Society of Medical Education & Research

2021, Volume 1, Page No: 123-128
ISSN: 3108-5059

Asian Journal of Ethics in Health and Medicine

Placebo Without Deception: Ethical Implications of Open-Label Treatments

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Abstract

Evidence is increasingly showing that open-label placebos (OLPs) can serve as an effective and safe approach for managing a variety of chronic health conditions. Because patients are fully informed that they are taking a placebo, OLPs are typically viewed as an ethically sound alternative to traditional placebo treatments, which rely on deception. Yet, despite their safety and potential therapeutic benefits, the counterintuitive nature of OLPs can make clinicians hesitant to offer them in practice. To overcome this challenge, we propose framing OLPs in clinical settings as a calculated gamble that patients and practitioners can consider together.

Keywords: Placebo, Ethical, Open-Label Placebos (OLPs), Treatment

Introduction

Is there a legitimate role for open-label placebos (OLPs) in clinical practice? At first glance, this question may appear paradoxical. Placebos have traditionally been considered effective only when patients are unaware that they are receiving an inert treatment, as in double-blind placebo-controlled trials or when administered deceptively. How, then, could clinicians ethically recommend a pill that patients know contains no active medication? Despite this counterintuitive premise, a growing body of research demonstrates that OLPs can be effective for a range of chronic conditions, including chronic low back pain, cancer-related fatigue, and irritable bowel syndrome (IBS) [1–10]. Meta-analyses suggest that OLPs can produce moderate to large effects in clinical populations [11].

Access this article online https://smerpub.com/

Received: 19 May 2021; **Accepted:** 16 August 2021

How to cite this article: Yu C, Na L, Qiang W. Placebo Without Deception: Ethical Implications of Open-Label Treatments. Asian J Ethics Health Med. 2021;1:123-8. https://doi.org/10.51847/w61rmL5Qzv

From an ethical perspective, OLPs are generally regarded as a more acceptable alternative to traditional deceptive placebos, in which patients are given inactive substances under the false impression that they are receiving active treatment [12]. In modern clinical practice, the use of deceptive placebos is uncommon. Here, we explore the ethical implications of OLPs for patients with chronic conditions who have not achieved sufficient relief from standard therapies, drawing a comparison with the widespread practice of prescribing off-label treatments that lack robust evidence of efficacy. Surveys indicate that physicians in countries including the USA, UK, and Germany sometimes prescribe "impure" placebos—active agents with limited or uncertain specific benefit for the patient's condition [13, 14]. Examples include vitamins for fatigue without deficiency, antibiotics for probable viral infections, homeopathic remedies, and various herbal preparations.

To structure our discussion, we present three hypothetical but clinically plausible scenarios, focusing on IBS, a chronic condition for which evidence supporting OLP efficacy is growing [8–10]. We contend that prescribing OLPs can be ethically defensible and, in some cases, preferable to off-label interventions, particularly for

chronic conditions with no clear biomedical explanation and a lack of effective evidence-based therapies. Furthermore, we suggest that clinicians and patients can frame OLP as a "worthwhile wager," providing a practical and ethically coherent approach to its use in clinical practice.

Over-the-counter medication

To begin, consider the opening stage of a typical clinical consultation for IBS.

James takes a seat next to Dr. Halden's desk and immediately describes his discomfort. "It was so painful," he says, clutching his abdomen, "I couldn't even make it to work this morning."

Dr. Halden asks about his symptoms, including his diet and bowel habits, and then asks him to lie down for an examination. "This pain has lasted three days?" she inquires.

"Yes, that's right," he confirms

They discuss the pain further. Dr. Halden explains that it is likely associated with James's Irritable Bowel Syndrome. "Previously, you took Buscopan, which helped with your symptoms," she notes while checking his records, "but we stopped it because of the side effects."

James responds, "Yes, it was terrible. I had so much trouble urinating it just wasn't worth it. Is there another option that won't cause so many issues?"

At this initial stage, James reports significant pain, which Dr. Halden attributes to IBS. IBS is a prevalent condition affecting the digestive system, causing symptoms such as abdominal pain, bloating, diarrhea, or constipation, which often fluctuate. This variability can make the condition frustrating and difficult to manage. While there is no cure, some medications can help control or alleviate symptoms. In James's case, Buscopan, an antispasmodic that relaxes gut muscles, caused intolerable side effects, leading him to discontinue treatment. Recognizing this, Dr. Halden suggests an alternative.

"Well, peppermint oil is another option," she says. "There's some evidence that it can help relieve abdominal pain like yours. Like most treatments, it can have side effects."

