

# Effect of Non-Deceptive Placebo on Weight Loss: A Preliminary Study

**Ann Carol Braswell**

The University of Alabama at Birmingham

**Mel Ebeling**

The University of Alabama at Birmingham

**Audria S. Wood**

The University of Alabama at Birmingham

**Taylor R. White**

The University of Alabama at Birmingham

**Marissa A. Lausen**

The University of Alabama at Birmingham

**Sasha Isaac**

The University of Alabama at Birmingham

**Mary Michelle Boggiano** (✉ [boggiano@uab.edu](mailto:boggiano@uab.edu))

University of Alabama at Birmingham <https://orcid.org/0000-0002-3662-155X>

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## Research Article

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# Abstract

## Purpose

The high global prevalence of obesity calls for the development of new weight loss strategies. Open-label placebo (OLP) has ameliorated symptoms of several medical and psychological conditions but has not been tested for obesity. With OLP, participants know they are receiving a placebo. This study investigated the effect of OLP pills to increase weight loss and reduce food craving.

## Methods

N=31 adults of diverse sex and ethnicity with a mean BMI of 35 underwent a simple eight-week long weight-loss intervention called Gut-Cued Eating. They were randomly assigned to take two pills daily for the entirety of the study (OLP group) or no pills (no-OLP group). All participants were weighed and completed baseline surveys. The OLP group also completed an original OLP survey which assessed compliance and perceived influence of putative mechanisms behind the efficacy of OLP on their change in weight.

## Results

OLP did not augment weight loss or further reduce food craving following GCE. Controlling for demographics and baseline trait suggestibility did not affect the results. While the study was preliminary due to a small sample and limited statistical power, the results did not approach significance. Furthermore, the OLP survey indicated that belief in the effect of the pills was very low to none. OLP may prove beneficial in obesity if general belief in OLPs is increased and if it is delivered in a modality different from a pill given the likely negative associations between weight-loss pills and successful weight loss.

## Level of Evidence

Level 1, experimental study

# Introduction

Novel treatments or treatment adjuncts for obesity are needed due to the sustained high prevalence and grave comorbidities of this disease [1, 2]. Open-label placebo (OLP) has been found to improve test anxiety [3], cancer-related fatigue, irritable bowel syndrome, menopausal hot flashes, ADHD, allergic rhinitis, chronic back pain, and migraine (see meta-analysis for studies [4]). Like placebos, OLPs are inert, i.e., not biologically active, but unlike traditional placebos, participants and patients know that they are taking a placebo. Hence, with OLPs, there is no need for deception which is an ethical barrier to the clinical use of placebos [2, 5].

To our knowledge, OLP has not been tested in obesity. Chang and Chiou [6] examined OLP in food intake. They found that 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. They suggested that participants may have placed too high an expectation on the supplement to help them lose weight which resulted in less effort to limit their intake. While this explanation is offered as a reason for the lackluster efficacy of weight-loss supplements, the study did not assess food consumption over time or change in body weight. Fontaine et al. [2] proposed that obesity treatments can be greatly *improved* by incorporating the factors that make traditional placebos effective. While the same factors are thought to underlie the effectiveness of open-label placebos, OLP has not been investigated as a treatment adjunct for obesity.

Therefore, in this first and preliminary study of OLP in obesity, individuals with a body mass index (BMI) ranging from overweight to Class III obesity underwent a new weight-loss protocol designed to make exceedingly few demands on the participants. It was hypothesized that participants on OLP pills would lose more weight and have lower food craving than those not on the pills. Finally, while specific mechanisms have been theorized to explain the effectiveness of OLPs [5], to our knowledge, participants have not previously been asked to opine on the influence of each of these mechanisms and other factors on their improved outcomes. Therefore, this study also obtained participant ratings on the perceived importance of these theorized mechanisms to affect their weight loss outcome.

## Methods

### Participants

The initial sample was  $N = 35$ , but results are reported for the  $N = 31$  that completed the intervention. Three of the non-completers were assigned to the OLP group and one to the no-OLP group. No reason was given for their attrition. The sample was students and employees from The University of Alabama at Birmingham (UAB), 22F/9M, 39% Black, 51% non-Hispanic White, and 10% other ethnicity with a mean age of 25 (range 18–60) and mean BMI of 34.9 (range 26.9 to 76.8).  $N = 15$  received OLP (OLP group) and  $N = 16$  did not (no-OLP group). Exclusion criteria included uncontrolled diabetes or hypertension, suicidal ideation in the last year, use of illegal recreational drugs, history of an eating disorder, current enrollment in a commercial weight-loss program, pregnancy or breastfeeding, and intent to stop or start an appetite-altering drug. The study was approved by the UAB Internal Review Board for Human Research.

