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## A systematic qualitative review of ethical issues in open label placebo in published research

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Open-label placebos (OLPs), which are transparently administered inert treatments, have gained increasing attention in the research community. They have the potential to harness placebo effects without deceiving the patient. The purpose of this study was to examine and synthesize prior research discussing ethical issues in OLPs. A systematic qualitative literature review was conducted (last search on January 2023) across multiple databases (e.g., MEDLINE, Embase, PsycInfo) using keywords related to OLPs. Publications were screened and assessed for eligibility. Seventeen articles explicitly addressing OLP ethics were included. Data were extracted and thematically analyzed following established qualitative content analysis procedures. 37 distinct ethical issues were identified, grouped into five overarching themes: (1) Sociocultural and Contextual Factors, (2) Implementation and Logistics, (3) Informed Consent, (4) Patient Health Behavior and Dynamics, and (5) Therapeutic Relationship. Frequently mentioned concerns focused on uncertainty of OLP efficacy, the need for further research, and complexities of dose-extending OLPs. The effective integration of OLPs into healthcare necessitates thoughtful consideration and responsible communication. This analysis shows that demonstrating the efficacy of OLPs becomes pivotal for their widespread adoption, underscoring the necessity for additional research to validate their effectiveness. This review was pre-registered on January 26th, 2023, in the Open Science Framework Registry under the identifier: DOI <https://doi.org/10.17605/OSF.IO/R6NKG>.

**Keywords** Open label placebos, OLP, Placebo research, Systematic qualitative review, Bioethics

The use of placebos in clinical practice has traditionally been a subject of ethical controversy due to several reasons: It often involves deception, conflicting with the ethical principle of informed consent and violating patient autonomy by not allowing informed decision-making<sup>1,2</sup>. Furthermore, administering a placebo without the patient's knowledge violates their autonomy by not allowing them to make an informed decision about their treatment. This can be seen as paternalistic and undermines respect for the patient's right to self-determination<sup>3</sup>. Additionally, placebos can prevent patients from receiving effective treatments, leading to potential harm<sup>4</sup>. Their use may compromise the integrity of the medical profession and erodes patient trust<sup>5,6</sup>. The efficacy of placebos is also highly variable, making them unreliable as a standard treatment<sup>7</sup>. The use of placebos without consent may have legal implications, potentially constituting malpractice or fraud<sup>8</sup>. Historically, placebos were administered covertly<sup>9,10</sup>, with patients unaware of the inert nature of the treatment. In recent years, open-label placebos (OLPs) have gained prominence as an innovative approach for medical treatment, effectively addressing a fundamental concern associated with traditional placebos—the element of deception. Unlike traditional placebos, OLPs are administered transparently, with patients knowingly receiving placebos. This approach leverages the psychological effects of belief, expectation, and hope in healing while avoiding deception. Several studies have shown that OLPs can still improve symptoms and promote well-being<sup>11–17</sup>. However, significant obstacles to the methodological integrity of OLP research have been identified in a number of other recent articles<sup>18–22</sup>. The effectiveness of OLPs in various clinical contexts and the psychological mechanisms underlying their effects are subjects of extensive inquiry<sup>23</sup>.

OLPs bring forth the question of whether they represent a mere adjunct to conventional treatment, potentially reducing the need for pharmacological interventions<sup>24–27</sup>. Conversely, some studies argue that open-label placebos might serve as an important complementary therapeutic tool, particularly in conditions with a strong

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psychological component<sup>28,29</sup>. The question of whether OLPs have the potential to revolutionize healthcare by harnessing the mind's ability to heal<sup>30</sup> is a topic of ongoing interest.

A substantial body of research has discussed the ethical implications of open-label placebos<sup>1,26,27,31–44</sup>. Nonetheless, there is currently no comprehensive overview available, and many researchers may not be fully cognizant of the potential ethical concerns that arise with OLPs.

Ethical considerations surrounding OLPs encompass a wide spectrum of topics, such as the necessity of unambiguous informed consent<sup>27,39,43,45</sup> and the impact of OLPs on patient-doctor relationships and autonomy<sup>1,27,34,38,41,46,47</sup>. The question of whether open-label placebos are ethically sound for specific medical conditions, like (chronic) pain<sup>11,39,40,46,48,49</sup> and irritable bowel syndrome<sup>50–52</sup>, remains an area of active debate. An empirical literature review provides concrete evidence and real-world examples to support the conceptual exploration of ethical concerns surrounding open-label placebo usage. Our primary objective was to explore which ethical principles and concerns have been identified and discussed in the context of OLPs.

## Methods

### Study design and rationale

We conducted a systematic qualitative review to synthesize ethical concerns specific to OLPs. This approach was selected because much of the OLP ethics literature is conceptual or theoretical, and the empirical studies available lack sufficient homogeneity for quantitative pooling. Hence, a meta-analysis was not feasible. A systematic qualitative review allows for an in-depth exploration of heterogeneous evidence—ranging from opinion pieces and conceptual analyses to empirical research—focusing on emergent ethical themes<sup>53,54</sup>.

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>55</sup>, adapted where necessary for qualitative evidence<sup>56</sup>. Where relevant, we also drew on previous systematic ethics review approaches for identifying and synthesizing conceptual issues in biomedical literature<sup>57–60</sup>.

### Search strategy; databases and search terms

On January 5th, 2023, we searched multiple databases via the Ovid platform—including MEDLINE (1946–2023), Embase (1974–2023), PsycInfo (1806–2022), and additional databases listed in Table 2—using the following abstract keywords: (“open label placebo\*” OR “open-label placebo\*” OR “non-deceptive placebo\*” OR “non deceptive placebo\*”).

We replicated the same search strategy on PubMed to account for variations in indexing and platform-specific algorithms<sup>61</sup>. Table 1 details the sources and date cutoffs.

All search results from Ovid ( $n = 539$ ) and PubMed ( $n = 187$ ) were exported into Covidence<sup>62</sup> for screening and deduplication.

### Eligibility criteria; inclusion criteria

153 publications were eligible because they explicitly addressed an ethical concern, conflict, or controversy arising from OLP use. Articles needed to either:

- Discuss OLP in the context of at least one core ethical principle (e.g., autonomy, beneficence, non-maleficence, or justice), or
- Discuss whether OLPs presented a clash between multiple ethical principles.

We employed principlism<sup>63</sup> as our overarching ethical framework, consistent with prior systematic ethics reviews<sup>57–60</sup>. Only explicitly stated ethical arguments or reflections were included; implicit or “between the lines” inferences were excluded.

### Eligibility criteria; exclusion criteria

136 publications were excluded because of three reasons: there was no ethical dilemma discussed in the paper that concerned OLPs (114 excluded), there were only abstracts available (16 exclusions) or there were not OLPs applied at all (wording in the article might have been similar but not the same topic, 6 exclusions).

