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Methodological considerations for designing and conducting open-label placebo trials

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Abstract

In pain and other research fields, placebos have traditionally been associated with deception, although harnessing placebo effects does not necessarily require deception. Open-label placebos (OLPs) represent a novel approach in which inert treatments are administered openly and transparently, allowing patients to knowingly receive an inert treatment while still experiencing therapeutic benefits (eg, pain relief). As OLP research grows, concerns have been raised regarding methodological rigor and the unique challenges posed by unblinded designs in both experimental and clinical contexts. Given the inherent transparency regarding treatment group allocation in OLP trials, particular attention is needed when defining appropriate control groups, implementing feasible blinding strategies, and providing a treatment rationale to adequately explain OLPs. Addressing these challenges is crucial to advancing both the scientific understanding of the psychoneurobiological mechanisms underlying OLP effects and their clinical relevance in pain. In this review, we outline key methodological considerations for designing and conducting OLP studies in pain research and beyond, providing guidance on control group selection, blinding strategies, and reporting standards. In addition, we integrate insights from the patient advisory board of the transregional Collaborative Research Center (CRC/TRR) 289 "Treatment Expectation" to incorporate patient perspectives on the feasibility and acceptability of OLPs. Aligning study designs with patient needs and expectations may foster a more meaningful, patient-centered approach to OLP research. By combining methodological guidance and emphasizing patient-centered insights, this review aims to enhance the quality, relevance, and clinical translation of OLP research in pain.

Keywords: Expectation, Nocebo, Methods, Patient-centered

1. Introduction

Placebos, once regarded solely as inert controls, are now understood to engage complex psychoneurobiological mechanisms that modulate symptom perception, with pain representing one of the most responsive clinical domains.[13,22,49,95] Indeed, numerous behavioral and neuroimaging studies have demonstrated that placebo-induced expectations can powerfully alter subjective pain experiences across both acute and chronic conditions.[15,85] While the clinical use of placebos is constrained by ethical concerns surrounding deception, open-label placebos (OLPs) address this dilemma by demonstrating that symptom improvement can occur despite full disclosure.[19,49]

Randomized controlled trials (RCTs) increasingly suggest that OLPs can elicit meaningful symptom relief across diverse conditions, including major depressive disorder, chronic low back pain, and irritable bowel syndrome.[30,76,78,137] For example,

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a recent meta-analysis covering 60 RCTs found moderate, statistically significant OLP effects across different populations and outcomes, with pain emerging as a highly responsive domain.[48] However, other results from the area of experimental pain and in healthy participants remain heterogeneous, including some null observations.[27,48,129] These findings underscore the urgent need for rigorous, transparent, and standardized research designs to identify the conditions under which OLPs prove beneficial and to define their boundary conditions.

The mechanisms underlying OLP efficacy remain far from being understood. Some of the proposed mechanisms engage processes that overlap with those of deceptive placebos—including classical conditioning, associative learning, and contextual cues,[12,14,29] as well as prior treatment expectations.[27,55] Several neuroimaging studies have demonstrated that OLPs can evoke responses in brain areas and neurotransmitters involved in pain perception and modulation.[4,14,81] Patient-provider interaction and communication represent a further potential dimension: full disclosure respects patient autonomy and may in itself enhance therapeutic outcomes.[137] Moreover, OLP outcomes can depend on the patient's active engagement and cognitive flexibility in reconciling the paradox of perceived symptom changes while knowingly taking an inert substance (eg, prediction errors).[6]

Previous critiques have raised important concerns about the methodological foundations and clinical relevance of OLP research,[2,74] highlighting the risk of conflating the placebo response (any observed outcome in a placebo group) with the placebo effect (the specific contribution of the placebo itself, beyond the natural course of illness and other control group effects). Other challenges include a lack of blinding, as well as diminutive sample sizes that may compromise both internal (eg, causal inference) and external validity (eg, generalizability).[17,19] These issues mirror the wider discord between trials tailored to meet rigorous scientific standards and trials developed with pragmatic, real-world relevance in mind.

Although methodological quality has repeatedly been identified as a central challenge in OLP research, available recommendations remain selective and dispersed. Existing work has addressed individual issues, including control group selection and intervention components,[18,21,34,43] but other key aspects, such as assessing potential moderators, accounting for nocebo effects and adverse events, and designing adequate follow-up measurements, remain insufficiently defined. Therefore, the present review synthesizes existing methodological suggestions and adds further considerations to provide a concrete and comprehensive, structured framework for designing, conducting, and reporting of OLP studies in pain research. Our goal is to strengthen the reliability and transparency of future (open-label) placebo research, by providing theoretical and empirical recommendations to improve its methodological quality and comparability.

Beyond methodology, there are concerns about the potential to mislead or stigmatize patients with chronic illnesses due to an implicit suggestion that their condition lacks sufficient legitimacy or severity,[93] underscoring the urgent need to involve patient perspectives in study conceptualization at an early stage.[63] To ensure that our scientific recommendations align with the perspective of individuals with lived experience while retaining clinical relevance, we collaborated with the Patient Advisory Board (PAB) of the transregional Collaborative Research Center (CRC/TRR) 289 "Treatment Expectation", funded by the German Research Foundation (DFG). The PAB involves individuals with personal experience of different treatments and with different research projects, with the aim of boosting relevance and strengthening the link between research and clinical care.[109] The PAB input directly shaped several methodological considerations presented here.

In sum, this article outlines evidence-guided, practical, patient-informed, and ethically grounded methodological recommendations to enhance the quality, relevance, and interpretability of future OLP studies. While not derived from a formal consensus process, our insights seek to catalyze further dialogue in the field and foster clinically meaningful OLP research. In the following, we (1) systematically identify key methodological features of OLP study designs, (2) discuss how these features may influence study outcomes and their interpretation, and (3) provide practical recommendations for future OLP research, informed by direct input from potential OLP study participants.

2. Planning open-label placebo studies

2.1. Selecting a study population

Open-label placebos can be administered to both clinical (eg, patients with chronic pain) and nonclinical (eg, cognitive enhancement in students) populations, with results varying considerably across groups.[18,123,137] While many studies have found positive effects of OLPs in clinical populations in need of symptom relief,[27,75,137] others have reported small or no effects in healthy participants without preexisting conditions.[34,64,82,129] This disparity likely reflects floor/ceiling effects, as healthy participants would not be expected to benefit significantly from active treatments. An exception exists for (elite) athletes, who have been found to show both classical placebo effects[107] and ergogenic effects of OLPs.[116]

Another challenge lies in counteracting potential biases in participant recruitment (see also section on Recruitment). Volunteers in OLP studies tend to be younger and more highly educated, as is common in medical and psychological research as a whole.[31] Moreover, OLP participants are more often female,[137] thus potentially limiting the generalizability of study results.