"Do you mean the kind you can buy at a health-food store?"

"Yes, exactly. Mint has been used medicinally for thousands of years. Modern peppermint oil comes in capsules, taken like any other medication, and works similarly to Buscopan by relaxing the muscles of the bowel wall."

James asks about side effects. "Some people experience heartburn, indigestion, dry mouth, or belching, although most do not," Dr. Halden explains.

"Alright. It seems more natural than the previous option. Let's try it."

"Great. I'll write down the recommended brand and dosage. Take one capsule 30 minutes before meals, three times daily, for six weeks. Book a follow-up appointment in six weeks, and contact me if you have any questions."

Given James's difficulty tolerating Buscopan, it is reasonable for Dr. Halden to suggest another antispasmodic, peppermint oil. While the supporting evidence is limited, research suggests it may relieve IBS-related abdominal pain. From an ethical standpoint, peppermint oil is presented honestly, just as Buscopan was. The treatment rationale is straightforward and aligns with what patients typically expect from conventional medicine, enhancing acceptability. Additionally, peppermint has a long history of medicinal use, which may further convince James of its potential effectiveness. However, Dr. Halden must also inform him of possible side effects, which, though necessary for informed consent, could potentially influence the treatment's outcome [15, 16].

Off-label prescription medication

Despite reasonable expectations that peppermint oil might alleviate some of James's IBS symptoms, a month later he experiences little improvement and returns to Dr. Halden seeking alternative treatments.

"Well," Dr. Halden says, "some experts suggest that amitriptyline, an antidepressant, can help with certain IBS symptoms. It may work by modifying gut motility and the sensitivity of your digestive tract. That said, the evidence is not definitive."

James asks, "What do you think? Do you think it will work?"

Dr. Halden responds, "It's difficult to predict, but it could be helpful. I've seen success with some patients. If we try it, we'd start at a low dose and monitor how you respond."

James expresses concern about side effects. "Aren't antidepressants associated with many side effects?"

"Like any medication, there can be side effects," Dr. Halden explains, "though many patients tolerate low doses well. Some report fatigue, constipation, dry mouth, or headaches. If you experience problems, we can

discontinue treatment. I'll prescribe 10 mg once daily in the evening and review your progress in four weeks. Of course, if any issues arise sooner, you can contact me immediately."

When first-line IBS treatments fail in primary care, the National Institute for Health and Care Excellence (NICE) recommends considering low-dose tricyclic antidepressants like amitriptyline for their analgesic effects. However, although meta-analyses of randomized controlled trials suggest potential benefits, these studies were not conducted specifically in primary care and are generally small and underpowered [17–19]. Consequently, amitriptyline is not licensed for IBS-related abdominal pain. Prescribing a drug outside its approved indication is referred to as off-label prescribing. Contrary to some assumptions, off-label prescribing is relatively common, representing an estimated 10–20% of primary care prescriptions [20, 21]. For amitriptyline, off-label use exceeds 80% in some reports [21, 22]. In relation to placebo discussions, off-label prescriptions are often considered "impure placebos," avoiding criticisms of the concept—namely, that truly inert treatments do not exist, so labeling something pure or impure can be misleading [23].

Two factors contribute to the high prevalence of off-label prescribing. First, the cost of clinical trials necessary for formal approval can deter pharmaceutical companies if anticipated revenue does not justify the expense, even when expert consensus suggests effectiveness. Second, certain populations—such as children, pregnant women, and older adults—are often excluded from trials that form the basis of a drug's official license, despite potentially benefiting from treatment. Nevertheless, by modern evidence-based medicine standards, prescribing a medication without strong supporting evidence increases risks, which carries important ethical implications.

In James's case, Dr. Halden presents amitriptyline in a favorable light and downplays possible side effects. As with Buscopan and peppermint oil, she notes some risks but emphasizes that many patients tolerate the low dose well. However, she does not highlight the broader risks associated with off-label use nor mention that the drug is unlicensed for IBS. This illustrates a common challenge with off-label prescribing: treatments may not always be presented fully transparently. Given the heightened risks, clinicians should ensure rigorous informed consent and shared decision-making, explicitly disclosing a treatment's off-label status to patients [24, 25].

Open-label placebo

A month later, James continues to experience discomfort and has developed notable side effects from amitriptyline, including drowsiness and blurred vision. During a follow-up appointment, Dr. Halden presents a final alternative.

"There is another option we could consider, though it may seem unconventional," she says. "Some studies with IBS patients suggest that open-label placebo (OLP)—pills that contain no active medication—can improve symptoms. We could try this and monitor your response." [8–10]

James looks puzzled. "I don't really understand. I thought the placebo effect only works if you think you're taking a real drug. How would it help now that I know these are placebos?"

