Open-label placebo clinical trials: is it the rationale, the interaction or the pill?

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10.1136/bmjebm-2019-111209

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To cite: Blease CR, Bernstein MH., Locher C. *BMJ Evidence-Based Medicine* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bmjebm-2019-111209

Abstract

National surveys of primary care physicians demonstrate that placebo use is prevalent. Against their widespread use, until recently, it was assumed among researchers that placebos must be deceptively prescribed for beneficial effects to be elicited. However, a new programme of research in placebo studies indicates that it may be possible to harness placebo effects in clinical practice via ethical, non-deceptively prescribed 'open label placebos' ('OLPs'). To date, there have been 14 small scale clinical and experimental trials into OLPs. Results suggest therapeutic potential of these treatments for a range of conditions and symptoms. In this evidence-based Analysis we identify conceptual issues that, if not given due consideration, risk undermining research methodologies in OLP trials. Counterintuitively, owing to the nuances posed by placebo terminology, and the difficulties of designing placebos controls in OLP trials, we suggest that experimentalists reflect more deeply when formulating adequate comparison groups. Further research is needed to disentangle which specific components of OLPs are effective, such as: the rationale provided to participants; the quality of provider interaction; and/or the action of taking the pills. We conclude with recommendations for how researchers might take up the significant challenge of devising optimal placebo controls for OLP clinical trials. Although these issues are intricate, they are not merely academic: without due diligence to conceptual, and as a consequence, methodological considerations, OLP effect sizes may be over- or underestimated. We conclude that there may yet be potential to use OLPs in medical practice but clinical translation depends on rigorously controlled research.

Introduction

Placebo use in clinical medicine is common. Recent survey research reveals that in the UK, 77% of general practitioners (GPs) prescribe placebos at least once per week, meanwhile, in the USA, around half of internists and rheumatologists (46%–58%) reported using placebos 'on a regular basis'.[1 2] Qualitative research suggests that physicians endorse a range of disparate views about placebos and placebo effects, and many GPs appear to believe that placebos necessitate deception.[3] This view is currently challenged by experts working within the field of placebo studies where a prominent new research programme explores the possibility of 'open-label' placebos.[4 5] The aim of this research agendum is to investigate whether placebos can be ethically prescribed within the clinical practice—that is, without deceiving patients.

So far, several prominent clinical trials of open-label placebos (hereafter, OLPs) have concluded that there are significant salubrious effects of using transparently described placebos for a range of conditions[6–11] (discussed further, below). Drawing on these findings, a systematic review and meta-analysis of OLPs concluded that 'OLPs appear to have positive clinical effects compared with no treatment' but that 'caution is warranted' due to the lack of blinding and the inclusion of positive messages included within research setups.[12] Kaptchuk and Miller have also emphasised limitations with current findings, including small sample sizes, and the short duration of studies.[13]

Building on these concerns, our aim is to present an evidence-informed conceptual Analysis of OLP clinical trials. To appraise the effectiveness of OLPs *using* the framework of placebo-controlled randomised clinical trials (RCTs), an appreciation of the conceptual distinction between placebos as methodological devices and placebos as treatments is crucial. Indeed, properly constructed, RCTs may provide a useful starting point to discover the mechanisms of action of OLPs.[14] We conclude with recommendations and next steps for improving clinical and experimental trials of OLPs.

Placebo concepts: disambiguating definitions

Before reviewing findings from OLP studies, it is crucial to clearly demarcate between two distinctive uses for the term placebo[15 16] (box 1). First, is the usage of placebos in RCTs. Here the term is often understood to refer to a certain kind of 'thing' (eg, saline injections or sugar pills). Strictly speaking, this interpretation is incorrect: instead, *placebos in RCTs* ought to be conceived as methodological tools since their function is to duplicate the 'noise' associated with clinical trials including spontaneous remission, regression to the mean, Hawthorne effects and placebo effects (box 1). Properly understood, then, these types of placebos are deployed as controls that are specifically designed to evaluate the difference—if any—between a control group and a particular treatment under scrutiny. Ideally, in RCTs, controls should mimic the appearance and modality of the

Box 1 Placebo concepts*

Placebos

(1) Methodological controls in RCTs

Placebos in clinical trials should ideally be indistinguishable from the particular treatment under the investigation, except for the latter's particular hypothesised remedial factor(s). Placebos in RCTs are methodological tools to screen out the 'noise' of clinical research (see Placebo Responses, below).