Often, study participants may have a preference to be assigned to one specific treatment arm. For example, one study found no OLP effects in a healthy sample that was significantly less satisfied with their OLP group allocation compared with the control group.[64] One suggested approach to address treatment preferences is to allow participants with strong preferences to select their study condition, while randomizing only those participants without treatment preference. This approach allows for a direct assessment of treatment satisfaction effects[134] and it seems plausible that treatment adherence is higher when participants receive their preferred treatment. However, this approach has several limitations, including the violation of randomization and selection bias, which precludes its recommendation at this time.

To enhance comparability across studies, a detailed characterization of participants' demographic and psychological characteristics, health status, and medical history, especially for patient populations, is crucial. Especially psychological and cognitive differences manifesting, eg, as desire for symptom relief, expectations about the treatment, and prior treatment experiences, need to be considered and measured as possible factors modulating the response to OLPs.[129] Future work could directly test these tentative hypotheses to better understand how treatment preference and choice may support OLP effects.

Besides healthy volunteers and the clinical population, there is a third category of participants for whom OLP effects might be

beneficial: the subclinical population. Several clinical trials have recruited participants with subclinical symptoms, ie, individuals whose symptoms do not meet diagnostic criteria, with samples including students or learners facing examination-related stress or emotional distress.[25,82,117,118]

In addition, study contexts range from highly controlled laboratory settings, in which clearly defined experimental paradigms are tested, to naturalistic clinical environments addressing complex symptoms and medical conditions. Context factors, eg, treatment location, noise level, and atmosphere, may also affect participants and outcome measures.[113] Therefore, the choice of study population and their psychosocial environment should be taken into account when evaluating OLP effects.

2.2. Choosing open-label placebo characteristics

Currently, the impact of the OLP administration mode and appearance on its efficacy remains unclear.[27] While invasive and personalized placebo interventions have traditionally been assumed to yield larger effects in deceptive placebo paradigms,[61,115] a current meta-analysis does not substantiate this assumption for OLPs, likely due to limited statistical power rather than a true absence of effect.[27] Moreover, invasive routes such as injections may reduce patient acceptability. Visual characteristics (eg, color, shape) may also influence outcomes.[99] For instance, Winkler et al.[140] demonstrated that the administration of nasal sprays yielded greater benefits for depressive symptoms than did capsules, contradicting participants' pretreatment beliefs that capsules would be most beneficial. Open-label placebos that resemble familiar types of medication or that match one's information about specific treatments might be more effective than those deemed unrealistic or unpleasant. The impact of dosing frequency (eg, pill intake once vs multiple times per day) is currently unknown. Once target populations' preferences are better understood, researchers might optimize OLP characteristics to align with personal preferences and/or expectations.

2.3. Defining the open-label placebo trial type

When designing a study, it is essential to determine whether the objective is to demonstrate OLP superiority, equivalence, or noninferiority. Superiority trials compare OLPs against no treatment (NT) or treatment as usual (TAU) to evaluate efficacy. Noninferiority trials may use comparisons with, eg, deceptive placebos or established treatments, to demonstrate that OLPs are not less effective than a control condition.[5,45] Depending on the research question, OLPs can thus be administered and investigated in various designs and contexts, which then inform the type of control group discussed in the following section.

2.3.1. Open-label placebo as a stand-alone treatment

Open-label placebos are the sole intervention for a symptom or condition, allowing for an assessment of the efficacy of OLPs in isolation, without the influence of other treatments, eg, in irritable bowel syndrome.[76] This design may be applicable for conditions for which no (sufficient) other treatment exists or where patients cannot take medication or do not wish to, eg, due to unwanted side effects.

2.3.2. Open-label placebo as an add-on

Open-label placebos are given in addition to TAU, allowing researchers to examine whether adding an OLP can enhance the overall therapeutic outcome of an existing treatment regimen, be it medication or a nonpharmacological therapy. For example, in patients receiving treatment for chronic back pain, an OLP may be added to TAU.[30,83] In cases where withholding active treatment would be unethical, OLPs should only be provided as an add-on.

2.3.3. Open-label placebo as part of a pharmacological conditioning design or tapering protocol

Open-label placebos are initially paired alongside an active drug to establish a conditioned response. Over time, the dose of the active drug is reduced or entirely discontinued, leaving the OLP as the only remaining treatment.[41,114] This "special case" of the add-on design is especially well-suited to investigate conditioned placebo effects aimed at maintaining treatment benefits and preventing rebound effects during dose reduction (eg, post-surgical opioid tapering).[50]

2.4. Selecting control groups

Designing appropriate control groups for OLP studies is a unique challenge given the inherently unblinded nature of the OLP intervention. Ideally, control groups should be structurally equivalent to the OLP condition, minimizing nonspecific differences in participants' time, attention, and care provided.[11] The choice of control group is critical, as it defines the interpretation of efficacy, and the optimal choice depends on the specific research question. Recent meta-analyses indicate that OLPs often outperform NT controls, but may not differ significantly from TAU.[27,137] Although crossover designs provide within-subject controls, they introduce challenges such as order and carry-over effects.[79,100,142]

In OLP research, a variety of control conditions may be used, each with its own distinctive advantages and limitations. There is no general rule that any one control condition is inherently superior to another; rather, the optimal choice depends on the specific research question. Nevertheless, the control group critically defines the interpretation of efficacy and the mechanisms underlying OLPs. For example, some control conditions are better suited for isolating and studying specific active components of OLPs, whereas others prioritize overall feasibility, efficacy, and safety in clinical practice. Depending on the study aim, one or several of the following types of control group may be considered (**Fig. 1**).

2.4.1. Control conditions for clinical trials

2.4.1.1. No treatment

Many OLP studies have used NT control groups,[76,119] which provide a baseline for nonspecific effects such as natural disease progression and symptom fluctuation.[56] While OLPs generally outperform NT, effect sizes vary across studies, ranging from small to large in both clinical and nonclinical populations.[27,34,137] However, NT does not account for nonspecific effects such as attention, time spent with experimenters/care providers, or awareness of being closely monitored[45] (see the Hawthorne effect, **Table 1**). Furthermore, NT participants often use self-initiated coping strategies, making the condition conceptually closer to a minimal TAU group than a true absence of intervention. Critically, providing NT participants with the full OLP rationale transforms the group into an active psychological control, as the rationale itself may induce positive expectations independently of pill intake.

