Title

A worthwhile wager: the ethics of open label placebo treatment in clinical practice

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Abstract

There is increasing evidence for the use of open label placebo (OLP) as an effective and safe treatment for a range of chronic conditions. OLP is generally conceived as an ethical alternative to classic placebo treatment because patients know that they are taking a placebo and are hence not deceived. However, despite its potential benefits and lack of side effects, the paradoxical nature of OLP may make it difficult to propose as a treatment option in clinical practice. To mitigate this issue, we propose a practical way for clinicians and patients to conceive of OLP in clinical practice: namely, as a worthwhile wager.

1. Introduction

Is there a legitimate role for open label placebo (OLP) in clinical practice? On its face, this question might seem nonsensical. It has long been assumed that placebos can be effective in relieving symptoms only if they are concealed, as in double-blind placebo-controlled trials or administered deceptively. How can clinicians recommend that patients take pills that they both know contain no medication? However, despite its counter-intuitive and paradoxical character, there is an increasingly robust evidence-base for the use of OLP to treat a range of chronic conditions [1], including chronic low back pain [2–4], cancer-related fatigue [5–7], and irritable bowel syndrome (IBS) [8–10]. Meta-analyses have demonstrated medium to large effects in clinical samples.[11]

Beyond questions of effectiveness, OLP treatment is generally considered an ethical alternative to classic deceptive placebo treatment – whereby a patient is given a sugar pill, or suchlike, but told it is an effective drug – because patients know that they are taking a placebo and are hence not deceived [12].[1] However, in modern clinical practice, classic deceptive placebo treatment is rare. Therefore, in this article we investigate the ethics of OLP, for patients with chronic conditions who have not received a satisfactory response to standard treatments, by way of comparison with the widespread practice of physicians prescribing off-label treatments to patients without solid evidence of efficacy. Surveys have revealed that physicians in the U.S., the U.K., Germany, and other countries occasionally or frequently prescribe "impure" placebos: active drugs that lack, or have equivocal, evidence of specific efficacy for the patient's condition.[13,14] These include vitamins for patients

[1] 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.

complaining of fatigue but lacking signs of vitamin deficiency, antibiotics for probable viral infections, homeopathic remedies, and various herbal treatments.

Our investigation proceeds by describing and reflecting on three hypothetical but realistic clinical scenarios. To make the scope of our investigation manageable, we focus on one chronic condition – IBS – for which there is increasing evidence for the effectiveness of OLP treatment.[8–10] We argue that prescribing OLP can be an ethically acceptable option, and potentially superior to prescribing off-label treatments, for some patients with chronic conditions for which there is no clear biomedical explanation and a lack of effective evidence-based treatments. We further argue that a practical way for clinicians and patients to conceive of OLP in clinical practice is as *a worthwhile wager*.

2. Over-the-counter medication

To get started, let us first consider the initial stage of an everyday clinical consultation involving the treatment of IBS.

> James sits down in the chair next to Dr Halden's desk and dives straight into the problem. "It was so painful," he says, holding his midriff, "I didn't even make it in to work this morning."
>
> Dr Halden talks to James about how he is feeling, his diet and his bowel movements. She instructs him to lie on the bed so she can examine him. "You've had this pain for three days?" she asks.
>
> "Yes, that's right."
>
> They discuss the pain for a while. Dr Halden suggests that it is very likely to be related to James's Irritable Bowel Syndrome. "You were taking Buscopan before and it helped relieve your symptoms," she says, looking at the computer, "but we stopped it because of the side effects."
>
> "Yes, it was awful. I was having such difficulty going for a pee it just wasn't worth it. Is there not something else you could recommend? Something that won't cause me so many problems?"

In this initial stage of the consultation, James reports that he is in considerable pain, which Dr Halden attributes to his irritable bowel. IBS is a common condition that affects the digestive system and can cause various symptoms, such as stomach pain, bloating, diarrhoea, or constipation, which can fluctuate over time. This can make IBS challenging and frustrating to live with. There is currently no cure for IBS, but some medicines can help some patients to control or relieve their symptoms. In this case, James had been taking Buscopan, an antispasmodic drug that relaxes the muscles of the gut. Unfortunately, as in James's case, Buscopan can cause unwanted side effects, such as difficulty passing water, which can lead patients to cease treatment. Given James's problems, Dr Halden suggests an alternative.

"Well, peppermint oil is another option," replies Dr Halden. "There is some evidence that peppermint oil can help to relieve abdominal pain such as yours, but, like most medicines, it has some potential side effects."

