The paradox of "open-label placebos": Recent trial results and implications for clinical practice

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The paradox of "open-label placebos": Recent trial results and implications for clinical practice

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Giving patients a transparent or open-label placebo (OLP) with the aim of promoting therapeutic benefit seems like a crazy idea. Isn't it obvious that patients must believe (or be uncertain about whether) the placebo is a real treatment in order to produce a placebo effect? Intriguingly, the results of several, albeit small, OLP trials in a variety of medical conditions suggest that patients can experience symptom relief from taking pills described honestly as lacking any medication.

Current status of placebo concept

"Placebo" is usually a pejorative term used to denigrate therapies deserving rejection: "It's no more than a placebo." In the last fifteen years, basic science research has demonstrated that while placebo treatments primarily modify subjective symptoms,[1] various neurotransmitters (e.g., endorphins, dopamine and cannabinoids), and specific, quantifiable, and relevant regions of the brain are activated.[2] Potential genetic markers have also been detected.[3] Importantly, clinical research has demonstrated that placebo effects are more than natural fluctuations and regression to the mean and can reduce symptoms that are defined by self-report.[4] Placebo effects have gained a new legitimacy. This raises a critical question: can placebo pills be used ethically in clinic 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 prescribing placebo pills.

Open-label placebo studies

In OLP RCTs performed to date, placebos are honestly prescribed to patients as pills containing no medication, and patients are randomized to receive OLP or no-treatment or treatment-as-usual (TAU) to control for patient-provider interactions and spontaneous improvement. In most of these experiments, patients are given a 10-15 minute description of placebo effects. This explanation includes a very brief overview of the results of placebo treatments in double blind RCTs of the target condition and the recent neurobiological and psychological evidence concerning placebo effects. If there is no evidence that OLP can work for the target complaint, this is also clearly explained.

The first OLP RCT was conducted with patients suffering from irritable bowel syndrome (IBS).[5] Eighty patients were randomized for three weeks to OLP + TAU versus TAU. Patients on OLP reported 60% global improvement compared to 35% improvement in TAU (p=.002). A second experiment was nested in a large randomized study of acute episodic migraine attacks.[6] Here, 66 patients (n=132 baseline attacks) served as their own control and received OLP or no-treatment (NT) during two different attacks. In this study, no information was provided about placebo effects. Patients on OLP had 15% improvement in

pain while those on NT worsened 15% (p=0.001). A third study involved chronic low back pain (cLPB) patients (n=83) who were randomized to OLP versus TAU.[7] A 10-15 minute discussion preceded randomization. At the end of 3 weeks, those receiving OLP had pain reduction of 28%, compared to 5% receiving TAU (p<0.001). Improvement on disability was 29% versus 0% (p<.001). Assessors were blind to treatment assignment in these studies. A recent meta-analysis of five OLP RCTs, including these studies of IBS and cLBP as well as smaller pilot studies of depression, allergic rhinitis and attention deficit hyperactivity disorder, found a positive effect for OLP with a standardized mean difference of 0.88 (p<0.00001).[8]

Because trial participants cannot be blind to whether they have received open placebo, report bias may be a factor influencing the observed results. However, the consistency and magnitude of symptomatic relief across these several studies suggest that a real therapeutic benefit is produced by the OLP intervention.

Psychological and Neurobiological Mechanisms

The psychological and neurobiological mechanisms underlying the observed effectiveness of OLP are unclear. Most OLP trial participants are refractory and have already visited multiple specialists before entering such trials. It is unlikely that the usually cited psychological processes connected with placebo responding—expectation and classical conditioning—can adequately explain therapeutic benefit associated with OLP trials. Participants frequently mention that the treatment seems “crazy”[9] and overwhelmingly deny initial positive expectations.[3] Furthermore, insofar as these participants have failed previous medication trials, the basis for a conditioned placebo response appears to be lacking.