"That's a reasonable concern," Dr. Halden replies. "We used to think that as well. But recent research shows that meaningful improvement can occur even when patients know they are taking placebos. Essentially, your body can respond automatically to the act of taking the pills. You don't need to believe in their efficacy, but it's important to take them exactly as instructed. I admit it sounds strange, but keeping an open mind may help—there are many biological processes we don't fully understand, and this might be one of them." [8–10]

"Well, it sounds unusual, but I trust you. Let's try it. It's better than nothing," James says.

As with Buscopan and peppermint oil, Dr. Halden presents OLP treatment honestly, explaining the key principles established in clinical trials: the placebo effect can be powerful; the body may respond automatically; a positive mindset may help but is not required; and adherence to instructions is critical. Current research indicates that OLP can be effective for some IBS patients. A 2021 six-week RCT demonstrated clinically meaningful improvements in both OLP and double-blind placebo (DBP) groups, with no significant differences in IBS Severity Scoring System (IBS-SSS) scores, suggesting that patient blinding may not be necessary for therapeutic benefit9. These findings imply that, given its efficacy and lower risk of adverse effects, OLP might be preferable to peppermint oil in some cases.

Similarly, a recent trial of low-dose, titrated amitriptyline as a second-line IBS treatment provides a useful comparison [26, 27]. While this double-blind, placebo-controlled study showed significant differences in IBS-SSS scores between amitriptyline and placebo groups after six months, symptom severity decreased

substantially in both groups, and the minimum clinically important difference of 35 points between treatments was not achieved [26, 27]. This highlights the strength of the placebo response in IBS patients. Considering that low-dose amitriptyline offers only modest benefits over placebo and carries substantial long-term side effects, there is an ethical argument for offering OLP before prescribing tricyclic antidepressants.

A worthwhile wager

Of course, treatment decisions are rarely straightforward for every patient and clinician. Acceptance of interventions—whether peppermint oil, low-dose amitriptyline, or open-label placebo (OLP)—can be influenced by both patient and clinician perspectives on complementary medicine, the placebo effect, off-label prescribing, and other factors. The clinician–patient relationship also plays a critical role. For instance, excessive skepticism about placebo efficacy may make proposing OLP challenging, while negative attitudes toward antidepressants may similarly complicate off-label amitriptyline use.

In fact, commentators on the previously discussed amitriptyline trial have suggested framing tricyclic antidepressants for IBS as "neuromodulators" rather than antidepressants to improve acceptance [27]—a finding consistent with qualitative research on physician prescribing in functional bowel disorders [28]. Therefore, as with other clinical decisions, clinicians must integrate this knowledge into individualized care plans, balancing medical evidence with patient context. This highlights how evidential, epistemological, and ethical considerations are intertwined in clinical practice, particularly in emerging approaches such as OLP.

Despite these complexities, evidence indicates that OLP can be a safe and effective second-line option for certain patients with chronic conditions [8–10]. We propose conceptualizing OLP as a "worthwhile wager" in clinical practice. This analogy draws on Pascal's Wager, Blaise Pascal's famous argument for believing in God: Pascal contends that one should wager on God's existence because the potential gain—eternal life—is immense, whereas the potential loss is minimal [29]. Critics have argued that belief cannot simply be willed, but Pascal advises that individuals can act as if they believe—participating in practices such as taking holy water or attending masses—which may gradually cultivate genuine belief [29].

This reasoning parallels OLP. Since patients are aware they are taking a placebo, initial belief in the pill's efficacy is absent. However, empirical research suggests that neither patients nor clinicians need to believe in OLP for it to be potentially beneficial; they need only act as if it might work [30]. This aligns with broader conceptualizations of the placebo effect as decoupled from explicit belief, instead relying on ritual, hope, and engagement of the imagination [31–34].

In practice, patients begin OLP without expecting benefit but agree to take the treatment as directed. Symptom improvement may arise through a combination of natural disease progression, regression to the mean, and the ritualized act of pill-taking within a supportive clinical context, which may stimulate endogenous healing. This dynamic is illustrated in studies of OLP for menopausal hot flushes, where participants reported that initial improvements increased hope and anticipation of further improvement, potentially creating a positive feedback loop [35]. Notably, patient experiences suggest that while individuals may not attribute symptom changes directly to OLP, their engagement is primarily motivated by hope and curiosity, rather than belief or expectation [36].