### Materials

#### Open-label placebo (OLP) groups and materials

*Groups.* Participants were assigned to an OLP or no-OLP group in alternating fashion by the order of their lab visit, blocking only for ethnicity to assure equal numbers of Black participants in both groups. *OLP pills.* The pills were medium-sized green and white gel capsules containing inert micro-crystalline cellulose (Remedies Pharmacy, Birmingham AL). *Instructions and Log.* Participants were instructed to

take one pill in the morning and one at night for the duration of the study. They were also provided with a pill log to remind them to take the pills. *Video*. Prior to obtaining the pills and log, OLP participants were shown a brief video educating them on placebos in general, on OLPs, conditions found to be improved by OLP, and a request to keep an open mind about their efficacy. The video content was adopted from [5].

## Gut-Cued Eating (GCE) weight-loss intervention

Details on the GCE protocol and results on body weight used here have been submitted elsewhere [7]. Participants were shown a four-minute video that distinguished eating for “stomach hunger” (physical hunger) vs. “mouth hunger” (eating for any reason other than metabolic need). They were then asked to follow these two instructions for the remainder of the 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.”

## Baseline Surveys

*Demographics*. This survey asked for age, sex, and ethnicity. *Short-Suggestibility Scale (SSS)*. This scale assessed trait tendency to readily believe information from others and the media [8] and was used to control for suggestibility on OLP effects.

## Measures

### Body Weight and BMI

Body weight was measured in pounds by an assistant on a calibrated digital scale after shoes and outer clothing was removed. BMI was obtained with height measured on a calibrated stadiometer and the formula  $\text{kg}/\text{m}^2$ .

### Food Craving Task

Participants viewed 24 palatable food images on a monitor representing sweets (e.g., chocolates), fatty proteins (e.g., BBQ ribs), carbohydrates (e.g., pasta), and mixed macronutrients (e.g., pizza). An all-foods category was calculated based on the mean of the 4 categories. Participants rated each food by how much they liked it and how much they would want to eat it if available right now. Because of this task, participants were asked to come to the lab not too hungry or too full. This was checked with a hunger scale prior to the task. Anyone rating the extremes of the scale was rescheduled.

### Open Label Placebo (OLP) Survey

This self-developed survey assessed: a) if all pills were taken (Y/N) and reasons for not taking all the pills (open-ended) and b) how much participants thought the pills contributed to their weight change (one Likert-like question). If they reported anything but “not at all” to the previous question, they then rated c) ways that OLP pills might have influenced their change in weight with twelve Likert-like items (**Table 1**). The phrasing of these and remaining questions aligned with whether the participant lost or gained weight. Finally, the entire OLP group rated d) the importance of other general and theorized factors [5] on their weight outcome with seven Likert-like items (**Table 2**).

# Pill-taking Compliance

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 pills) were skipped. Compliance was verified if the returned pill bottle contained  $\leq 10\%$  of the pills.

## Procedures

On Visit 1, all participants provided demographics, were weighed, completed the Craving Task, and were given the GCE information. Those in the OLP group then watched the placebo video, received the pills and log, and had any questions answered. On Visit 2, 3, and 4, which took place two, three, and three weeks later, respectively, participants were weighed and interviewed as part of the GCE protocol [7]. On Visit 4, all completed another Craving Task, and those in the OLP group completed the OLP Survey.

## Statistical Analysis

Data were normality tested with histograms. ANOVA assessed differences between the OLP and no-OLP group on body weight, BMI, and food craving difference scores (Visit 1 minus Visit 4). Results for BMI were reported only if found significant for body weight. Demographics, weight measures, and SSS scores were entered as fixed factors or covariates. Alpha was set at 0.05 for significance. Data are reported as means  $\pm$  SEM.