"Like what you can get from the health-food shop?"

"Yes, that's right, you can just get it over the counter. Mint has been used for medicinal purposes for thousands of years. Modern peppermint oil comes in capsules that you take just like any other drug. It works, much like Buscopan, by helping the muscle of the bowel wall to relax."

"Ok. You mentioned that I might get some side effects?"

"Like anything else there are some potential side effects. In the case of peppermint, some people do experience heartburn or indigestion, dry mouth, and sometimes belching. Although most people do not experience these."

"Ok, right. Well it seems more natural than the other option. Let's give it a go."

"Great. I'm going to write down the brand of capsule that I recommend. You can get this over the counter at your local pharmacy. I'll also write down the dosage. Take one capsule 30 minutes before meals, three times a day, for six weeks. If you have any questions just let me know. Book an appointment at reception for six weeks' time and we'll see how you are getting on."

Given James did not tolerate taking Buscopan, it is logical for Dr Halden to propose another antispasmodic medication – peppermint oil – instead. Although the evidence is not robust, there is some support for the effectiveness of peppermint oil in treating stomach pain caused by IBS.[15–18] From an ethical perspective, peppermint oil is, like Buscopan, honestly and openly presented to James. Moreover, peppermint oil has a simple rationale that is easily explained. Although it might not be considered mainstream medicine by some patients, the kind of explanation given – i.e. biomedical – is one that most patients would expect and of the same kind that is given for most mainstream medicine. There is also a long cultural history of people taking mint medicinally. This may help to convince James that it works. However, in presenting peppermint oil openly and honestly to James, Dr Halden must also make him aware of the notable side effects that could occur; so doing could negatively affect treatment outcomes.

3. Off-label prescription medication

Despite the reasonable expectation that peppermint oil might help to alleviate some of James's symptoms, a month later he is still not receiving any notable relief and feeling desperate, so he returns to see Dr Halden about other options.

> "Well, some experts think that amitriptyline, an antidepressant, can help with some IBS symptoms" says Dr Halden. "It can work by altering gut mobility and the sensitivity of your digestive tract. Although, I have to say that some of the evidence for this is inconclusive."
>
> "Ok. What do you think about it? Do you think it will work?" asks James.
>
> "It's hard to say I'm afraid, but it might be helpful. I have had some success with other patients in the past. If we do go down this route, we would start you off on a low dose and see how we get on."
>
> "Aren't there also lots of side effects with anti-depressants though?"

> "Like any medication there can be some side effects, although many patients do not experience them, especially at a low dose. Some patients have experienced things like fatigue, constipation, dry mouth and headaches. However, if you feel uncomfortable then we can just stop the treatment. I will write you a prescription for 10 milligrams to start with, to be taken once a day in the evening. We'll review it after four weeks. Obviously it's an open door before then if you are having any problems."

When first-line therapies for IBS in primary care are ineffective, the National Institute for Health and Care Excellence (NICE) suggests that clinicians should consider low-dose tricyclic antidepressants, such as amitriptyline, for their analgesic effect. However, despite meta-analyses of randomised controlled trials (RCTs) suggesting that tricyclic antidepressants might be beneficial for patients, such as James, none of the contributing trials were conducted specifically in primary care, and most of them are small and underpowered.[19–21] Given these limitations, tricyclic antidepressants, such as amitriptyline, are not licensed for treating abdominal pain associated with IBS. Prescribing medication for an indication for which it has not received approval is commonly referred to as 'off-label prescription'.

Contrary to what some patients might think, off-label prescription is common, with some reports suggesting that it accounts for 10-20 percent of all prescriptions in primary care.[22,23] For amitriptyline specifically, off-label prevalence rates of over 80% have been reported.[23,24] With respect to placebo treatment, the prevalence of off-label prescription is important because what some researchers term "impure placebos" are, in clinical practice, more commonly conceived of as off-label prescription. Conceiving of impure placebos as off-label prescription sidesteps problematic critiques of the impure placebo concept; notably, that nothing is actually inert, insofar as one can treat any substance, even a sugar pill, in physico-chemical terms if one chooses to do so, therefore the pure/impure distinction seems mistaken.[25]

There are two main reasons for the high prevalence of off-label prescription. First, the high cost of conducting the necessary clinical trials required for relabelling, which dissuades pharmaceutical companies if the revenue associated with a particular indication is not offset, even if expert consensus suggests that the drug is effective. Second, certain populations – such as children, pregnant women, and older adults – are regularly excluded from clinical trials from which drugs derive their on-label license, despite likely befitting from the treatment. Such issues notwithstanding, by the standards of modern evidence-based medicine, if there is no convincing scientific evidence supporting the use of a particular medication for a particular indication, then the risks of prescribing that medication are notably increased. This, in turn, has significant ethical implications.