Source	Range/cut-off date
Books@Ovid	December 27, 2022
Ovid Full Text Journals plus Abstracts	1974 to 2023 January
Ovid Full Text Journals (LWW, PsycARTICLES, Nature Reviews)	1974 to 2023 January
APA PsycArticles Full Text	1974 to 2023 January
Embase	1974 to 2023 January
Ovid MEDLINE(R) ALL	1946 to 2023 January
APA PsycInfo	1806 to 2022 December
PSYNDEXplus Literature and Audiovisual Media	1977 to 2022 November
PSYNDEXplus Tests	1945 to 2022 November

**Table 1.** Sources and date ranges searched for relevant papers.

### Screening and selection process

After Covidence removed duplicates ( $n=416$  total across both Ovid and PubMed results), 279 unique abstracts remained. One reviewer (M.R) screened all abstracts ( $n=279$ ) for relevance based on predefined inclusion and exclusion criteria. During this initial screening, 126 abstracts were excluded for being off-topic, typically because they addressed topics like “open-label medication” rather than specifically OLPs. Subsequently, the full texts of the remaining 153 articles were retrieved for detailed review. Upon thorough examination of these 153 articles, an additional 136 studies were excluded for reasons such as being available only as abstracts ( $n=16$ ), not involving the application of open-label placebos ( $n=6$ ), or failing to discuss ethical dilemmas specifically in the context of open-label placebos ( $n=114$ ). Ultimately, 17 studies satisfied all criteria and were included in the review.

A PRISMA flow diagram (Fig. 1) depicts the entire selection process. For each of the 17 included studies, we extracted Publication Details: author(s), year, study design, sample size, population, aim and journal, which can be consulted in Table 3.

Figure 1 PRISMA flowchart overview.

### Data analysis

We employed conventional qualitative content analysis<sup>64,65</sup> to synthesize ethical themes across the included studies. This process was performed using MAXQDA software<sup>66</sup> to ensure consistency. A subset was double coded (for a discussion on intercoder reliability see<sup>67</sup>). Table 2 shows a step-by-step breakdown on the analysis.

### Results

From the initial pool of 279 non-duplicate records, 17 articles met the inclusion criteria (see Fig. 1). As shown in Table 4, most of these articles were published between 2019 and 2023 (11 out of 17). The studies vary in design, with most being qualitative studies or conceptual analyses, and one randomized controlled trial (Publication 12). Sample sizes and populations differ widely; most papers (10 out of 17) were conceptual pieces while the empirical ones focus on healthcare professionals (e.g., surgeons, physicians) or patients with specific conditions such as chronic pain.

### Ethical issues

In total, we inductively derived 37 discrete ethical issues (“codes”) from the 17 articles. Each distinct concern was assigned a single code. Through iterative qualitative analysis, these codes were grouped into five overarching themes:

1. Sociocultural and contextual factors.
2. Implementation and logistics.
3. Informed consent.
4. Patient health behavior and dynamics.
5. Therapeutic relationship.

Each theme captures related ethical discussions that cut across multiple articles. In the following section, we inspect the five themes with their 37 corresponding codes. In Table 4 we list the theme, code, corresponding publication (numbered as per Table 3), a brief explanation of the code and an example quote<sup>68–71</sup>. This allows readers to see both a concrete instance (via the quote) and the scope (which publications) for each code (a discussion on using quotes in qualitative studies can be found here<sup>72</sup>). After Table 4 we provide a summary text for each theme, where codes are printed bold, and publication numbers are mentioned again.

### Sociocultural and contextual factors

The theme of Sociocultural and Contextual Factors became apparent in the discourse on placebo use. This theme encompasses the intricate and often contentious perspectives that various stakeholders hold regarding the legitimacy and utility of placebos within healthcare settings.

Publications coded under Alternative Medicine (Publications: 17, 5, 6, 9, 10, 13) reveal a recurrent concern regarding the potential for placebo use to foster or reinforce beliefs in the efficacy of the placebo itself or the broader concept of mind-body healing. A salient quote from publication 17 encapsulates the apprehension that such beliefs could be mistakenly held as sufficient for curing serious illnesses, thus neglecting established treatments. This suggests a risk of placebos contributing to an overvaluation of “positive thinking” in healing, possibly leading to the avoidance of medically proven interventions. Publications 3, 7, 13 and 14 also suggest a possible paradigm shift that pertains to the cultural and ethical discourse around placebo treatments potentially advancing and redefining their role within medical practice. A forecasted change, as detailed in publication 13, might see placebo therapy integrated into a legitimate clinical method, albeit in specific situations delineated by clear guidelines. The theme further engages with the influence of social norms (Publications: 3, 13) on patient-physician interactions, particularly how patients’ expectations of treatments are constructed and sometimes confronted in the context of OLPs. Publication 3 provides an account of a participant suggesting that OLPs could challenge social conventions, indicating a potential shift in the dynamics of patient-clinician relationships. Lastly, publications 8, 13 and 17 contribute to a discussion on how the use of placebos might affect patient and parental attitudes view on medicine. A noteworthy concern is that an increased reliance on placebos could inadvertently escalate the expectation for immediate “treatments” for every symptom, potentially exacerbating issues within medical practice as highlighted by publication 17. In summary, this theme underscores a complex interplay between sociocultural and contextual factors and the use of placebos to justify the use of alternative