## Results

### Effect of OLP on body weight and craving

Overall, participants lost significant weight after the GCE intervention ( $p=0.003$ ) [7]. However, OLP did not augment the weight loss.<sup>1</sup> That is, there was no significant difference between the mean weight lost by the OLP and no-OLP group (3.32 lbs.  $\pm$  1.03 vs. 1.48 lbs.  $\pm$  1.03,  $p=0.22$ , ns). Controlling for demographics, initial body weight (or BMI), or SSS scores did not change this null result. Regarding food craving, the sample had less craving after the intervention, but there was no difference between the OLP and no-OLP group in the all-foods category ( $0.59 \pm 0.23$  vs.  $0.88 \pm 0.33$ ,  $p=0.38$ , ns) or other food categories, all  $p>0.25$ , ns.

### Pill-taking compliance and attribution of OLP to weight loss

Only 47% of the OLP group (N=7 of 15) complied with taking the pills. This lack of pill-taking compliance was incongruent with their full compliance during the GCE intervention; all 15 completed all four visits. However, the 47% that complied did not lose more weight than the non-compliers,  $p=0.19$ , ns. Reasons reported for not taking the pills as prescribed in order of frequency included forgetting, dizziness, fear that the pills would affect other medications, and stomach issues. All in the OLP group, regardless of weight gain or loss, rated a mean of  $1.25 \pm 0.39$  (equal to “a small amount”) to how much they thought the pills

had anything to do with their weight change. As shown in **Table 1**, GCE protocol components were most endorsed while direct effects to appetite or their biology were less endorsed.

<sup>1</sup> The study was administratively stopped due to the COVID-19 outbreak and could not be continued remotely. At that point, complete data was available only for the 31 participants analyzed here (from Visit 1 to Visit 4). However, we also analyzed weight-change data at the end of each visit which included a greater number of participants (N=57 at Visit 2 and N=44 at Visit 3). Despite a mean decrease in overall body weight at each of these visits [7], ANOVA detected no difference in weight change between the OLP and no-OLP groups,  $p=0.80$  at V2 and  $p=0.34$  at V3, ns.

**Table 1. Mean attribution of ways that the OLP pills might have influenced weight loss in those who lost weight after the GCE intervention**

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	0.60
Made me less hungry	1.00	0.49
Made me feel fuller after eating	1.00	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	0.30
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

<sup>a</sup> Response scale was 0="Not at all", 1="A small amount", 2="Some", 3="More yes than no", 4="Very Much"

\*Theorized mechanisms for effectiveness of OLP [5]

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 2. Mean importance ratings by OLP participants who lost weight of general factors that might have influenced their weight loss**

Factors Important to Weight Loss	Mean <sup>a</sup>	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	3.00	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

<sup>a</sup> Response scale was 0="Not at all", 1="A small amount", 2="Some", 3="More yes than no", 4="Very Much"

## Discussion

This study was the first to investigate the potential therapeutic effect of OLP in obesity. The results are preliminary because of the small sample size and low statistical power. However, it was randomized, longitudinal, controlled, and included methods successfully used in previous OLP studies [4]. It also included the assessment of perceptions regarding the influence of theorized mechanisms of OLP on weight change. Results found that while the eight-week GCE intervention decreased mean body weight, BMI, and food craving, OLP did not augment these outcomes. We consider three potential reasons for not observing an OLP effect.

First, the pills might have been found effective if tested in a larger sample (Type II error). The small sample size and limited statistical power were limitations. However, we found no trends approaching significance between OLP conditions on weight loss even when analyses included more participants.<sup>1</sup> Nonetheless, the use of OLP in obesity should not be dismissed until larger studies are conducted. Results may also differ in an older than college-aged population.

Second, the OLP pills might have aided weight-loss but were overridden by the effects of the GCE intervention. This is suggested by the finding that those on the OLP pills who lost weight ranked the GCE instructions as first in importance for their weight loss. A future study could test if OLP has an independent benefit on weight loss by employing no other intervention *but* OLP. At most, the "intervention" could be to simply have participants come into the lab to be weighed. However, real-world application of OLP in obesity is likely to be as an adjunct therapy to dietary, cognitive, and/or other lifestyle change protocol. Therefore, validation of OLP as an efficacious adjunct means an intervention must yield greater or more sustained weight loss with it, than without it. In our study, OLP did not meet this standard.

