Is Open Labelled Placebo a Plausible Treatment for Patients with Chronic Pain? A Scoping Review

Master´s Thesis

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Abstract

Introduction:

Chronic pain is a prevalent global health challenge, affecting approximately 30% of the population and imposing significant socio-economic burdens. Despite the broad spectrum of available treatments, the placebo effect is the most significant factor influencing treatment efficacy. Research has shown that placebo, even when administered openly, remained effective on physical and psychological outcomes.

Objectives:

To examine the efficacy, mechanisms, and practical applications of open-label placebos (OLP) and conditioned open-label placebos (COLP) in chronic pain management.

Methods:

Following PRISMA guidelines for scoping reviews, we conducted a PIO-search and a terminology-focused search in PubMed, Cochrane, Embase, and PsycINFO databases for studies published prior to March 2024. Inclusion criteria encompassed per-reviewed records, investigating the impact of OLP on chronical pain. Moreover, records were included when investigating COLP on pain management. Exclusion criteria encompassed non-empirical records. Data were charted, synthesized, and assessed for risk of bias by one researcher.

Results:

In total, 1,432 records were screened for eligibility. The review included 16 RCTs, 3 reviews, and 7 qualitative studies. The overall evidential quality was moderate. OLP had a statistically significant effect reducing pain intensity and medication use, while improving function. Clinical relevance remained inconclusive, with most prominent findings on chronic secondary pain conditions, such as knee osteoarthritis and irritable bowel syndrome. However, the efficacy in chronic primary low back pain remained controversial and one study showed an increase in complementary and alternative treatments. COLP showed potential in reducing opioid consumption post-surgery, but its efficacy seemed diminished in chronic pain patients. Moreover, patients were more likely to accept OLP and COLP as potential treatment options when proven effective or when no other treatment was available. Providers raised concerns on ethics, missing guidelines, and potential mistrust in the healthcare system and scientifical approaches.

Conclusions:

OLP and COLP presented controversial but cost-effective treatments for chronic pain, where efficacy may depend on pain mechanisms. Further research is needed to standardise methods and guidelines, explore long-term effects, assess efficacy across different chronic pain conditions, and address ethical considerations for clinical integration.

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Introduction

Chronic pain represents one of the most significant challenges in global healthcare, impacting around 30% of individuals worldwide (1,2). While prevalence rates continue to increase, their complexity not only strains healthcare systems but also imposes substantial social and economic burdens (3,4). Globally, pain is the main reason to seek medical care (5). When pain persists for more than three months, it is classified as chronic (6). Chronic pain is the leading cause of years lost to disability worldwide (7), moreover in Denmark, it also counts as the main reason to retire early (3). In addition to the socio-economic consequences, chronic pain contributes to an increased risk of suffering and comorbidity for the individual citizen. This includes significant emotional and social consequences, such as unemployment, loss of identity, social isolation, anxiety, and depression (6,8).

To date, while a cure for chronic pain has yet to be found, a broad spectrum of treatments are accessible (6,9,10). The most effective treatment for chronic pain demands an interdisciplinary, biological, psychological, and social approach (2,11). Possible approaches range from non-pharmacological interventions, including psychological, physical, and manual therapy, to more invasive options like medication and surgeries (2,3,6). Despite treatment choice, the placebo effect plays a significant determinant of therapeutic outcomes. Various non-pharmacological treatments, such as manual therapy, acupuncture and psychotherapy have encountered challenges in establishing efficacy that significantly exceeds that of placebo responses (12–16). However, more invasive routes of administrations seem to even increase the placebo effect, proposing that injections have greater placebo efficacy compared to pills (17). Comparing surgical interventions to sham operations, research even estimates that up to 78% of pain relief may be attributable to the placebo effect (18,19). Focusing on chronic pain conditions only, a systematic review estimates the placebo effect to account for 87% (20). Investigating analgesics, new guidelines recommend not to prescribe opioids for acute neck- and backpain, since the effect remains no better than a placebo (21).

It appears that the psychological role in pain perception and management is a powerful factor that remains underexploited in clinical settings (22–24). The consideration of treating with placebo is tempting because of its efficacy, the reduction in healthcare costs, and due to the various side effects of using conventional medicine and surgery. For ethical reasons, however, the patient must be informed about being prescribed a placebo. One might think that openly labelled placebos would nullify a beneficial effect. However, research has identified a significant placebo effect, even in patients aware of taking inactive medication, leading to the concept of open label placebo (OLP) (25). OLPs are placebos without deception, consciously administered from healthcare providers, in the sense that

patients are fully aware of receiving a placebo. Recent studies highlight the advantages of combining genuine medication intake with OLP for both physical and psychological conditions. This approach, known as conditioned open-label placebo (COLP), leverages the benefits of traditional medications alongside the psychological effects of placebos. COLP is purported to decrease pharmacological side effects by reducing the dosage of analgesics while maintaining effective pain relief (26,27).

A systematic review conducted in 2021 investigated the effects of OLP and revealed significant improvements, including pain intensity and physical disability reductions. These benefits were represented through various chronic conditions, including two studies specifically addressing chronic musculoskeletal pain (25). Subsequently, a more recent systematic review in 2023, to which this research team contributed, specifically focused on OLP effects in musculoskeletal pain, which is a subgroup of chronic pain conditions. Our review identified four additional studies, underscoring the rapidly growing interest in this area (28–31). Both reviews highlighted the need for further research, particularly due to the ambiguous results concerning the long-term efficacy of OLP. Furthermore, both reviews did not incorporate COLP-related studies.

This scoping review aims to:

1. Explore the potential effects of open label placebo treatments: Investigate which chronic pain subpopulations could benefit from OLP and COLP and to what extent these treatments can provide pain relief, focusing on patient-centered approaches.
2. Understand the mechanisms: Examine how OLP and COLP provoke analgesic responses, shedding light on the biological and psychological pathways involved.
3. Assess practical application: Evaluate the integration of OLP and COLP into existing healthcare frameworks, determining patient receptiveness and coping mechanisms with such treatments.
4. Lay groundwork for future research: Establish a foundation for ongoing research and clinical trials that will expand on the preliminary findings and potentially lead to substantial advancements in pain management.

Scientific Question

Is open labelled placebo a plausible treatment for patients with chronic pain?

Theory

Having established that the placebo effect accounts for a significant portion of the analgesic effect across multiple interventions for chronic pain, it is crucial to delve deeper into this phenomenon. Understanding the substantial influence of placebo effects on treatment outcomes can offer insights to the scope and novel approaches in pain management.

Understanding Chronic Pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (32). Central to the discussion of pain is its inherently subjective nature, highlighting the biopsychosocial model (11,32). This approach recognizes pain as not merely a physiological symptom but as an experience influenced by an individual's biology, psychology (thoughts, emotions, and behaviours), and social context (10,11,32). Unlike acute pain, which serves an evolutionary purpose, chronic pain does not contribute to any known advantage (33,34). Acute pain is a dynamic psychophysiological response to the prevention of tissue damage and often associated with inflammatory processes, providing survival value by promoting healing. However, once the immediate threat dissipates, this pain shifts from being protective to burdensome, transitioning into a condition in itself (2,10,34). Although there is no precise moment when acute pain transitions into chronic pain, it is commonly recognized that pain, lingering beyond the typical healing timeframe, becomes a disease (11,33,34). The disease can be classified as chronic primary pain, being pain itself as the primary cause of pain, or chronic secondary pain, distinguishing a biological cause (e.g. postsurgical or cancer-related pain) (35). Such distinctions are crucial for understanding the mechanisms underlying pain and guiding to effective treatment strategies (2,36,37). The underlying mechanisms include nociceptive pain, signalling damaging or potentially harmful stimuli due to activation of nociceptors, neuropathic pain, caused by a lesion or disease of the somatosensory nervous system, and nociplastic pain, arising from altered nociception despite no clear evidence of actual or threatened tissue damage is causing the pain (2,38).

However, pain is not merely a simple transmission of noxious signals from peripheral nerves to the brain but involves a sophisticated psycho-neuro-endocrine-immunological network (39). This network includes numerous brain circuits and neurotransmitter systems that contribute to the perception and modulation of pain (40,41). When noxious stimuli ascend the central nervous system, they reach diencephalic regions such as the thalamus, the periaqueductal gray (PAG), and the amygdala (11,40). The thalamus acts foremost as a critical relay station (11). From here, signals are directed to cortical

regions, such as the insula, which helps coordinating the signals to structures, encompassing emotional and cognitive regions, like the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) in the prefrontal cortex (PFC) (40,41). Simultaneously, the thalamus directs signals to the somatosensory cortex where the sensory quality and location of pain are mapped. Together, this allows us to not only perceive physical sensations but also to interpret them (11,40). Signals, evaluated as harmful, will thereby release neurotransmitters (NS) like cortisol and cholecystokinin, whereas positive interpretations release NS, including serotonin, norepinephrine, and dopamine (39,40,42). The neuroendocrine transmission affects PAG, which, in interaction with the parabrachial nucleus and rostroventral medulla (RVM), plays a magnificent part in the descending pain regulation (43). The descending pain modulation either amplifies or suppresses afferent stimuli in the central nervous system, depending on the individual's signal interpretation (40,41,43). Exacerbated negative affections, such as pain catastrophizing or kinesiophibia, can therefore increase the experience of pain (40,44,45).

When pain becomes chronic, studies have shown alterations in the insula, ACC, thalamus, and PAG, including allostasis (46,47). While homeostasis is the process by which a dynamic system tries to return to its equilibrium after a change, the equilibrium in allostasis is adaptively. Allostasis thereby marks the brain's ability to adapt to new situations by adjusting the brain area volume, neural activity, endocrine balance, and immune system, often marked by increased cortisol and cytokines compared to the healthy populations (11,39,40,46). Additionally, synapses in the dorsal horn alter, including an increasing number of excitatory receptors and ion channels, as well as inhibitor neuron degeneration, potentially decreasing GABA-related pain inhibition (11). These favours decreased activation threshold, enhanced response, and increased firing.