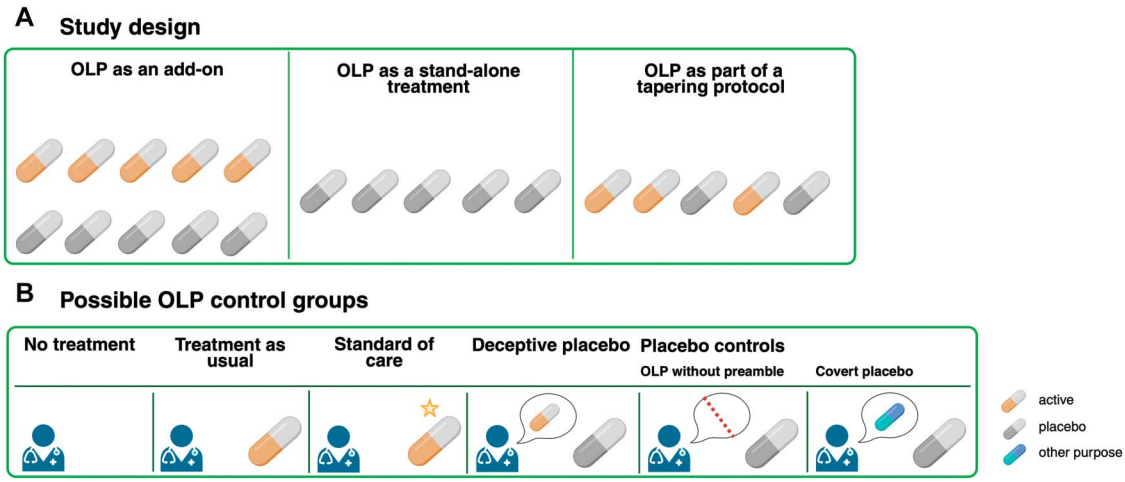

Figure 1. Illustration of designs for open-label placebo studies (A) and the control conditions (B). (A) Different OLP treatment designs: "OLP as an add-on treatment" includes both an active treatment (orange capsules) and an OLP (gray capsules); "OLP as a stand-alone treatment" shows OLPs (gray capsules) administered without any other treatment; and "OLP as part of a tapering protocol" shows the gradual replacement of the active medication with OLPs (exact design of tapering protocols may vary). (B) Possible control conditions used in OLP studies: "No treatment" represents a situation in which no intervention in given; "treatment as usual" refers to a usual treatment (represented by an orange capsule); "standard of care" refers to the optimal treatment, eg, guideline-based; in the "deceptive placebo" condition, the patient receives a placebo, which is labeled as an active treatment by the provider (represented by the orange capsule in the speech bubble and with the gray capsule being provided); in the "OLP without positive preamble" group, the OLP (gray capsule) is provided without a positive framing and explanation; and in the "covert placebo" group, a placebo is given with a distracting reason. Created in BioRender.com. OLP, open-label placebo.

The knowledge of not receiving treatment may even introduce negative effects (eg, disappointment),[76] particularly if potential OLP benefits were mentioned before group assignment (see the section on Rationale).[18,56] Withholding the rationale from NT would alter the treatment core and risk confounding prior information-related mechanisms with differences in attention or engagement. Framing NT as general symptom monitoring, without explicit comparison with an OLP group, may mitigate this issue. Many OLP trials also offer voluntary crossover to the OLP treatment group to minimize cognitive bias and disappointment.[30,83,84] Notably, waitlist control groups, which have been used in few OLP studies,[78,141] constitute a special form of NT, in which the anticipation of future treatment may influence current behavior and outcomes.[36,103]

2.4.1.2. Treatment as usual and standard of care

A TAU control group, in which participants continue their existing treatment regimen, is common in add-on OLP trials.[30,68,83,88] This design approximates real-world conditions and controls for ongoing treatment effects,[52] but can be confounded by high variability in individual treatments.[96] Moreover, TAU is often insufficiently monitored and reported, leading to potential structural inequivalence across studies.[137] Thus, each participant's treatment components should be documented in detail to ensure balanced distribution across groups, changes in TAU during participation should be registered, and preregistered study protocols should predefine how such changes will be handled.

By contrast, standard of care (SOC) uses a stricter, per-protocol, a priori defined, evidence-based treatment with or without OLP as an add-on, eg, a guideline-based treatment. Most published OLP studies have used TAU,[137] likely because OLPs are often tested in conditions in which patients remain symptomatic after SOC or in which no single SOC exists. However, in acute clinical settings or experimental trials, SOC controls might homogenize treatment and establish potential interactions on its efficacy through the addition of OLPs.[126] On the other hand, SOC (compared with TAU) might limit the generalizability of results to clinical populations. Finally, any direct comparison of an established treatment alone vs OLP alone naturally requires careful ethical evaluation, as it could be perceived as withholding effective therapeutic intervention.[38]

2.4.1.3. Deceptive placebo controls

Deceptive placebo controls, in which participants are told that they are receiving an active treatment,[40,89] allow for a direct comparison of OLP and deceptive placebo effects, especially in noninferiority trials or for the assessment of mechanistic effects. However, even if a deceptive placebo is labelled as an "active treatment," participants may not expect a benefit (eg, because its sensory properties or effects do not match prior expectations). Therefore, it is crucial to assess expected benefits and suspected group allocation at multiple time points. Because these beliefs can change over time, repeated assessments during and after the study are advisable and the potentially differential influence of expectations regarding deceptive vs open-label placebo treatments has to be considered.

2.4.2. Control conditions for mechanistic studies

To disentangle the psychological mechanisms underlying OLPs, several studies have incorporated experimental conditions that systematically modify specific components of the OLP treatment while keeping others constant (see eg, Druart et al.[42] for a recent study protocol). These designs typically vary elements such as the treatment rationale, the provider's interaction behavior, or the duration and style of the clinician–patient interaction, while keeping the basic treatment-taking ritual constant. It has been proposed that forms of control that are feasible in clinical trials, such as NT and TAU, should ideally be used in conjunction with such more mechanistically informative "placebo controls". This approach of varying specific components of the OLP treatment can only be used to a limited extent when it comes to translation and large clinical trials.

Table 1

Potential biases in open-label placebo research and suggestions for mitigating them.

