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Effect of Non-Deceptive Placebo on Weight Loss: An Exploratory Study

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Abstract

Background: The continued high prevalence of obesity calls for novel treatments or treatment adjuncts. Open-label placebos (OLPs) can improve medical conditions despite that patients know they are receiving a placebo. OLP has not been tested in obesity.

Aim: To explore if OLP augments weight loss.

Methods: N=31 adults, mean BMI 34.9, were assigned to an OLP or no-OLP group during a weight-loss intervention. Body weight, compliance, suggestibility, and perceived importance of theorized factors on weight change were assessed with questionnaires.

Results: OLP failed to augment weight loss. Only 45% of the OLP group took the pills as instructed, consistent with report of little-to-no belief that they affected body weight.

Conclusions: Results question if OLP benefits generalize to conditions requiring action from patients and to studies with objective outcome measures. In either case, it is clear that the potential of OLPs to enhance obesity treatments hinges foremost on increasing belief in them.

Keywords: Obesity; Intervention; Treatment; Open-label Placebo; Suggestibility; Eating Behavior

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Introduction

The sustained global prevalence of obesity calls for novel treatments or novel treatment adjuncts [1]. Like placebos, open-label placebos (OLPs) are inert, but unlike traditional placebos, patients are aware that they are taking a placebo [2]. OLPs have been found to improve symptoms in various medical and psychiatric conditions including irritable bowel syndrome [3], cancer-related fatigue, postmenopausal hot flashes, ADHD, allergic rhinitis, chronic back pain, migraine [4,5], and test anxiety [6]. Conditioned OLP, where OLP pills are first paired with real medication, was found to decrease amount of postoperative opioid consumption [7,8]. OLPs have the added benefit of not needing to deceive patients, which is a barrier to the clinical use of traditional placebos [2].

To our knowledge, OLP has not been tested in obesity as a weight-loss treatment or treatment adjunct. One study examined effects of a placebo supplement on food consumption [9]. Participants who were told they were on an active weight-loss supplement ate more at a buffet than those told they were on a placebo (an OLP condition). The surprising outcome was explained as placing too high an expectation on the supplement such that less effort was made to limit intake. However, the researchers did not consider that OLP might have reduced intake and the study did not assess food consumption over time nor change in body weight.

Therefore, the aim of this study was to explore the effect of OLP to augment weight loss in individuals undergoing a simple weight-loss intervention. In view of OLP benefits on other conditions, we initially hypothesized that participants on the OLP pills would lose more weight than those not on the pills and that pill-taking compliance would be high. However, a growing body of OLP research is finding that efficacy is generally not observed when objective vs. subjective outcomes are employed [10-14]. Weight loss is a clear objective measure. Hence, the study became more exploratory than hypothesis-driven. Lastly, the study differs from previous OLP studies not only in its clinical application, obesity, but in its requirement that participants engage in a behavior to affect the desired outcome. With the exception of the buffet eating experiment, outcomes of the aforementioned studies relied on a change in sensation or autonomic function. Patients did not have to act. The opioid studies did require patients to make a choice of how many pain killers to consume, but OLP was first conditioned with an unconditioned stimulus - real opioid medication. In the present study, no unconditioned stimulus was paired with OLP.

Methods

Participants

N=57 students and employees from The University of Alabama at Birmingham (UAB) were enrolled after screening ([15] for I/E criteria). N=22 were forced to stop the study because of a university-mandated closure due to the COVID-19 outbreak. Prior to this, four participants dropped out for reasons unknown (three in the OLP and one in the no-OLP group). Results are provided for OLP effects on weight change in the 57 and 44 able to complete the first study and second study, respectively. However, body weight and all other results described are from the main study sample of N=31 that completed all four visits and were thus able to complete critical assessments that could only be administered on the last visit. This sample included 22 females and 9 males; was 39% Black, 51% non-Hispanic White, and 10% other ethnicity; had a mean age of 25, SD=11.1, and mean BMI of 34.9, SD=9.1. The study was approved by the UAB Internal Review Board for Human Research.

Open-label Placebo (OLP) Groups and Materials

Participants were randomly assigned to an OLP (N=15) or no-OLP (N=16) group. Assistants were blind to their participant's group assignment until they disclosed it from a sealed envelope to the participant. For all participants, this occurred at the end of the first of four visits (V1-V4) after viewing a brief video. The video explained placebos in general, OLPs, conditions improved by OLPs, and that this study would help determine if OLPs could benefit weight loss. It also asked the participant to keep an open mind regarding the efficacy of the pills. The video content was adopted from previous and successful OLP studies [3-5]. Those in the OLP group were then given medium-sized green and white gel capsules containing inert micro-crystalline cellulose (Remedies Pharmacy, Birmingham AL) in an amber plastic pharmaceutical bottle. They were instructed to take one pill in the morning and one at night daily for the eight-week duration of the weight-loss intervention and were given a pill log to remind them to take the pills.