In James's case, one could argue that Dr Halden presents amitriptyline in a favourable light and downplays the potential side effects. As with peppermint oil and Buscopan, in openly presenting amitriptyline as an option, Dr Halden does note some potential side effects. But she also notes that many patients do not experience them, especially at the low dose that she will prescribe, and does not present the more general risks associated with off-label prescription. Moreover, Dr Halden does not mention that amitriptyline is not licensed to treat IBS. One might therefore argue that, as is often the case with off-label prescription, amitriptyline is not presented completely transparently. Given the higher risk associated with off-label prescription, clinicians should even more rigorously ensure that informed consent and shared decision making processes are implemented in consultations, including clear disclosure about a treatment's off label status.[26,27]

4. Open label placebo

Unfortunately, another month later James is still in some discomfort and is experiencing drowsiness and blurred vision, notable side effects associated with amitriptyline. In a follow-up visit, Dr Halden offers James a final alternative treatment.

> "There is something else we could try, but it's a bit out there. The surprising results from some studies with IBS patients suggest that openly taking placebo pills – by that I mean pills that don't contain any medication – might be effective for treating your symptoms. We could give that a go and see how you get on."
>
> "I'm sorry, I don't really understand. Doesn't the placebo effect only work if you think you are taking something else? How will it work now you have told me I will be taking placebos?"
>
> "Well, that's right insofar as that's what we used to think. But recent results suggest that you can get meaningful improvement even if you know you are taking placebos. Essentially, the way it works is that your body can automatically respond to taking the placebo pills. So the treatment works by triggering processes that are already there in your body. You don't have to believe that placebos work to experience benefit, but it is important that you take the pills exactly as I instruct you to. To be honest, I do share your puzzlement, but keeping an open mind can really help on this. There are lots of processes we don't fully understand, and this might just be one of those."
>
> "Well, it sounds a bit odd, but I trust you so let's give it a go. It's better than nothing!"

As with the instances of prescribing Buscopan and peppermint oil, Dr Halden presents OLP treatment honestly and openly, giving an explanation that covers the key points outlined in OLP trials: the placebo effect is powerful; the body can automatically respond to taking placebo pills; a positive attitude can help but is not essential; and you must take the pills exactly as instructed.[8] And, as Dr Halden notes in the consultation, recent research suggests that OLP can be an efficacious treatment for IBS symptoms for some patients. In particular, a 2021 6-week RCT showed clinically meaningful improvement in IBS symptoms in both OLP and double-blind placebo (DBP) groups, and showed that OLP and DBP groups did not differ significantly on IBS Severity Scoring System (IBS-SSS) improvement, suggesting that blinding may not be necessary for placebos to be effective.[9] One might therefore argue that, given recent research suggests that OLP is an effective treatment for treating IBS symptoms but is associated with less adverse events, OLP is preferable to peppermint oil. A similar,

albeit less conclusive inference could be made from a recent clinical trial investigating low-dose and titrated amitriptyline as a second-line treatment for IBS.

Given the questionable generalisability of extant findings on the use of tricyclic antidepressants for treating IBS symptoms, noted previously, a recent double-blind placebo-controlled trial assessed whether titrated low-dose amitriptyline was effective as a second-line treatment for IBS in primary care.[28] Although the results showed a significant difference in IBS-SSS mean scores between patients in the amitriptyline and placebo groups at six months, IBS symptom severity dropped substantially in both groups, and the 35-point minimum clinically important difference between treatment groups was not met.[28,29] Thus, although the trial does provide support for the use of low-dose amitriptyline for treating IBS symptoms, it also demonstrates the strength of placebo in patients with IBS.[29] Given the therapeutic benefit of low-dose amitriptyline was only modestly above placebo, and given research suggests that OLP treatment can be as effective as DBP for treating IBS symptoms, one might infer that the trial also indirectly supports the use of OLP for treating IBS symptoms. Moreover, given tricyclic antidepressants have significant long term side effects, one might argue that there are ethical grounds for clinicians proposing OLP as a treatment option before proposing low-dose amitriptyline.