Or

(2) Interventions used in patient care

Interventions that, owing to their intrinsic properties, are ineffective for a particular condition or symptom(s), but which may be intentionally or unintentionally administered in clinical settings or experimental placebo research with the aim of 'pleasing' 'difficult patients' and/or to elicit *placebo effects*. The ethics and motivations behind placebos in primary care are keenly debated by medical ethicists and social scientists.

Placebo Effects and Nocebo Effects

To date, there is a scientific consensus that placebo effects constitute genuine psychobiological events that engage perceptual and cognitive processes to produce therapeutic benefits among patients for a range of self-reported conditions and symptoms, including depression, anxiety, pain and irritable bowel syndrome. Nocebo effects, on the other hand, refer to adverse effects that arise from perceptual and cognitive responses associated with anticipating a treatment, including its possible negative side effects.

Placebo Responses

Placebo effects should be disambiguated from the concept of 'placebo response'; the latter encompasses the full range of outcomes (the 'noise') that may arise after the administration of placebos ('controls') in RCTs; such factors include spontaneous remission, regression to the mean, Hawthorne Effects and so on. Placebo responses may (under the right conditions) also include *placebo effects*.

*Adapted from Blease, C. and Annoni, M., 2019. Overcoming disagreement: a roadmap for placebo studies. *Biology & Philosophy*, *34*(2), p.18.[16]

RCT, randomised clinical trial.

particular treatment or medical intervention under investigation.[15 16] In contrast, placebos in clinical contexts are interventions that may be intentionally or unintentionally administered by practitioners either with the goal of placating patients and/or of eliciting *placebo effects*.

OLP studies

Clinical trials of OLPs present a unique context where researchers require a sound appreciation of these distinctive, nuanced definitions of placebos. Specifically, experimentalists need to control for all aspects of the OLP arm *other than* the component that they consider to be therapeutically significant—for example, this could be the ingestion of a placebo pill. In table 1, we list 14 studies that included at least one OLP arm. To date, in 12 trials, OLPs have been compared with no treatment or treatment as usual.[6–11 17–22] Two studies involved a single-group design[23 24]; and two studies examined the efficacy of OLPs among healthy volunteers[17 20] (table 1)

Methodological considerations

While positive claims have been made for the efficacy of OLPs,[12] we suggest results must be approached tentatively in light of trial designs. Below, we discuss three methodological considerations derived from the foregoing conceptual distinctions that require the attention of investigators.

Lack of rigorous control groups

First is a lack of rigorous control groups in the trials that have been conducted to date. As noted, ideally controls should be structurally equivalent conditions when compared with the active treatment, that is, OLP. Structural aspects comprise number and duration of patient-clinician/researcher consultations; format of the treatment; and the quality of the interaction.[25] To date, many clinical trials appear to have made important efforts to achieve structural equivalency but these strides may have been subtly hampered with the inclusion unblinded assessments with PIs, and the frequently applied control condition of treatment-as-usual (TAU) (table 1). With regard to the latter, TAU controls are in most cases 'anything but usual'[26] ; the care that is actually provided under TAU is usually not monitored or adequately reported.[27] This means that inferences regarding structural equivalence are often impossible. Thus, although aspects which are monitored and described in the study design (eg, number and length of visits, length of intervention and person who is providing the treatment) might be equivalent between the intervention and the control group(s), 'usual' treatments or 'waiting for a treatment' most probably consist of other treatment components (or a lack of those) which are not accounted for. This concern applies not just to OLP versus TAU comparisons but to OLP+TAU versus TAU comparisons as well. (One of the studies came closest to describing TAU:'Participants were allowed to continue their chronic lower back pain medications (eg, paracetamol, non-steroidal anti-inflammatory drugs and son on) as long as they agreed to not change their medication routine or dosage during the trial, nor make any major life-style changes (eg, starting a new diet or changing their exercise pattern) during the study'.[7])

Relatedly, some clinical studies undertook a comparison of OLP with some form of no treatment including waitlist controls.[6 9 18] Problematically, OLP waitlist comparisons do not sufficiently differentiate between placebo responses and placebo effects; for example, in OLP studies, we suggest that participants receiving placebos—versus those who do not—may experience elevated Hawthorne effects or be more susceptible to responder biases. An additional challenge is the possibility that 'no treatment control' groups contribute to nocebo effects among participants.[28] Nocebo effects in the waitlist group might be particularly likely to occur in OLP trials for the following reason: randomisation to OLP or a control group typically occurs *after* the experimenter discusses the potential advantages of placebos[6 7 9 11 18 20] (table 1). In other words, patients in a control group are told why placebos might work, and then informed they will not receive a placebo. In one early OLP study, it was suggested that this concern was mitigated because 76% of participants in the control group were not disappointed about their lack of placebos,[6] however, we caution that self-report is notoriously inaccurate and vulnerable due to social desirability biases.