Bias	Relevance for OLP	Mitigation methods
Social desirability bias: the tendency of participants to respond to questions in a manner that they believe will be viewed favorably by others rather than answering truthfully	Owing to the transparent nature of the intervention, OLP trials may be particularly prone to social desirability bias. Participants know they are receiving a placebo, which may encourage them to report improvements to align with researchers' expectations or to conform to the belief that they should experience benefits.	*Anonymity in response collection:* Ensuring anonymity in responses reduces pressure to conform to social norms and encourages honesty.[57,132] *Neutral phrasing of questions:* Using neutral language in surveys and interviews minimizes social desirability bias by avoiding leading questions.[105,136] *Training researchers to avoid leading questions:* Researchers should be trained to use open-ended questions and maintain a neutral demeanor to reduce bias.[58,86]
(Self-)Selection bias: the methods and criteria used to recruit and select participants lead to a sample that is not representative of the broader population	OLP studies are often advertised as studies on mind–body interaction or as studies on the power of placebo. Such advertisements might attract participants who are generally more open and interested in the topic and who would be more willing to believe that placebos work for them, which can result in nonrepresentative samples.	*Diverse recruitment strategies:* Use various channels, such as online platforms, community boards, patient advocacy groups, social media, and traditional media to reach a broad audience. Community engagement builds trust and encourages participation, effectively reducing recruitment bias and increasing retention.[73] *Multicenter trials:* Conduct trials across multiple centers at different geographical locations to enhance participant diversity and reduce location-specific biases. Multicenter trials improve generalizability and reduce recruitment bias.[37] *Neutral framing during recruitment:* Use neutral phrasing in advertising material to avoid attracting mainly participants interested in placebo and mind–body interaction topics. *Inclusive criteria:* Design inclusion and exclusion criteria that align with study objectives without being overly restrictive. Avoid excluding participants based solely on age or minor health conditions unless directly related to the study. Well-defined criteria can reduce recruitment bias.[54]
The Hawthorne effect: unwitting confounding of outcome variables by the study itself, eg, participants modify their behavior because they are aware of being observed (note, however, that the use of the term Hawthorne effect has been criticized; instead, referring to the specific psychological and social variables that might have affected the outcome variable is suggested)[139]	In OLP studies, participants may feel motivated to report positive outcomes because they know their responses are being closely monitored (demand characteristics). In addition, regular interactions with researchers can create a supportive environment that encourages positive reporting[97] or greater adherence.	*Minimizing visibility of monitoring activities:* Reduce the apparent intensity and frequency of monitoring to reduce participants' awareness of being observed. Use unobtrusive methods for data collection, such as passive monitoring tools, and limit the frequency of direct interactions with participants to necessary check-ins only. *Standardizing interaction levels:* Ensure that all participants receive the same amount and type of interaction with study personnel to control for any additional placebo effects that might arise from varied levels of attention. Develop a consistent protocol for personnel–participant interactions that applies equally to all participants. *Anonymized data collection:* To alleviate pressure to achieve specific results and to allow for more natural behavior, data should be collected as anonymously as possible. *Use of digital self-report tools:* Using digital self-report tools, such as apps or online platforms, can also reduce direct interaction with study personnel, which may make participants feel less observed and more inclined to provide authentic responses. However, because the usage of digital apps might exclude older patients or those with impairments, relying on these methods may promote selection biases.[131]

(*continued on next page*)

Table 1 (*continued*)

Bias	Relevance for OLP	Mitigation methods
The Rosenthal effect: a bias due to the experimenter's knowledge of participants' group assignment	In OLP studies, it can be difficult to blind the person who provides the OLP to the participant. This may lead to (subconscious) changes in behavior toward participants in one or the other treatment condition.	*Use as much blinding as possible:* Although it may be difficult to blind the person providing the preamble, all other study personnel should be blinded, especially those performing the data analysis and those collecting the outcome measurements (eg, study nurses who measure blood pressure, hand out questionnaires, or perform interviews/behavioral assessments). *Different personnel for explaining OLP and providing treatment as usual:* If any active treatment is provided alongside the OLP, the treatment as usual (eg, physiotherapy or prescription of active medication) should be provided by a different person than the one explaining the OLP rationale. Train experimenters: Because the experimenter who explains the OLP rationale will most likely be unblinded, he or she could be trained to treat participants in all experimental conditions as similarly as possible. *Use of video-based instructions:* Instead of having a person explain the OLP, standardized written, video, or audio instructions can be used but may have a different effect.

OLP, open-label placebo.

2.4.2.1. Covert placebos

A recent approach involves a "covert" placebo condition.[48,59,129] Here, the physical placebo is administered with a cover story that diverts attention away from the primary outcome (eg, by citing a technical reason for its use) instead of explicitly labeling it as a placebo. As such, it is given "openly" regarding its substance but "covertly" regarding its intended effect. This design helps isolate effects of explicit placebo induction from those of the treatment-taking ritual itself.

2.4.2.2. Open-label placebo without positive preamble (OLP−)

Participants receive the OLP without the standard explanatory rationale. This design aims to isolate the effect of the "treatment-taking ritual" from the explicit rationale explaining the reasoning for the treatment.[27,92] In two nonclinical samples, OLP− performed worse than NT, pointing to the importance of the treatment rationale.[27] However, results are mixed and likely context-dependent: Studies using OLP− report weaker or no effects regarding pain intensity, performing worse than OLP with rationale and similarly to no treatment. Conversely, in clinical conditions such as allergic rhinitis, OLP has shown efficacy even without an extended rationale, performing similarly to OLP with rationale.[120] By omitting the rationale, OLP− conditions can help disentangle placebo effects from the ritual of taking a pill and from spontaneously generated thoughts about the treatment, which might arise when patients attribute random symptom improvements to the new OLP medication.

Existing frameworks such as the CoPPS statement[69] and the TIDieR-Placebo checklist[70] provide further guidance on designing, implementing, and reporting control interventions in placebo research.

2.5. Recruiting and advertising

Beyond careful study design, participant recruitment and the framing of study aims critically influence outcomes and generalizability. As with any research relying on voluntary participation, some degree of self-selection bias is unavoidable. Similar to deceptive placebo studies, individuals with higher outcome expectations, a holistic attitude, or a stronger desire for symptom relief may be disproportionately likely to volunteer for OLP studies, potentially limiting generalizability to more skeptical populations.[125] Recruitment framing is known to affect participation and expectations in placebo research more broadly,[1,20] yet its impact on sample composition and outcomes in OLP studies has not been examined systematically.[42] For example, people may react differently to a study investigating "mind-body self-healing processes"[76] or "psychophysical interactions"[120] (both of which may avoid some participant-related biases) compared with a study announced as investigating "the efficacy of open-label placebos" (which may indeed lead to a sample that is especially open-minded to the concept of placebos). On the other hand, not informing participants upfront that the study uses placebos might lead to dissatisfaction or disappointment, potentially biasing results in the other direction. Open-label placebo researchers are encouraged to explicitly consider potential self-selection or allocation-related effects, report recruitment materials transparently, and reflect on how recruitment strategies may have influenced their study sample and findings (see also section below on patient perspectives).

