



ANALYSIS

Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits?

Results from small clinical trials suggesting that placebos can be ethically and effectively used in clinical practice warrant further study, argue **Ted Kaptchuk and Franklin Miller**

Ted J Kaptchuk *professor of medicine*¹, Franklin G Miller *professor of medical ethics*²

¹Program in Placebo Studies, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA; ²Weill Cornell Medical College, New York, NY USA

Placebo treatments in randomised controlled trials produce significant improvement in many subjective symptoms.¹ Until recently, it has been presumed that placebo pills can produce therapeutic benefit only if patients do not know that they have received a placebo. Intriguingly, the results of several, albeit small, randomised trials of open label placebo suggest that patients can experience symptom relief from taking pills that they know lack any medication.

The placebo concept

For biomedicine, if an intervention is equivalent to placebo treatment it warrants rejection. In the past 20 years, basic science research has shown that although placebo treatments primarily modify subjective symptoms, various neurotransmitters (eg, endorphins, dopamine, and cannabinoids) and specific, quantifiable, and relevant regions of the brain are engaged.² Potential genetic markers are emerging.³ Importantly, clinical research has shown that placebo effects are more than spontaneous improvement and regression to the mean.⁴ Placebo effects have gained a new legitimacy.

This raises a critical question: can placebo pills be used ethically in clinical practice? Conventional wisdom has assumed that deception or concealment is necessary for placebos to work. Until recently, this belief has posed an insurmountable barrier to ethically harnessing placebo effects.

Open label placebo studies

One of us (TK) has been an investigator in four randomised trials of open label placebo, each in different conditions, each with over 60 patients. In these four studies patients were randomised to receive open label placebo (pills described as “inert placebos containing no medication”) plus usual treatment or usual treatment (and in one case no treatment.)

To control for provider interaction and time, patients in three of the studies received information about both groups, had identical patient-provider interactions, and were assigned to

either arm only after all discussion was complete. During the 10-15 minute orientation researchers sought to remove negative connotations about placebo by describing placebo responses in double blind trials for the target condition. Patients were told that it was not known whether open label placebo worked for their condition and testing this question was the purpose of the trial, with information provided transparently and neutrally. They were told about neurobiological and psychological evidence concerning placebo effects in general. The dialogue emphasised, “let’s see what happens.”⁵

The first trial involved people with irritable bowel syndrome⁶ and included 80 patients followed for three weeks. Patients receiving placebo reported 60% global improvement compared with 35% improvement among those getting only usual treatment (P=0.002). In the second trial, in 83 people with chronic low back pain, participants randomised to placebo plus usual treatment had a 28% reduction in pain after three weeks compared with 9% in the usual treatment group (P<0.001). Pain disability was reduced 29% versus 0.02% (P<0.001).⁷

A third study in 74 patients with cancer related fatigue found that, after three weeks, those randomised to open label placebo reported 29% improvement in fatigue compared with 10% for the usual treatment control (P=0.008). Disruption of quality of life caused by fatigue improved by 39% versus 5% (P=0.002).⁸

The fourth study was a prospectively nested randomised trial of episodic migraine attacks.⁹ For the open label placebo part of the study, 66 patients served as their own control and received placebo or no treatment during two separate episodes. Patients did not have an orientation regarding placebo responses. Nonetheless, patients reported a 15% improvement in pain when taking the open label placebo and 15% worsening of pain with no treatment (P=0.001).

Assessors were blind to treatment assignment in these studies. The consistency and magnitude of symptomatic relief across these studies—performed in hospitals on two continents—suggest that open label placebo may have a real

therapeutic benefit. Three smaller pilot or feasibility clinical studies of open label placebo—two in people with allergic rhinitis (n=25, n=45)^{10 11} and one in depression (n=20)¹²—also suggest potential benefits. In addition, two independent studies in chronic low back pain (n=127) and cancer related fatigue (n=40) recently reported significant positive results.^{13 14}

However, because trial participants cannot be blind to whether they have received open label placebo, report bias may affect the observed results. Additionally, given that successful small trials are often followed by failed large scale trials, we do not know whether the benefits of open label placebo will be seen in larger replications.

How might open label placebo work?

