Topical Review

PAIN 164 (2023) 2139–2142

PAIN®

Time to reflect on open-label placebos and their value for clinical practice

Caitlin M.P. Jones[a,b,*], Chung-Wei Christine Lin[a,b], Charlotte Blease[c,d], Jen Lawson[e], Christina Abdel Shaheed[a,b,f], Christopher G. Maher[a,b]

1. Introduction

Basic science has found limited evidence from small studies of genuine positive effects on health and wellbeing outcomes, caused by positive treatment expectations, known as placebo effects.[1] Naturally, many researchers and clinicians are curious about how to harness the placebo effect in clinical practice to improve patient outcomes. Research examining open-label placebos (OLPs) caused excitement when findings suggested that the positive effects of the placebo could be elicited without the need for deception, which made the concept more appealing.[32] Unfortunately, misunderstandings stemming from flawed research design and faulty assumptions about how these research findings can be ethically applied to clinical settings have provided a platform for the questionable proposal of prescribing OLPs to treat patients.

2. The fundamental misunderstanding of concepts and research methods

To discuss the misunderstandings in OLP research, it is important to first discuss the misunderstandings in placebo research in general. Unlike the placebo *effect*, the placebo *response* is any outcome seen in those who were assigned to a placebo group in a clinical trial, including but not limited to natural history and regression to the mean (**Fig. 1**). A Delphi study clarified these 2 concepts in 2019[4]; however, the error is still repeated today.

Many research articles report on the within-group change seen in placebo arms of trials and incorrectly conclude it to be the placebo effect.[10,18,28] This conflates the placebo effect with placebo response and leads to mistaken conclusions that the placebo effect is large and important (**Fig. 1**). Further to this, studies that incorrectly report the placebo response as the "placebo effect" are highly vulnerable to bias including (but not limited to) lack of blinding and lack of control for the time and interaction with a clinician.[5,7,16] Studies that use the more accurate method of calculating the between-group difference between a placebo group and a no-treatment group find much smaller estimates of the placebo effect but are still vulnerable to bias such as those described above, as well as small sample sizes and mild baseline pain.[15] Experimental placebo research has also been criticised because of mistaking the placebo response for the placebo effect, studying evoked pain, and having brief follow-ups.[7,8]

3. Placebos in clinical care

Recent expert commentaries have called for OLPs to become part of clinical care.[19,31] Although our best evidence is that merely offering placebos elicits small effects, surveys have found that the use of placebos in clinical practice does occur. Surveys from 2008, 2010, and 2019 conducted in primary care settings in Australia and the United States found that many doctors have prescribed a placebo at least once (from 55% to 80%).[12,14,30] Surveys from 2019 and 2020 conducted in Australia and the United States have also found that people with symptoms believed by the doctors to be psychosomatic, medically unexplained, and pain- or fatigue-related conditions (such as postviral syndromes) were more likely to be prescribed a placebo.[2,12] Despite a large percentage of doctors reporting using placebos, the frequency of placebo prescribing is not known. Nonetheless, surveys do offer clear evidence of an inclination for placebo use by clinicians. Currently, there are no guidelines that recommend using placebos clinically for specific conditions. The American Medical Association's code of ethics warns against using placebos to "mollify" a "difficult" patient but says that they can be considered if the patient is aware that it is a placebo and can therefore provide informed consent. This has given rise to the potential use of OLPs.

4. Are open-label placebos the answer?

The concept of an OLP is where the clinician delivers the treatment (a pill or procedure) with open disclosure that the intervention itself is not effective but that the patient may expect improvements because of the placebo effect. There is some enthusiasm for this approach, evidenced by recent commentaries, as it is thought of as a way of providing benefit to patients with conditions where there is no known effective treatment and avoids the unacceptable element of deception associated with undisclosed placebos[19,31]. Others say that OLPs should not be used because of a lack of unbiased research and that there are risks to patients including stigmatising and shaming (that have only been studies in self-selected research recruits and not in real patients), and may delay them from receiving real treatments.[6,21] We suggest now is the best time to examine this issue. We

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] *Sydney Musculoskeletal Health, The University of Sydney, Sydney, Australia,* [b] *The Institute for Musculoskeletal Health, The University of Sydney and Sydney Local Health District, Sydney, Australia,* [c] *Department of Women's and Children's Health, Uppsala University Sweden,* [d] *Digital Psychiatry, Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, United States,* [e] *Patient Advocate, Kalamazoo, Michigan, United States,* [f] *The University of Sydney, School of Public Health, Sydney, Australia*