Weight-loss Intervention

Participants underwent "Gut-Cued Eating" (GCE). See [15] for protocol and weight change details. Briefly, on V1, participants watched a video that distinguished stomach-hunger (eating triggered by physical hunger sensations in the stomach) from mouth-hunger (eating triggered by emotions, craving, external stimuli; anything other than stomach hunger). They were then asked to follow two instructions for the remainder of the eight-week study:

1. "Start to eat only when you are stomach hungry" and
2. "Stop eating when you are satisfied, but before you feel completely full."

Short-Suggestibility Scale (SSS)

The SSS was completed at V1. It assessed trait tendency to readily believe information from others and the media [16]. Scores were used to control for suggestibility on OLP effects.

Dependent Measures

Body weight and BMI: were measured at each visit by an assistant using a calibrated scale and stadiometer after shoes and outer clothing were removed. Body weight is reported in pounds (lb) and BMI was calculated as kg/m^2.

The OLP survey: was developed for the study to assess pill-compliance and help elucidate how much the pills and other factors were perceived to affect weight loss. It was completed only by the OLP group at V4. The survey first asked if all pills were taken (Y/N), reasons for not taking all pills (open-ended), and how much the pills were thought to contributed to their change in weight (one Likert question). Those reporting anything but "not at all" and that lost weight then rated how important they perceived 12 methods to be by which the pills may have contributed to their weight loss (Table 1). Lastly, this subgroup rated how important they perceived seven general factors to be on achieving weight loss (Table 2).

Pill-taking compliance: was defined as answering "yes" to the first OLP survey question or answering "no" to this question but reporting that no more than 11 pills (~10% of total) were skipped. Reports were verified by examining the returned pill bottles at the end of the study.

Analyses

Data were normality tested with histograms. Repeated measures ANOVA assessed differences in weight and BMI from V1 to V2, to V3, and to V4 with OLP as the between-subjects factor. Initial weight, demographics, and SSS scores were added separately as fixed factors/covariates. Univariate ANOVA assessed weight change between OLP groups at V2 for the N=57 and at V3 for the N=44 samples. Alpha=0.05 for significance, and results are reported as means and SEM (±).

Results

Effect of OLP on Body Weight

Weight decreased significantly from V1 to V3 and V1 to V4 across the sample of N=31 participants for a final 2.4 lb mean decrease (range -4.0 to 11.6 lb loss; p=0.003). BMI also decreased (p=0.024; see [15]). However, OLP did not augment weight loss or BMI as OLP groups did not differ in weight loss at any of the visit intervals (OLP=3.3 ± 1.0 lb vs. no-OLP=1.5 ± 1.03 lb at V4; p=0.22). Controlling for initial body weight, demographics, or SSS scores did not alter the null effect of OLP on change in weight.

In the initially enrolled sample of N=57, 26 were in the OLP and 31 in the no-OLP group. At V2, while mean weight decreased (p<0.001), weight loss between OLP groups did not differ (p=0.80). In the N=44 sample able to complete V3, 18 were in the OLP and 26 in the no-OLP group. Again, mean weight decreased (p<0.001), but there was no difference in weight loss between OLP groups (p=0.34).

Pill-taking Compliance and Attribution of OLP Pills to Weight Loss

Despite completing all study visits, only 47% of the OLP group (N=7 of 15) met defined pill-taking compliance. However, the 47% that complied did not lose or gain more weight than non-compliers (p=0.19, ns). Reasons in order of most-to-least commonly reported were forgetting, dizziness, fear the pills would affect other medications, and stomach issues. All in the OLP group, regardless of weight gain or loss, rated a mean of 1.25 ± 0.39 (equal to "a small amount") to how much they thought the pills had contributed to their weight change. As shown in Table 1, those in the OLP group that lost weight endorsed factors related to the GCE intervention for the weight loss while effects on appetite were among the least endorsed. Finally, as shown in Table 2, placebo pills were rated low as a factor important to weight loss, second only to compensation as the least important factor.

Table 1: Mean perceived importance of possible methods by which OLP pills might have contributed to weight loss in OLP participants that lost weight after the GCE intervention.

Possible Methods	Mean[a]	SEM
Made it easier to follow GCE	2.57	0.48
Reminded me that I was getting personal care* with my weight-loss efforts	2.29	0.47
Learned from past experience that taking pills helps with other conditions*	1.71	0.57
I was expecting them to help me*	1.29	0.57
Made me eat less of the food I craved	1.14	0.6
Made me less hungry	1	0.49
Made me feel fuller after eating	1	0.54
Gave me more energy which made me more active	0.86	0.46
Increased my metabolic rate	0.71	0.36
Made me crave less of specific food(s)	0.43	0.3
Changed my mood	0.29	0.18
Interacted with my particular biological/genetic makeup*	0.14	0.14

OLP=Open-Label Placebo; GCE=Gut Cued Eating; a Response scale was 0="Not at all," 1="A small amount," 2="Some," 3="More yes than no," 4="Very much," Scale was part of OLP survey. *Theorized mechanisms for effectiveness of OLP [3].