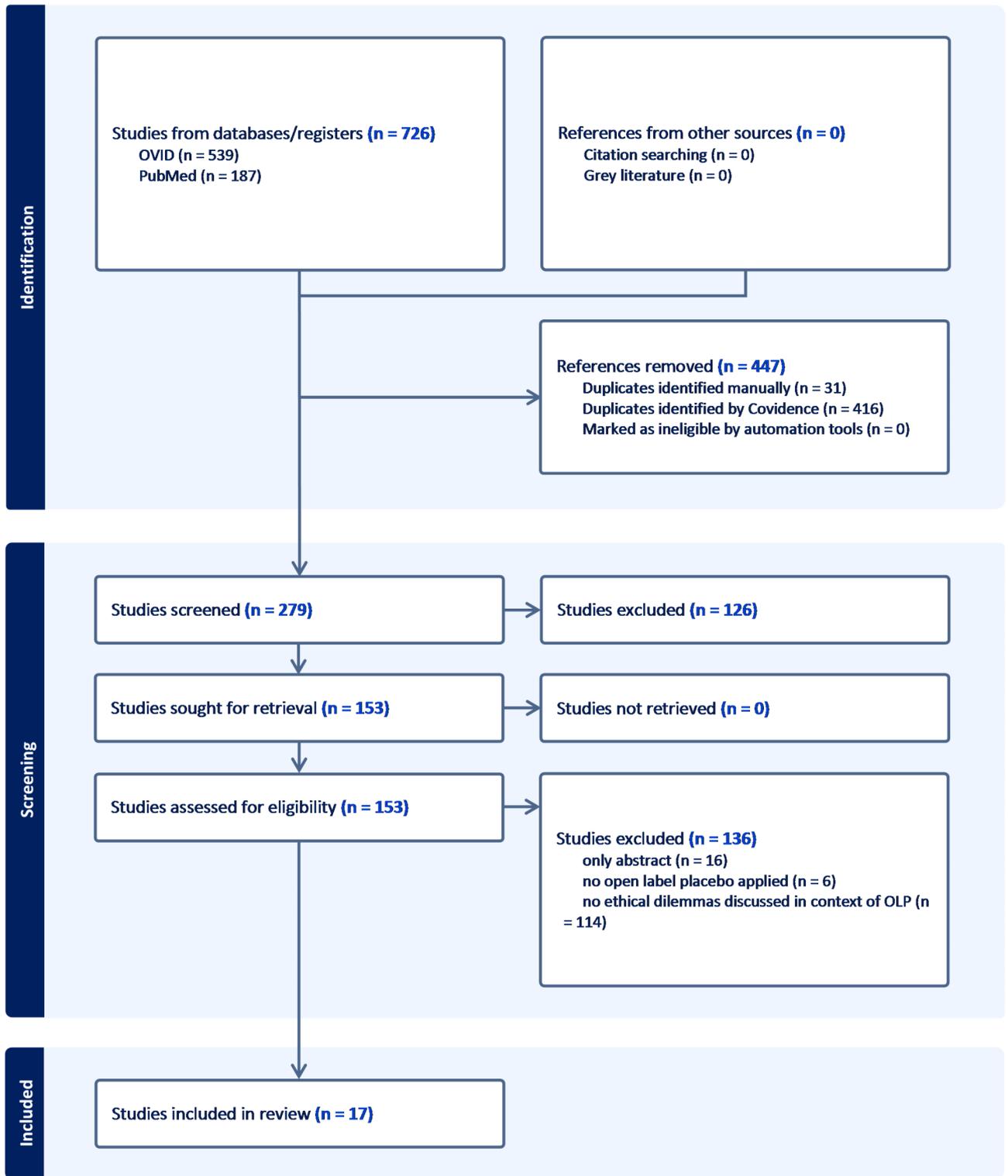


Fig. 1. PRISMA flowchart overview.

medicine. The data indicates both concern for the potential misappropriation of placebos and an optimistic outlook for their ethical integration into medical practice, subject to ongoing cultural and ethical discourse.

### Implementation and logistics

The exploration of OLPs within the systematic review highlighted a nuanced spectrum of implementation and logistical considerations critical to their integration into medical practice. Acceptability was a pivotal concern, with intervention preference varying widely; some patients exhibited a readiness to embrace OLPs as an extension

Step/section	Description
1. Initial coding	The first coder (M.R.) performed an inductive open coding of four articles to generate a preliminary code list
2. Double coding	Two of these articles were independently coded by M.B. to assess intercoder reliability. Discrepancies were resolved through discussion, leading to refinements and additions to the initial code set
3. Full coding	M.R. applied the revised codebook to the remaining 13 articles, adding new codes only when novel ethical concerns were identified
4. Hierarchical categorization	Codes were grouped into broader categories (e.g., “Therapeutic Relationship,” with subthemes such as “trust,” “paternalism,” and “patient agency”)
5. Final synthesis	The coding framework was reviewed in iterative discussions (M.R., M.B.) to ensure accuracy and consensus. This process yielded a set of overarching ethical themes reflecting the major concerns and debates in the literature

**Table 2.** Overview of data analysis.

of their current treatment regimen (Publications: 2, 3, 4, 5, 6, 7, 8, 9). However, the potential for OLPs to serve as a dose extending OLP alongside active medication was met with both intrigue and scepticism, prompting calls for more definitive evidence to validate this application (Publications: 2, 3, 4, 8, 9, 11, 13, 15, 17). The issue of blinding in placebo-controlled trials was also broached, with publications indicating a challenge in maintaining the rigour of double-blind placebo research design when comparing open with hidden placebos and evaluating them against the best available treatment (Publications: 8, 9, 14). Doubts concerning the clear efficacy of OLPs were prevalent, with several studies suggesting a strong imperative for future research to provide solid evidence for their effectiveness, as OLP efficacy not clear yet (Publications: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 16, 17). Indeed, future work is needed by large-scale, pragmatic randomized trials to assess the true potential of OLPs, which was a recurrent theme, emphasizing the importance of robust, evidence-based conclusions (Publications: 1, 4, 5, 6, 7, 8, 9, 11, 12, 16). Legal aspects emerged as a barrier to the prescription of OLPs, with practitioners expressing concern over the consequences of possible negative outcomes from OLP use (Publications: 3, 4). Opinions were divided; some viewed OLPs as comparable to other prescriptions, while others called for additional provider training or patient education to ensure appropriate use, which is summarized under the code ‘logistics’ (Publications: 3, 7, 8, 9, 17).

‘OLP by Proxy’ was acknowledged as a phenomenon, particularly in paediatric care, where the belief systems of parents could significantly influence the placebo response in children, highlighting a complex dynamic in placebo use (Publications: 10, 11). The cost of OLPs was another factor affecting their acceptability, with patients hesitant to incur costs for an inert substance, suggesting economic factors need to be considered in the implementation strategy (Publications: 2, 7, 14).

Lastly, the notion of replacing drugs by OLPs was contemplated, especially in the context of treatments for conditions such as ADHD, where the goal might be the gradual withdrawal from active drugs. This theme suggested a careful and considered approach to introducing OLPs into the treatment regimen (Publications: 2, 9, 11).

Throughout this theme, it was apparent that while there is an underlying positive sentiment towards OLPs, their acceptance and practical application hinge on a multitude of factors that span the spectrum of ethical, legal, logistical, and economic considerations. The synthesis of these insights portrays a healthcare landscape cautiously navigating the potentialities of OLPs, with a clear consensus on the need for continued investigation and dialogue.

### Informed consent

In the context of informed consent within the use of OLPs, this theme has uncovered several dimensions of concern and consideration. The ambiguity inherent in the disclosure process was highlighted, with some practitioners opting for vague language to introduce placebos to patients. This strategy involves offering OLPs with phrases like “here’s something you could try and let’s see if it works,” which, while avoiding definitive claims about the treatment keeping up ambiguity, could lead patients to assume they are receiving an active medical intervention (Publications: 1, 6, 7). The necessity for clinician OLP literacy is underscored, pointing to a need for comprehensive training to ensure that the wider adoption of OLPs is accompanied by accurate patient understanding and expectation management (Publications: 5, 7, 8, 9, 11). Publications suggest that OLPs are consistent with IC values and it is both achievable and necessary to mitigate the ethical risks associated with OLP use (Publications: 5, 7, 13, 16, 17).

