sensory Testing and Human Experimental Models

Before Quantitative Sensory Testing (QST) became commonly used, researches used nerve conduction studies (NCS) whereby only large nerve fibres could be assessed. This limitation has been overcome in QST, which is a non-invasive method involving a battery of psychophysical tests through which both small and large nerve fibres can be evaluated. However, it should be noted that NCSs are objective, while QST may be affected by several subjective factors. [55] [56] Nevertheless, QST has shown promise as a tool to monitor the nociceptive excitability of the peripheral and central nervous system, using various stimuli modalities. As previously mentioned in the section regarding peripheral nociceptive mechanisms, different nerve fibres are activated depending on the type of stimuli. This knowledge allows for an investigation of the underlying mechanisms of different pain pathways, as information regarding the difference between healthy and pathophysiological pain responses can be obtained hereby.

Preclinical animal models, primarily based on rodents, have long been used to study nociceptive mechanisms, which has resulted in many important findings. An example hereof is the discovery of Diffuse Noxious Inhibitory Controls (DNIC), which is the phenomenon of "pain inhibits pain", where one painful peripheral stimulation, applied to one body site of the animal, is used to inhibit nociceptive signals in another site. [57] [58] Furthermore, animal models allow for more invasive investigations and ensures that interventions or medical equipment is safe before using them in the human population. [59] Despite the advantages of this type of model, a major disadvantage is the fact that not all results are translational to humans, which leads to the need of human experimental models.

The combination of QST and human experimental pain models has led to further advances in pain research, as studies conducted in healthy participants are more likely to be unbiased by other symptoms. This makes them suited for both mechanistic studies and drug trials, in which researchers might attempt to mimic various aspects of chronic pain disorders by activating specific nociceptive mechanisms and pathways. However, not all characteristics of chronic pain can be mimicked in healthy participants. [60] [61] Consequently, a method including both patients and healthy participants might be advantageous, as this would allow baseline measurements from healthy participants to be compared to measurements in chronic pain patients. For example, a study by Graven-Nielsen et al. [62] (48 patients and 21 healthy participants) and a study by Arendt-Nielsen et al. [63] (48 patients and 24 healthy participants) found that Conditioning Pain Modulation (CPM), which is the human equivalent of DNIC, was impaired in patients compared to healthy participants. The same pattern has been found in studies regarding OA, where a study by Zhang et al. [15] (17 patients and 17 healthy participants) a study by Szikszay et al. [16] (26 patients and 26 healthy participants) and a study by Kobinata et al. [17] (12 patients and 12 healthy participants) found that patients had a significantly lower OA response compared to healthy participants.
3. Interventions

To understand the reason behind each study’s choice of intervention, the current knowledge regarding the biochemical mechanisms between the type of intervention and pain are described in the following sections.

Adrenergic Interventions

Clonidine

Clonidine is an α-2 adrenergic agonist and antagonist, commonly used to treat hypertension and attention deficit hyperactive disorder (ADHD). The underlying mechanisms of the analgesic effects of Clonidine are still not fully understood, but research has indicated that it binds to receptors on multiple levels of the CNS. [22] [64] [65] In the dorsal horn, it activates α-2 adrenoceptors, which reduces the release of neurotransmitters from primary afferent nociceptors, and consequently the transmission of nociceptive signals to second- and third-order neurons. [64] [22] In the locus coeruleus, which is a noradrenergic nucleus in the pons of the brainstem, it primarily binds to presynaptic α-2 adrenoceptors, in turn causing a reduction in the release of norepinephrine. [64] [66]

Propranolol

Propranolol is a non-selective β adrenergic antagonist, commonly used to treat a number of diseases, including hypertension and irregular heartbeats. Like Clonidine, the mechanisms behind the analgesic effect of propranolol are still uncertain. [25] The primary function of propranolol is blocking β-1 and β-2 adrenoceptors, by which the release of epinephrine and norepinephrine is inhibited, [67] but studies have found that it also increases heart rate variability, thus affecting the PSNS. [68] This makes it a candidate for pain relief, as reduced heart rate variability has been associated with experimental pain, and chronic pain disorders [69] [70] such as fibromyalgia [71] and postsurgical pain [72]. Furthermore, Propranolol has been shown to reduce pain caused by serotonin, indicating that it may also act as an antagonist of specific serotonin receptors [73].

Serotonin Norepinephrine Reuptake Inhibitors

Venlafaxine

Venlafaxine is an SNRI, used to treat a range of diseases, such as depression, anxiety, chronic neuropathic pain, ADHD and fibromyalgia. While the two latter are for off-label use, Duloxetine, which is also an SNRI, has been approved for these purposes. [74] While the effect of SNRIs on pain is still not fully understood, there is consensus that they act by inhibiting serotonin and norepinephrine reuptake, resulting in an increase in both [75] [76]. Venlafaxine primarily inhibits serotonin reuptake, while inhibition of norepinephrine reuptake requires a larger dose. [75] [74]

NSAID and Acetaminophen

Both Paracetamol (Acetaminophen) and Ibuprofen (NSAID) are commonly used pain relievers, but the exact underlying mechanisms of their effects are still not completely understood. While evidence shows that Ibuprofen acts through cyclooxygenase (COX) pathways [45] [46], it has been suggested that Paracetamol acts through the descending serotonergic, opioid, nitric oxide, cannabinoid and/or COX pathways. However, unlike Ibuprofen, Paracetamol does not seem to have anti-inflammatory properties. [77] [78]
N-Methyl-D-Aspartate

Ketamine is an NMDA receptor-channel blocker, mainly used for pain relief. One of the changes found in patients with chronic pain is central sensitisation, in which an upregulation of NMDA receptors at dorsal horn synapses takes place, resulting in hyperexcitability. Evidence shows that Ketamine acts by blocking these receptors, creating an analgesic effect. [79] [80] [81] Other suggested effects of Ketamine include: enhancement of descending inhibition, anti-inflammatory properties [80] and dopamine receptors [81].

Opioids

Opioid Agonists

While Acetaminophen and NSAIDs are some of the most commonly used drugs for mild to moderate pain, opioids are the most common choice for severe pain. [82] [83] [84] All opioid agonists used in the included articles are µ-opioids: Remifentanil, Oxycodone, Tapentadol and Hydromorphone. This type of opioid agonists activates µ-opioid-receptors, which are found in the descending pain modulatory pathways, leading to a decrease in neurotransmitter release and consequently pain inhibition. [82] [83] [84]

Opioid Antagonists

Naloxone, the only drug of this type, is a µ-opioid antagonist, which is commonly used to reverse the effects of opioid agonists. It has the opposite effect of µ-opioid agonists, and acts by blocking µ-opioid-receptors, inhibiting the descending pain modulatory pathways. [24] [14]

Isometric Exercise

Exercise is an important part of managing chronic pain disorders, and previous studies have indicated that exercise-induced hypoalgesia might be associated with descending pain modulatory pathways. [85] [86]
REFERENCES


[87] Grünenthal, CHANGE PAIN.