Table 1 OLP studies

Study	Disorder/Problem	N	Duration	Control group(s)	Study structure: (a) Blinding: assessment (b) Blinding: visit midpoint (c) Placebo briefing before randomisation	Structure OLP: (a) No. of interactions (b)Length of interaction(s) (c) Length of intervention (d) Provider and assessor interactions	Structure control(s): (a) No. of interactions (b) Length of interaction(s) (c) Length of intervention (d) Provider and assessor interactions
Aulas and Rosner (2003)[24]*	Minor anxiety and somatoform symptoms	34	7 days	None	(a), (b), (c): Not applicable—single group study, no randomisation	(a) Not reported (b) Not reported (c) 1 week (d) Physician	No control group
Carvalho *et al*,[7] 2016†	Chronic lower back pain	83	3 weeks	TAU	(a) A registered nurse blinded to treatment assignment conducted all assessments (b) Unblinded PI: reminded participants receiving placebo pills about the 4 discussion points and reminded participants in the TAU arm that they could start the placebo pills at the end of the 3 weeks (c) 4 discussion points on placebo effects	(a) 3 visits (b) 15 min a priori script; 10–15 min midpoint visit (c) 3 weeks (d) Blinded nurse; interaction with unblinded PI at midpoint	(a) 3 visits (b) 15 min a priori script; 10–15 min midpoint visit (c) 3 weeks (d) Blinded nurse; interaction with PI unblinded at midpoint
Hoenemeyer *et al*,[11] 2018†	Fatigue among cancer survivors	74	3 weeks	TAU	(a) All assessments were performed by a research assistant blinded to randomisation allocation (b) Unblinded PI (an oncology behaviour specialist) phone call to inquire about patients' health changes and answer questions (c) 4 discussion points on placebo effects	(a) 2 visits+1 phone call at midpoint (b) Not reported (c) 3 weeks (d) Blinded research assistants and blinded research specialist; interaction with unblinded PI (an oncology behaviour specialist) at 2 visits+phone call	(a) 2 visits+1 phone call at midpoint (b) Not reported (c) 3 weeks (d) Blinded research assistants and blinded research specialist; interaction with unblinded PI (an oncology behaviour specialist) at 2 visits+phone call
Kam-Hansen *et al*,[21] 2014*	Episodic migraine	66	7 migraine attacks	No treatment drug (Maxalt)	(a) All study personnel were blind to treatment allocation (b) Not applicable (c) Intake instructions and content of Maxalt and placebo	(a) Not reported (b) Not reported (c) 6 attacks after baseline attack (d) No reported interactions; patient self-report	(a) Not reported (b) Not reported (c) 6 attacks after baseline attack (d) No reported interactions; patient self-report
Kaptchuk *et al*,[32] 2010†	Irritable bowel syndrome	80	3 weeks	NT	(a) All assessments were performed by a researcher who was blind to treatment assignment (b) Blinded with research assessors. Potential for unblinding in interaction with physician PI; patients receiving placebos received a short reminder regarding the '4 discussion points'. In the no treatment arm, patients were encouraged and thanked for helping make a successful study (c) 4 discussion points on placebo effects	(a) three visits (b) 30 min initial interview process; 15 min midpoint (c) 3 weeks (d) Blinded assessors; midpoint interaction with unblinded physician PI	(a) 3 visits (b) 30 min initial interview process; 15 min midpoint (c) 3 weeks (d) Blinded assessors; midpoint interaction with unblinded physician PI
Kelley *et al*,[18] 2012†	Major depressive disorder	20	4 weeks (intervention group); 6 weeks (waitlist control)	Waitlist control	(a) Blinded clinicians assessed patients at baseline and every 2 weeks thereafter (b) Not applicable (c) 4 discussion points on placebo effects	(a) 3 visits, 1 blinded (b) Not reported (c) 4 weeks (d) Blinded clinicians	(a) 4 Visits‡, 1 blinded (b) Not reported (c) 6 weeks (2 weeks waitlist, 4 weeks OLP) (d) Blinded clinicians
Locher *et al*,[17] 2017*†	Heat pain experiment with healthy participants	160	1.5 hours	NT OLP-DP	(a) Unblinded study investigators knew the allocation code of participants at the start of the trial (b) Not applicable (c) No briefing before randomisation	(a) 1 visit (b) Not reported (c) Not reported (d) Unblinded researchers	For all controls: (a) 1 visit (b) Not reported (c) Not reported (d) Unblinded researchers