These changes, also called central sensitisation, are indicative of the brain's neuroplastic adaptation to prolonged exposures (47). Chronic pain thereby alters the immune system and endocrine-balance in favour of pain-related NS and brain activity. This imbalance not only exacerbates future pain provocations and prolong the period of experienced pain, but also affects mood and behaviour negatively, potentially leading to disorders such as loss of function, depression, and anxiety (11,40,46).

Understanding Pharmacological Pain Management

In the context of placebo, in chronic pain management, it is essential to consider the analgesic efficacy of various interventions, particularly in how they interact with the body's physiological mechanisms. Surgical interventions often target specific peripheral structures to alleviate pain, aiming to rectify physical sources of pain. On the other hand, pharmacological treatments typically have a broader impact. Addressing both peripheral and central neurotransmitter mechanisms, they alter different

pain-related brain circuits, thereby effectively modulating the brain's processing and perception of pain (48). In Denmark, the most common pharmacological analgesics include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, anticonvulsants, and antidepressants (49). Respectively, they target different mechanisms and pathways to alleviate pain.

NSAIDs primarily inhibit cyclooxygenase enzymes (COX-1 and COX-2) in the peripheral tissues to reduce inflammation, thereby inhibiting noxious afferent axion potentials (50,51). Opioids work by binding endorphin and enkephalin to opioid receptors primarily in the brain and spinal cord. This binding affects areas responsible for descending pain inhibition, altering the perception and emotional response to afferent stimuli. The specific brain regions involved include the PAG, thalamus, hypothalamus, hippocampus, amygdala, and the cingulate cortex. (11,48). Anticonvulsants primarily affect neuronal ion channels, thereby decreasing neuronal excitability, and are particularly effective in managing neuropathic pain. They mainly modulate activity in the spinal cord and various cortical areas, like ACC and OFC (11,52). Antidepressants, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants, influence pain processing by altering neurotransmitter levels in the CNS, especially serotonin and noradrenalin, which are crucial for the descending inhibitory pain pathway involving the spinal cord, brainstem, and cerebral cortex (52,53).

While pharmacological treatments provide measurable benefits through direct interaction with pain-related neurochemistry, the power of the mind in pain management reveals another intriguing aspect of treatment. As we transition from the concrete mechanisms of analgesics to the more elusive yet potent influences of placebo, we approach pain management from a psychological and neurobiological perspective, without influencing them biologically with interventions consisting of active ingredients. This shift underscores the complex interplay between mind and body, where belief and expectation can significantly modify the perception of pain, revealing the substantial impact of placebo effects in clinical settings.

Understanding Placebo Effects

Research continues to aim for a comprehensive understanding of how OLP function and the specific underlying placebo mechanisms that occur. However, research has shown different mechanisms being able to occur simultaneously (11). Placebo treatments are known to trigger neurobiological changes in the brain by releasing neurotransmitters like endorphin and dopamine (23,54–56). These neurotransmitters are the same, which get activated by pharmacological medicine and can modulate pain and mood (22,23,55–57). Such observations prove that the brain has the ability to produce its own pain-relieving endocrines in response to a placebo, also called endogenous placebo analgesia

(22,37,58). Notably, analgesic endogenous systems such as the opioid, endocannabinoid, dopaminergic, oxytocinergic, and vasopressinergic systems have repeatedly been observed with increased activity through placebo effects on both healthy subjects and chronic pain patients (54,58,59). The endogenous opioid system is particularly dominant and well-studied (42,59). It increases activity in the rostral ACC, amygdala, and PAG. Other well-studied areas, such as PFC, hypothalamus, thalamus, insula, nucleus accumbens (NCA), lateral OFC, and the somatosensory cortex, are additional key regions within placebo analgesia (42,59). Through complex neuroendocrine interactions, these regions play a crucial role in perception, memory, and cognition, thereby influencing pain, emotional regulation, and decision-making (37,42,59).

Conversely, the nocebo effect demonstrates that an effective treatment can become less efficient. Nocebo, Latin for "I will harm," serves as the counterpoint to placebo. Unlike the placebo effect, which improves health outcomes, the nocebo effect involves neurophysiological mechanisms that operate in the opposite direction. This effect negatively influences descending pain modulation, leading to poorer outcomes. It occurs when negative expectations diminish the effectiveness of a beneficial intervention or transform an innocuous treatment into a harmful one (11,60). Despite its significant impact, the nocebo effect has not been as extensively studied as the placebo effect. However, it is anticipated that its magnitude is comparable to the placebo effect, though in a detrimental direction (11,24,37). For instance, comparing the CoViD19 vaccine with a control group, receiving an injection without active ingredients, a meta-analysis involving over 45,000 participants determined that as many as 76% of the adverse side effects was due to the nocebo effect (60). Comparable to the placebo effect, the nocebo effect has neurobiological circuits, altering the experience of pain. This pain modulating, can be triggered through complex and coexisting mechanisms, including patient expectations, conditioning, and emotional states (23,24,61,62). Positive emotional states, especially when individuals anticipate beneficial outcomes from treatment, lead to increased activity in the ACC, dorsolateral PFC, and the PAG. These enhancements in neural activity, coupled with a favourable endocrine environment, significantly amplify the placebo effect (25,57,63). In research on expectancy-induced placebo analgesia, key factors such as verbally induced expectations and observing others are identified as effective in pain management (63,64). Positive feelings, such as optimistic expectation, but also hope and trust, mediate this effect by fostering a psychological framework that promotes the release of opioid and dopamine-based pain-relieving mechanisms (62,63). Conversely, negative emotions such as doubt, fear, and pain catastrophizing, can diminish the placebo effect due to adverse expectations, linked to an increased activation of brain circuits, enabling NS like cortisol and cytokines (11,39,57,63,65). Together, these complex mechanisms provide the foundation for understanding the

depth and complexity of how inactive treatments, such as OLP, could positively impact chronic pain conditions.

In conclusion, the intricate dynamics of pain management in chronic conditions underscore a sophisticated psycho-neuro-endocrine-immunological interplay. By integrating the tangible benefits of analgesics with a nuanced understanding of placebo mechanisms, we can enhance therapeutic outcomes and explore innovative avenues for alleviating chronic pain. As research continues to unravel the complexities of both pharmacological efficacy and the body's natural pain-relieving processes, it paves the way for more informed and patient-centered pain management strategies. This dual perspective not only enriches our clinical practices but also deepens our understanding of pain as a multi-dimensional experience, guiding us towards more effective and compassionate healthcare solutions.

Methods

This scoping review follows the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (66). Emphasizing transparency and reproducibility, a protocol was developed, serving as the foundation for the systematic methodology.

Development of Review Protocol and Search Strategy

Prior to the literature search, a comprehensive review protocol was established, guiding the review's scope and objectives. The protocol outlines the eligibility criteria, information sources, and planned analysis to ensure methodological transparency.

Based on the research question, an exhaustive search strategy was formulated. To cover the subject area and background knowledge, preliminary searches were conducted using citation and free text search in PubMed and Google Scholar. References of the identified articles were looked up and relevant peers have been consulted. Similar scientifical records were checked for their keywords, search terms, and search strategy. Similarly, it was investigated which questionnaires could be relevant to use in relation to the outcome.

The search, conducted in March 2024, aimed to capture the nuances of chronic pain treatment with OLPs, reflecting both health and psychological dimensions. A PIO (Population, Intervention, Outcome) framework has been developed, combining indexed terms and free-text phrases across the databases PubMed/Medline, Cochrane, Embase, and PsycINFO. A detailed search strategy for PubMed, ensured

a comprehensive retrieval of relevant studies (see Table 1) and got adapted to other databases by addressing their individual search criteria such as emtree and thesaurus (see Appendix 1-3). No filters were applied to ensure that all available research was included.

Pubmed/MEDLINE search 1: PIO (P = chronic pain; I = Open-Label Placebo; O = improved pain, function, quality of life, or decreased medication)		
1	chronic pain[MeSH Terms] OR Chronic* Pain[Title/Abstract] OR Persistent pain[Title/Abstract] OR recurrent pain[Title/Abstract]	68,202
2	open-label* placebo* OR open label* placebo* OR OLP OR non-decept* placebo* OR nondecept* placebo* OR without decept* OR non blind OR non-blind OR nonblind OR unblind OR without conceal OR no conceal OR none conceal OR noneconceal OR Condition* open label placebo* OR Condition* open-label placebo* OR C-OLP OR COLP OR active open label placebo* OR active open-label placebo* OR AOLP OR A-OLP OR Conditioning, Psychological/drug effects[Mesh] OR Conditioning, Classical/drug effects[Mesh]	69,286
3	Disability OR Impairment OR quality of life OR NRS OR numeric rating scale OR VAS OR visual analogue scale OR EuroQol OR EQ-5D OR McGill pain questionnaire OR MPQ OR short-form 36 OR SF-36 OR SF 36 OR chronic pain grade scale OR CPGS OR Self-efficacy OR self efficacy OR PSEQ OR Örebro OR Orebro OR Oerebro OR ÖMPQ OR Timed up and go OR TUG OR Roland-Morris disability OR Roland Morris Disability OR RMQ OR Opiod reduc* OR Morphine reduc* OR Medicine reduc* OR Drug reduc* OR Dose reduc* OR pharmaco-behavior* OR pharmaco* behavior* OR Quality of life [MeSH] OR Visual analogue scale [MeSH] OR Self-efficacy [MeSH] OR Pain measurement [MeSH]	4,217,748
4	1 AND 2 AND 3	275

Table 1: PIO search in PubMed.

Due to its novelty, COLP might be overlooked if not explicitly addressed. Therefore, an additional terminology-focused search was conducted across several key databases, including Embase, PubMed/MEDLINE, PsycINFO, and the Cochrane Library (see Appendix 4-6). This search aimed to capture all literature pertaining to "conditioned open-label placebo" (see Table 2). Additionally, records identified through alternative sources such as Google Scholar, peers' assistance, as well as those found in the references of relevant articles, were included. The staff of the AAU libraries assisted in retrieving records that were otherwise unavailable. When full texts remained inaccessible, the authors were contacted directly.