**Corresponding author. Address: Sydney Musculoskeletal Health, Level 10N KGV Building, Missenden Road, Camperdown 2050, Australia. Tel.: +61 2 8627 6270. E-mail address: caitlin.jones@sydney.edu.au (C.M.P. Jones).*

http://dx.doi.org/10.1097/j.pain.0000000000003017

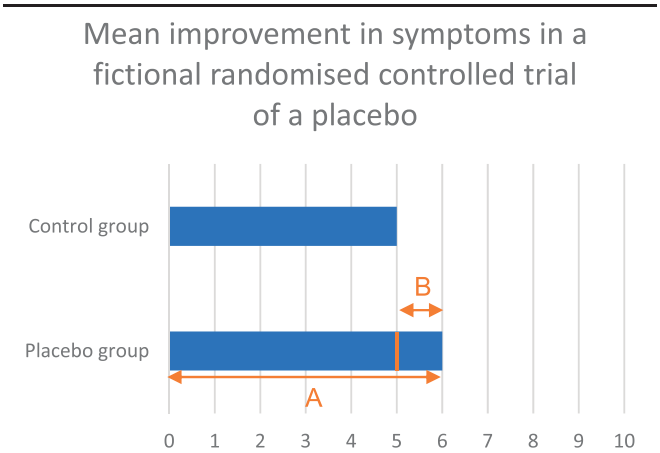

Figure 1. Conceptual drawing defining terms. (A) The within-group effect (any effect observed during the trial within the placebo group). In placebo trials, this is called the placebo response. (B) The between-group effect (the effect seen in the placebo group on top of the effect that was also seen in the control group). The placebo effect lies within the range labelled "B," but other effects may be also contributing to that difference depending on the trial design. The vertical orange line marks the point where any effect to the right of the line can be considered causal to being assigned to the placebo group but is not likely purely the placebo effect because of lack of blinding.

caution that OLPs should not be used, even for patients with conditions where there is no effective treatment, until we better understand their efficacy and acceptability among patients.

Clinicians may like the idea of an OLP because it offers them something to prescribe when there is pressure from patients to do "something."[14] A growing body of research into OLPs suggests that the concept is attractive to researchers too. A search on PubMed of "open-label placebo" shows a clear increase in number of articles published in recent years, for example, only 2 published in 2011 compared with 33 in 2022. The concept may be appealing to some patients. A 2014 qualitative study of 58 healthy recruits in the United Kingdom found mixed opinions, but a prominent theme was that healthy recruits considered placebo prescribing to be acceptable if there was no "deception,"[3] and that if the placebo "worked," then the mechanism was unimportant. A 2013 survey of 853 people treated for a chronic illness within the previous 6 months, conducted in the United States, found that almost 80% thought placebo prescribing was acceptable at least in some circumstances.[17] The participants believed "honest," open discussion about trialling a placebo was appropriate as a shared decision-making option. Moreover, as participants in these surveys were either healthy recruits or people with an unspecified chronic illness, it is unclear if these views are representative of people with difficult-to-treat conditions, who may be the people most likely to be offered OLPs.[2,12] Furthermore, it is not known whether responses were biased by participants recruited into placebo studies.

Currently, pure placebo tablets are not approved by regulatory bodies, eg, the Therapeutic Goods Administration in Australia. However, growing enthusiasm for OLPs evidenced by increased research output should give prudent reasons for the research and clinical communities to pause to critically examine the issue before going any further. Outstanding limitations with the strength of foundational evidence and important ethical considerations need to be carefully considered before risking unintended harm (like stigma, shame, or delaying proper treatment, discussed below) to patients who may already be living with a chronic illness or even conditions that have not yet been properly diagnosed.

5. Open-label placebo research programs lack rigour and patient codesign

Like much of the evidence from open-label trials, research into OLPs lack unbiased, convincing evidence of their efficacy. Studies of OLPs do not properly control for the positive preamble delivered alongside the placebo pill.[7] Although some studies do make an attempt by providing the positive preamble to both the OLP group and the control group,[20] they do not blind the participant to their treatment allocation. If anything, this would increase the bias as now the nontreatment groups believe they are missing out on the promising treatment that is OLP. A better control would be a preamble that sells no-treatment delivered with equal enthusiasm/credibility as the preamble that sells OLP. The trials also lack adequate researcher-clinician—patient blinding, and self-selection bias based on trial recruitment procedures.[5,7,10,18,28] Therefore, it is uncertain if OLPs have any therapeutic effect. An ideal OLP study would use control group that also receives the positive preamble about the recovery that can be expected because of the natural history of their condition, equal time with clinicians, blinding to treatment allocation, and blinded assessors where possible. This is incredibly methodologically challenging, and so it may be impossible to infer whether placebo effects drive the improvements seen in OLP studies. In addition triallists evaluating OLPs should follow best practice guidance for the design, conduct, and reporting of trials that apply in general when evaluating interventions. For example, in a recent systematic review of 13 OLP trials, the median sample size was only 66, and all trials had concerns about risk of bias.[32]