Continued

Table 1 Continued

Study	Disorder/Problem	N	Duration	Control group(s)	Study structure: (a) Blinding: assessment (b) Blinding: visit midpoint (c) Placebo briefing before randomisation	Structure OLP: (a) No. of interactions (b)Length of interaction(s) (c) Length of intervention (d) Provider and assessor interactions	Structure control(s): (a) No. of interactions (b) Length of interaction(s) (c) Length of intervention (d) Provider and assessor interactions
Mathur *et al*,[20] 2018†	Wound healing in healthy volunteers	65	10 days	NT	(a) Blinded co-investigator dermatologist assessing wound healing at visit 3 (b) Not reported (c) 4 discussion points on placebo effects	(a) 3 visits (b) 25 min for the first session; 10 min for first follow-up; 15 min for final follow-up (c) 10 days (d) Blinded co-investigator dermatologist	(a) 3 visits (b) 25 min for the first session; 10 min for first follow-up; 15 min for final follow-up (c) 10 days (d) Blinded co-investigator dermatologist
Park and Covi (1965)[23]*	Neuroticism	14	1 week	None	(a), (b), (c): Not applicable—single group study, no randomisation	(a) 2 visits (b) 75–90 min for initial visit. Time not provided for second visit (c) 1 week (d) 1 unblinded psychiatrist	No control group
Sandler and Bodfish, 2008[10]§	Juvenile ADHD	26	4 weeks baseline and 4 weeks dose reduction	Full dose group Partial dose group (ie, medication dose reduction without OLP)	(a) School teachers were the only blinded raters during the study (b) Not applicable (c) No briefing before randomisation	(a) Not reported (b) Not reported (c) 8 weeks (d) Interaction with unblinded physician PI; assessments by unblinded parents and blinded school teachers	For all controls: (a) Not reported (b) Not reported (c) 8 weeks (d) Interaction with unblinded physician PI; assessments by unblinded parents and blinded school teachers
Sandler *et al*,[22] 2010§	Juvenile ADHD	99	4 weeks baseline and 4 weeks dose reduction	Full dose group Partial dose group (ie, medication dose reduction without OLP)	(a) Unblinded parents; blinded school teachers (b) Not applicable (c) No briefing before randomisation	(a) Not reported (b) Not reported; children randomised to the OLP group had an additional discussion of the placebo with the study physician. (c) 8 weeks (d) Interaction with physician PI; assessments by unblinded parents and blinded school teachers	For all controls: (a) Not reported (b) Not reported (c) 8 weeks (d) Interaction with physician PI; assessments by unblinded parents and blinded school teachers
Schaefer *et al*,[9] 2016†	Allergic rhinitis	25	2 weeks	TAU	(a) Not reported (b) Not applicable (c) 4 discussion points on placebo effects before randomisation	(a) 2 visits (b) Not reported (c) 2 weeks (d) Not reported, nor whether blinded	(a) 2 visits (b) Not reported (c) 2 weeks (d) Not reported, nor whether blinded
Schaefer *et al*,[8] 2018*†	Allergic rhinitis	46	2 weeks	TAU+, TAU−, OLP−	(a) The experimenter was blind to treatment assignments. (b) Not applicable (c) Basic information about placebos	(a) 2 visits (b) Not reported (c) 2 weeks (d) Experimenter	For all controls: (a) 2 visits (b) Not reported (c) 2 weeks (d) Experimenter
Zhou *et al*,[19] 2018*	Cancer-related fatigue	40	3 weeks	NT	(a) Not reported if research assistants who conducted phone calls were blinded. Other assessments: not reported (b) Not applicable (c) Study rationale, information on possible impact of placebo on cancer-related fatigue, prior evidence of the impact of placebo on symptoms including fatigue	(a) 1 visit+2 phone calls (b) Not reported (c) 3 weeks (d) Research assistants	(a) 1 visit+2 phone calls (b) Not reported (c) 3 weeks (d) Research assistants

*Open placebo is provided not as a dose-extender, and without the aforementioned four discussion points.