Pubmed/MEDLINE search 2: COLP		
1	((((((nondeceptive placebo[Title/Abstract]) OR (non deceptive placebo[Title/Abstract])) OR (non-deceptive placebo[Title/Abstract])) OR (placebo without deception[Title/Abstract])) OR ((placebo with no deception[Title/Abstract])) AND (condition*[Title/Abstract])) OR (((condition*[All Fields] AND open label placebo[Title/Abstract]) OR (condition*[All Fields] AND open label placebo[Title/Abstract]) OR COLP[Title/Abstract] OR C-OLP[Title/Abstract]))	85

Table 2: Terminology-focused search in PubMed.

Selection and Data Management

Inclusion and exclusion criteria were precisely defined to find peer-reviewed studies addressing chronic pain through OLP interventions, published in Danish, German, or English (see Table 3). To carefully integrate ethical considerations, articles that would fail to address ethical considerations in accordance with the Helsinki Declaration would have been evaluated for potential exclusion. The selection process, from deduplication in Zotero to sequential screening of titles, abstracts, and full texts, was meticulously carried out by the author, with ambiguous cases reviewed by peers and the supervisor.

Inclusion criteria	**Exclusion criteria**
All study designs Peer reviewed Chronic pain OLP Article language in Danish, German, or English	Protocols Acute Pain No available abstract or full text Failed to address ethical concerns according to the Helsinki declaration Animal studies Non-empirical

Table 3: In- and exclusion criteria for PIO search.

Given the novelty of COLP, a secondary selection criteria framework was developed for the terminology-focused search and all other conducted records regarding COLP. This approach was designed to comprehensively capture approaches with the potence to reduce pharmacological dosages in chronic pain conditions (see Table 4).

Inclusion criteria	**Exclusion criteria**
All study designs Peer reviewed COLP Article language in Danish, German or English	Protocols No available abstract or full text Failed to address ethical concerns according to the Helsinki declaration Animal studies Non-empirical

Table 4: In- and exclusion criteria for terminology-focused search.

Data Charting and Appraisal

For the included studies, a data charting form was devised to systematically capture critical information. This form was pre-tested and facilitated a uniform data extraction process. Additionally, a critical appraisal using the Joanna Briggs Institutes (JBI)s checklists was conducted to assess the quality of the evidence (67).

Synthesis Approach

The synthesis aimed to qualitatively compare the studies, focusing on different study extractions. Key themes were identified and synthesised into a qualitative description to scope OLPs in chronic pain management. This involved creating a narrative synthesis supplemented by tables for visual clarity following guidelines for narrative reviews and scoping review methods (66,68,69).

Firstly, included articles were categorised after design (experimental, qualitative, and empirical review). Mixed methods, providing information for the multiple approaches, will be synthesized within all relevant assessments. Secondly, the analysis and comparison of studies were structured based on the nature and methodology of each type of research: Experimental studies were evaluated based on their publication date, pain of interest, population characteristics, intervention, placebo education, and outcomes. Qualitative research was, besides publication date, analysed in terms of its objectives, methods employed, demographic data, findings, and subsequent recommendations. Empirical reviews were assessed by examining their publication date, objectives, results, discussions, and perspectives. However, extraction and comparison in all three subgroups focuses on answering the scientific question.

To reduce potential bias, the risk of bias and evidence assessment will be described and presented after included articles were systematically evaluated with the JBI checklists (67).

Results

As depicted in the flow-chart (see Figure 1), a total of 1,608 records were initially identified through databases regarding the PIO search, and 209 records through the terminology-focused search on COLP. Additional nine records were sourced from other means. After duplicate removal, 1,432 records were retained for further title and abstract screening. Of these, 66 records met the eligibility criteria. Following exclusions for protocols, no full text available, letters to the editor and other non-empirical records, 25 records were ultimately included in this review. This final selection comprised 15

experimental studies, 3 empirical reviews, and 6 qualitative approaches, and 1 mixed methods, consisting of an RCT and a qualitative approach.

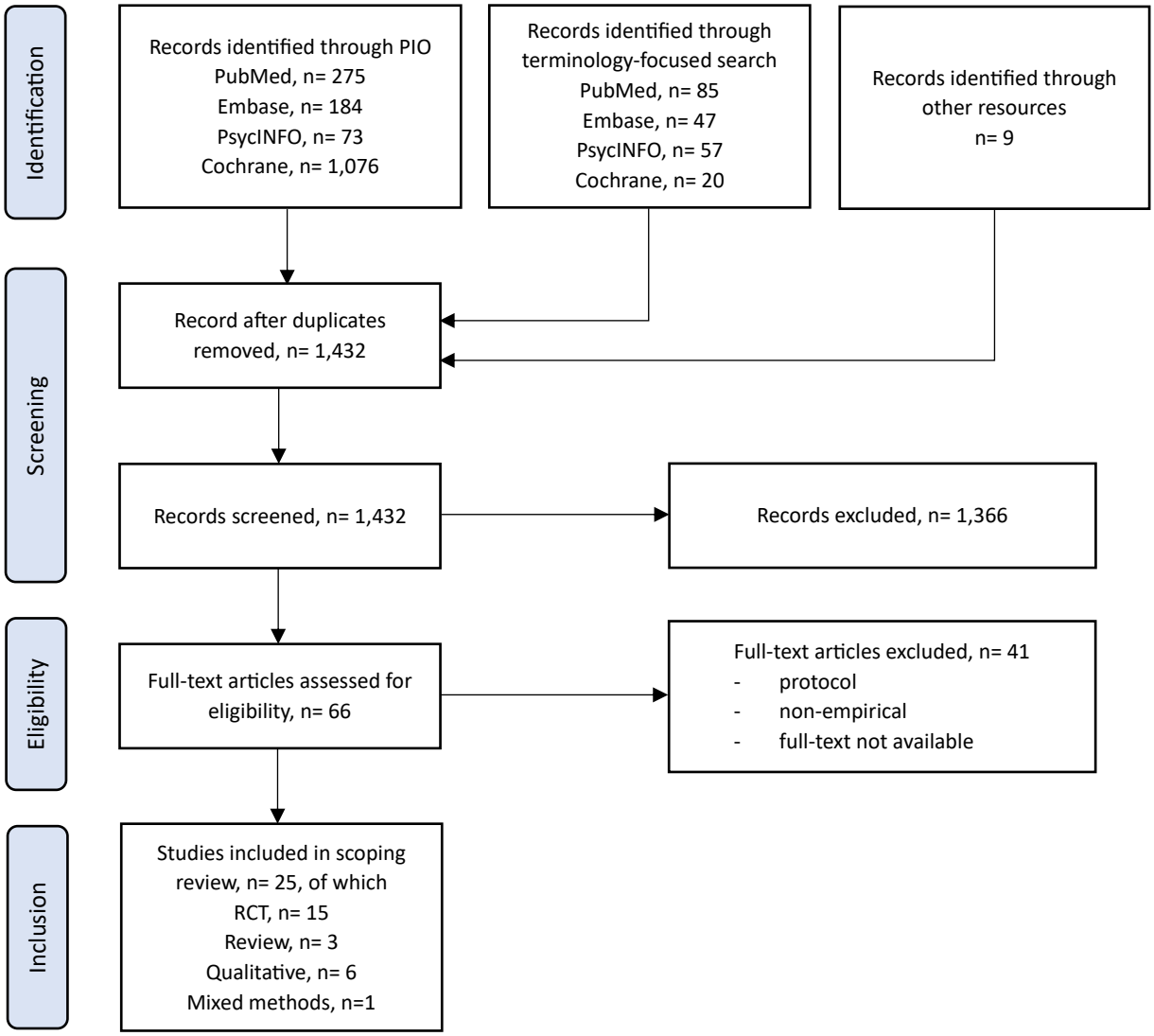

Figure 1: Flow-chart.

The 16 experimental studies were all RCT-designs and conducted between 2010 and 2023. The collective research efforts spanned globally with dominant emphasis within the United States (eight studies), alongside notable studies conducted in Germany (three studies), Portugal (two studies), Denmark (two studies), and Japan (one study). Three of those were follow-up studies. Their parent studies were likewise included in this scope. A total of 1,477 patients have completed across all studies (follow-up studies not included). While one study did not yield data on age specifics, the other 15 provided mean ages per study ranging from early 40s to late 60s. Meanwhile two other studies did not provide sex specifics, whilst the others in total encapsulate 60% females. A total of 13 out of 16 captured RCTs explicitly focused on chronic pain conditions, encompassing chronic low back pain (cLBP) (six studies), irritable bowel syndrome (IBS) (three studies), knee osteoarthritis (kOA) (three studies), and episodic migraines (one study). Complementing the chronic pain-centric research, three studies have delved into COLP for opioid reduction, whereas two studies examined COLP following spine surgery and one examined COLP with opioid use disorder. Furthermore, 13 studies relied on OLP-pills, consumed from 6 days to 12 weeks, either one or two pills, between one and three times daily. Meanwhile, the three remaining studies used OLP-injection, either given once or four consecutive times in between 7 weeks. While one parent study and its follow-up did not educate patients pre-interventional about the potential of a placebo-effect, the other 14 studies used either video or verbal education, though with different content.

The three empirical reviews contained one systematic review from 2017, one systematic review and meta-analysis from 2021, and one network meta-analysis (NMA) from 2023. They respectively consisted of two, four, and eight studies on OLP and chronic pain conditions, while the NMA additionally contributed with three studies regarding COLP. Mention worthy, while all studies from the 2017 analysis were represented in the 2021 analysis, the NMA from 2023 lacked one of the four studies from the 2021 review (Kam-Hansen et al. (2014)). All reviews concentrated on quantitatively assessing the efficacy and application of OLP. They interrogated the mechanisms that might influence the outcomes of placebo research and offered reflective insights on the broader applications of OLPs in therapeutic practices. They broadened the conventional scope of placebo research by delving into the roles of expectation, the patient-provider interaction, and the different administration of placebo.