The medium of recruitment (print, online media, recruitment in clinics) and possible barriers to participation may also influence participation. For instance, responding to a newspaper advertisement requires different abilities and effort than agreeing to participate in a study when offered during a routine clinical visit or on social media platforms.

2.6. Designing the open-label placebo rationale

In OLP trials, the treatment can be conceptualized as a combination of (1) the physical placebo administration and (2) the accompanying rationale explaining how placebos may produce effects even when known to be inert. In some cases, (3) context effects such as the patient-provider interaction may

also play a role. Usually, the rationale is designed to induce openness and a positive attitude toward placebo effects, thereby creating positive expectations[7] and promoting well-being.[120] Nevertheless, the role of expectations for OLP efficacy is still a topic of debate (see section 2.8.4. on evaluating expectations).

The rationale typically follows 4 recommendations outlined by Kaptchuk et al.[76]: (1) Remove the stigma of placebo effects by openly and truthfully talking about them, "Placebos are powerful"; (2) Explain that placebo responses can occur automatically, without conscious effort; (3) Facilitate positive reactions by mentioning hat there is no requirement to believe; and (4) Emphasize adherence, ie, stressing the importance of the physical ritual of taking the pill.

More recent studies have also added a fifth recommendation, namely informing participants that OLPs have demonstrated efficacy in past research (eg, Ref. 27, 137 for meta-analyses). Strategies for optimizing the rationale have been reviewed by Heiss et al.[65] and Locher et al.[92]; see also Wessels et al.[138] for a study example.

Preliminary evidence suggests that merely providing information about placebo mechanisms (without actually administering OLPs) has been shown to improve well-being, suggesting that awareness of placebo mechanisms may itself be therapeutic.[120] This aligns with findings on "imaginary placebos," according to which imagining a pill intake reduced test anxiety[25,26] and improved emotion regulation[121] compared with physical OLPs—representing a promising avenue for patients who are averse to pill-taking.

Interestingly, in pain research, OLP analgesia requires the rationale to be provided. An RCT found that pain relief did not seem to occur with placebo disclosure alone,[92] highlighting the importance of rationale for future pain research. Conversely, debate continues regarding which specific components—rationale, provider interaction, or ritual—drive efficacy, emphasizing the need for appropriate control groups.[18]

2.6.1. Wording

The wording of the rationale requires careful attention to both methodological and ethical considerations and might be reported (eg, video).[18,82] While researchers may want to induce openness and belief in efficacy, making overly optimistic and unrealistic promises risks deception and undermines informed consent.[19,46] Therefore, it is crucial to strive for a balance between presenting empirically supported information (eg, the results of meta-analyses demonstrating the potential benefits of OLPs) and being realistic about the limitations of OLPs (eg, that not everyone[18] and not all symptoms may benefit from placebo treatments). An emerging perspective suggests that uncertainty within the rationale may also play a functional role. Rather than stating certainty, inviting patients to remain "open to possibility" may activate self-reflective and self-evaluative processes that contribute to symptom improvement,[75,101] contrasting with the more traditional assumption that strong positive expectations are necessary for placebo responses. Future research should clarify whether uncertainty enhances OLP effects or simply reflects personal meaning-making, while ensuring that such framing remains compatible with transparent disclosure.

2.6.2. Language

The language and complexity of the information should further be adjusted to match the participants' level of education and prior knowledge to maximize understanding and acceptability. A verbatim script of the rationale, while a relevant aspect in all scientific studies, may be especially helpful for experimenters in OLP studies. Ideally, adherence to this script should be verified by a second rater. Such a script also serves as an indispensable part of the methods to be shared upon publication, allowing for close replication in future work and assessment of differential results regarding OLP efficacy.

2.6.3. Delivery

For delivering the OLP treatment rationale, print leaflets, videos, and direct explanation by the study personnel can all be considered separately or in combination.[138] While observational learning can induce placebo effects,[80] one study found that combining it with an OLP rationale did not enhance placebo analgesia, hinting at redundancy.[24] The choice of delivery mode depends on study goals and feasibility: Video instructions minimize provider variability and are suitable when direct interaction effects should be avoided.[18,123] Conversely, print or video formats are practical for naturalistic or multicenter trials due to standardization and resource efficiency.

2.6.4. Experimenter interaction

Effects of OLPs in in-person studies might additionally depend on experimenter-related effects, such as quantitative aspects of the interaction (eg, duration), the quality of the interaction, perceived experimenter characteristics, and context, although no study has isolated which components drive outcomes. Regarding the quality of the interaction, qualitative studies in particular consistently highlighted the importance of trust, communication quality, and therapeutic relationships for patient acceptance and experience of OLPs.[53,91,101] Participants report greater willingness to try OLPs when experimenters invest time in providing explanations and convey genuine care, leading to the feeling that they are "in good hands."[91] Clinical interaction alone might thus be insufficient for symptom improvement: Pan et al.[102] found that only the OLP group improved whereas the NT group did not, despite comparable involvement of healthcare professionals in both groups. Although evidence on the role of warmth and friendliness remains limited[72] (see also section 4 below for patient perspectives on this topic), provider attentiveness, empathy, and communication style should be considered as integral intervention components. The question remains, however, whether these interpersonal factors are truly necessary or merely provide optional benefits for creating a positive study environment and boosting OLP effects.[18] Experimenter sex, age, and ethnicity may also influence perceived credibility and efficacy. These variables have the most impact in face-to-face interactions, but also apply to remote studies, for example, using video instructions.[18,82,124] Kube et al.[88] found a greater effect of an augmented vs limited remote clinical encounter. In completely remote designs, participants may weigh given information higher when there is no experimenter interaction, a hypothesis that warrants further testing. Although more systematic studies on this topic are needed, the TIDieR-Placebo checklist[70] includes a list of relevant experimenter descriptors applicable to OLP studies.

2.7. Blinding and bias assessment in open-label placebo research

2.7.1. Blinding

Blinding is considered the standard in RCTs, as it minimizes expectancy and performance effects by ensuring that neither

participants nor study personnel are aware of group allocation. In OLP studies, however, participants are explicitly informed about their treatment condition, and this transparency is an inherent, theoretically and ethically necessary part of the intervention rather than a methodological flaw. This creates an apparent mismatch between standard clinical trial methodology and the nature of OLP research.

To minimize experimenter or participant effects, several strategies have been proposed. One option is a single-blind design in which study personnel interacting with participants are blinded to group allocation.[64,84] In addition, control conditions can be matched for time, interaction, and attention while omitting only the explanatory rationale. This approach balances engagement across groups without compromising the theoretical integrity of the OLP intervention. Thus, rather than violating the RCT framework, OLP research adapts it—replacing concealment with transparency as a deliberate experimental manipulation.