Perhaps an even more pressing issue with OLP research is that patients have not been involved in co-designing this program of research. Increasingly, medical funding calls for patients' contributions to shift from merely passive recipients to active co-designers of research programs.[25] We are not aware of any OLP studies that have systematically engaged patients as co-producers of research in this way. Although some studies have interviewed self-selected research participants who are open-minded to OLP based on their interest in joining such a study,[11,24] the real patient perspective has yet to be properly engaged. Testimonies from individuals (such as a coauthor of this article) suggest that OLPs may not be acceptable to some patients (**Fig. 2**).

The question at hand is whether it is ethical to offer patients an OLP. How honest and adequate are the ethics of informing patients of evidence that OLPs have positive effects, in light of the limitations with that evidence? How comfortable should we be when the potential for stigmatising patients is uncertain, and the risks of harm with OLP prescribing are unknown? Perhaps the ethical acceptability of OLPs might differ according to clinical contexts or among diverse patient populations. For example, in cases where there are effective treatments, most agree that there is no role for OLPs.[3] In the context of conditions where there is no known effective treatment, proposing OLPs as an option in the shared decision-making process is a gamble with unfavourable odds, when we do not know yet whether patients would likely find this stigmatising and offensive. Despite the perceived transparency when offering an OLP, there is an issue with deception unless we are properly informing patients about the limitations of the evidence.

The next logical step from here is to properly investigate patient acceptability, to know whether investigating the utility of OLPs as a shared decision-making option is even worth pursuing. The

> *"When doctors offer me treatments that they can't justify aside from 'let's just try, it might help,' I lose hope in that doctor. It is disheartening and frustrating. I have developed confidence over time to ask for their reasons for wanting to try new things, and I say no if the reasons aren't good enough. But you must be diplomatic. You're balancing the need to advocate for yourself against the risk that you will upset the doctor and they will put something in your permanent record that affects your care in the future. I have been offered treatments that I believe were intended as active placebos, and it is like they're telling me my symptoms are not physical. Like it's in my head and I am the problem. That doubt creeps in and eventually you are believing it yourself. I have trauma related to people not believing that I am in pain. I am done with that. I have done enough self-shaming."* – Jen Lawson has hypermobile Ehlers-Danlos syndrome, and other morbid conditions including life-long chronic pain

Figure 2. A patient's perspective.

issue here is that it is unclear whether we can properly elicit the patient perspective when we cannot offer reliable information about the effectiveness of open-label placebos compared with other treatments (or no intervention). As a priority, patient acceptability must be examined in the groups who are more likely to be offered an OLP based on the findings from surveys of prescribers, eg, difficult-to-treat conditions like chronic pain and chronic fatigue.[2,13] These patients often experience external and internalised stigma caused by doubt and suspicion from doctors about the symptoms that they report.[8,22,23,27] They are the most at-risk of psychological harm and erosion of trust by the vernacular, discrediting "it is all in your head" message—with connotations that the patient's pain is not real, made up, or exaggerated—that an OLP prescription may imply.[26]

Another risk of proceeding with OLPs without due critical reflection is the direct-to-consumer market. Although clinician prescription of placebos is currently prohibited because of the need for approval from medical regulators, there is no barrier to companies selling direct-to-consumers. There are numerous companies (eg, Zeebo and Silver Bullet) who legally sell OLP tablets over the internet. They uncritically cite studies of within-group change in support of "proven" effectiveness. Direct-to-consumer products are not regulated in the same way prescription medicines are, and so come with a risk of harm from contaminated products. One example of this from recent history is a direct-to-consumer imported placebo pill that was found to contain undeclared clenbuterol (a substance not approved for human use in Australia and other countries).[29]

Our hope is that this article gives clinicians and researchers pause to critically reflect on whether OLPs can and should be used in clinical care. Previously, other researchers have suggested that more research is required to determine the role for OLPs.[9,19] We echo their view and suggest the following steps from here. We must seek patient involvement and co-design in this research program. If OLPs are not of interest to those who are proposed to benefit from it, it may be unethical to invest public money into further enquiry. Next, we must aim to optimise control groups in OLP research. If it is too methodologically challenging to do so, we must acknowledge the uncertainty and temper conclusions accordingly. We must then make decisions about how to proceed by carefully considering the limitations of research to date and balancing the potential for OLPs to benefit patients with the risk of harms. In the meantime, clinicians should aim to promote the positive effects of positive expectations (eg, via reassurance). To encourage positive treatment expectations from a treatment that lacks solid evidence of efficacy such as OLP is ethically questionable at best.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgements

Professors Lin and Maher are supported by the National Health and Medical Research Council fellowships. The authors report no financial arrangements that might represent a possible conflict of interest.