The seven included qualitative studies were conducted from 2014 to 2024. Within these, the majority took place in the United States, which hosted five studies. One study was conducted in Portugal, and another in Austria. Across all studies, a total of 983 participants were involved, with a substantial representation from one study, containing 806 participants (Schienle et al., 2024). While one study of

25 participants did not provide sex-specifics, the others contained between 33% to 73% female, 71.3% on average. Most of the qualitative assessments focused on OLP (four studies), while two others investigated the administration of placebo itself, and one investigated COLP. Their approach ranged from interviews (three studies), internet-based surveys (two studies), focus groups (one study), and a single multi-modal qualitative research method. The qualitative studies aimed to understand patient and provider perspectives on placebo, OLP, and COLP, their ethical use, long-term effects on pain management, and factors influencing willingness to use or prescribe them in clinical practice.

In the next section, we will expand on the extracted data, starting with the analysis of the experimental studies, followed by the reviews, and qualitative approaches. After a critical appraisal of all records, a synthesized summary will elucidate the principal findings from this review.

Critical Appraisal

In the critical appraisal of 16 randomised controlled trials, all studies utilized true randomisation and consistent methods for measuring outcomes. Due to the nature of open-label treatments, none of the trials employed blinding for participants or those delivering the treatment, which is typical in such study designs to ensure transparency and informed consent. Allocation of treatment groups was not concealed for the same reason. Although these factors could introduce bias, outcomes assessors were blinded in most studies, reducing some risk of bias and enhancing the credibility of the results. The trial designs and statistical analyses were appropriate, validating their inclusion in the scoping review. Overall, the risk of bias was moderate (see Appendix 7).

The empirical reviews had similar findings regarding their critical appraisal assessment. They supported an overall moderate risk of bias throughout their OLP studies. They reported that risk of bias was exacerbated by small sample sizes and selective reporting of results. Furthermore, insufficient randomisation and concealment of allocation compromised the integrity of these studies. Additionally, they highlighted critical methodological shortcomings that needed attention to fortify the foundation of evidence in this field. The reviews revealed a substantial degree of heterogeneity across OLP studies, attributed to variations in study design, patient demographics, specific conditions addressed, and the methods of administering OLPs. Such diversity posed significant challenges in drawing consistent conclusions and comparing outcomes across different studies, as these variations substantially influenced the results.

In the critical appraisal of the three empirical reviews, each study clearly articulated its review question and adhered to appropriate inclusion criteria and search strategies (see Appendix 8). All reviews

employed robust methods to minimize errors and ensure independent critical appraisal. Although one review had unclear assessments of publication bias, the others effectively utilized methods to assess this bias. Recommendations and directives for future research were well-supported by data, enhancing the validity of their conclusions.

In the critical appraisal of the seven qualitative studies, they all demonstrated congruity between their philosophical perspectives, research methodologies, and objectives, ensuring methodological consistency (see Appendix 9). Each study adhered to ethical standards, with documented approvals. However, cultural and theoretical positioning by researchers was uniformly absent, and in one study, the influence of the researcher on the research was unclear, while another failed to address this influence altogether. Participants' perspectives were effectively represented in all studies, strengthening the credibility of the findings. Overall, these qualitative studies were methodologically robust, providing trustworthy insights into the research questions posed.

Experimental Studies

	Study Specifics	Content of Placebo Intervention	Results Regarding Placebo
Chronic Primary Low Back Pain	Carvalho et al., 2016 (70)	*Intervention*: 2 pills, twice a day for 21 days *Education*: 15min verbal instruction. Placebo was inactive but might still trigger powerful effects. They could prompt automatic responses and that a positive attitude helps, though it's not essential.	Significant reductions in pain and disability were observed in the OLP group compared to TAU.
	Carvalho et al., 2021 (28)	*Intervention*: 2 pills, twice a day for 21 days *Education*: 15min verbal instruction. Placebo was inactive but might still trigger powerful effects. They could prompt automatic responses and that a positive attitude helps, though it's not essential.	Pain intensity decreased by 40% and disability scores also showed substantial reductions. Medication use significantly decreased from 87% at baseline to 31% at the 5-year follow-up.
	Kleine-Borgmann et al., 2019 (71)	*Intervention*: Pills. Twice a day for 21 days. *Education*: Video. Positive effects shown in clinical trials, the automatic nature of placebo responses explained in simple terms, the effectiveness of placebos regardless of belief.	There were significant reductions in pain intensity, functional disability ratings, and depression scores in the OLP group compared to the TAU group. No significant changes in spine mobility between groups.
	Kleine-Borgmann et al., 2023 (29)	*Intervention*: Pills. Twice a day for 21 days *Education*: Video. Placebo has no active ingredients but could still relieve pain effective through psychological effects.	Pain intensity, functional disability ratings, and depression scores did not significantly differ between OLP and TAU groups over the 3-year follow-up period.
	Ikemoto et al., 2020 (30)	*Intervention*: 2 pills, twice a day for 12 weeks. *Education*: Placebos are inactive, but the effect is strong and physiological changes are confirmed in research. A positive attitude helpful but not vital.	OLP and TAU improved significantly, but OLP showed no superior findings compared to TAU group regarding pain intensity and functional disability.
	Ashar et al., 2022 (72)	*Intervention*: One saline injection *Education*: Two videos describing how placebo treatments can effectively alleviate pain even when known to be inert.	OLP injections were less effective than PRT, but more effective than TAU. At 1 year follow-up PRT had reduced pain with NRS 2.59, OLP with NRS 1.31 and TAU with NRS 1.1. Statistical data for group comparison is not provided.

Irritable Bowel Syndrome	Kaptchuk et al., 2010 (73)	*Intervention*: Two pills, twice a day. *Education*: Verbal instruction. Placebo is inert but can improve IBS symptoms through its effect potency and physiological responses.	OLP significantly improved IBS-SSS and IBS-AR compared to the no-treatment control. A trend favouring OLP was observed for IBS-QoL. Study backs involving patient expectations and beliefs within therapy.
	Lembo et al., 2021 (74)	*Intervention*: One pill, designed to match the real medication, three times a day. *Education*: Placebos can bring positive results in trials, likely through psychological and neurobiological means, though not fully understood.	The OLP group had a significant reduction in IBS-SSS and IBS-GIS compared to the no-pill control group and was comparable to the double-blind placebo group.
	Ballou et al., 2022 (75)	*Intervention*: 3 pills a day for 6 weeks. *Education*: Verbal instruction. Placebo intake in double-blind conditions can relieve symptoms significantly. It's uncertain if placebos work open labelled. Belief in placebos isn't required for treatment benefits.	Significant psychological predictors included low pain catastrophizing and high visceral sensitivity for better response in OLP, which was contrasted with their effects in double-blind placebo and no-pill control groups.
Knee Osteoarthritis	Bandak et al., 2022 (76)	*Intervention*: saline injections at week 1, 3, 5, and 7. *Education*: Neutral script equally emphasized the benefits of both the exercise program and the placebo injections, including a possible placebo effect even though open labelled.	OLP was as effective as exercise and education program (GLA:D) for pain intensity and functional improvements.
	Henriksen et al., 2023 (77)	*Intervention*: saline injections at week 1, 3, 5, and 7. *Education*: Neutral script equally emphasized the benefits of both the exercise program and the placebo injections, including a possible placebo effect even though open labelled.	OLP and exercise and education program (GLA:D) had both significant benefits for kOA, with no significant differences in between groups.
	Olliges et al., 2022 (31)	*Intervention*: Pills. Twice a day for 21 days. *Education*: Verbal instruction. The placebo effect is powerful, and the body can respond physiologically. A positive attitude is helpful but not necessary.	Pain intensity significant improved in OLP-treated groups. Functional disability and mobility of the knee did not change significantly across the groups.
Migraine	Kam-Hansen et al., 2014 (78)	*Intervention*: 7 pills, one for each migraine attack. *Education*: It was verbally explained that the pill labelled 'Placebo' is inert and contains no active medication.	Under OLP, the average placebo effect was significant and amounted to approximately 30.9% effectiveness compared to 51.6% in the control group.

Conditioned Open-Label Placebo	Morales-Quezada et al., 2020 (79) *Postsurgical pain after spinal surgery after injury and polytrauma.*	*Intervention*: Pills, initially given together with oxycodone, but continuously replaced until OLP only. *Education*: Participants were specifically taught about the association between the placebo effect and conditioning.	The COLP group had significantly opioid use reduction of 66% ($p = 0.0094$) and a significantly but not clinically relevant pain reduction.
	Flowers et al., 2021 (27) *Postsurgical pain after spinal fusion surgery*	*Intervention*: one pill, three times daily together with real medication. *Education*: Overview of placebo, OLP, and COLP and their pain reduction evidence; clarification that belief is not essential for efficacy; assurances of unrestricted access to analgesics post-surgery.	COLP group consumed significant less daily opioids compared with TAU group (approx. 30%). Daily worst pain scores were lower in the COLP group by an average of 1 NRS. No significant difference was detected in average daily pain between the groups
	Belcher et al., 2023 (80) *Opioid use disorder*	*Intervention*: Placebo pills. Initial 2 weeks given together with methadone, then OLP only for 10 weeks. *Education*: Both verbal and video. Prove of effectiveness in clinical trials, automatic responses based on neurobiological and psychological conditioning, non-necessity of belief in their efficacy.	Mean methadone doses had no significant differences between the groups. Treatment retention was significantly higher in the COLP group (77.9%) compared to the TAU group (61.1%). COLP group had significant improved sleep quality compared to TAU group.

Table 5: Results from collected RCTs. OLP: Open-Label Placebo. TAU: Treatment as Usual. PRT: Pain Reprocessing Therapy. IBS: Irritable Bowel Syndrome. IBS-SSS: Irritable Bowel Syndrome - Severity Scoring System. IBS-AR: Irritable Bowel Syndrome - Adequate Relief. IBS-GIS: Irritable Bowel Syndrome - Global Improvement Scale. IBS-QoL: Irritable Bowel Syndrome - Quality of Life. COLP: Conditioned Open-Label Placebo. GLA:D: Good Life with osteoArthritis in Denmark. kOA: Knee OsteoArthritis. NRS: Numerical Rating Scale. Green: study shows significant efficacy. Yellow: Study shows uncertain efficacy or improvement, yet not clinically significant. Red: Study shows no significant difference.