2.7.2. Bias assessment

The transparent nature of OLP trials introduces unique sources of bias at several levels. While standard instruments, such as the Cochrane Risk of Bias tool (RoB2),[67] automatically classify lack of blinding as a high risk, in OLP designs, nonblinding is an intentional and essential feature of the treatment. It is therefore important to distinguish between (1) unintended systematic distortion (eg, due to differential recruitment, reporting, or experimenter behavior) and (2) intended transparency. Because current risk-of-bias assessment frameworks were developed for blinded RCTs, they require contextual interpretation for OLP research. For instance, recruitment bias is a particular concern (as in all RCTs), because individuals who consent to participate in an "open-label placebo" study may differ systematically from the general population in expectancy, openness, or prior experience with placebo treatments. **Table 1** summarizes biases that may be particularly relevant to OLP studies and suggests practical strategies to mitigate them.

2.8. Assessment considerations

2.8.1. Outcome measures

The choice of outcome measure, including both subjective, ie, patient-reported outcomes, and objective measures, bears significant implications for evaluating treatment effectiveness.[27,129] While no single outcome measure is inherently superior, it should reflect the study's objectives. Most OLP studies have focused on patient-reported symptoms, such as pain, mood, and fatigue (for an overview, see Chapman et al.[33]). However, supplementing these outcome measures with "objective" physiological measurements such as heart rate, cortisol levels, or movement parameters can provide a more nuanced understanding of treatment effects, especially when directly relevant to the condition. For instance, a study on the effects of OLP in chronic low back pain found that subjective improvements were not paralleled by changes in objective spinal mobility,[83] and another study also found OLP-related improvements in multiple subjective but none of the objective outcomes.[84] Defining a broader core outcome set may capture a more diverse range of symptom or disease aspects. Because patients are rarely affected by one single symptom, this would improve our understanding of which symptoms may be amenable to OLP effects.[84,106]

Given that most OLP studies have focused on short-term outcomes,[77] future research should also explore the ideal frequency and timing of outcome measurements. While patient burden should be kept to a minimum, it may be necessary to collect outcome measures more frequently to gain insights into the time course of effects or to introduce longer follow-up periods to characterize the duration of possible OLP benefits. These additional measurements may be valuable even when there is some level of participant attrition.

2.8.2. Treatment adherence

While treatment adherence is relevant to all interventional trials, it deserves special attention in OLP studies. Two different scenarios are conceivable if participants are aware that they are receiving an inert substance, compared with an active treatment: they could either become less adherent (believing it to be futile) or more adherent (lacking a fear of side effects). Because proper treatment adherence is crucial for the comparability of different treatment arms, it should be continuously monitored and reported. Objective measures (eg, electronic medication packaging) can quantify adherence, while subjective measures can elucidate reasons for nonadherence (for an overview of adherence measures, see Lam and Fresco[90]). Moreover, strategies to improve adherence, including behavioral and educational interventions, have been suggested.[39,112,135] To account for dropout and nonadherence, intention-to-treat analyses should take precedence over per-protocol analyses as the standard analytical approach.[133]

2.8.3. Acceptability assessment for both patients and healthcare providers

2.8.3.1. Patients

Studies have reported mixed attitudes toward OLPs, with some respondents expressing skepticism[60,91] and others expressing more openness, particularly when OLPs are suggested as an add-on treatment.[51] In one study, healthy volunteers receiving an OLP for cognitive enhancement were less satisfied with their group allocation than those in the NT condition,[64] suggesting that OLPs may be perceived as unnecessary or as a burden by participants who do not need symptom relief. Concerns have been raised that patients with chronic disease might feel stigmatized by the suggestion that a placebo could alleviate their symptoms.[17,60,74] Nevertheless, many quantitative and qualitative studies conducted in diverse settings,[28,44,71] including primary care,[108] and various demographic groups (eg, parents),[122] have not substantiated this concern. In fact, many patients express curiosity and a willingness to try OLPs.[60,87,101,108] To the best of our knowledge, such reports of patients' ambivalence after being offered an OLP are rare,[60] it is essential to document patients' perspectives and satisfaction to identify whether, to what extent, and for whom the suggestion of an OLP treatment might lead to undesired effects.[87] Alternatively, a partially randomized patient preference design may be used, allowing those participants with a strong treatment preference to choose their treatment while randomizing undecided participants. However, the effects of such a design on OLP efficacy are still in need of systematic investigation.

2.8.3.2. Healthcare providers

The perspectives of healthcare providers, including those who provide OLPs, have rarely been investigated.[16] The feasibility of clinical implementation, attitudes, potential skepticism, and

ethical concerns among clinicians require consideration, particularly in large-scale, more naturalistic clinical trials, where healthcare providers are not part of the research team. Understanding provider attitudes and how they affect the receiving side, participants of OLP trials, will be crucial for successfully integrating OLPs into routine care.

2.8.4. Evaluating expectations

The rationale provided along with an OLP treatment has the goal to induce an openness toward OLP treatment. While research on deceptive placebos consistently demonstrates positive expectations as a key mechanism, current OLP research paints a more heterogeneous picture (see eg, Ref. 8 for an overview). A recent meta-analysis demonstrated that OLP interventions are more effective when at least minimal positive treatment expectations are evoked, especially for nonclinical samples with a single OLP administration.[94] More specifically, OLP interventions delivered without positive treatment expectations were less efficacious than interventions with the induction of some treatment expectations.[27] This suggests that an open attitude and expectation building may in fact be important for OLP interventions (albeit less than for deceptive placebos) and that merely prescribing an inert treatment is not sufficient. By contrast, other studies found that OLP effectiveness did not increase with higher expectations and patients did not identify expectations as a key driver.[60] In addition, positive treatment expectations were not sufficient to evoke an OLP effect.[55] A recent study by Barnes and Faasse[8] may help to reconcile some of these inconsistencies by showing that OLP-related expectations may initially be uncertain and loosely held, becoming predictive of outcomes only after participants have accumulated some treatment experience. This is consistent with Bayesian and computational models of the placebo effect in which expectations and outcomes update each other dynamically, and suggests that heterogeneous findings on expectations as an OLP mechanism may partly reflect timing of measurement rather than absence of effect. A further conceptual issue concerns the distinction between expectation and hope. Following Kube et al.,[89] expectation can be understood as a primarily cognitive construct tied to a relatively high subjective probability of an outcome. Hope, on the other hand, refers to a desire for an outcome that can be sustained even when its probability is judged to be low, and it carries a stronger affective component. This distinction is particularly pertinent for OLPs, given that the rationale explicitly states that belief in the treatment is not necessary, which may evoke hope or openness to possibility rather than confident expectation. This aligns with Kaptchuk's third recommendation for the OLP rationale, that belief in the treatment is not required for it to work.[76] In sum, the underlying working mechanisms of OLPs remain an underexplored phenomenon that extends beyond expectations and potentially engages multiple other factors.[8] Owing to the heterogeneous and mismatching nature of the literature, we nevertheless recommend OLP researchers (especially those who also include a treatment rationale in some form) to measure resulting expectations at multiple timepoints if their study design allows for it.