Table 2: Mean perceived importance of general factors to have contributed to weight loss in OLP participants that lost weight after the GCE intervention.

Factors	Mean[a]	SEM
GCE instructions	3.83	0.17
Attention/care from lab assistants	3.25	0.22
My motivation to lose weight	3.17	0.39
My greater expectation of losing weight from info received in lab	3.08	0.34
Anticipation of getting weighed	3	0.39
OLP pills	1.42	0.38
Compensation ($60 gift card or research credits)	0.58	0.26

OLP=Open-Label Placebo; GCE=Gut Cued Eating; a Response scale was 0="Not at all," 1="A small amount," 2="Some," 3="More yes than no," 4="Very much," Scale was part of OLP survey.

Discussion

To our knowledge, this was the first study to test OLP in obesity. While participants lost weight after the GCE intervention, OLP failed to augment weight loss. We observed no trend for significant results even when a greater number per OLP group were analyzed. Despite the exploratory nature of this study, assignment to the OLP conditions was blind to participants and their assistant when intervention and OLP expectations were explained, data were longitudinal, and the protocol methods were adopted from previous successful OLP studies [3-5]. Pill-taking compliance was much lower than expected, but we do not believe this contributed to the null effects of OLP because the same participants completed all visits of the intervention, weight loss of compliers was not greater than that of non-compliers, and those that lost weight ranked the pills next to last, only above monetary compensation, as influencing their weight loss.

Fontaine and colleagues [2] proposed that obesity treatments can be improved by incorporating factors that make traditional placebos effective. A foremost factor is belief in the treatment's therapeutic potential [2,3,6, and 17]. Our lab witnessed this power of belief in a study that used transcranial direct current stimulation (tDCS). Participants who were told they were receiving real tDCS ate significantly less even if they received sham tDCS. Those told they were receiving sham tDCS ate significantly more, even if they received real tDCS [18]. In that study, participants were pre-informed of the eating and craving-suppressing effect of tDCS. That is in contrast to the present study. Since this was the first study to investigate OLP (i.e., a non-deceptive placebo condition) on weight loss, we could not tell participants that OLP had been found to augment weight loss. This may have lowered belief in the pills. Belief in placebos was not directly assessed, but controlling for trait suggestibility did not alter the results. Additionally, the OLP survey revealed that participants had very little, if any, belief in the pills, despite having seen a video touting the benefits of OLP and asking them to keep an open mind. While it is tempting to consider that increasing positive pre-information about OLP and weight loss may yield better results on weight reduction, the point of OLP is to avoid deception.

The study's limitations were a low sample size when only OLP participants were analyzed, self-report nature of the surveys, and lack of a no-intervention group which may have ensconced OLP effects. However, as a successful treatment adjunct, OLP should enhance weight loss achieved from a real intervention. Despite these limitations, the results raise valuable issues to consider in future investigations:

- Are OLPs effective when patients are required to take voluntary action such as following instructions on when to start/stop eating? This differs from most conditions in which OLP has proved beneficial, conditions that did not require voluntary action for positive outcomes, e.g., alleviation of pain, fatigue, anxiety, etc. [3-6]; and
- The results add to growing evidence that OLP benefits are not as likely to be observed when outcome measures are subjective vs. objective or blinded [10-14].

Conclusions

Validation of OLP as a clinical tool for obesity will require systematic investigations testing active vs. passive requirements from patients for a positive outcome and should employ as many objective vs. subjective measures as possible. Finally, if belief in OLPs in general can be increased, we believe there is still hope for nondeceptive placebos to boost the efficacy of obesity treatments.

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Declarations

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Availability of Data and Materials: Available from the corresponding author upon request.

Ethics Approval and Consent to Participate: All procedures were approved by the UAB Institutional Review Board for Human Use in accordance with the 1964 Helsinki declaration and later amendments. Informed consent was obtained from all participants.

Consent for Publication: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Author's Contributions: Ann Carol Braswell coded and analyzed OLP data, made the OLP video, and wrote the initial manuscript;

Mel Ebeling created electronic surveys for the intervention;

Audria S Wood and Taylor R White trained assistants and performed background literature searches;

Marissa A Lausen and Sasha Isaac screened, contacted, and scheduled participants.

All above carried out procedures and provided feedback on materials prior to the study.

Mary M Boggiano conceived of the study, developed original materials, guided analyses and edited writing.

All authors approved the final version.

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