Conclusion

Evidence supporting the use of open-label placebo (OLP) for a variety of chronic conditions continues to grow. By examining a typical clinical scenario involving OLP for IBS, we illustrate how this approach can be integrated into practice in an ethically sound manner. OLP may offer benefits comparable to off-label treatments while avoiding many of their associated side effects. Thus, despite its counterintuitive nature, OLP may hold a legitimate place within modern evidence-based medicine, which emphasizes expert clinical judgment, individualized application of evidence, and the centrality of the clinician–patient relationship. Whether clinicians and patients will embrace this seemingly paradoxical intervention in routine care, and whether it consistently produces meaningful therapeutic outcomes, remains to be determined. Nevertheless, we propose that one practical framework for realizing its potential benefit is for clinicians and patients to view OLP as a worthwhile wager.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: This accords with the American Medical Association (AMA) guidance on the use of placebo in clinical practice, whereby physicians may only use placebo if they enlist the patient's cooperation, obtain their consent to administer a placebo, and avoid giving a placebo merely to mollify a patient.

References

1. Ballou S, Kube T. Open-label placebo is an evidence-based treatment option for many chronic conditions. Pain. 2024;165:487–8.
2. Carvalho C, Caetano JM, Cunha L, Pinto-Ribeiro F, Leite-Santos N, Tavares I, et al. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain. 2016;157:2766–72.
3. Carvalho C, Pais M, Cunha L, Leite-Santos N, Caetano JM, Pinto-Ribeiro F, et al. Open-label placebo for chronic low back pain: a 5-year follow-up. Pain. 2021;162:1521–7.
4. Ashar YK, Sun M, Knight K, Wong A, Louie K, Barbot A, et al. Open-label placebo injection for chronic back pain with functional neuroimaging: a randomized clinical trial. JAMA Netw Open. 2024;7:e2432427. doi:10.1001/jamanetworkopen.2024.32427
5. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR, Kerr CE, McManus C, et al. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. Sci Rep. 2018;8:2784. doi:10.1038/s41598-018-21211-2
6. Zhou ES, Hall KT, Michaud AL, Kaptchuk TJ, Leventhal H, Weinstock-Guttman B, et al. Open-label placebo reduces fatigue in cancer survivors: a randomized trial. Support Care Cancer. 2019;27:2179–87. doi:10.1007/s00520-018-4516-7
7. Yennurajalingam S, Azhar A, Lu Z, Hui D, Shamieh O, Bruera E, et al. Open-label placebo for the treatment of cancer-related fatigue in patients with advanced cancer: a randomized controlled trial. Oncologist. 2022;27:1081–9. doi:10.1634/theoncologist.2022-0033
8. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One. 2010;5:e15591. doi:10.1371/journal.pone.0015591
9. Lembo A, Kelley JM, Nee J, Ballou S, Kaptchuk TJ, Kokkotou E, et al. Open-label placebo vs double-blind placebo for irritable bowel syndrome: a randomized clinical trial. Pain. 2021;162:2428–35. doi:10.1097/j.pain.0000000000002191
10. Nurko S, Saps M, Kossowsky J, Brown E, Van Tilburg MA, Scheinbaum J, et al. Effect of open-label placebo on children and adolescents with functional abdominal pain or irritable bowel syndrome: a randomized clinical trial. JAMA Pediatr. 2022;176:349–56. doi:10.1001/jamapediatrics.2021.5973
11. von Wernsdorff M, Loef M, Tuschen-Caffier B, Watzke B, Meyer S, Köhler S, et al. Effects of open-label placebos in clinical trials: a systematic review and meta-analysis. Sci Rep. 2021;11:3855. doi:10.1038/s41598-021-82865-2
12. Blease C, Colloca L, Kaptchuk TJ. Are open-label placebos ethical? informed consent and ethical equivocations. bioethics. 2016;30:407–14. doi:10.1111/bioe.12240
13. Linde K, Friedrichs C, Alscher A, Weidenhammer W, Melchart D, Witt CM, et al. Use of placebos and nonspecific and complementary treatments by german physicians - rationale and development of a questionnaire for a nationwide survey. Complement Med Res. 2013;20:361–7. doi:10.1159/000351164
14. Hardman DI, Geraghty AW, Lewith G, Bishop FL, MacPherson H, Howick J, et al. From substance to process: a meta-ethnographic review of how healthcare professionals and patients understand placebos and their effects in primary care. Health (Lond). 2020;24:315–40. doi:10.1177/1363459319845831
15. Nee J, Ballou S, Kelley JM, Lembo A, Kaptchuk TJ, Jensen KB, et al. Peppermint oil treatment for irritable bowel syndrome: a randomized placebo-controlled trial. Am J Gastroenterol. 2021;116:2279–85. doi:10.14309/ajg.0000000000001487
16. Weerts ZZRM, Masclee AAM, Witteman BJM, Kruimel JW, van Dijk SM, Otten RHJ, et al. Efficacy and safety of peppermint oil in a randomized, double-blind trial of patients with irritable bowel syndrome. Gastroenterology. 2020;158:S123–36. doi:10.1016/j.gastro.2019.12.046
17. Black CJ, Yuan Y, Selinger CP, Andrews JM, Ford AC, Whorwell PJ, et al. Efficacy of soluble fibre,