Participants' treatment expectations can be assessed systematically using validated tools (eg, TEX-Q,[127] GEEE,[111] ETS,[9] and CEQ[39]). These may include both treatment-related and symptom-related expectations, as well as constructs such as expectation of improvement, worsening, and side effects, which are at least partially independent constructs.[10] The timing of such assessments (pre/postexpectation induction, pre/postrandomization),[8] as well as measures of treatment credibility, satisfaction with group allocation, and participant preferences, can also be reported and may provide valuable information on the mechanisms and interindividual responsiveness of OLP treatments.

2.8.5. Safety and tolerability assessment

2.8.5.1. Safety

Although safety has not been seen as a major concern in OLP studies, adverse effects (AEs) may be underreported, particularly given evidence that OLP administration itself can elicit nocebo-like responses, including increased symptom reporting and negative mood relative to untreated controls.[47] Periodic open-ended questions (eg, "Are you experiencing any other symptoms?") may be helpful to capture AEs, but may not prevent underreporting.[110] The form of administration may further modulate AE reporting, as different OLP delivery formats (eg, capsule vs nasal spray) have been associated with distinct symptom attribution patterns.[140] Therefore, a structured assessment of defined AEs, whether general (eg, the General Assessment of Side Effects)[110] or condition-specific (eg, the Opioid-Related Symptom Distress Scale for OLPs used in opioid-sparing or conditioned OLPs,[3] or the Pittsburgh Side Effect Rating Scale when OLPs are used as a stimulant)[104] is recommended. Analogous to pharmacological studies, OLP trials must assess side effects and iatrogenic outcomes for a thorough risk-benefit analysis, as patients' attribution of symptoms to the "drug" influences adherence, satisfaction, and provider interaction. Beyond physical AEs, unwanted psychological effects should be assessed, although consensus on measurement tools is currently lacking[66] and efforts should be made to reduce possible side effects.

2.8.5.2. Tolerability

Patient-centered research requires a more precise evaluation of tolerability (ie, the extent to which AEs of a treatment can be endured). Studies indicate that the term "tolerability" is often used inaccurately, with claims of good tolerability frequently lacking supporting data, leading to potentially misleading conclusions.[130] While tolerability is inherently subjective, treatment discontinuation due to intolerable AEs provides an objective measure. To evaluate the tolerability of OLPs, documenting and transparently reporting instances in which patients withdraw consent due to distressing events is thus essential. The event-specific Tolerability Index (TI) provides a quantifiable measurement of tolerability.[110]

2.8.6. Concomitant treatment

In OLP studies, as in other clinical trials, it is important to accurately record and report any concomitant treatment, ie, any additional therapies or medications that participants are using alongside the study intervention; this is particularly relevant in TAU control groups. Currently, there is great variability in the handling and reporting of concomitant treatments, as no specific guidelines or protocols are available. Some studies allow the continuation of usual medication,[76] others restrict treatment changes during the study period,[30] and many only report baseline medication use.[68] Recent meta-analyses highlight significant heterogeneity in OLP outcomes,[27,137] which may be partly attributed to inconsistent reporting of concomitant treatments. Beyond pharmacological effects, participants may adopt other health-related behavioral and lifestyle changes—such as improved sleep, increased exercise, nutrition changes, or relaxation

routines—which could influence study outcomes. Suggestions on handling concomitant treatment and changes in health-related behavior may be:

(1) **Comprehensive baseline assessment**: Documenting all ongoing treatments at study entry, including recent changes in medication or dosage. In addition, relevant health-related behaviors such as sleep, exercise, and diet may be assessed.
(2) **Regular monitoring:** Implementing a system for participants to report changes in their treatment regimen or health behavior throughout the study, eg, through patient diaries or ecological momentary assessments.
(3) **Quantification of use:** Measuring and reporting actual use (eg, session number/duration, daily dosage), which may differ from prescriptions.
(4) **Analysis and discussion of implications:** Considering concomitant treatments as potential covariates in statistical analyses and discussing their implications for OLP effect interpretation.

3. Reporting and publishing of open-label placebo studies

As in any other field of research, transparent reporting is paramount. Given the relevance of context-induced treatment effects in OLP research, it is crucial to report all potentially relevant details of the participant/patient collective, recruitment strategies, study design and procedure (eg, time, place, and environment of data acquisition), and instructions provided by the experimenter or by video. A great level of detail is necessary here, to ensure the reliability and reproducibility and to facilitate meaningful comparisons across studies.[62,98]

Existing guidelines offer a solid foundation. The CONSORT extension for nonpharmacologic treatments[23] and the TIDieR-Placebo checklist[70] can be adapted for OLP-specific aspects, such as detailed reporting of recruitment nuances and single-blinding procedures. Moreover, documenting participant refusals and reasons for nonparticipation is necessary to understand potential biases and the generalizability of the findings, which should in turn enhance credibility and support clinical integration.[46]

While publication bias is a concern in emerging fields, it has been formally assessed in previous OLP meta-analyses. In clinical trials, there is limited evidence of publication bias.[137] Similarly, a meta-analysis of experimental OLP studies with nonclinical samples[129] found no evidence of publication bias. However, given the limited number of trials, these findings should be interpreted with caution, and monitoring of publication patterns must continue.

Embracing open science principles, such as publishing study protocols, registered reports, and preprints, as well as open access publishing, is important to transparently advance the field of OLP research.[32] This fosters a collaborative scientific environment in which data can be scrutinized, validated, and built upon by others.

4. Patients' perspectives on conducting open-label placebo studies

To ensure a patient-centric approach, we conducted a focus group discussion with members of the Patient Advisory Board (PAB) of the Collaborative Research Center (CRC) 289 "Treatment Expectation," funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) (www.treatment-expectation.en). The PAB aims to actively involve people with lived experience in all phases of research projects to enhance research relevance and strengthen the connection between scientific research and clinical care. Comprising 16 individuals who are patients, representatives of patient organizations (eg, German Pain League), and former study participants, the PAB provides diverse perspectives on medical treatment.