†Open Placebo is provided with four discussion points identical or very similar to what was originally discussed by Kaptchuk et al.[6]

‡The difference between 4 visits in control and 3 visits in OLP is due to the fact that patients initially assigned to control were later switched to the OLP condition for 4 weeks, meaning they were technically in the study for 2 weeks longer than patients initially assigned to OLP. Of note, the authors examined between-subject differences comparing 2 weeks of OLP vs 2 weeks of waitlist, as well as within-subject differences comparing before and after 4 weeks of OLP.

§Placebo issued as a dose-extender; some information about the placebo effect might be given.

DP, deceptive placebo; NT, no treatment; OLP, open label placebo; OLP−, OLP without a rationale; PI, principle investigator; RCTs, randomised controlled trials; sign., significant; TAU, treatment-as-usual.

Bias of clinician experimenters

Blinding of clinician experimenters in clinical trials is crucial to avoid subtle, non-conscious communication of positive biases to participants during interaction phases and in evaluating their outcomes.[29] In OLP clinical trials, there are two possible forms of bias that may influence outcomes of OLP trials: researcher/investigator allegiance; and clinician/therapist allegiance. The former, well-known phenomenon forms the rationale for blinding in clinical trials; the latter bias arises when researchers with an allegiance to a particular treatment and who may be subtly motivated in its success, non-consciously influence the delivery of the intervention. Indeed, a recent meta-analysis of psychotherapy treatments for depression found that after controlling for researcher allegiance, the differences between placebos and treatments disappeared.[30] We observe that OLP treatments appear to be conceived as something of a hybrid between a medical intervention (ie, administration and swallowing of a pill) and a psychological intervention (eg, plausible rationale with four discussion points with a 'positive framing with the aim of optimising placebo response').[6] If the presentation of a psychological rationale and positive framing are considered necessary to the intervention, then OLPs are vulnerable to comparable methodological hurdles arising in psychotherapy research where allegiance—and potential bias—plays a large role in outcomes.[29] We strongly suggest that allegiance effects may have confounded results in the OLP studies. Although several studies reported blind assessors of patient outcomes,[6 7 11 18] some failed to report whether assessors were blind at all points of the trial.[9 17 18] In other highly cited studies, unblinded investigators met with participants at the mid-point.[6 7 11]

Inclusion of rationale

The inclusion of a rationale is a particularly tricky aspect of OLP studies as this renders the placebo treatment open and transparent to the patient, and also renders blinding (for the patient, at least) impossible. Here, again, the issue of structural equivalence arises, raising questions about the adequacy of the 'placebo' control condition. Conceivably, the inclusion of a rationale may play a role in augmenting patients' perceptions of practitioner competence and empathy, which in turn may enhance placebo effects.[31 32] We suggest that clinical researchers must be clear about whether they hypothesise that the rationale forms a (potentially) remedial aspect of the OLP treatment and control groups should be designed accordingly. One study compared the provision of OLP both with a rationale and without, concluding that OLP was only associated with pain reduction when there was a rationale.[17] In two of the studies, participants were reminded of the rationale at the mid-point (day 11) of the trial which may have boosted the outcome for those allocated to the OLP arm of these studies.[7 32]

Recommendations and next steps

To summarise, OLPs may yet prove beneficial as future therapeutic tools—used either alone or complementing existing treatments—for patients suffering from conditions or symptoms that are responsive to the placebo effect. Before clinical translation ensues, however, further research is necessary to address shortcomings that are perhaps inevitable in a nascent interdisciplinary research programme such as placebo studies. Below, we detail three broad categories of recommendations that researchers conducting OLP studies ought to consider (table 2). We suggest that it may not be possible for every study to implement all of these elements but our aim is to help move the conversation towards generating the highest quality test of OLP efficacy.

First, for the reasons discussed, we suggest that waitlist controls do not provide an adequate 'placebo' control for OLP studies. Instead, counterintuitive as it may sound, adequate *OLP controls* must be devised. We concede that OLPs present a complex object of scrutiny for clinical trialists and we suggest that resourcefulness and ingenuity are required to meet the challenge.