Contributors and sources: C. M. P. Jones is postdoctoral research associate investigating the effects of opioid medicines, particularly against placebo, in musculoskeletal pain at the University of Sydney. Professor C.-W. C. Lin is an expert in evaluating the benefits and harms of treatments for musculoskeletal pain, having led multiple trials of medicines for musculoskeletal pain that have changed guidelines worldwide. Doctor C. Blease is a philosopher of medicine, interdisciplinary health researcher, and co-founder of the Society for Interdisciplinary Placebo Studies. She is based at General Medicine and Primary Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston. J. Lawson has hypermobile Ehlers–Danlos syndrome and other comorbid conditions and has a lifetime of experience advocating for herself within the medical system. She has been offered active placebos to treat her painful conditions. Doctor C. A. Shaheed's expertise is in the quality use of medicines across a range of conditions, including having led multiple high-quality systematic reviews. Professor C. G. Maher is the codirector of Sydney Musculoskeletal Health with expertise in low back pain research. Ms Jones, Dr Abdel Shaheed, and Professors Lin and Maher jointly conceived the idea for the manuscript. Ms Jones, Dr Blease, Dr Abdel Shaheed, and Professors Lin and Maher jointly worked on an outline for the manuscript. Ms Jones drafted the first version, and the others provided critical feedback. Ms Lawson provided critical feedback on later drafts of the manuscript and provided the quote in the Figure 2. Ms Jones is the guarantor of this article. Sources used in this article were systematic reviews that aimed to quantify the placebo effect for any condition, reviews summarising the body of evidence, and media stories reporting placebo research to the lay

public. Patient involvement: Jen Lawson provided an interview about her experiences with receiving placebos in clinical care, which was summarised in the quote shown in Figure 2. Ms Lawson also provided critical comments on the manuscript content. Ms Lawson has hypermobile Ehlers–Danlos syndrome and other morbid conditions, including chronic pain. She gave consent for her medical history to be disclosed and for her quote to be used in this article.

Funding: Professors Lin and Maher are funded by investigator grants from the National Health and Medical Research Council, Australia. Dr Abdel Shaheed is supported by a fellowship from The University of Sydney.

Data availability: No data (outside of citing prior research in the placebo field) were used in this article.

Article history:
Received 6 March 2023
Received in revised form 19 June 2023
Accepted 24 June 2023