The psychological mechanisms underlying the observed effectiveness of open label placebo are unclear. The usually cited psychological processes connected with placebo response—expectation and classic conditioning—are unlikely to adequately explain the therapeutic benefits seen in the trials.¹⁵ Most of the participants in the main trials of open label placebo described above experienced refractory symptoms and were frustrated by multiple unsuccessful treatments.^{5 15} Although some participants seemed to enjoy the novelty of open label placebo, many also described the intervention as “crazy” and overwhelmingly denied initial positive expectations during their intake and exit interviews.^{5 15} They did, however, often express “hope” connected to despair—a kind of “tragic optimism” that allowed them to continue to seek treatment even from a counterintuitive intervention.

Recent neuroimaging evidence showing that non-conscious mental processes can initiate placebo effects is compatible with open label placebo.¹⁶⁻¹⁸ Furthermore, parallel research in cognitive science concerning prediction processing, bayesian brain, and embodied cognition underscores the idea that the brain can operate as an automatic prediction machine independent of conscious awareness.^{15 19} We speculate that the dissonant and contradictory open label placebo message—“it’s an inert pill without physiological effects” versus “it could help you, let’s see what happens”—may weaken the central sensitisation involved in many subjective complaints.²⁰ The response probably involves some of the same neurotransmitters associated with concealed placebo effects, but more research is required.²¹

Which conditions respond?

Despite the identification of a neurobiological substrate for placebo effects, there is little evidence that placebo treatments change underlying pathophysiology beyond the manifestation of symptoms.²² We hypothesise that open label placebo may be valuable for conditions with self reported outcomes where placebo responses in double blind trials are substantial and rival the active intervention. For example, placebo effects do not shrink oncological tumours, but open label placebo might be worth investigating for cancer related symptoms with high placebo responses such as nausea, pain, and hot flushes, as we have seen already in cancer related fatigue.^{23 24} Patients with malaria or high cholesterol levels, on the other hand, are unlikely to benefit from open label placebo.

Implications for clinical practice

Many patients seem prepared to try placebo if it is honestly prescribed. We carried out a telephone survey of attitudes towards placebos among 853 patients in a large US healthcare

system. After being read a vignette based on the study in irritable bowel syndrome described above, 62% of patients (529) reported that they would probably or definitely take open label placebo in this context if recommended by a doctor.²⁵ A focus group study of 58 people in the UK had similar findings.²⁶

If positive evidence accumulates from larger studies would clinicians be willing to adopt open label placebo as a therapeutic strategy? A potential barrier is that it goes against the grain of medical training and norms of medical practice in which physicians prescribe drugs with biochemical properties known to promote therapeutic benefit. However, survey research indicates that physicians often use placebo treatments in routine care.²⁷ For example, a US randomised survey of 1200 internists and rheumatologists found that about half of the physicians (46-58%) prescribe placebo treatments regularly.²⁸ Although placebo pills or saline are rarely used (2-3%), physicians often adopt the ethically dubious and paternalistic practice of “impure placebos,” such as vitamins to treat fatigue in the absence of any evidence of vitamin deficiency (38%) or using over-the-counter analgesics only for their placebo value (41%).²⁸ Ethical analyses have found that open label placebo conforms with ethical standards of transparency and informed consent.²⁹

Moving research forward

Open label placebo research has thus far consisted of small studies of short duration. Replication with larger sample sizes and longer duration is needed, and the psychological and neurobiological mechanisms underlying the observed effectiveness of open label placebo need to be investigated.

Whether the effects seen in open label placebo studies can be translated into routine clinical care is not clear. The observed outcomes, at least to some extent, may be a product of the experimental context of deploying a counterintuitive intervention by investigators with at least some interest in showing that open label placebo can relieve symptoms.

We need more information on the duration of open label placebo’s effects, who responds, optimal and ethical ways to present open label placebo to patients, and how to discuss failure to respond. Clinician education, training manuals, and workshops might help with initial implementation. Qualitative research needs to elucidate what makes patients and physicians comfortable with open label placebo. However, if confirmatory evidence increases, open label placebo could offer a possible supplementary intervention in some chronic conditions and an honest approach for a watch-and-wait strategy.

Key messages

Placebo pills in randomised trials can significantly benefit patients’ subjective symptoms

Using placebo pills clinically is an ethical challenge as prevailing wisdom asserts that deception or concealment is required

Recent small randomised trials suggest that openly prescribing placebo can evoke meaningful therapeutic benefits

More research is required to determine the role for open label placebo and the conditions in which it is effective.

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