Therefore, second, and at the outset, we recommend that investigators formulate clear theories about the factors that they wish to investigate as therapeutically significant in eliciting placebo effects. For example, if the rationale embedded in the disclosure is considered valuable as a mechanism for eliciting placebo effects,

Table 2 Summary of recommendations for future OLP studies

Problem	Recommendation
Lack of adequate placebo controls	Treatment control groups ('placebos') should be structurally equivalent to OLP groups differing only in the factor(s) hypothesised to be therapeutically significant Waitlist controls, and treatment-as-usual may be employed but only in addition to adequate 'placebo controls'
Lack of clarity on how OLPs might work	Researchers should formulate clear hypotheses about how OLPs, including what they conjecture to be the active component of the treatment For example, if the mechanism of action is hypothesised to be: *(a) The rationale:* The OLP group might receive a statement including the rationale for the treatment; the placebo group should receive a statement without the rationale. Interactions should be the same for both groups *(b) The quality of the clinician interaction:* Interactions should be structurally equivalent between OLP and placebo groups (eg, same length, number, and content) but differ in the level of specific clinician behaviours (eg, level of empathy, confidence and so on). Judgements about the quality of interactions should be independently assessed *(c) The action of taking pills:* Participants should receive disclosures in closed envelopes. Both placebo and OLP groups might be informed: "the provision of placebo pills *or* emotional support and meeting regularly with a supportive individual may be helpful in eliciting powerful placebo effects'. Those allocated to the OLP group would also receive the instructions 'placebo effects may be elicited by placebo pills and it is important to take the pills as prescribed'. Both groups should experience structurally-matched clinician interactions of the same quality of care which should be video-recorded and evaluated by independent assessors
Researcher bias	Researchers should be blind to patient allocation at all times to avoid investigator bias, and any potential bias relating to OLP treatment allegiance. Two independent assessors should be employed: one to measure primary outcomes, the other to look up the condition to which participant was assigned. If necessary, interactions should be conducted by clinicians blind to study hypotheses

OLP, open-label placebo.

Box 2 Key Questions and Findings

What is already known about this topic?

- Surveys demonstrate that placebo use is widespread in primary care.
- Deceptive placebos undermine ethical duties to be open and honest with patients; open-label placebos may provide an ethical means of eliciting therapeutic placebo effects.
- Clinical trials into open-label placebos (OPL) appear to show promise for a range of self-reported conditions but have been hampered by small sample sizes and short duration.

What are the new findings?

- Placebo concepts refer to: (1) 'methodological controls'; or (2) 'mind–body treatment interventions'.
- Failure to distinguish between placebo concepts can undermine research methodology: the quality of OLP studies—just like in other randomised placebo-controlled trials—is dependent on the adequacy of placebo controls.
- Inclusion of waitlist controls or treatment-as-usual (TAU) do not constitute OLP placebos: those in waitlists may experience nocebo effects, and TAU groups are not usually monitored or structurally matched to OLPs.
- A number of prominent OLP trials included unblinded investigators; others failed to report whether assessors were blind at all points of the trial, yet it is recognised that researcher allegiance can undermine the integrity of participant outcomes.

How might these results change the focus of research?

- Clarity over placebo concepts can enhance the rigour of clinical trials in OLP research.
- Going forward, as far as possible, placebo controls in clinical trials should be structurally equivalent to OLPs.
- By formulating clear hypotheses about the factors that investigators consider therapeutically significant in OLPs, future research can better reveal whether the rationale provided to participants; the quality of interaction; and/or the action of taking the pill influences the size of placebo effects.

then this might be controlled for using an alternative set of instructions for the 'placebo' control group. Although both groups would receive placebo pill and interactions should be the same for both groups, both the 'placebo' control and the OLP groups might receive two different statements, one with a rationale for the treatment and one without, that should be delivered to participants without any interpersonal interaction to avoid confounding factors, such as researcher allegiance, and any other factors associated with the quality of the patient–practitioner interaction in delivering the information.

Similarly, if the interaction is considered therapeutically significant, then the interactions should be structurally equivalent (same length of time and same content) but differ in terms of level of 'practitioner' (or confederate) behaviours (eg, level of empathy, confidence and so on)[32] ; judgements about the quality of interactions would then, ideally, be independently assessed.