References

[1] Benedetti F, Maggi G, Lopiano L, Lanotte M, Rainero I, Vighetti S, Pollo A. Open versus hidden medical treatments: the patient's knowledge about a therapy affects the therapy outcome. Prev Treat 2003;6:1-19.
[2] Bernstein MH, Locher C, Stewart-Ferrer S, Buergler S, DesRoches CM, Dossett ML, Miller FG, Grose D, Blease CR. Primary care providers' use of and attitudes towards placebos: an exploratory focus group study with US physicians. Br J Health Psychol 2020;25:596–614.
[3] Bishop FL, Aizlewood L, Adams AEM. When and why placebo-prescribing is acceptable and unacceptable: a focus group study of patients' views. PLoS One 2014;9:e101822.
[4] Blease C, Annoni M, Blease C, Annoni M. Overcoming disagreement: a roadmap for placebo studies. Biol Philos 2019;34:2.
[5] Blease C, Colagiuri B, Locher C. Replication crisis and placebo studies: rebooting the bioethical debate. J Med Ethics 2023. doi: 10.1136/JME-2022-108672.
[6] Blease CR. The role of placebos in family medicine: implications of evidence and ethics for general practitioners. Aust J Gen Pract 2019;48: 700–5.
[7] Blease CR, Bernstein MH, Locher C. Open-label placebo clinical trials: is it the rationale, the interaction or the pill? BMJ Evid Based Med 2020;25: 159–65.
[8] de Carvalho Leite JC, Drachler MdL, Killett A, Kale S, Nacul L, McArthur M, Hong C, O'Driscoll L, Pheby D, Campion P, Lacerda E, Poland F. Social support needs for equity in health and social care: a thematic analysis of experiences of people with chronic fatigue syndrome/myalgic encephalomyelitis. Int J Equity Health 2011;10:1–17.
[9] Colloca L, Howick J. Placebos without deception: outcomes, mechanisms, and ethics. Int Rev Neurobiol 2018;138:219–40.
[10] de Craen AJM, Tijssen JGP, de Gans J, Kleijnen J. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. J Neurol 2000;247:183–8.
[11] Druart L, Vauthrin O, Pinsault N, Locher C, Blease C. 'It's not my greengrocer, it's someone from the medical profession': a qualitative study regarding acceptability of deceptive and open-label placebo prescribing in France. Br J Health Psychol 2023;28:273–90.
[12] Faasse K, Colagiuri B. Placebos in Australian general practice: a national survey of physician use, beliefs and attitudes. Aust J Gen Pract 2019;48: 876–82.
[13] Faasse K, Colagiuri B. Placebos in Australian general practice: a national survey of physician use, beliefs and attitudes. Aust J Gen Pract 2019;48:876–82.
[14] Fässler M, Meissner K, Schneider A, Linde K. Frequency and circumstances of placebo use in clinical practice—a systematic review of empirical studies. BMC Med 2010;8:15.
[15] Hróbjartsson A, Gøtzsche PC; Cochrane Consumers and Communication Group. Placebo interventions for all clinical conditions. Cochrane Database Syst Rev 2010;2010:CD003974.
[16] Hróbjartsson A, Kaptchuk TJ, Miller FG. Placebo effect studies are susceptible to response bias and to other types of biases. J Clin Epidemiol 2011;64:1223–9.
[17] Hull SC, Colloca L, Avins A, Gordon NP, Somkin CP, Kaptchuk TJ, Miller FG. Patients' attitudes about the use of placebo treatments: telephone survey. BMJ 2013;347:f3757.
[18] Jones BDM, Razza LB, Weissman CR, Karbi J, Vine T, Mulsant LS, Brunoni AR, Husain MI, Mulsant BH, Blumberger DM, Daskalakis ZJ. Magnitude of the placebo response across treatment modalities used for treatment-resistant depression in adults: a systematic review and meta-analysis. JAMA Netw Open 2021;4:e2125531.
[19] Kaptchuk TJ, Miller FG. Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? BMJ 2018;363:k3889.
[20] Kleine-Borgmann J, Schmidt K, Hellmann A, Bingel U. Effects of open-label placebo on pain, functional disability, and spine mobility in patients with chronic back pain: a randomized controlled trial. PAIN 2019;160: 2891–7.
[21] Maher CG, Traeger AC, Abdel Shaheed C, O'Keeffe M. Placebos in clinical care: a suggestion beyond the evidence. Med J Aust 2021;215:252–3.e1.
[22] McManimen S, McClellan D, Stoothoff J, Gleason K, Jason LA. Dismissing chronic illness: a qualitative analysis of negative health care experiences. Health Care Women Int 2019;40:241–58.
[23] McManimen SL, McClellan D, Stoothoff J, Jason LA. Effects of unsupportive social interactions, stigma, and symptoms on patients with myalgic encephalomyelitis and chronic fatigue syndrome. J Commun Psychol 2018;46:959–71.
[24] Pan Y, Frank ML, Kaptchuk TJ, Nestoriuc Y. "Let's see what happens:"—women's experiences of open-label placebo treatment for menopausal hot flushes in a randomized controlled trial. PLoS One 2022; 17:e0276499.
[25] Riggare S. Patient researchers—the missing link? Nat Med 2020;26: 1507.
[26] Specker Sullivan L. More than consent for ethical open-label placebo research. J Med Ethics 2021;47:e7.
[27] Stone L. Managing the consultation with patients with medically unexplained symptoms: a grounded theory study of supervisors and registrars in general practice. BMC Fam Pract 2014;15:192.
[28] Stridh A, Pontén M, Arver S, Kirsch I, Abé C, Jensen KB. Placebo responses among men with erectile dysfunction enrolled in phosphodiesterase 5 inhibitor trials: a systematic review and meta-analysis. JAMA Netw Open 2020;3:e201423.
[29] Therapeutic Goods Administration. Placebo Tablets . 2017. Available at: https://www.tga.gov.au/alert/placebo-tablets. Accessed May 31, 2022.
[30] Tilburt JC, Emanuel EJ, Kaptchuk TJ, Curlin FA, Miller FG. Prescribing "placebo treatments": results of national survey of US internists and rheumatologists. BMJ 2008;337:a1938.
[31] Uchendu SN, Wang A. Less pain, more gain: should placebo be a clinical therapeutic? Arthritis Rheumatol 2020;72:511–4.
[32] von Wernsdorff M, Loef M, Tuschen-Caffier B, Schmidt S. Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. Sci Rep 2021;11:3855.