Hope, as a psychological construct, has defied simple definition, but is likely more relevant than expectancy or conditioning. Interviews with trial participants suggest that patients hope enough to seek help even from a counter-intuitive intervention, but keep hopes in check to avoid the ever-present possibilities of despair.[10,11] Furthermore, the novelty of OLP and its cognitive dissonance may be helpful, as it appears to bring a noticable playful spirit to the research. Patients in these studies, who have often been frustrated by failed medication trials, report being empowered. An empathic clinician is likely to be crucial.[5]

It seems reasonable to assume OLP involves some of the same neurotransmitters involved with deceptive or concealed placebo effects.[12] Recent neuroimaging evidence demonstrating that non-conscious mental processes can initiate placebo effects is compatible with OLP.[13,14] Furthermore, parallel research in computational biology concerning error processing and embodied cognition underscores the idea that the brain can operate as an automatic prediction machine independent of conscious awareness.[15] It seems possible

that the paradoxical message of OLP disrupts the central sensitization that underlies many conditions with distressing symptoms that are placebo responsive. The psychological and neurobiological mechanisms underlying the observed effectiveness of OLP need to be investigated.

Conditions likely to be responsive to OLP.

Despite the identification of a neurobiological substrate for placebo effects, there is little evidence that placebo treatments change underlying pathophysiology beyond symptomatic manifestations.[16] We hypothesize that it is worth investigating OLP for conditions with subjective outcomes where placebo responses in double-blind treatment are almost as large as the active intervention. For example, placebo effects do not shrink oncological tumors, but OLP could be helpful for symptom management of cancer-related nausea, pain, hot flashes or fatigue. Malaria and high cholesterol are unlikely candidates for OLP.

Implications for clinical practice

A large telephone survey of patients' attitudes towards placebos was undertaken at a major healthcare system in the US (n=853). After being read a vignette based on the first IBS OLP study described above, 62% of patients reported that they would probably or definitely take OLP in this context if recommended by a doctor.[17] A more recent focus group study (n=58) found that patients were comfortable with OLP if prescribed transparently by physicians.[18] It seems that many patients would be prepared to try OLP if it is honestly prescribed.

If positive evidence accumulates for OLP would clinicians be willing to adopt it as a therapeutic strategy? A potential barrier is that this goes against the grain of medical training and norms of medical practice in which physicians prescribe medications that are indicated to promote therapeutic benefit by virtue of their biochemical properties. However, substantial survey research indicates that physicians frequently use placebo treatments in routine care. Most of the time these are "impure placebos," such as vitamins to treat fatigue in the absence of any evidence of vitamin deficiency.[19] Microcrystalline cellulose or sugar pills or saline injections are rarely used. While the transparency of prescribing pills lacking medication has no ethical problems,[20] it may be more difficult for clinicians than the ethically dubious prescription of impure placebos.

Moving OLP research forward

Heretofore, OLP research has consisted of small studies of short duration. Because successful small trials are often followed by failed large-scale

trials, replication of these preliminary findings with larger sample sizes and longer duration is desirable.

Whether the positive results suggested by OLP studies can be translated into routine clinical care is an open question. The observed outcomes, at least to some extent, may be a product of the experimental context of deploying a counter-intuitive intervention – the ritual of treatment via taking a pill known to lack medication – by investigators with at least some interest in demonstrating that OLP can work to provide symptomatic relief. Physicians in routine practice may be skeptical about the potential benefit of OLP even if they are willing to try it with some patients. In other words, the seeming paradox of OLP efficacy observed in RCTs would need to be duplicated in the clinical setting.

Conclusion

OLP is disruptive. Besides raising new perspectives on placebo effects, OLP challenges exclusive reliance on medical technology to promote therapeutic benefit. OLP may be a trigger for engaging self-healing mechanisms in conditions that often resist successful treatment. The use of OLP in the context of a supportive therapeutic alliance is one way to acknowledge the interpersonal core of medicine, which encompasses the influence of words, behaviors, engagement, rituals, mutual trust, emotional support, and empathic witnessing.

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