In addition, recently some placebo theorists have proposed that 'embodied cognition', the idea that one's physical interactions with the world influence cognitive processes, as a possible mechanism of placebo effects.[5] In light of this theory, if the physical action of taking the pill is hypothesised to be a key active component of the OLP condition, this too needs to be controlled for. Although this presents an extremely tricky problem in designing OLP trials, we tentatively suggest one way forward. Participants in both arms might be advised that they are enrolled in a trial to test different kinds of placebo interventions. Disclosure processes would be provided via closed envelopes to ensure blinding, and so that both groups are not privy to the range of OLP interventions being trialled. Both groups would be informed: 'placebo effects are powerful, mind-body responses that may be able to reduce symptoms for certain conditions,' and that, 'the provision of placebo pills, or emotional support and meeting regularly with a supportive individual may also be helpful in eliciting placebo effects, and alleviating symptoms.' However, those allocated to the OLP group would also receive additional instructions in their disclosure to the effect that 'placebo effects may be elicited by placebo pills' and 'it is important to take the pills as prescribed.' The singular key difference between the OLP 'placebo' control and the OLP pill treatment is that participants randomly allocated to the latter group invoke the embodied action of taking placebo pills. Ideally, in both groups, matched interactions would involve experimenters who are trained to provide the same level of care; such interactions should be structurally similar, equally convincing and ideally be video-recorded and independently evaluated for quality of interactions.

Third, and as already alluded to, we strongly recommend the importance of minimising researcher allegiance effects. When possible, all assessments measuring primary outcomes should be conducted by research staff blind to patient allocation. This may be difficult to implement, because it is simultaneously useful to obtain information about placebo adherence, where the researcher must know group assignment. However, we suggest that two assessors could be used: Assessor One could measure primary outcomes, and then Assessor Two might look up the condition to which the participant has been assigned, and measure placebo adherence. To reduce the likelihood of demand characteristics – the scenario whereupon participants are aware of the purpose of the experiment, and non-consciously change their behaviour to fit this understanding – we also advise that all non-blinded interactions with participants, when they do occur, be conducted by researchers who are blind to study hypotheses. Interactions with the PI should ideally be avoided all together.

Conclusions

For an effective translation of OPL into clinical practice we need to be clear about how to interpret the results of OLP trials; these outcomes, in turn should be informed by well-designed, methodologically robust studies (box 2). To achieve these goals, no less than for placebo RCTs of other medical or psychological interventions, OLP clinical trials require much clearer reflection about conceptual matters and, as a consequence, greater attention to designing adequate placebo controls. Well-replicated studies are also important if we are to better educate clinicians about the necessary components of OLP treatments so that clinicians might: (a) implement these components effectively; and (b) where necessary, communicate the therapeutic value of the components truthfully to patients. Without robust clinical trials, which, in turn,

can enhance mechanistic research into OLP, clinicians may adopt a 'medical model' and assume that the prescription of the pills is sufficient to induce placebo effects. Thus, OLP research is not merely an academic pursuit. OLPs carry the potential to reduce patient suffering across a variety of conditions, and may even represent one useful approach for tackling the opioid crisis.[33] Only if future, methodologically robust, studies show that OLPs are still efficacious, will it be time to open up the conversation about using OLPs in clinical practice.

Acknowledgements The authors thank two anonymous reviewers for their generous feedback on an earlier version of this paper.

Contributors CRB: conceived the manuscript and drafted it; CL devised Table 1. All authors contributed to multiple revisions & in contributing to intellectual content (CRB, MB and CL) and all signed off on the final version.

Funding CRB was funded by an Irish Research Counci-Marie Skłodowska-Curie Global Fellowship (CLN/2017/226); MB was funded by a National Institute of Health grant (T32DA016184); CL was funded by a Swiss National Science Foundation grant (P400PS_180730).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