Effectiveness of OLP Across Pain Conditions and Interventions

As seen in Table 5, nine studies attempted to find answers regarding the placebo effects on chronic musculoskeletal pain conditions, three investigated in referred visceral pain, one in migraine, and three attempted to explore COLP. Overall, the utilized outcomes were pain intensity, physical disabilities, mental state, and medication dose reduction. However, they have employed divergent outcomes and measurement tools, including NRS, applied medication, and various questionnaires for their functionality in daily life and mental health outcomes, including depression, anxiety, and stress.

Six of these studies investigated in cLBP, whereas two demonstrated significant reductions in pain and medication use through the administration of OLP. Notably only one of these reported sustained long-lasting effects in their 5-year follow-up, whereas the second reported no effects after a 3-year follow-up. Meanwhile, contrasting outcomes were seen in the other studies. Ikemoto et al. (2020) noted overall improvements from baseline, but OLP was not statistically different from treatment as usual (TAU). Ashar et al. (2022) did not provide specific statistical data to directly compare OLP with TAU but found that Pain Reprocessing Therapy (PRT) showed statistically and clinically relevant improvements compared to both OLP and TAU.

Three studies looked at kOA. Bandak et al. (2022) reported that OLP injections were as effective as exercise (GLA:D) in managing knee kOA, highlighting the magnitude of placebo interventions. In their follow-up, Henriksen et al. (2023) even confirmed sustained effects after one year. Similarly, Olliges et al. (2022) found statistically significant improvements with OLP pills for kOA.

Three other studies explored the effectiveness of OLP in managing IBS. Both Kaptchuk et al. (2010) and Lembo et al. (2021) reported significant symptom improvement with OLP treatments, utilizing similar outcome measures. Notably, Lembo et al. (2021) extended this research by comparing the efficacy of OLP directly with double-blind placebos, finding comparable efficacy. Additionally, Ballou et al. (2022) reinforced these findings, highlighting that psychological factors such as low pain catastrophizing and high visceral sensitivity were associated with better responses to OLP treatments for IBS.

Kam-Hansen et al. (2014) observed a robust effect of OLP pills regarding episodic migraine attacks, emphasizing the impact of patient expectations and treatment labels on efficacy. However, compared with double-blind treatments, the effect of OLP was less. They suggested that different placebo mechanisms were observed in OLP and blinding events.

Three studies provided information on the role of COLP in managing opioid dependency. Two studies investigated postsurgical pain, suggesting that the psychological components of COLP interventions can

significantly enhance traditional pain management strategies. Flowers et al. (2021) demonstrated that the combination of OLP with opioids reduced opioid usage by approximately 30% to TAU, while daily pain scores remained comparable. Meanwhile, Morales-Quezada et al. (2020) found a notable 66% decrease in opioid consumption in patients with spinal cord injuries when medication was combined with COLP. Moreover, pain scores significantly (but not clinically relevant) decreased in COLP group.

Belcher et al. (2023) explored the use of COLP within individuals with opioid use disorder. Their study found improved treatment retention and sleep quality among participants receiving COLP, while opioid dosage where not significantly reduced. They concluded that OLP could enhance the overall effectiveness of conventional therapies in the context of addiction treatment.

The duration of intervention influenced outcomes some of the time. Notably, Ashar et al. (2022), using a single injection approach, did not yield as favourable results as Bandak et al. (2022), who employed multiple injections. However, the duration of placebo intervention with pills did not yield this statistic, whereas 12 weeks with placebo pill intervention (Ikemoto et al. (2020)) were not associated with better outcomes than 3 weeks (Carvalho et al. (2016 et 2021); Kleine-Borgmann et al. (2019)). Besides chronic primary LBP, chronic pain conditions were more affected when administered with injections compared to pills.

Reviews

Study	Titel	Results	Discussion and Perspectives
Charlesworth et al. 2017 (81) OLP + CPain: 2 COLP: 0 Other: 3	Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis	The study found that OLP, when used transparently with participants informed, they were receiving a placebo, still produced beneficial effects on pain management and opioid usage post-surgery. This supported the efficacy of OLP even when patients were aware that they were not receiving active medication.	Based on the findings, the researchers recommended the consideration of OLPs as a safe and effective option for reducing opioid consumption post-operation. They emphasized the need for further research to explore how the benefits of OLP can be maximized when integrated into standard medical practice without deception.
Wernsdorff et al. 2021 (25) OLP + CPain: 5 COLP: 0 Other: 8	Effects of open-label placebos in clinical trials: a systematic review and meta-analysis	The review found a significant overall effect of OLPs in various conditions, with a standardised mean difference of 0.72, indicating a robust effect across different disorders. OLPs were effective compared to no treatment, supporting their potential as a beneficial intervention in clinical settings.	The authors highlighted the importance of the narrative accompanying OLP administration, suggesting that positive expectations and patient education about the placebo effect could enhance treatment outcomes. They also pointed out limitations due to high heterogeneity and a moderate risk of bias in the included studies, recommending more rigorous and larger-scale studies to confirm these findings.
Buergler et al. 2023 (82) OLP + CPain: 8 COLP: 3 Other: 26	The roles of expectation, comparator, administration route, and population in open-label placebo effects: a network meta-analysis	The review found that OLPs had beneficial effects in both clinical and nonclinical populations, with larger effects observed in clinical settings. Positive treatment expectations were crucial for achieving these effects. The type of control group used influenced the perceived efficacy, highlighting the importance of comparative context in OLP research.	The review emphasized the significant role of patient expectations in enhancing OLP effects and suggested that the method of administration did not markedly influence outcomes. It underscored the need for further studies to explore how different aspects of OLP administration affect outcomes across varied conditions. The review called for more comprehensive guidelines on implementing OLPs in practice, considering the ethical implications and potential benefits of non-deceptive placebo use in clinical settings.

Table 6: Results, discussion, and perspectives from collected reviews. OLP: Open-Label Placebo. CPain: Chronic Pain. COLP: Conditioned Open-Label Placebo. Mainly positive findings. Yellow: Mainly ambiguous findings (no study represented). Red: Mainly negative findings (no study represented).

OLPs Implication on Pain-Related Conditions

Across the three empirical reviews, consistent findings showed that OLP significantly decreased pain and pain-related symptoms in various conditions, including chronic pain (see Table 6). Wernsdorff et al. (2021) found a significant effect size of a standard mean difference (SMD) of 0.72, demonstrating a medium-to-large effect size impact of OLPs. They indicated that OLPs had a substantial influence on symptom alleviation in clinical settings. This effect size derived from five studies across various pain-related conditions such as cLBP, IBS, and episodic migraine attacks, and eight studies from non-pain-related conditions, including menopausal hot flushes, ADHD, allergic rhinitis, cancer-related fatigue, and depression. All of their chronic pain-related studies were analysed within this scoping review.

While specific effect sizes for different interventions were not detailed in the review from Buergler et al. (2023), the effectiveness of OLPs varied mostly due to patient expectations and the clinical context, especially in clinical examples. Their review captured eight OLP RCTs on chronic pain conditions, three studies investigating COLP, and 15 studies on non-pain-related, psychological origin. They highlighted, that OLP in general seemed to be better than “nothing”, as for example a waiting list, but no better than “something”, as they, depending on the control group, often could not exceed TAU-groups. However, COLP seemed to outstand both waiting list as also TAU, even though limitations occurred due to assumptions being made on two studies only.

They found no statistically significant difference in the route of administration and highlighted this finding to be controverse to deceptive treatments. However, they noted that larger differences in standard mean differences in clinical context, compared to non-clinical, suggesting underpowered sample sizes. They underscored that the route of administration might differ for pain-related conditions. However, this phenomenon has until today only been discovered in deceptive administrations, and they emphasized the need for further research to determine differences in administration routes for OLP.

The review by Buergler et al. (2023) implied that the efficacy of OLPs may differ with different types of interventions, whether they be psychological, physical, or a combination of both. They indicated that efficacy variability pointed to the importance of tailoring placebo interventions to individual patient needs and clinical scenarios to maximize their effectiveness. This differentiation in intervention strategies could lead to a range of effect sizes, indicating that some placebo protocols may be more effective depending on the targeted condition and patient expectations.

Ethical Implications and Clinical Integration

The ethical considerations concerning the use of OLPs in clinical practice were comprehensively addressed in all three empirical reviews. Their discussions emphasized the intersection of clinical efficacy and ethical practice, advocating for the development of robust guidelines that uphold the ethical use of OLPs. Such guidelines were addressed as crucial in recognizing the potential benefits of OLPs and ensuring adherence to non-deceptive practices in patient care.

Despite the inherent ethical advantages of OLPs, such as their transparency and absence of deception, their practical application and acceptance extended beyond these theoretical benefits. For an effective implementation, Wernsdorff et al. (2021) required patients to fully understand OLPs and the potential benefits. This understanding necessitated clear communication and a deep comprehension of patient expectations and psychological dynamics. Thus, the ethical use of OLPs transcended mere permissibility, focusing also on ensuring patients were well-informed about their treatment options and the possible outcomes.

Furthermore, the ethical use of OLPs represented a significant shift in the traditional paradigms of patient care. Especially Buergler et al. (2023) challenged conventional notions of treatment and the placebo effect by proposing a model where the psychological engagement of the patient was as pivotal as the biological efficacy of conventional drugs. They suggested that patient care should incorporate both psychological and physiological considerations to enhance treatment efficacy.