antispasmodic drugs, and gut–brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:117–31. doi:10.1016/S2468-1253(19)30354-4
18. Ruepert L, Quartero AO, de Wit NJ, Muris JWM, Bolk JH, Linders SW, et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2011;2011:CD003460. doi:10.1002/14651858.CD003460.pub3
19. Ford AC, Lacy BE, Harris LA, Quigley EM, Moayyedi P, Saito YA, et al. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. Am J Gastroenterol. 2019;114:21–39. doi:10.1038/s41395-018-0243-6
20. Eguale T, Buckeridge DL, Winslade NE, Hanley JA, Bate A, Tamblyn R, et al. Drug, patient, and physician characteristics associated with off-label prescribing in primary care. Arch Intern Med. 2012;172:781–8. doi:10.1001/archinternmed.2012.202
21. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 2006;166:1021–6. doi:10.1001/archinte.166.9.1021
22. Wong J, Motulsky A, Abrahamowicz M, Smolina K, Brophy JM, Buckeridge DL, et al. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. BMJ. 2017;356:j603. doi:10.1136/bmj.j603
23. Howick J. The relativity of 'placebos': defending a modified version of Grünbaum's definition. Synthese. 2017;194:1363–96. doi:10.1007/s11229-015-0886-2
24. Wilkes M, Johns M. Informed consent and shared decision-making: a requirement to disclose to patients off-label prescriptions. PLoS Med. 2008;5:e223. doi:10.1371/journal.pmed.0050223
25. Furey K, Wilkins K. Prescribing "Off-Label": what should a physician disclose?. AMA J Ethics. 2016;18:587–93. doi:10.1001/journalofethics.2016.18.6.ecas3-1606
26. Ford AC, Wright-Hughes A, Alderson SL, Moayyedi P, Quigley EM, Lacy BE, et al. Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment in primary care (ATLANTIS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;402:1773–85. doi:10.1016/S0140-6736(23)01418-3
27. De Wit N, Keszthelyi D. Low-dose amitriptyline in irritable bowel syndrome: ready for primary care? Lancet. 2023;402:1727–8. doi:10.1016/S0140-6736(23)01420-1
28. Ongaro G, Ballou S, Kube T, Lembo A, Kaptchuk TJ, Kelley JM, et al. Doctors speak: a qualitative study of physicians' prescribing of antidepressants in functional bowel disorders. Cult Med Psychiatry. 2023;47:669–83. doi:10.1007/s11013-023-09828-0
29. Pascal B. Pensées. London: Dent; 1910.
30. Hardman D. A fictionalist account of open-label placebo. J Med Philos. 2024;49:246–56. doi:10.1093/jmp/jhaa033
31. Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? Ann Intern Med. 2002;136:817–25. doi:10.7326/0003-4819-136-10-200205210-00011
32. Kaptchuk TJ. Placebo studies and ritual theory: a comparative analysis of Navajo, acupuncture and biomedical healing. Phil Trans R Soc B. 2011;366:1849–58. doi:10.1098/rstb.2010.0376
33. Kaptchuk TJ, Shaw J, Kerr CE, Conboy LA, Kelley JM, Csordas TJ, et al. "Maybe I made up the whole thing": placebos and patients' experiences in a randomized controlled trial. Cult Med Psychiatry. 2009;33:382–411. doi:10.1007/s11013-009-9143-x
34. Hardman D, Ongaro G. Subjunctive medicine: a manifesto. Soc Sci Med. 2020;256:113039. doi:10.1016/j.socscimed.2020.113039
35. Pan Y, Frank ML, Kaptchuk TJ, Lembo A, Kaptchuk TJ, Kelley JM, et al. "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. doi:10.1371/journal.pone.0276499
36. Haas JW, Ongaro G, Jacobson E, Kelley JM, Kaptchuk TJ, Lembo A, et al. Patients' experiences treated with open-label placebo versus double-blind placebo: a mixed methods qualitative study. BMC Psychol. 2022;10:20. doi:10.1186/s40359-022-00726-7