The definition of OLPs was also a focal point of debate. It was proposed that recent discussions around OLPs, which often include considerations of communication, empathy, and other contextual factors, should not blur the conceptual boundaries of OLP and other non-specific effects (Publications: 3, 9, 15). OLP Disclosure practices are central to the ethical deployment. Evaluating whether the disclosures made in open-label placebo studies would be ethically acceptable in clinical encounters first requires a clear understanding of what is divulged to participants. Publications stressed that the disclosures and informed consent in clinical trials must be subject to careful moral scrutiny to differentiate them from disclosures in other therapeutic contexts (Publications: 1, 2, 5, 7, 9, 11, 15). Furthermore, the influence on decision-making was considered important. It was posited that the way in which OLPs are presented could independently influence how patients understand their illness and symptoms, and thus their maintenance and healthcare-seeking behaviour (Publications: 1, 11). A critical concern raised was the potential for patients not to fully understanding the consent and hence the concept of OLPs, raising alarms about the consistency of messaging and comprehension across care teams and between clinicians and patients (Publications: 7, 8, 11). Moreover, the notion of patients’ right to ‘not know’ or to know less was discussed, emphasizing the ethical complexity in ensuring that patients can consent to OLP use

Theme	Code	Publications	Explanation	Example quote
Sociocultural and contextual factors	Alternative Medicine	17, 5, 6, 9, 10, 13	Worries that emphasizing placebo or mind-body healing might overshadow established treatments or foster illusory “positive thinking” cures.	More concerning is the possibility that placebo use could lead patients to develop false or misguided beliefs either about the placebo compound itself or the concept of “mind-body healing” overall. It is possible that patients and/or parents could equate the benefits they receive from placebos with a legitimization of other forms of so-called alternative medicines, or develop the inaccurate belief that “positive thinking” is sufficient to cure all manner of serious illnesses, forgoing proven treatments. (17,p2)
	Paradigm-Shift	13, 3,7,14	The idea that legitimizing OLPs in mainstream practice could redefine how society and the medical profession view placebos.	Alternatively, the cultural and ethical discussion regarding placebo treatments will advance, develop, and perhaps expand the bounds of medical practice; eventually turning placebo therapy to a legitimate clinical method - though restricted to specific situations delineated with clear guidelines - but implemented when appropriate and in the service of patient well being. (13, p186)
	Social Norms	3, 13	Considers how cultural expectations and societal beliefs influence the acceptance or skepticism of OLP usage.	More strongly, one participant suggested that OLPs contravened social conventions in patient-physician interactions, where patients held particular expectations of the treatments that would be offered. (3, p607)
	View on Medicine	17, 8,13	How OLPs are prescribed and disclosed may influence patients' views on medicine in general.	Perhaps more importantly, placebo use could potentially have a negative impact on broader patient and parental attitudes toward medicine and health care. It is possible, for example, that the widespread use of placebos would intensify the widely held expectation of “treatments” for every symptom, potentially exacerbating the problem of inappropriate overprescription of other medications. (17, p2)
Implementation and logistics	Acceptability	2, 3, 4, 5, 6, 7, 8, 9	Whether patients/clinicians find OLP appropriate or appealing. Some patients might get upset or lose trust if their MD suggests OLP, others not.	Intervention preference was far from unanimous, suggesting acceptability of placebos may be patient-dependent. (9, p274)
	Dose extending OLP	2, 3, 4, 8, 9, 11, 13, 15, 17	Using OLP alongside or replacing a dose of active medication to maintain or enhance therapeutic effect while reducing drug load.	Although participant's initial reactions to OLPs were more mixed, nearly all agreed they would take an OLP if it were prescribed as an adjunct to active medication. (2, p10)
	Double blind placebo	8, 9, 14	Dilemma of how to maintain rigorous methodology when participants know they're receiving a placebo in open-label studies.	Importantly, all these trials are characterized by the lack of blinding that can be achieved by comparing open placebos vs. hidden placebos and the comparison with the best available treatment to estimate the relevance of open placebo potential effectiveness. (8, p222)
	OLP efficacy not clear	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 16, 17	Uncertainty about consistent, measurable benefits, with many calling for additional data and larger trials.	We strongly suggest future studies should focus on providing solid evidence for the effectiveness of OLP before clinical use can be considered. Our study identified the importance to patients of establishing clinical effectiveness of placebo interventions. To date, the small number of studies, their heterogeneity and the risk of bias calls for caution when drawing conclusions on efficacy, (9, p287)
	Future work needed	1, 4, 5, 6, 7, 8, 9, 11, 12, 16	Emphasizes the embryonic stage of OLP research, calling for more rigorous and/or large-scale investigations.	Future large scale, pragmatic randomized trials should investigate the potential of open-label and dose-extending placebos to improve outcomes and reduce side effects (8, p235)
	Legal aspects	3, 4	Concerns about regulatory or malpractice issues when prescribing an inert substance, e.g., liability or fraud accusations.	Two physicians flagged potential legal issues as a barrier to prescribing OLPs: Somebody starts freelancing with this, the first few people that start doing it, and there's one bad outcome... I occasional[ly] serve [as a] witness for legal cases. I could just see what the opposing attorney would do. They gave the patient what? (3, p608)
	Logistics	3, 7, 8, 9, 17	Practical barriers, including prescribing format, availability, cost coverage, and documentation requirements.	Participants were unsure of how OLP prescribing might look different from prescribing other medications. Some expressed the view that OLPs could be treated like any other prescription medication, whereas others felt additional information may need to be provided to either the provider (e.g., specific training) or the patient (e.g., package insert) before prescribing could be possible. (7, p762)
	OLP by proxy	10, 11	In pediatric contexts, parents' attitudes can greatly shape children's placebo responses and raise unique ethical concerns.	Evidence related to “placebo by proxy” supports this extension, demonstrating, perhaps unsurprisingly, that sometimes placebo effects in children may be mediated more by their parents than by their doctor. (10, p5)
	Costs of OLP	2, 7, 14	Ethical question of whether patients should bear any financial cost for an inert substance, and broader economic implications of widespread OLP use.	Patients were not happy to pay a prescription charge for what they saw as an inert pill (14, p7)
	OLP rationale	7, 8, 9, 11	Considers the scripts or reasoning provided to patients about why an OLP might help.	Third, the positive suggestions often delivered alongside open-label placebos could involve an element of deception, depending on their wording.(8, p234)
	Replace drug by OLP	2, 9, 11	Weighs the possibility—and risks—of fully discontinuing active medication in favor of OLP for certain conditions, demanding strong evidence of efficacy.	On the other hand, OLPs could be applied as a treatment alternative to the use of ADs. In this case, OLPs could either replace ADs completely (i.e., children and their parents aim for the total withdrawal of ADs) or could be the primary choice of treatment from the beginning (i.e., children and their parents aim to use OLPs instead of ADs in the first instance). (11, p2)
	Continued			