5. A worthwhile wager

Of course, for particular patients and clinicians in particular situations, treatment decisions are not so simple. The acceptance of all treatments – including peppermint oil, low-dose amitriptyline and OLP – is, in part, affected by patients' and clinicians' views on complementary medicine, the placebo effect, off-label prescribing of antidepressants and other issues. It is also affected by the relationship a patient has with their clinician. For example, some clinicians and/or patients might be overly sceptical about the effectiveness of placebo, which may make it difficult to propose OLP as a treatment option. Similarly, some

clinicians and/or patients might have negative perceptions of antidepressants, making off-label prescription of low-dose amitriptyline equally difficult; indeed, in a comment article on the trial previously discussed, researchers suggested reframing tricyclic antidepressants in the context of IBS as 'neuromodulators' rather than antidepressants to overcome this very issue. [29] This also accords with qualitative findings of how physicians prescribe tricyclic antidepressants in functional bowel disorders.[30] Thus, as with treatment decisions more widely, clinicians need to incorporate this information into their approach in order to tailor their advice, based on medical evidence, to the individual patient and particular situation. This foregrounds the entanglement of evidential-epistemological and ethical issues in clinical practice, which are especially important in emerging treatment paradigms, such as OLP.

Such issues notwithstanding, given there is evidence that OLP can, for certain patients, be an effective and safe second-line treatment for certain chronic conditions, we propose a practical way to conceive of OLP treatment in clinical practice: namely, as a worthwhile wager. We can make sense of this by analogy with "Pascal's Wager", the name given to Blaise Pascal's famous argument for believing (or at least taking steps to believe) in God. Put simply, Pascal argues that we should wager that God exists because there is much to gain, especially the gift of eternal life, but nothing to lose in doing so. However, one critique of Pascal is that, if he is arguing that you should *believe* in God, we cannot simply do so at will. Pascal's response to this objection – his response to the non-believer – is well-known.

> But at least learn your inability to believe, since reason brings you to this, and yet you cannot believe… You would like to attain faith, and do not know the way; you would like to cure yourself of unbelief, and ask the remedy for it. Learn of those who have been bound like you, and who now stake all their possessions. These are people who know the way which you would follow, and who are cured of an ill of which you would be cured. Follow the way by which they began; by acting as if they believed, taking the holy water, having masses said, etc. Even this will naturally make you believe, and deaden your acuteness.[31]

Pascal thus offers a central piece of advice: it is not that one must try to *believe* in God at will but only, at least in the first instance, act *as if* one believes. And this certainly involves actions one can perform at will. Again, there is a direct analogy with OLP. Given that belief in the effectiveness of the pill is, unlike in deceptive or concealed placebo treatment, absent in OLP, a recent alternative explanation – grounded in empirical investigations into patient experiences – argues that patients and clinicians do not have to believe that OLP works but only act *as if* it does.[32] This explanation accords with broader accounts in which the placebo effect is decoupled from belief, grounded instead in ritual efficacy, hope, and an appeal to the imagination.[33–36]

On this view, at the outset of taking OLP there is no expectation of benefit or belief that it is likely to work, but the patient is willing to act as if OLP is a treatment that can work. During the course of taking OLP, as directed by a clinician, the natural history of the patient's condition/regression to the mean may contribute to symptom improvement. While the underlying mechanism of symptomatic improvement remains unclear, we suggest that, in addition, the ritual act of taking OLP, in the context of clinical care, stimulates endogenous healing. This dynamic is reflected in an investigation of women's experiences of open-label placebo treatment for menopausal hot flushes, insofar as "feeling improvement increased their hope and built anticipation for more improvement, potentially creating a positive cycle."[37] What seems clear from investigations into experiences of OLP treatment, however, is that not only are patients generally ambivalent about attributing symptomatic improvement directly to OLP, but when questioned about their drive to engage with OLP treatment they foreground hope and curiosity, rather than belief or expectation.[38]

6. Conclusion

There is increasing evidence for the use of OLP to treat a range of chronic conditions. Through careful consideration of an everyday clinical situation involving OLP treatment for

one such condition – IBS – we highlight how OLP may be adopted in clinical practice in an ethically appropriate way. OLP may be no less beneficial than off-label treatments, without the potential for side effects. Therefore, despite being paradoxical, OLP may have a legitimate role to play within the context of modern evidence-based medicine, which promotes the importance of expert clinical judgement, the role of individualised evidence, and the significance of the clinician-patient relationship. It remains to be seen whether, in the routine practice of medicine, clinicians and patients are prepared to adopt the paradoxical treatment of OLP and whether it succeeds in producing therapeutic benefit. However, one way in which such therapeutic benefit might be practically realised, we argue, is for clinicians and patients to conceive of OLP as a worthwhile wager.

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