The third possible reason OLP failed to enhance weight-loss in our preliminary study is because, at least in its delivery as a pill and among younger adults, OLP may simply not be effective against obesity. We

found that the participants' belief in the OLP pills to exert an effect on body weight was very low, if any. This was despite viewing a tutorial about published benefits of OLP on other conditions and a request to suspend any disbelief or low expectation. Specifically, participants who lost weight ranked the OLP pills next to last, only above compensation for the study, in importance to their weight loss (Table 2). We believe lack of belief in OLP was also behind the overall poor rate of adherence to the pill-taking instructions. Arguably, not taking the pills could be attributed to their failure to enhance weight loss, but we found no trend of greater weight loss in those who took the pills as prescribed compared to those who did not take them as prescribed. It also cannot be said that the participants were not generally compliant because they complied well with the GCE-protocol, i.e., completed all visits. In support of lack of belief in the OLP pills for the null results on weight loss, Leibowitz et al. [9] found that an OLP cream reduced allergy responses to a histamine prick only in those with a strong belief in placebos.

Lastly, it should be noted that while OLP has been reported to benefit several conditions [3,4], publication favors positive over negative findings such that null effects may not be known. Exceptions include two studies on depression where OLP did not yield the positive effects hypothesized [10,11]. However, like the present study, both were preliminary and merit investigations in larger samples. Closer to obesity, in the buffet-eating study, participants who were told they were taking a weight-loss supplement ate more than those told they were taking a placebo pill [6]. But, without knowing how much they would have eaten without an intervention (with no pill), this is not evidence that the OLP pills *reduced* consumption. It will be interesting to learn if there are better clinical targets than others for OLP. Knowing what the targets have in common would be medically and psychologically valuable.

In conclusion, although this study was preliminary and we report that OLP did not augment weight loss or lower food craving, it provided valuable insight into compliance behavior and perceptions surrounding OLPs in those seeking to lose weight. These are insights that can inform ways of making OLPs effective for obesity. A good start appears to be boosting belief in non-deceptive placebos [9]. Finally, the ideal OLP modality for obesity may not be a pill. In a previous study in our lab, participants learned that noninvasive brain stimulation could suppress eating and craving. We found that participants who were told they were receiving real brain stimulation ate and craved significantly less, whether they received real or fake stimulation. Those told they were receiving fake stimulation ate and craved significantly more, even though half received real stimulation [12]. In sum, the most effective OLP for obesity may be one that patients believe in and that least resembles diet pills, diet food, work-out gear, or any stimuli associated with past attempts at treating their condition.

## **Strength and limits**

**Strengths:** The study is the first to investigate effects of open-label placebo (OPL) as an adjunct treatment for obesity. It is also novel in its assessment of participant perceptions on the importance of various mechanisms theorized to drive beneficial effects of OLP. Novel too is that it controls for trait suggestibility. The study is longitudinal, controlled, and participants were randomly assigned to experimental groups. It uses methodology that has been successful in previous OLP studies and includes

food craving in addition to weight loss as a dependent variable. The sample is sex- and ethnically-diverse, and spans a BMI range from overweight to Class III obesity.

Limitation: As mentioned in the Discussion, limitations are a small sample size, low statistical power, a mostly college-aged sample, and the possibility that the successful weight-loss intervention overshadowed an independent effect of the OLP pills on weight loss.

### **What is already known**

OLP has been reported to improve symptoms of cancer fatigue, irritable bowel syndrome, menopausal hot flashes, ADHD, allergic rhinitis, chronic back pain, migraine, and test anxiety. OLP was less effective in depression.

### **What this study adds**

This study adds obesity to the list of clinical conditions targeted for possible treatment with OLP. It adds weight loss effort and food craving as behaviors now tested with OLP. It adds original measures of participant perceptions to better understand outcomes in OLP studies. It adds knowledge to indicate that increased trait suggestibility may not affect OLP efficacy. Lastly, it adds support for the evidence-based proposal that boosting belief in OLPs may increase their effectiveness and it introduces the idea that the type of OLP used should differ from stimuli that are naturally associated with the condition being tested or treated.

## **Declarations**

### **Funding**

The study was supported by Psychology Merit Funds (to MMB) and the UAB Nutrition Obesity Research Center (NIH-P30DK056336).

### **Conflicts of interest/Competing interests**

The authors declare that they have no conflict of interest.

### **Ethics approval**

All procedures involving human participants were approved by the UAB Institutional Review Board for Human Use in accordance with the 1964 Helsinki declaration and later amendments.

### **Consent to participate**

Informed consent was obtained from all individual participants in the study.

### **Consent for publication**

Not applicable.

## Availability of data, material, and code

**Raw data were generated at UAB. Derived data** supporting the findings of this study are available from the corresponding author (MMB) on request.

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## Supplementary Files

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