Theme	Code	Publications	Explanation	Example quote
Informed consent	Ambiguity	1, 6, 7	Partial or vague disclosure that may undermine true informed consent.	Some who were open to offering placebos to patients stated that they would use language like, 'here's something you could try' and 'let's see if it works' when offering the placebos. This kind of vague language avoids making false claims about the placebo treatment—that is, the physician does not use the word 'medication'. Nonetheless, when physicians use these vague phrases, patients might reasonably assume that they are being offered a medication with an active ingredient known to be effective for their condition. Thus, this vague language may cause patients to have false beliefs about what they're taking, and is arguably deceptive.(7, p761)
	Clinician OLP literacy	5, 7, 8, 9, 11	Importance of educating practitioners about the rationale, communication strategies, and ethical nuances of OLP.	Our findings, while preliminary, suggest that wider adoption of OLPs will require physicians to be trained in their use (7, p762)
	Consistent with IC values	5, 7, 13, 16, 17	Addresses how OLP use can align with or uphold autonomy, honesty, and trust—core values in informed consent—when presented transparently with proper disclosure.	Importantly, in this scenario full informed consent can be obtained and the physician continues to foster patient trust. (13, p184)
	OLP definition	3, 9, 15	Challenge of articulating a precise definition to ensure patients know they're receiving a non-active treatment.	If more recent debates now primarily revolve around entirely different triggers of expectations for improvement—such as communication, empathy, and other so-called contextual factors—they should conceptually be distinguished from that original model. Otherwise, depending on the perspective, there is a risk of losing sight of its specific problem of deception or, conversely, projecting critically onto the other contexts. (15, p686) <sup>a</sup>
	OLP disclosure	1, 2, 5, 7, 9, 11, 15	Focuses on the type and depth of information shared with patients about OLP's.	In order to evaluate whether the disclosures made in open-label placebo studies would be ethically acceptable in clinical encounters, we first need to know what is divulged to participants in the open-label studies. Clearly, disclosures and informed consent in clinical trials must be subject to different moral evaluations from those disclosures that occur in clinical contexts.(5, p5)
	Influence decision-making	1, 11	How the presentation of OLPs can affect patient choices, healthcare-seeking behavior, and adherence.	For example, it may be that consenting to open-label placebos independently influences how patients understand their illness and symptoms, and that this (in turn) may influence medication-seeking behaviour and attendance at the doctor. (5, p10)
	Not understanding consent	7, 8, 11	Argues that OLP use requires a targeted, open disclosure process respecting autonomy while avoiding undue persuasion.	Participants also raised concerns that patients would not comprehend what an OLP is, particularly if there was not consistent messaging and understanding among care team members. (7, p762)
	Right to 'not know'	13	Explores whether patients can choose not to have full transparency about their treatment. Some argue forced disclosure can remove the 'ignorance is bliss' benefit or override patient preference to remain partially uninformed.	Without being asked they are deprived of the right to "not know" or "know less" and consequently enjoy the benefits of a safe and possibly useful treatment for depression. (13, p186)
Continued				

Theme	Code	Publications	Explanation	Example quote
Patient health behaviour and dynamics	Expectations	5, 9, 11	Highlights how patients' prior beliefs and hopes for improvement influence their openness to an OLP.	Our results found acceptability of both types of placebo treatments was dependent on the perception patients had about the treatment solving their problem as well as the doubts they had regarding the effectiveness of placebo treatments (9, p285)
	Harms vs. benefits	3, 7, 9, 13, 15	Tension between possible symptomatic relief and concerns about neglecting effective medical interventions.	For widespread use of OLPs to actually catch on, physicians will need to have familiarity and comfort with them, and perceive them to have a favourable risk/benefit ratio. (7, p762)
	Influence help-seeking	5, 6, 16	Considers how prescribing OLPs might alter people's subsequent behavior in seeking medical advice—either eroding trust in conventional care or wrongly legitimizing unproven alternative methods.	Third, and relatedly, it is unknown how OLPs influence help-seeking. It is conceivable, for example, that as a result of being prescribed placebos, some patients may lose faith in mainstream medicine; others may erroneously believe that placebos legitimise complementary and alternative treatments. (6, p703)
	Nocebo effects	2, 3, 8, 9, 17	Risk that negative expectations can cause or worsen symptoms, complicating ethical justification for OLP usage.	(...) raising concerns about the potential for unknown risks or “nocebo effects,” whereby the expectation of an adverse effect by patients precipitates or exacerbates the experience of that symptom. (17, p2)
	Overestimating positive effects	2, 5, 7, 10, 11,	Warns against overstating placebo/OLP power. Patients or clinicians might assume greater benefits than evidence supports, risking neglect of essential or more effective treatments.	While there is a significant amount of research yet to be done that will better allow us to demarcate the boundaries of placebo potential, it is important to be as honest as possible at this point about what placebo responses can and cannot do for people. (10, p6)
	Overprescription drugs	17	Concern that OLPs might entrench a culture of “a pill for everything,” even if it's a non-active medication.	It is possible, for example, that the widespread use of placebos would intensify the widely held expectation of “treatments” for every symptom, potentially exacerbating the problem of inappropriate overprescription of other medications. (17, p2)
	Structural injustice	16	Fear that OLPs could widen healthcare inequities if marginalized populations receive them in place of full treatment.	As argued above, the assumptions that physicians make about when patients are giving reliable testimony can be grounded in biases and power imbalances between social groups. When OLPs are then investigated with a majority of participants from social groups that have been historically disbelieved and devalued and for conditions that affect those social groups primarily, this runs the risk of reinforcing these imbalances, even if they are not explicitly grounded in assumptions about social worth. (16, p5)
Continued				

Theme	Code	Publications	Explanation	Example quote
Therapeutic relationship		2, 3, 10, 14, 15	Focuses on how OLPs could affect trust, rapport, and communication dynamics between patient and clinician, including risks of paternalism or misunderstanding when discussing an inert treatment.	In a context where the explosive growth of medical expertise, the proliferation of multilingual medical jargon, and patients' increasing demands for healthcare services are uniting doctors as members of an overwhelmed community, their unconscious and unintended isolation from patients is not an unusual group psychological phenomenon. Combating this isolation might be a prerequisite for the implementation of effective placebo-based patient communication. (15, p689) <sup>b</sup>
	Agency	3, 9, 10, 11	How OLPs can either bolster or undermine patient self-determination, depending on disclosure and framing.	The first implication is that recognizing the role of agency in placebo effects takes us beyond the clinical context and requires us to see the potential for promoting placebo effects in several other realms. Rather than thinking only of the question of whether doctors should lie to patients for their medical benefit, examining the mechanisms underlying placebos and how they can promote agency reveals the significant role that placebo effects play in many domains of our lives (10, p5)
	Autonomy	7, 9, 10, 14, 17	Ensuring patients freely choose OLP use with full awareness of what it entails.	(...) some patients feel it is important for any placebogenic practice to respect patient autonomy. (14, p7)
	Deception	1, 5, 8, 15	Potential moral challenge if "transparent" placebos are still perceived as deceptive or manipulative in how they are presented.	However, it's important to note that deception begins when intentionally false hopes are raised, prognoses are embellished, or risks are downplayed. Particularly when it involves imprecisely formulated and ambiguous messages (often with good reason) rather than hard prognostic data, the temptation for doctors to want to foster more positive expectations than what is objectively justified may be strong. Yet, even though the line between justified and exaggerated confidence is notoriously blurry, deception is difficult to control in this context, and optimistic disclosure is emotionally more pleasing for both parties than pessimistic disclosure, placebo-based approaches must still operate within the bounds of truthfulness. (15, p688) <sup>c</sup>
	Blame	6, 9, 10, 11, 14, 17	Raises questions about culpability for treatment outcomes when the therapy is inherently inert.	Second, the long-term health impact of using OLPs among different patient groups is unknown. Some patients, especially those for whom placebo effects carry the most potential, may self-stigmatise or feel guilt, perhaps by diminishing the medical importance of their symptoms as being 'all in their heads'. This risk may be most acute among vulnerable patients, such as those who have pain, depression or medically unexplained symptoms, and for whom practitioners may consider OLPs a possible intervention, particularly if other treatment options have failed (6, p703)
	Paternalism	15, 16	Danger that clinicians override patient preferences by prescribing an OLP assuming they "know best."	(...) when researchers believe that some patients' experiences can be studied through a psychogenic mechanism such as a placebo rather than a physiological 'little blue pill', they act paternalistically, even if participants in these studies have given consent. (16, p5)
	Responsibility	10	Unclear who bears ethical/legal responsibility for outcomes when prescribing non-active treatments.	Looking beyond the white walls and white coat leads to difficult ethical questions related to what falls within the bounds of medicine and what the responsibilities of health-care professionals might be in relation to placebo responses that take place outside of their territory. If it is the case that many factors that may influence placebo responses are outside of the health-care system, is there a responsibility to communicate with patients about these influences within the process of informed consent? If so, what should they be told? (10, p5)
	Trust	5, 9, 12, 13, 14, 17	Key concern that OLP might undermine trust to physicians for several reasons, for example patients might feel they are not being taken seriously.	Finally, it is possible that the prescription of placebo treatments could damage trust in physicians, particularly if carelessly implemented (17, p2)