Following a structured protocol based on current guideline recommendations,[63] the PAB was invited to participate in a moderated focus group discussion. Five PAB members (3 women and 2 men) participated, all of whom had personal experiences with different medical treatments (eg, for pain); notably, one had used OLPs for analgesic dose reduction and another had participated in a preoperative anxiety OLP trial. The focus group discussion lasted for 1.5 hours and was moderated by 2 of the authors (J.A., J.W.) with direct experience in OLP research. First, the theoretical basis of placebo effects and existing research on OLPs were briefly presented. Next, 3 essential aspects of OLPs were addressed, with 2-3 guiding questions for each topic (eg, What reasons would motivate you to participate in an OLP study?): (1) potential risks and benefits, (2) recruitment, and (3) patient information strategies. Patients were encouraged to provide their personal viewpoint based on their own experiences and the experiences within their patient organizations. The session was recorded, independently documented by K.S., J.W., and J.A., and analyzed using a structured content analysis approach.

The PAB members generally had a positive attitude and expressed strong support for OLP research and explicitly advocated for its expansion in areas such as reducing anxiety and treating chronic pain, where conventional drug regimens often lead to escalating doses and unwanted side effects. They highlighted the relevance of several important outcomes for OLPs, including dose reduction of conventional medications, minimization of side effects, and improvements in patients' subjective well-being and quality of life. They did not identify any indications that would preclude the administration of OLPs as an add-on treatment. Minor concerns were raised that being offered an OLP treatment could imply that physical symptoms are not taken seriously. Consequently, they emphasized that OLPs should complement rather than replace standard treatments, particularly in the case of severe conditions. The PAB members also addressed the need for clear, quantifiable metrics to evaluate the efficacy of OLPs, particularly in patient-reported outcomes.

For recruitment to OLP studies, the PAB members underscored the pivotal role of trust in healthcare providers as a determinant of patients' willingness to engage in studies, aligning with findings that physician recommendation drives OLP acceptance.[51] To foster trust, the PAB recommended a gradual introduction focusing on clinical benefits rather than complex psychobiological mechanisms. Owing to potential initial skepticism, they suggested avoiding the term "open-label placebo" or "placebo" during initial recruitment (eg, on flyers) and instead using terms that emphasize well-being and self-efficacy. Furthermore, they highlighted the significance of timing and context in which patients are approached, and proposed recruiting patients for an OLP trial when they are more amenable, for example following initial consultations or during less intensive phases of their standard treatment.

The PAB members emphasized the necessity of providing transparent and easy-to-understand information about the trials to ensure that patients understand the objectives, risks, and potential benefits of their study participation. They encouraged the use of figurative language (eg, using placebos to "unlock the body's own pharmacy" or to "support the activation of the body's

natural healing mechanisms") and incorporating personal stories and testimonials to enhance patient engagement. Finally, from the perspective of the PAB members, participation in an OLP trial would prompt similar deliberations and considerations to the initiation of any novel therapy in their treatment plan—requiring information, transparency, and empathic communication to enable active engagement in a decision-making process informed by evidence. They recommended introducing OLPs as a novel adjunct therapeutic option rather than as a substitute for the patients' ongoing therapy because discontinuing an existing treatment to participate in an OLP trial may be unethical and clinically inadvisable.

5. Conclusion and future directions

In this review, we presented key methodological considerations to improve the reliability and reproducibility of OLP studies and to establish a robust, patient-centered framework for future research on the mechanisms and usability of OLPs.

Careful consideration of these recommendations when designing and presenting recruitment material and delivering information about OLPs may further improve the quality and applicability of OLP research. Although there is currently no empirical guidance on "optimal" recruitment wording in OLP trials, our PAB advised against using the explicit term "open-label placebo" in initial recruitment materials to engage patients who may be more skeptical, a preference that aligns with recent qualitative work showing that patients are unfamiliar with, or initially skeptical about, the OLP concept.[91]

One key challenge remaining in OLP research is the selection of appropriate control groups (**Fig. 1**) to isolate the effects of OLPs and to draw valid conclusions about their efficacy. At the outset, researchers should determine whether the primary objective is to demonstrate the superiority or noninferiority of OLPs compared with existing treatments and to select control groups accordingly. Moreover, it is important to distinguish whether a study aims to demonstrate the overall efficacy of OLP treatment or whether different mechanisms of action should be disentangled, ie, the treatment rationale, the type of OLP, or changes in health behavior. Furthermore, biases and blinding remain pertinent issues in the context of OLP studies (**Table 1**). While efforts shall be made to reduce biases, it should be noted that similar challenges are common in other nonpharmacological interventions (such as physiotherapy) and even in pharmacological trials with opioids, where side effects jeopardize blinding. Difficulties with blinding should thus not discourage researchers from systematically investigate OLPs.

The PAB strongly endorsed investigating OLPs as a valuable add-on to conventional treatments, particularly for reducing side effects of active medication and promoting patient empowerment. Because OLPs inherently bridge psychological and somatic mechanisms, they actively engage patients in the treatment process, fostering empowerment and self-efficacy—key factors in managing chronic conditions. While the PAB emphasized the significance of empathic communication and trust in healthcare providers as a crucial element to motivate patient involvement in all studies, including OLP studies,[51] this may present a challenge for researchers if their aim is to maintain a neutral and professional relationship with participants throughout the course of a study. Assessing how the experimenter or study nurses were perceived by patients and consider possible differences in the analyses may therefore be beneficial. Although several studies have demonstrated a general acceptability of OLPs by patients, particularly as an add-on treatment and for dose reduction, such as in chronic pain,[51,60,71,83,87,101] it is essential to incorporate the perspective of healthcare providers into future OLP research and implementation. These insights are based on 5 German patients or patient representatives and may not be generalizable to other populations. As perspectives on OLPs are likely to vary across personal experience, culture, and healthcare context, broader, cross-cultural qualitative research is warranted.[35]

Ethical considerations also warrant attention in the context of OLP trials. Recent reviews have highlighted broader issues regarding informed consent, therapeutic relationships, and sociocultural factors.[109,128] Moreover, ethical OLP research requires more than transparent disclosure alone, pointing to broader structural considerations such as avoiding paternalistic assumptions about which patient populations are deemed appropriate for placebo treatment. While a comprehensive ethical analysis is beyond the scope of this methodological review, these issues are important for the responsible development and clinical translation of OLP research. Future work should explicitly integrate methodological rigor with ethical guidance.

Ultimately, if OLPs are to be integrated into clinical practice, they will have to undergo the same evaluation as established medical or psychological treatments, including efficacy and cost-effectiveness evaluations. By confronting these methodological challenges and embracing a patient-centered approach, OLP research has the potential not only to deepen our understanding of placebo effects but also to expand the range of treatment options for patients in various clinical contexts.

Conflict of interest statement

The authors have no conflict of interest to declare.

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