References

1. **Howick J**, Bishop FL, Heneghan C, *et al*. Placebo use in the United kingdom: results from a national survey of primary care practitioners. *PLoS One* 2013;**8**:e58247.
2. **Tilburt JC**, Emanuel EJ, Kaptchuk TJ, *et al*. Prescribing "placebo treatments": results of national survey of US internists and rheumatologists. *BMJ* 2008;**337**:a1938.
3. **Bishop FL**, Howick J, Heneghan C, *et al*. Placebo use in the UK: a qualitative study exploring GPs' views on placebo effects in clinical practice. *Fam Pract* 2014;**31**:357–63.
4. **Evers AWM**, Colloca L, Blease C, *et al*. Implications of placebo and nocebo effects for clinical practice: expert consensus. *Psychother Psychosom* 2018;**87**:204–10.
5. **Ballou S**, Kaptchuk TJ, Hirsch W, *et al*. Open-label versus double-blind placebo treatment in irritable bowel syndrome: study protocol for a randomized controlled trial. *Trials* 2017;**18**:234.
6. **Kaptchuk TJ**, Friedlander E, Kelley JM, *et al*. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One* 2010;**5**:e15591.
7. **Carvalho C**, Caetano JM, Cunha L, *et al*. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain* 2016;**157**:2766.
8. **Schaefer M**, Sahin T, Berstecher B. Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. *PLoS One* 2018;**13**:e0192758.
9. **Schaefer M**, Harke R, Denke C. Open-label placebos improve symptoms in allergic rhinitis: a randomized controlled trial. *Psychother Psychosom* 2016;**85**:373–4.
10. **Sandler AD**, Bodfish JW. Open-label use of placebos in the treatment of ADHD: a pilot study. *Child Care Health Dev* 2008;**34**:104–10.
11. **Hoenemeyer TW**, Kaptchuk TJ, Mehta TS, *et al*. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. *Sci Rep* 2018;**8**:2784.
12. **Charlesworth JEG**, Petkovic G, Kelley JM, *et al*. Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *J Evid Based Med* 2017;**10**:97–107.
13. **Kaptchuk TJ**, Miller FG. Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? *BMJ* 2018;**363**:k3889.
14. **Solomon M**. *Making medical knowledge*. USA: Oxford University Press, 2015.
15. **Locher C**, Gaab J, Blease C. When a placebo is not a placebo: problems and solutions to the gold standard in psychotherapy research. *Front Psychol* 2018;**9**:2317.
16. **Blease C**, Annoni M. Overcoming disagreement: a roadmap for placebo studies. *Biol Philos* 2019;**34**:18.
17. **Locher C**, Frey Nascimento A, Kirsch I, *et al*. Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain* 2017;**158**:2320–8.
18. **Kelley JM**, Kaptchuk TJ, Cusin C, *et al*. Open-label placebo for major depressive disorder: a pilot randomized controlled trial. *Psychother Psychosom* 2012;**81**:312–4.
19. **Zhou ES**, Hall KT, Michaud AL, *et al*. Open-label placebo reduces fatigue in cancer survivors: a randomized trial. *Support Care Cancer* 2019;**27**:1–9.
20. **Mathur A**, Jarrett P, Broadbent E, *et al*. Open-label placebos for wound healing: a randomized controlled trial. *Ann Behav Med* 2018;**52**:902–8.
21. **Kam-Hansen S**, Jakubowski M, Kelley JM, *et al*. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci Transl Med* 2014;**6**:218ra5–218.
22. **Sandler AD**, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in ADHD? *J Dev Behav Pediatr JDBP* 2010;**31**:369.
23. **Park LC**, Covi L. Nonblind placebo trial: an exploration of neurotic patients' responses to placebo when its inert content is disclosed. *Arch Gen Psychiatry* 1965;**12**:336–45.
24. **Aulas JJ**, Rosner I. [Efficacy of a non blind placebo prescription]. *Encephale* 2003;**29**:68–71.
25. **Baskin TW**, Tierney SC, Minami T, *et al*. Establishing specificity in psychotherapy: a meta-analysis of structural equivalence of placebo controls. *J Consult Clin Psychol* 2003;**71**:973–9.
26. **Watts SE**, Turnell A, Kladnitski N, *et al*. Treatment-as-usual (TAU) is anything but usual: a meta-analysis of CBT versus TAU for anxiety and depression. *J Affect Disord* 2015;**175**:152–67.
27. **Mohr DC**, Ho J, Hart TL, *et al*. Control condition design and implementation features in controlled trials: a meta-analysis of trials evaluating psychotherapy for depression. *Transl Behav Med* 2014;**4**:407–23.
28. **Furukawa TA**, Noma H, Caldwell DM, *et al*. Waiting list may be a nocebo condition in psychotherapy trials: a contribution from network meta-analysis. *Acta Psychiatr Scand* 2014;**130**:181–92.
29. **Munder T**, Brütsch O, Leonhart R, *et al*. Researcher allegiance in psychotherapy outcome research: an overview of reviews. *Clin Psychol Rev* 2013;**33**:501–11.
30. **Cuijpers P**, Driessen E, Hollon SD, *et al*. The efficacy of non-directive supportive therapy for adult depression: a meta-analysis. *Clin Psychol Rev* 2012;**32**:280–91.
31. **Howe LC**, Goyer JP, Crum AJ. Harnessing the placebo effect: Exploring the influence of physician characteristics on placebo response. *Health Psychol* 2017;**36**:1074–82.
32. **Kaptchuk TJ**, Kelley JM, Conboy LA, *et al*. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 2008;**336**:999–1003.
33. **Bernstein MH**, Magill M, Beaudoin FL, *et al*. Harnessing the placebo effect: a promising method for curbing the opioid crisis? *Addiction* 2018;**113**:2144–5.