**Table 4.** Themes, codes, Article numbers and example quotes.

without forfeiting their right to fully informed consent or the benefits of a safe and transparent patient-clinician relationship (Publication: 13). In synthesizing these insights, it becomes evident that informed consent for OLPs is a multifaceted issue that intersects with ethical, communicative, and educational domains, each demanding careful attention to uphold the integrity of patient care and the ethical standards of clinical practice.

### Patient health behaviour and dynamics

In the sphere of patient health behaviour and dynamics, this theme presents a multifaceted view informed by patient expectations and the perceived harms versus benefits of OLPs. Expectations play a crucial role in the acceptability of placebo treatments, with outcomes depending greatly on how patients anticipate the effectiveness of treatment (Publications: 5, 9, 11). Physicians need to carefully evaluate harm vs. benefits (Publications: 3, 7, 9, 13, 15). The potential influence of OLPs on healthcare-seeking behaviour is complex. On the one hand, they can empower patients, providing a sense of control and comfort. Yet, there are once more concerns that by being prescribed placebos, some patients may lose faith in mainstream medicine, erroneously believing that placebos legitimize complementary and alternative treatments, which influences help-seeking behaviour (Publications: 5, 6, 16).

The phenomenon of nocebo effects—where an inactive substance causes negative outcomes—is also a significant concern. This includes the potential for unknown risks or 'nocebo effects,' where the expectation of an adverse effect by patients precipitates or exacerbates the experience of that symptom (Publications: 2, 3, 8, 9, 17). Moreover, there is the issue of overestimating the positive effects of OLPs. While considerable research remains to be done, there is a need for honesty about the current understanding of the boundaries of placebo

Number	Study Ref.	Title	Study design	Sample size	Population	Aim/content
1	Annoni (2016) <sup>31</sup>	Placebo effects and the ethics of therapeutic communication: a pragmatic perspective	Conceptual	N/A	N/A	In this article we explore the ethics of manipulating verbal information for the sake of influencing health outcomes through placebo and nocebo responses.
2	Bernstein (2021) <sup>27</sup>	Treating pain with open-label placebos: a qualitative study with post-surgical pain patients	Interviews	11	(Wrist surgery) Patients	This qualitative study examines how hand surgery patients view OLPs, which are placebos described honestly as inactive pills.
3	Bernstein (2020) <sup>32</sup>	Primary care providers' use of and attitudes towards placebos: An exploratory focus group study with US physicians.	Focus groups	15	US Physicians	Examine how primary care physicians define placebo concepts, use placebos in clinical practice, and view open-label placebos (OLPs).
4	Bernstein (2021b) <sup>33</sup>	How orthopedic surgeons view open label placebo pills: Ethical and effective, but opposed to personal use	Online survey	687	US Orthopedic Surgeons	To examine attitudes of Open Label Placebos (OLP) among a national sample of US orthopedic surgeons.
5	Blease (2016) <sup>1</sup>	Are open-label placebos ethical? informed consent and ethical equivocations.	Conceptual	N/A	N/A	In this article we focus on the content of disclosures in distinctive open-label, transparently disclosed placebo studies and inquire whether they might be said to invoke deception in clinical contexts, and if so, whether the deception is unethical.
6	Blease (2019) <sup>34</sup>	The role of placebos in family medicine: Implications of evidence and ethics for general practitioners	Conceptual	N/A	N/A	The aim of this article is to synthesise state-of-the-art scientific and bioethical research to provide up-to-date recommendations on placebo use for general practitioners.
7	Bliamptis (2021) <sup>35</sup>	Physician perspectives on placebo ethics.	Focus Groups	14	US Physicians	Focus groups to explore physician attitudes about clinical use of placebos, including non-disclosed and OLPs, and physician attitudes about the underlying ethical issues.
8	Colloca (2018) <sup>36</sup>	Placebos without deception: outcomes, mechanisms, and ethics	Conceptual	N/A	N/A	We present the state-of-the-art evidence and ethical considerations about open-label and dose-extending placebos, discussing the perspective of giving placebos with a rational, as dose extension of active drugs, or expectancy boosters.
9	Druart (2023) <sup>37</sup>	'It's not my greengrocer, it's someone from the medical profession': A qualitative study regarding acceptability of deceptive and open-label placebo prescribing in France	Interviews	8	Healthy Participants	Explore participants' views regarding clinical use of deceptive placebo (DP) and open-label placebo (OLP) treatments.
10	Friesen (2019) <sup>38</sup>	Placebos as a source of agency: evidence and implications	Conceptual	N/A	N/A	This paper is looking beyond the paradigmatic clinical encounter involving deceptive placebos and towards many other routes that bring about placebo effects.
11	Locher (2019) <sup>39</sup>	Placebos are part of the solution, not the problem. An exemplification of the case of antidepressants in pediatric chronic pain conditions.	Conceptual	N/A	N/A	Investigating on the use of OLP or its underlying processes in the treatment of chronic pain conditions in children and adolescents.
12	Mundt (2017) <sup>40</sup>	A comparison of deceptive and non-deceptive placebo analgesia: efficacy and ethical consequences.	Randomised Controlled Trial	75	Healthy Adults	This study aimed to investigate the consequences of deceptive placebo analgesia in terms of ethical/psychological effects and efficacy.
13	Nitzan (2014) <sup>41</sup>	Using placebo medications in the clinical setting - an intellectual game or a possible reality?	Conceptual	N/A	N/A	We discuss whether placebo treatments can be ethically used in clinical practice as an alternative to standard therapy, and propose an innovative conceptualization of the factors involved in the exclusion of placebo treatments from the clinical setting.
14	Ratnapalan (2020) <sup>42</sup>	Placebos in primary care? a nominal group study explicating UK GP and patient views of six theoretically plausible models of placebo practice	Nominal Group Technique	41	GPs&Patients	To better understand which theoretically plausible placebo techniques might be acceptable in UK primary care.
15	Schone-Seifert (2020) <sup>43</sup>	Placebos and placeboids in clinical practice: conceptual and ethical considerations	Conceptual	N/A	N/A	Reflecting on results of recent placebo research, this article analyzes relevant key concepts and ethical positions.
16	Specker Sullivan (2020) <sup>44</sup>	More than consent for ethical open-label placebo research	Conceptual	N/A	N/A	With research into placebo effects in particular, this author argues that the history of clinical placebo use grounds special considerations for OLP research that go beyond respect for the autonomy of individual patients through informed consent and encompass structural concerns about the type of patient for whom a placebo has historically been thought appropriate.
17	Trogen (2017) <sup>36</sup>	The Ethics of Open-Label Placebos in Pediatrics.	Conceptual	N/A	N/A	Perspective to suggest a possible limited role for open-label placebos in pediatric clinical practice.