Qualitative Analysis

	Study Specifics	Design and Methods	Findings
Chronic Pain Condition	Kisaalita et al. 2014 (83) *All kinds of chronic pain conditions*	Survey methodology. Internet-based survey.	The study highlighted that the acceptability of OLPs was significantly influenced by the context in which it was used. In scenarios where no other treatments were available, or as an adjunct to existing treatments, OLPs were seen as more acceptable. The effectiveness of OLP in alleviating symptoms further reduced concerns over the deception typically associated with placebo use, improving trust in providers and reducing negative moods among patients.
	Carvalho et al. 2021 (28) *Chronic Primary Low Back Pain*	Qualitative study nested within RCT. Individual interviews.	Patients shared positive experiences and perceptions regarding the effectiveness of OLP in managing chronic low back pain. Many reported a lasting reduction in pain and improved quality of life, which they attributed to their participation in the OLP intervention.
	Haas et al., 2022 (75) *Irritable Bowel Syndrome*	Mixed methods. Qualitative study nested within a RCT. Semi-structured interviews.	Both open-label and double-blind placebo participants expressed feelings of hope and curiosity regarding their treatments. OLP participants engaged more in self-reflection and were more ambivalent about attributing symptom improvement to the treatment.
Post Surgical Pain	Bernstein et al., 2021 (84) *OLP following hand or wrist surgery*	Qualitative study with thematic coding consistent. Semi-structured interviews.	The study identified that postsurgical pain patients perceived OLP as an ethical and potentially effective treatment for pain management, noting that the transparency of OLP contributed to its ethical reception. Patients were open to using OLPs, especially if prescribed by a trusted doctor.
	Hruschak et al., 2023 (85) *COLP following spine surgery*	Qualitative thematic analysis. Semi-structured qualitative interviews.	Participants' experiences with COLP varied, with insights on the psychological impact on pain management and opioid use. Some noted COLP provided a distraction from pain or helped in reducing opioid consumption, though efficacy was uncertain for many.
OLP in General	Bernstein et al., 2020 (86)	Two semi-structured focus groups.	Physicians expressed mixed opinions about OLPs, highlighting a nuanced understanding of placebos within clinical contexts. Some physicians saw OLPs as potentially beneficial and harmless, while others viewed them as potentially disrespectful to patients. Additionally, concerns about the lack of guidelines, legal issues, and reputational risks were highlighted as barriers to OLP use in clinical practice.
	Schienle et al., 2024 (87)	Cross-sectional survey methodology. An online survey.	The survey revealed polarized attitudes towards using OLPs for themselves and their children, with a third of participants being highly receptive and another third holding exceedingly unfavourable views. Willingness correlated with beliefs in OLPs' effectiveness on emotional and physical issues.

Table 7: Findings from qualitative studies. OLP: Open-Label Placebo. COLP: Conditioned Open-Label Placebo. RCT: Randomised Controlled Trial. Green: Mainly positive findings. Yellow: Mainly ambiguous findings. Red: Mainly negative findings (no study represented).

Perspectives of OLP Treatments in Pain Management

The research methodologies employed in the seven studies on OLP treatments encompassed qualitative thematic analysis, semi-structured interviews, focus groups, and surveys (see Table 7). The understanding and perceptions of OLP treatments varied significantly among both patients and healthcare providers. Patients' initial responses to OLPs ranged from intrigue and ethical skepticism to surprise at the therapeutic benefits. The 2024 cross-sectional survey by Schienle et al. (2024) suggested a societal shift towards accepting placebos if proven effective, though ethical concerns remained. Many patients felt empowered by their active involvement in treatment decisions, even when those treatments were placebos. This sense of empowerment and agency emerged as a prominent theme across studies, with increased acceptance of placebo treatments over time, particularly when outcomes were positive and the mechanisms were transparently explained. However, Carvalho et al. (2021) found significant changes in patients use of treatments relying on complementary and alternative medicine (CAM), going from 18% pre-study to 29% post-study.

Healthcare providers also had complex views on OLP treatments. Carvalho et al. (2021) documented some providers' positive views due to the long-term benefits of OLP for cLBP, viewing it as a viable alternative where conventional methods fail or lead to dependency issues. Meanwhile, Bernstein et al. (2020) revealed that while primary care providers acknowledged the potential therapeutic benefits of placebos, they called for more robust clinical evidence to justify wider adoption in practice. They expressed concerns about the ethical implications and maintaining trust and transparency when prescribing inert treatments. Ethical concerns were the most outstanding theme among providers. The 2014 study by Kisaalita et al. highlighted discomfort regarding the use of deception in placebo use, even with openly labelled placebos. Providers emphasized the need for rigorous consent processes to ensure patients were fully informed about their treatment. Haas et al. (2022) found that providers saw the value in using OLP as part of a comprehensive treatment plan but stressed the importance of maintaining ethical standards.

Besides ethical concerns, providers reputational risks were prominent. Kisaalita et al. (2014) and Bernstein et al. (2020) noted providers' wariness about how their professional peers and the broader medical community might perceive the use of placebos. They feared it could be seen as less scientifically rigorous. Additionally, Haas et al. (2022) pointed out that while younger providers were more open to incorporating innovative treatments like OLP into their practice, older providers were more concerned about potential criticism from within the medical community.

Summary of Synthesis

16 RCTs, 3 empirical reviews, and 7 qualitative studies were included in the scope. The critical appraisal indicated some limitations, especially due to the lack of blinding in the RCTs and missing cultural and theoretical positioning by researchers in the qualitative assessments. However, the overall level of evidence was moderate. Meanwhile, the data-extraction indicated a comprehensive overview of the scientific question; is open labelled placebo a plausible treatment for patients with chronic pain?

Potential Effects of Open Label Placebo Treatments

The RCTs indicated that OLP and COLP had varying degrees of effectiveness in different chronic pain conditions. For cLBP, studies showed mixed results. In contrast, interventions for kOA, IBS, and episodic migraine attacks showed significant improvements. Some research showed that OLPs could be as effective as exercise in managing pain and improving functional outcomes. Only three studies investigated COLP. Of these only one investigated a chronic condition, whereas the other two investigated postsurgical pain management. While COLP seemed to have promising benefits regarding postsurgical short-term interventions, the efficacy for patients with opioid use disorders diminishes substantially.

Understanding the Mechanisms

The qualitative studies, while primarily focused on participant experiences, hinted at psychological mechanisms contributing to the analgesic responses seen with OLP and COLP treatments. Patients often expressed a belief in the treatment despite knowing these were placebos, indicating the power of psychological factors such as expectation and conditioning. Empirical reviews further underscored the role of cognitive engagement, suggesting that understanding and believing in the treatment process may enhance the therapeutic outcomes of OLPs.

Assessing Practical Application

The integration of OLP and COLP into existing healthcare frameworks appeared feasible but was contingent on patient receptiveness, which varied. Some studies reported high levels of acceptance and perceived effectiveness when patients were involved in treatment decisions and fully informed about the nature of their treatment. However, ethical concerns and the variability in healthcare provider support could affect the broader acceptance and practical application of these interventions. Missing guidelines due to a continuous need for research, seemed to impede its inclusion as a viable treatment in scientific medicine.

Discussion

Efficacy of OLP and COLP in Chronic Pain Subgroups

Overall, placebos administered without deception appeared to have a significant impact in chronic pain patients. This includes reductions in NRS scores, improved physical function, enhanced mental state, and decreased medication use. However, the clinical relevance of these findings was often not addressed. Clinical relevance, such as minimal important change (MIC), distinguished between statistically significant differences and those that were meaningful for patient care. While statistical significance indicates that an observed effect is unlikely to be due to chance, clinical relevance assesses whether this effect is substantial enough to impact patient outcomes. This limited the applicability of their results to patient centred care and made them more research focused. Nevertheless, Bandak et al. (2022) demonstrated that the effect size of OLP was comparable to that of a structured exercise program, with benefits persisting up to the 1-year follow-up. Conversely, Ashar et al. (2022) found that PRT was more effective than OLP, although the comparison between OLP and TAU was not elaborated upon.

The empirical reviews tried to quantify OLP efficacy, showing medium-sized to large clinically relevant effects on self-reported outcomes, comparable to deceptively administered placebos. However, their analysis included non-clinical trials and non-pain-related conditions.

COLP showed promising effects on reducing opioid consumption in postsurgical patients. However, varying reductions between 30-66% demonstrated uncertainties in effect size, indicating reliability and validity concerns. Additionally, they reported a significant reduction in pain, though this reduction was not clinically relevant. Belcher et al. (2023) found no reduction in methadone use in patients with opioid disorders. However, the COLP group had significantly improved sleep quality and the treatment retention increased from 61.1% to 77.9%, compared to TAU. While results showed promising effects on postsurgical pain patients, efficacy seemed compromised when compared to people with long-lasting opioid disorders. It could be hypothesized that patients with short-term prescribed medications could have a more positive and optimistic attitude than patients with several years of opioid dependency. Another possible explanation for conflicting results could be due to mechanisms from the placebo or hawthorne effect. Patients' behaviour reactivity in response to their awareness of being observed may alter throughout time. They may no longer have felt a connection to the study, have lost attention or motivation, and there was no longer an active intake of a provided pills from professionals. Therefore, it remained uncertain whether COLP did affect patients with chronic pain conditions.

In general, all chronic subpopulations experienced positive outcomes except those with cLBP. While all seven studies focusing on IBS, kOA, and episodic migraine attacks reported positive results, only three out of six studies on cLBP showed positive outcomes. One of the studies without positive findings compared OLP with PRT, without addressing OLP versus TAU. Ikemoto et al. (2020) found significant benefits compared to baseline, but no difference compared to TAU. Regarding long-term effects, only Carvalho et al. (2021) demonstrated a persistent effect in their 5-year follow-up, whereas Kleine-Borgmann et al. (2023) found that the earlier improvements were absent in their 3-year follow-up.

Variability in OLP responses might have had an explanation in study method variability, differences in patient education, outcome measures, settings, and interventions (e.g. pill vs injection and intervention durations). Ashar et al. (2022), consisting of mostly well-educated patients, had great effects with PRT. They used several one-on-one sessions in their intervention group, containing cognitive, behavioural, and somatic techniques. Meanwhile, Bandak et al. (2022) and Henriksen et al. (2023) compared OLP to GLA:D, containing exercise and group sessions. Due to its novelty, there was no standard, and the diversity of study methods was enormous. These differences might have impacted placebo analgesia. While Buergler et al. (2023) implied that patient expectations played a significant role, which are known to affect neurobiological mechanisms. Together with methodological differences, they contributed to divergent outcomes.

