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

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

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For many conditions, placebo treatments in randomized controlled trials (RCTs) produce significant improvement for 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, RCTs of open-label placebo (OLP) suggest that patients can experience symptom relief from taking pills honestly described as "inert" placebos lacking any medication.

Current status of the placebo concept

"Placebo" is usually a pejorative term used to denigrate therapies deserving rejection. In the last twenty years, basic science research has demonstrated that while placebo treatments primarily modify subjective symptoms, various neurotransmitters (e.g., endorphins, dopamine and cannabinoids), and specific, quantifiable, and relevant regions of the brain are engaged.[2] Potential genetic markers have also been detected.[3] Importantly, clinical research has demonstrated that placebo effects are more than spontaneous improvement and regression to the mean and can reduce subjective symptoms.[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 prescribing placebo pills.

Open-label placebo studies

To our knowledge, to date, there have been four OLP RCTs in four different medical conditions involving over 60 patients each. (There are two feasibility studies in depression and allergic rhinitis of no more than 25 patients each that are too small to consider as serious evidence.) In these four studies patients were randomized to receiving OLP, pills honestly described as "inert

placebos containing no medication" + treatment-as-usual (TAU) versus TAU (or in one case no-treatment.) To control for provider interaction and time, all patients in three of the studies received orientation about both groups, 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 RCTs for the target condition. Patients were clearly told that it was unknown whether OLP worked for their condition and testing this question was the purpose of the RCT. Mention was made of neurobiological and psychological evidence concerning placebo effects in general. All information was transparent, accurate, and lacked any positive adornment or suggestion. The dialogue emphasized, "let's see what happens." [5]

The first OLP 3-week RCT was conducted with patients with irritable bowel syndrome (IBS).[6] Eighty patients were randomized for three weeks to OLP + TAU versus TAU alone. Patients on OLP reported 60% global improvement compared to 35% improvement in TAU (p=.002). A second RCT involved chronic low back pain (cLPB) patients (n=83) who were randomized to OLP + TAU versus TAU. After 3 weeks, pain was reduced 28% compared to 9% (p<.001) and pain disability was reduced 29% versus 0.02% (p<.001). Sixty-five percent of participants reported decreasing their medication on OLP. A third study randomized patients (n=74) with cancer-related fatigue to OLP + TAU or TAU; after three weeks, those receiving OLP reported 29% improvement in fatigue compared to 10% in TAU (p=0.008) and fatigue-disrupted quality of life improved 39% versus 5% (p=0.002).[7] A fourth study was different and was prospectively nested in an elaborate RCT of episodic migraine attacks (n=459 baseline headaches).[8] For the OLP part of the study, 66 patients (n=132 baseline attacks) served as their own control and received OLP or no-treatment during two different attacks. Patients did not have an "orientation" regarding placebo responses. Nonetheless, patients on OLP had 15% improvement in pain

while those on no-treatment worsened 15% (p=0.001). Assessors were blind to treatment assignment in these studies.

Because trial participants cannot be blind to whether they have received OLP, report bias may be a factor influencing the observed results. However, the consistency and magnitude of symptomatic relief across these several studies – performed in different hospitals in two continents involving four medical conditions -- suggest that a real therapeutic benefit may be involved with OLP intervention.

Psychological and neurobiological mechanisms of OLP

The psychological mechanisms underlying the observed effectiveness of OLP are unclear. It is doubtful that the usually cited psychological processes connected with placebo responding—expectation and classical conditioning—can adequately explain therapeutic benefits associated with OLP trials.[2] Most OLP trial participants are refractory and frustrated by multiple failed medications. While patients seem to enjoy the novelty of OLP, participants frequently describe the treatments as "crazy" and overwhelmingly denied initial positive expectations on exit interviews."[5] Nonetheless, patients often expressed "hope" connected to despair -- a kind of "tragic optimism" -- that allowed them to continue to seek treatment even from a counter-intuitive intervention. Recent neuroimaging evidence demonstrating that non-conscious mental processes can initiate placebo effects is compatible with the efficacy of OLP.[9,10,11] Furthermore, parallel research in computational biology concerning prediction processing and embodied cognition underscores the idea that the brain can operate as an automatic prediction machine independent of conscious awareness.[12] The dissonance embedded in the OLP may be an important factor triggering psychological and neurobiological mechanisms. We speculate that such dissonance may disrupt central sensitization and aberrant amplification of nociceptive signals involved in many subjective complaints.[13] OLP probably

involves some of the same neurotransmitters involved with concealed placebo effects.[14]

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.[15] We hypothesize that OLP may be valuable for conditions with subjective outcomes where placebo responses in double-blind RCTS are substantial and rival 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, as we have seen, 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.[16] A more recent focus group study (n=58), performed in the UK, found that patients were comfortable with OLP if prescribed transparently by physicians.[17] Many patients seem prepared to try OLP if it is honestly prescribed.

If positive evidence from larger studies 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. While placebo pills or saline injections are rarely used, physicians often use the ethically dubious and paternalistic route of "impure placebos," such as vitamins to treat fatigue in the absence of any evidence of vitamin deficiency.[18] Ethical analyses have found that OLP conforms with ethical standards of informed consent and transparency.[19] If the evidence of OLP continues to be positive, physicians may see the value of this ethical possibility of harnessing placebo effects, especially in conditions for which pharmaceutical management is a challenge.

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. The psychological and neurobiological mechanisms underlying the observed effectiveness of OLP need to be investigated.

Whether 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 by investigators with at least some interest in demonstrating that OLP can work to provide symptomatic relief. Nonetheless, if further confirmatory evidence continues, OLP may offer an honest approach for a watch-and-wait strategy before medication prescribing. It would be desirable to investigate whether OLP efficacy observed in RCTs can be duplicated in routine clinical practice. Clinician education, training manuals, and workshops might help for initial implementation of this paradoxical intervention.

Conclusion

OLP research is disruptive. At the very least, it suggests that placebo pills do not need duplicity to benefit patients. 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. If the effectiveness of OLP is validated, it may become an ethical therapeutic strategy for promoting placebo effects in clinical practice, offering symptom relief for hard-to-treat conditions.

Key Messages:

- Placebo pills in RCTs 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 RCTs suggest that open-labeled placebo (OLP) pills honestly prescribed can evoke meaningful therapeutic benefits.
- More research is required, but preliminary work suggests that OLP may offer a valuable therapeutic approach for promoting symptomatic relief in a variety of medical conditions.

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