**Table 3.** Overview and basic information on included articles. The column on the far-right comprises quotations from the referenced manuscript.

potential and the realistic communication of what placebo responses can and cannot do for people (Publications: 2, 5, 7, 10, 11). Overprescription of drugs is a concern tied closely to the use of OLPs. The widespread use of placebos could intensify the already prevalent expectation for treatments for every symptom, potentially leading to an overreliance on medication in general, which may crowd out other forms of care or lead to the devaluation of non-pharmacological treatments and to overprescription of drugs (Publication: 17). Lastly, the issue of structural injustice was addressed. Assumptions made about patients when they are giving testimony can be rooted in biases and power imbalances between social groups. When OLPs are integrated within minority

or participant groups that have been historically disbelieved or devalued, there is a risk that this might reinforce social disparities. This runs the risk of exacerbating these imbalances (Publication: 16).

### Therapeutic relationship

The dynamics within the therapeutic relationship are critically reflected upon within this theme. In environments where medical expertise is rapidly expanding and the lexicon becoming ever more specialized, the relationship between healthcare providers and patients is strained, with the latter often feeling overwhelmed and isolated (Publications: 2, 3, 10, 14, 15). Agency, particularly in the context of OLPs, is emphasized as a key component of the therapeutic relationship. It is recognized that the role of agency in placebo effects is complex and traverses the clinical context, necessitating a broader view of potential for promoting placebo effects in various domains. This involves understanding the underlying mechanisms of how they can promote agency and benefit patient outcomes (Publications: 3, 9, 10, 11). Additionally, the concept of autonomy within the therapeutic relationship is underscored, highlighting the importance of patient autonomy in any placebo-centric practice. The review suggests that autonomy plays a critical role in domains far beyond the immediate clinical encounter (Publications: 7, 9, 10, 14, 17).

Deception is a contentious issue that can include offering false hope, the downplaying of risks and ambiguously formulated messages that may foster more positive expectations than the evidence justifies. The fine line between justified optimism and exaggerated confidence presents a moral dilemma, where placebo-based approaches must operate within the bounds of truthfulness (Publications: 1, 5, 8, 15).

The impact of OLPs on long-term health outcomes and the potential for blame was discussed, acknowledging the uncertainty about how different patient groups may internalize the use of OLPs. There is a risk that patients, especially those with medically unexplained symptoms, may internalize blame, which could be mitigated by how practitioners frame the use of OLPs (Publications: 6, 9, 10, 11, 14, 17). Paternalism in the therapeutic relationship was also critiqued, particularly when researchers assume a psychogenic mechanism for patients' experiences, leading to the use of placebos rather than a conventional pill, potentially even without the patients' full understanding or consent (Publications: 15, 16). Responsibility in prescribing OLPs is highlighted, posing the question of the ethical considerations that fall within the bounds of medicine and what is considered difficult care. The necessity for clear communication about the influences on placebo responses is emphasized, especially regarding informed consent processes (Publication: 10). Lastly, trust is identified as a cornerstone of the therapeutic relationship, with concerns that the prescription of placebo treatments could undermine trust in physicians, particularly if there is a perceived imbalance in the relationship (Publications: 5, 9, 12, 13, 14, 17).

### Discussion

To our knowledge, this is the first systematic qualitative review of the full range of ethical issues discussed in the OLP literature. As can be seen in the PRISMA-Flowchart, we excluded articles that mention ethical issues surrounding OLPs but do not reflect on them. Those excluded fifty-four papers mainly mention deception as the primary or sole ethical issue with "traditional" placebo but then argue that there is no ethical concern with OLP due to the lack of deception<sup>6</sup>. However, as we have uncovered through this comprehensive analysis, there are several ethical issues that have been raised surrounding OLPs. Since, ideally, research leads to policy and implementation, it is important that researchers and ethicists grapple with these concerns as the ethical considerations associated with OLPs may not be alleviated by the mere absence of deception. On the contrary, the ethical considerations of OLP in medical practice are multifaceted, encompassing patient choices, the role of CAM, transparent communication, logistical challenges, and the complex dynamics of therapeutic relationships. Careful consideration and responsible communication are imperative to navigate these complexities and ensure the ethical and effective incorporation of OLPs in healthcare.

We did do an analysis of the most occurring codes and several articles stated that it is pivotal to further demonstrate the efficacy of OLPs as the widespread adoption of OLPs hinges on the confirmation of their effectiveness. We decided to put these results into the discussion section due to the echo-chamber concerns (explained below). i.e., we rank Table 5 according to most to least different publications that mentioned the specific ethical issue). As summarized in Table 6, "OLP Efficacy Not Clear" was the most frequently mentioned code (13 of 17 articles), closely followed by "Future Work Needed" (10 of 17), "Dose Extending OLP" (9 of 17), and "Acceptability" (9 of 17). Notably, these four most frequent codes all fall under the Implementation and Logistics theme, making it the most widely discussed theme across the included literature.