Impact of Open-Label Placebos on Pain Mechanisms

Pain Pathways

Variability in outcomes among subgroups with chronic pain could be attributed to different pain mechanisms. Studies investigating chronic secondary pain conditions, like kOA and IBS, found positive results with OLP. In contrast, all studies on cLBP had excluded primary causes, therefore focusing solely on chronic primary LBP. Due to their controverse findings, it could be hypothesized that OLP had a significant effect on chronic secondary pain, while its effectiveness on chronic primary pain remained inconclusive.

Delving deeper in the mechanisms, OLP may have altered nociceptive and nociplastic pain differently. For kOA and IBS, although specific mechanisms aren't fully understood, inflammation played a significant role. Pro-inflammatory markers, such as interleukins, exacerbate nociceptors and contribute to nociceptive pain (11). Over time, central sensitization can worsen pain experiences, indicating that kOA involves more than just nociceptive pain. However, the pain mechanisms for cLBP might be more complex. 85-95% of acute LBP cases are considered non-specific, meaning no definitive pathological source is identified through current scientific methods, including physical examination and imaging

diagnostics (11,88). “Non-specific” does not exclude nociceptive pain, but especially when transitioning into cLBP, embraces nociplastic origins. The lack of a clear mechanical source in cLBP could have exacerbated negative thoughts, such as doubt and frustration, and activated brain circuits and NT, decreasing the placebo effect. The most effective treatments for cLBP involve nuanced multimodal approaches, including pain neuroscience education, exercise, and engagement in painful yet meaningful activities (72,89,90). These approaches demand resourceful therapy sessions, where OLP group education or videos might have been lacking adequate procedures. Conversely, patients suffering from kOA, IBS, and post-operative pain might have experienced fewer negative thoughts since the source of their pain is more likely understandable. Therefore, convergent outcomes among studies embraced the hypothesis that OLPs were more effective for nociceptive pain than for nociplastic pain.

In conclusion, the effectiveness of OLP/COLP may vary depending on whether chronic pain is of primary or secondary character. This variability could be due to differences in pain pathways (nociceptive, nociplastic, or neuropathic) or the patient's confidence in their diagnosis. CLBP might show mixed benefits due to a potentially higher rate of nociplasticity, while visceral and nociceptive mechanical pain might yield more promising results.

Placebo Mechanisms

Expectations

As Buergler et al. (2023) indicated, expectations had a significant impact on placebo responses. Contributing to higher expectations of pain relief, most researchers educated similar content, including the placebo effect being powerful and contributing to neurobiological responds even when known to be inert. While most studies briefly clarified what content has been taught, and what didactive methods have been used, the specific details remained unknown. However, there seemed no immediate connection between type and content of education and OLP efficacy. For instance, Bandak et al. (2022) had great results, even without enhancing placebos potential (see Appendix 10). Notable, even though an association between used placebo education and OLP outcome in the RCTs seemed missing, other expectational factors might have altered the overall effect. As so to speak, qualitative studies elucidated that disbelief in the placebo effect and missing trust in the provider diminished the outcome. Therefore, motivation, personality, and beliefs of the educator could have influenced patients’ expectations in both directions. As elucidated from qualitative studies, medical providers concerns were addressed regarding uncertainty in placebo effect and its ethical use. Moreover, even when educated about placebos efficacy, they might have feared for their professional reputation in the context of ethics and science.

Conditioning

Especially the combination of OLP together with opioids showed promising results in post-operative patients. However, opioid reduction efficacy diminished when looking at patients with prolonged opioid consumption. It has been observed that prolonged drug consumption, especially opioids, has led to brain alterations including multiple NT-systems, such as glutamatergic, GABAergic, opioidergic, endocannabinoid, cholinergic, serotonergic, and noradrenergic (91,92). These systems are known for several pain pathways and placebo mechanisms. Together with decreased dopamine receptors in people with opioid disorders, these alterations contributed to a reduced capability to produce NT on its own (92–94) and established the hypothesis of decreased ability of conditioning placebo-efficacy.

Even though not unanimously, OLP seemed to decrease pharmaceutical needs. When OLP was combined with opioids, opioids could even be reduced by 30-66%. A possible explanation could be in conditioning placebo, known to produce similar neurotransmitters as genuine medicine when previously applied. In the COLP studies, the application happened simultaneously with the consummation of OLP. However, remaining OLP studies relied on the hypothesis that every participant had experienced benefits from either pills or injections earlier in their lifetime. When these experiences varied or lacked efficacy, it may have altered placebo analgesia efficacy.

The clinical setting could likewise have influenced conditions. Patients might have had less pain-relieving experiences from community centres, compared to a well-established university hospital. Lastly, injections have a potential more profound placebo effect than a pill, making some studies difficult to compare (17). Even though no clear connections could be detected in the outcome of the RCTs, as well as the NMA regarding clinical setting or placebo administration, it could be hypothesized that a mere effect could have occurred within more invasive administrations.

Emotions

Research suggested that observing others could alter the experience of pain (64). Being educated about the efficacy of placebos through hearing and seeing their success in various studies could have enhanced positive emotions such as hope and optimism. These emotions are known to increase the placebo effect. Conversely, negative emotions such as pessimism and doubt are known to diminish the placebo response. Additionally, Ballout et al. (2022) specified that increased pain catastrophizing was associated with decreased placebo analgesia in patients with IBS, receiving OLP. In studies involving cLBP, negative emotions might be exaggerated to a higher degree than other conditions. While most cLBP cases are non-specific, stigmatisation of “invisible conditions”, accounts for a major challenge, contributing to psychological issues, including shame and depression, as well as social problems, such

as social isolation and a lack of accept and support of others (11,95). Meanwhile Ashar, main-author for the comparison of TAU, OLP, and PRT, identified a correlation between positive outcome in PRT with an increased attribution of mind- or brain-related causes of pain, and decreased beliefs of injuries and activities to be the cause of pain (96). Haas et al. (2022) confirmed this assumption within their qualitative assessment, providing evidence that higher abilities for self-reflection correlated with better outcomes. Therefore, a potential positive effect of OLP could be associated with conquering sub-challenges within stigmatisation of cLBP, especially in the perspective of self-compassion. Hypothetically, it could have contributed to decreased feelings of shame, perceived mental weakness, or even anger and frustration.

A novel understanding of kOA questions the mechanical explanation as a solely cause of pain since no causal correlation has been found between the degree of bone degeneration and pain (97,98). However, unlike cLBP, the origin of kOA as a mechanical issue, is widely accepted. This discrepancy in global understandings of mechanical issues and pain could have contributed to the controversial effects of cLBP compared to the other studied conditions.

Lastly, another possible explanation for the controversial outcomes within the six different OLP-studies regarding cLBP could be reinforced due to cultural and geographical aspects. While most qualitative assessments were conducted in the United States, with only one taking place in Portugal, it remained unclear whether worse outcomes in Germany and Japan were due to a lower level of placebo acceptability, differences in stigmatisation, or other factors.

Endogenous system

Currently, no OLP-study investigated neurobiological changes, such as under the lens of an fMRI, PET-scan, or counterconditioning such as the opioid-antagonist naloxone. Therefore, endogenous alterations on behalf of OLP remain primarily hypothetical.

Placebo education, similar to pain neuroscience education, could have enhanced the belief, that pain always is an output of the brain and, especially when chronic, has little to do with tissue damage (99). This change in pain narrative and beliefs could have occurred with activity changes in the frontal cortex and limbic systems – brain circuits which are able to inhibit afferent noxious stimuli through descending pain modulation.

In conclusion, there is evidence to suggest that OLP altered expectations, conditioning, and emotions, contributing to changes in the endogenous system favourable towards placebo analgesia. Some studies even showed long lasting effects, reporting less pain and improved function. Long lasting altering of

brain function, including activity of respective brain areas and NS, has been observed to reverse allostasis in stress-related conditions (47,100). However, the hypothesis that improved pain-related outcomes over time correlate with reversing allostatic remains to be empirically validated.

Practical Application & Integration

Considering the application and integration of OLP into clinical practice, the included studies implied patient and provider perspectives. In this scope, patient perspectives covered whether patients found OLP helpful and recommendable, while provider perspectives addressed ethics, guidelines, iatrogenic consequences, and overall provider acceptability.

Patient Perspective

Qualitative assessments revealed varying experiences and acceptance levels of OLP. Factors influencing patient acceptance included trust in the provider and belief in the effectiveness of OLP for emotional and physical issues, which were positively correlated with increased acceptability and willingness to recommend OLP to others. Kisaalita et al. (2014) found that acceptability was higher in scenarios where no other treatments were available. Conversely, concerns about integrating OLP correlated with negative beliefs, such as doubts about OLP's effectiveness.

Schienle et al. (2024), whose study involved the highest number of patients, advocated for psychoeducational programs to increase OLP acceptance. They emphasized the importance of setting realistic expectations about OLP's effectiveness in managing symptoms and suggested that educating both healthcare providers and patients about placebo mechanisms could help normalize and potentially enhance the use of OLP in the treatment. This statement was reinforced by the overall outcome of the qualitative analysis.

Similarly, Bernstein et al. (2021) recommended to consider COLP as an adjuvant treatment to potentially reduce reliance on prescription opioids. Their study suggested that COLPs could be integrated into pain management strategies, given their acceptance among postsurgical patients and the potential to alleviate post-operative pain with decreased risks associated with traditional analgesics. Evidence showed that postsurgical decreased opioid use and improved sleep quality were positively associated with a reduced risk of transitions to chronic pain in hip and knee replacements (101). This suggests that postsurgical applicated COLP treatment might have the potential to reduce the risk of pain transitioning into chronic pain.

Provider Perspective

Concerns about ethics were prevalent among providers, particularly when there was a lack of patient education regarding OLP. The absence of clear guidelines and standards were seen as barriers to creating a more ethical environment for OLP integration. Additionally, there was an underlying fear among providers of diminishing their reputation. Qualitative analyses highlighted that providers worried their peers might perceive them as lacking scientific competence if they adopted OLP practices.