Whilst (concealed) placebos have been a topic of investigation for many decades, OLPs have emerged only in recent years and are still relatively unknown. Hence the codes that appeared the most in this review are not surprising (OLP efficacy not clear & more research needed). There has been one review and meta-analysis that pointed to the efficacy of OLPs in certain conditions compared to no-treatment<sup>23,73</sup>. This review found a

Theme > code	How many articles mentioned this issue
Implementation and logistics > OLP efficacy not clear	13
Implementation and logistics > future work needed	10
Implementation and logistics > dose extending OLP	9
Implementation and logistics > acceptability	9
Informed consent > OLP disclosure	7

**Table 5.** Binary occurrence of most occurred codes in the seventeen articles.

Area	Topic
Research focus and state of the field	Relative Infancy of OLP Field: The field is described as being in relative infancy, emphasizing the need for more studies to support effectiveness before considering clinical use.
Research methodology and scope	Need for Larger Studies: Emphasis on the necessity for larger, more comprehensive studies to confirm the clinical effectiveness of OLPs.
Physician perspectives and involvement	Physician Attitudes and Barriers: Exploration of physician barriers to clinical use of OLPs and understanding their attitudes toward prescribing.
Education and integration	Training for Prescribing OLPs: Recognition that physicians may need additional training and evidence before feeling equipped to prescribe OLPs. Exploration of what this training could entail. Integration into Medical Education: Suggestion to integrate information about OLPs into medical education, potentially through pain management curricula or instructional videos. Consideration of implementation strategies.
Ethical considerations	Ethical Considerations: Emphasis on determining lay understanding of OLPs and ensuring their ethical deployment.
Mechanisms of action and further investigation	Role of Embodied Condition: Call for further research to investigate the role of embodied condition in explaining how OLPs work. Comparison with Undisclosed Placebos: Physician desire for comparisons of OLPs and undisclosed placebos in clinical trials. Dose Extending Placebos: Suggestions for studying dose extending placebos in clinical trials with specific methodological considerations.
Variability in OLP forms and effects	Exploration of Different Forms of OLPs: Suggestion to explore various forms of OLPs (topical creams, injections) and assess their effectiveness compared to traditional pills. Long Term Effects of OLPs: Call for studies examining the long-term effects of OLPs, with consideration for robust control groups to understand contributing factors.
Patient centric considerations	Importance to Patients: Emphasis on the importance to patients of establishing the clinical effectiveness of placebo interventions.
Age specific considerations	Focus on Children and Adolescents: Recognition of the need for future research to study OLP in children and adolescents with chronic pain conditions.

**Table 6.** Suggested topics for future research.

significant overall effect favouring OLPs but also points out that the research is in its infancy and more work is needed. The prevailing scientific consensus is evident in our own analysis, which explicitly states that, despite the promising nature of the approach, it is too early for the clinical implementation of OLPs.

When we examined the articles included in this review, we noticed that there is a lack of author heterogeneity within the papers discussing OLPs highlighting a potential limitation in the breadth and diversity of perspectives being presented. The frequent recurrence of a limited group of scholars across multiple articles within our dataset suggests a risk of an echo chamber<sup>74</sup>, where the repetition of specific ethical considerations by the same authors could inadvertently create the illusion of a broader consensus, when it is in fact reflective of a single group's viewpoint. In our opinion, this observation underscores the critical need for broadening the field to include a wider range of voices and perspectives, thereby enriching the ethical discourse surrounding OLPs and ensuring a more balanced and inclusive exploration of their potential and limitations.

Also, it is noteworthy that in another high occurring code in the reviewed articles many discussions revolved around implementing OLPs in form of a dose extension rather than a complete replacement of an active medication. Further research into dose extension via OLPs and possible reduction of active medication as well as minimization of side-effects of active ingredients is indicated which is an important step towards possible implementation of OLPs. Research thus far has been promising as some studies have observed OLPs can reduce prescription pain medication<sup>75</sup>. Moreover, Kirchof and colleagues found that open placebos paired with a conditioned stimulus could have a positive immunological function<sup>76</sup>.

The most controversial issue in our eyes is the role of CAM, which has also been brought up prominently by Fabrizio Benedetti in his talk at the fourth international conference of the society of interdisciplinary placebo studies (SIPS 2023): "Today many quacks say their bizarre interventions work because of a placebo effect, thus they justify them. Paradoxically, research on placebo effects supports this assertion. What can we do to avoid this worrisome tendency?"<sup>77</sup>. As per today, no such investigation has been undertaken.

### Limitations

Abstract screening was performed by a single reviewer, which, despite careful adherence to predefined criteria, might have introduced unintended selection bias or oversight. Future research involving multiple reviewers could strengthen the robustness of the selection process. Additionally, variations in coding practices or differing research foci across studies included in this review could influence the identification and interpretation of ethical issues. Furthermore, it is important to recognize that ethical issues identified here may not universally apply across different healthcare settings, patient populations, and cultural contexts, highlighting opportunities for further investigation and contextual validation. Finally, potential language bias should be acknowledged, as we only included English and German papers.

### Outlook

The current outlook suggests a multifaceted research agenda that addresses the complexities of OLPs through an interdisciplinary lens, blending scientific inquiry with ethical considerations and patient-centred approaches. The first step on this path is a concerted effort to expand the evidence base through larger, more comprehensive studies that can verify the effectiveness and safety of OLPs across various conditions. These studies must be designed to not only test efficacy in a controlled environment but also to understand the real-world implications of prescribing OLPs in routine clinical practice. Understanding the mechanisms through which OLPs exert their effects remains an important objective. This includes further biological research to unravel the neurobiological pathways involved, as well as psychological research to explore the role of patient expectations, the therapeutic relationship, and the power of suggestion. As the body of evidence grows, there could be a shift towards the

integration of OLPs into clinical practice, necessitating robust physician education programs. These programs should focus on when and how to effectively prescribe OLPs, manage patient expectations, and navigate the complex ethical terrain that surrounds their use.

The code “Future Work Needed” emerged among the top four in Table 5, reflecting a strong consensus that further investigation is required. Table 6 distils the recommendations from these segments, encompassing:

- **Calls for Larger Studies:** Multiple authors advocate for robust clinical trials to ascertain OLP efficacy and guide best practices.
- **Mechanisms of Action:** Future research could delve deeper into how embodiment, conditioning, and expectancy influence OLP outcomes.
- **Physician Training:** Many publications suggest integrating OLP education into medical curricula, with emphasis on communication strategies and ethical considerations.

Such recommendations align with the high frequency of codes like “OLP Efficacy Not Clear” and “Dose Extending OLP,” indicating that while the potential of OLPs is compelling, the scholars have argued it is still in its early stages and requires more empirical substantiation.

The ethical dimension of OLP research will continue to be a critical area of focus. Future research must ensure that the use of OLPs adheres to the highest standards of patient consent and autonomy, with clear communication strategies developed to inform patients about the nature of OLPs and their potential benefits and limitations. With the rise of personalized medicine, the tailoring of OLP interventions to individual patient profiles could enhance therapeutic outcomes<sup>78</sup>. This precision approach would consider genetic, environmental, and lifestyle factors that may influence the effectiveness of OLPs. In paediatric and geriatric populations, where OLP research is particularly sparse, future studies should strive to fill this gap, considering the specific ethical, physiological, and psychological considerations that are unique to these age groups. The potential for OLPs to reduce reliance on pharmacological treatments, especially in the context of chronic pain management and psychological disorders, is another promising avenue for exploration. This could have significant implications for public health, offering a cost-effective and low-risk alternative to long-term medication use.

## Data availability

All data generated or analysed during this study are included in this published article.

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## Author contributions

M.R. planning, writing manuscript, PRISMA, coding. M.B double coding, editing, and revising manuscript. J.G. editing, B.E. planning, editing, and revising manuscript.

## Declarations

## Competing interests

The authors declare no competing interests.

## Ethical approval and informed consent

This article does not contain any studies with human participants performed by any of the authors.

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