On the positive side, providers saw the potential to empower chronic pain patients, fostering higher self-efficacy and reducing the "fix me" attitude. However, a follow-up study observed an increase in the use of CAM treatments from 18% to 29% post-study. This finding supports several researchers' warnings about placebo treatments. Benedetti, known for centuries of placebo research, is one of them and claimed that underestimated or not considered side effects might enhance a general distrust in the scientific healthcare system and warns of adverse consequences (102). While other studies lacked investigating this attitude, concerns remain that this or other undiscovered consequences might be enhanced with OLP treatments.

Equivalent to findings in patient perspectives, providers' attitudes also matched with beliefs about OLP's effectiveness. This reinforced Schienle's advocation for psychoeducational programs to increase OLP acceptance among healthcare providers and patients.

Overall, while there were significant concerns about the ethical implications and professional reputation, there was also recognition of the potential benefits of OLP for patient empowerment and symptom management.

Strength and Limitations

This review consists of strengths and limitations. These will be discussed in the upcoming section, divided into used methods and results.

Methods

Primarily limitation was the review being conducted by a single researcher, which may have introduced bias and limited the depth of the analysis. Furthermore, the limited timeframe constrained the comprehensiveness of the review, including the search. While the absence of grey literature narrowed the scope, the review could have accessed further databases, resulting in further records. Full-text availability issues also restricted the inclusion of some articles. Meanwhile, the novelty of the topic posed a challenge, potentially leading to the omission of essential articles. Additionally, other critical

appraisals, such as GRADE, could have gathered a more constructive insight regarding the evidential validity (103).

Despite these limitations, the review had notable strengths. The adherence to the PRISMA framework for scoping reviews ensured a systematic and transparent methodology. The comprehensive search strategy and critical appraisal processes, although limited, provided a robust overview of the current state of research on OLP for chronic pain management.

The choice of a scope allowed for capturing a wide range of studies, providing a comprehensive understanding of the topic. This inclusivity helped identify gaps in the current research, guiding future investigations. However, the extensive range of included studies made the review resource-intensive and time-consuming. The broad scope also risked diluting the focus by incorporating some irrelevant studies. While this approach offered a broad overview, it lacked the depth needed for a detailed analysis of specific issues within OLP treatments. Meanwhile, the subjective choices made in defining the scope may have introduced bias, affecting the objectivity of the review.

Results

The primary limitation regarding the results, was the inherent variability in the methodologies and outcome measures used across the included RCTs. Meanwhile cultural and geographical differences contributed to difficulties in reliable comparison, challenging consistent and generalizable conclusions.

The critical appraisal regarding the qualitative studies highlighted a uniformly absent statement of the researchers, locating them culturally or theoretically. Also, two studies failed to ensure the researchers' influence. Potential conscious or unconscious manipulation might have influenced the patients' answers or the interpretation of the researcher in both directions.

Additionally, OLP studies per definition lack blinding, increasing the risk of bias, such as the hawthorne effect. The absence of long-term follow-up data in most studies limited the understanding of the sustained effects of OLP. Moreover, missing adherence to clinical relevance limited the strengths of the result.

Despite the noted limitations, the results provided valuable insights into the potential of OLP and COLP in managing chronic pain. Through the method, a robust finding comprehensively discussed the research question, including experimental and qualitative studies, as well as empirical reviews. While the experimental studies gave an inside of OLP efficacy, the qualitative studies reflected a strategic approach to balance depth with breadth in understanding the intricacies of placebo in pain management. This offered a deeper understanding of the psychological mechanisms and patient and

provider experiences associated with OLP treatments. Simultaneously it gave insights on feasibilities of integration into clinical practice.

It has been mentioned that multiple factors, such as cultural backgrounds, societal norms, healthcare settings, and differences in the researchers' communication skills and attitudes might have impacted outcomes. However, the heterogeneity in outcomes, especially for chronic secondary pain, strengthened the validity of the result.

Across the three empirical reviews, findings suggested unanimously that OLPs can significantly decrease pain and related symptoms in various conditions. As mentioned before, all three reviews build their data on similar articles, highlighting, that different researchers partly were looking at the same data and came to the same conclusion. Coming to the same conclusion, even after new studies were added, made their assumptions more trustworthy.

Furthermore, these results were supported by the general consumption that opioids in the management of acute LBP are no better than placebo. Meanwhile, pain education is known to alleviate pain, contributing to the theory of pain relief being supported by psychological interventions.

Future Research

Understand the Mechanisms

The identification of specific pain conditions, such as chronic primary or chronic secondary, where OLP showed benefits, provided a focused direction for future research. This focus allows researchers to tailor their investigations and develop targeted OLP interventions for these conditions. This knowledge enhances our understanding of placebo mechanisms, paving the way for potentially more effective treatment modalities.

Future studies should focus on the differences in the efficacy of OLP on various pain mechanisms, such as nociplastic, nociceptive, and neuropathic pain. Understanding these differences could lead to the development of more effective OLP treatments and lay the groundwork for tailored patient education strategies. By addressing specific pain mechanisms, researchers may optimize OLP interventions to suit individual patient needs, potentially improving overall treatment effectiveness.

To date, no fMRI or PET studies have been conducted on non-deceptive, pain-related placebo interventions to confirm hypotheses about the underlying mechanisms. Neuroimaging studies could reveal whether placebo analgesia due to COLP responds to conditioning or expectation-induced

mechanisms, providing valuable insights into the neurobiological processes involved. Moreover, counterconditioning NS could improve insights in endogenous OLP mechanisms.

Likewise, COLP should be tested on chronic pain together with different pharmacological interventions, including NSAID, SNRI, and anticonvulsive. Potential benefits of reduction of genuine medication on different pharmacological interventions could improve knowledge on placebo mechanisms and potentially reduce side effects.

Explore the Potential Effects of OLP Treatments

Although the statistically significant efficacy of OLP is consistently highlighted across most RCTs, there is a lack of evidence quantifying the magnitude and clinical relevance of this effect. Future meta-analyses should aim to quantify the magnitude of OLP efficacy and compare it with MICes in chronic pain related conditions only. This approach, combined with qualitative studies, would provide a more objective estimate of the clinical value of OLP treatment, and justify its use in clinical practice.

Since OLP efficacy depended on contextual factors such as the control group, it should be examined in combination and comparison to other treatment modalities for chronic pain conditions, including psychological interventions and exercise. Beneficial outcomes may exacerbate a paradigm shift away from the biomedical “fix-me” paradigm towards shared decision-making and patient-empowerment.

Exploring whether OLP works similarly to COLP and how it might be combined with non-pharmacological interventions, such as pain neuroscience education, pain clinics, surgery, or other pain interventions, could provide a broader application framework. This integration could enhance the overall effectiveness of pain management strategies and offer new avenues for research and clinical practice.

Assess Practical Application

To enhance the practical application of OLP treatments, future research should aim for standardised protocols. Establishing comprehensive guidelines for educating patients about the nature and expected outcomes of OLPs, as well as training healthcare providers in the ethical administration of these treatments, could ensure consistency and improve patient outcomes. Developing a consensus on these elements may create more comparable and reproducible results across different studies.

Implementing multi-center trials could help generalize findings across different geographic, cultural, and clinical settings, enhancing the external validity of the research. This approach would also contribute to the diversity of participants, which is crucial for assessing the effectiveness of OLPs across

various populations. Multi-center trials can provide more comprehensive data and ensure that findings apply to a wider range of patients.

Conducting longer-term and larger-scale studies is essential to address the limitations of novel treatment modalities and follow-up periods. Long-term studies would provide more robust data and allow for more definitive conclusions about the efficacy and safety of OLPs. Understanding the duration of the placebo effect and any potential long-term benefits or side effects is crucial for assessing the practical application of OLP treatments.

An important consideration in the application of OLPs is their impact on trust in the evidence-based healthcare system. While OLPs can be beneficial, there is a concern that their use might inadvertently boost pseudoscience. While some researchers, like Benedetti, signal warning for this to happen, little is known about inappropriate attitudes or mistrust in the healthcare system after OLP interventions. Therefore, future studies should address these concerns and investigate how to reduce them.

Conclusion

The primary research question was whether OLP treatments were a plausible option for patients with chronic pain. The findings from this scoping review provided substantial evidence supporting the efficacy of OLP treatments across various chronic pain conditions. The 16 RCTs indicated that OLP significantly reduced pain intensity and medication use, while improving function across various chronic pain conditions. Unanimous results were seen in chronic secondary pain conditions, such as kOA and IBS, while controverse outcomes were reported in chronic primary LBP. Meanwhile, the duration of efficacy remained uncertain. While the short-term effect was significant, long-term efficacy might depend on the population or condition. Likewise, the magnitude of efficacy remained questionable, whereas clinical value was poorly addressed throughout most RCTs. Meanwhile, COLP had a significant and clinically relevant impact on the experience of pain and reduction of medication in post-operative pain management. However, the efficacy seemed diminished when observing chronic pain populations.

The mechanisms underlying the analgesic responses to OLP and COLP were explored, revealing that psychological factors such as patient expectations, emotions, and conditioning played a crucial role. Patients generally exhibited positive receptiveness, particularly when well-informed and involved in the decision-making process, which helped them develop effective coping strategies. However, barriers such as ethical concerns, the need for robust clinical guidelines, and potential attitudinal side effects—such as increased mistrust in the healthcare system and the promotion of pseudoscience—remained.

These challenges necessitate continued education and research to facilitate broader acceptance and implementation.

Due to uncertainty in efficacy, missing guidelines, as well as concerns about ethics and attitudinal side effects, OLP should not be integrated into clinical healthcare practice yet. However, further research should address these issues, since OLP potentially may benefit treatments for chronic pain in healthcare practice, which is needed. Moreover, the overall evidential quality was moderate, and limitations were identified in this scoping review, suggesting caution in generalizing the findings and highlighting the need for more rigorous and comprehensive studies.

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