

Open-label placebo vs double-blind placebo for irritable bowel syndrome: a randomized clinical trial

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Abstract

It is commonly believed that blinding to treatment assignment is necessary for placebos to have an effect. However, placebos administered without concealment (ie, open-label placebos [OLPs]) have recently been shown to be effective in some conditions. This study had 2 objectives: first, to determine whether OLP treatment is superior to no-pill control (NPC) in irritable bowel syndrome (IBS) and, second, to compare the efficacy of OLP against double-blind placebo (DBP). In a 6-week, 3-arm, randomized clinical trial, participants were randomized in equal proportions to 3 arms: OLP, DBP, or NPC. Two hundred sixty-two adults (72.9% women), with a mean age of 42.0 (SD = 18.1) years, participated in the primary study. The mean improvement on the IBS Severity Scoring System from baseline to the 6-week end point was significantly greater in OLP compared with that in NPC (90.6 vs 52.3, $P = 0.038$). Open-label placebo and DBP did not differ significantly on IBS Severity Scoring System improvement (100.3 vs 90.6, $P = 0.485$). Standardized effect sizes were moderate for OLP vs NPC ($d = 0.43$) and small for OLP vs DBP ($d = 0.10$). Participants treated with OLP reported clinically meaningful improvements in IBS symptoms that were significantly greater than those on NPC. Open-label placebo and DBP had similar effects that did not differ significantly, suggesting that blinding may not be necessary for placebos to be effective and that OLP could play a role in the management of patients with refractory IBS.

Keywords: Irritable bowel syndrome, Placebo, Chronic abdominal pain

1. Introduction

Placebo-controlled, randomized, double-blind trials are considered the gold standard for assessing treatment efficacy. Shortly after their development and then widespread adoption, Henry Beecher published a landmark article in 1955, “The Powerful Placebo,” in which he assumed that patients must be blinded to treatment assignment for placebos to have clinical effects.² The assumption that placebos require concealment or deception became imbedded in biomedicine. In 2010, we reported a pilot randomized controlled trial (RCT) of nonconcealed, “open-label”

placebos (OLPs) as treatment for irritable bowel syndrome (IBS) that challenged this conventional belief.¹⁷ The study showed that participants receiving OLP reported greater improvement in IBS symptoms with meaningful clinical impact compared with a control group who did not receive placebo (ie, “no-pill control [NPC]”). This pilot study was the first RCT to test OLP for any condition. Supporting the credibility of our finding in IBS, subsequent RCTs—all in patients with subjective symptoms who exhibit high placebo response in RCTs—involving chronic low back pain, knee pain, cancer-related fatigue, migraine headaches, and allergic rhinitis have also suggested that OLP may be an effective method to elicit placebo effects without deception in these conditions.^{6,14,16,22,24,27} This evidence suggests the importance to further investigate OLP in patients with IBS. In addition, if the presumption that concealment or deception is necessary for placebos to be effective is false, then many theories about the mechanisms that drive placebo effects may need modification or be inaccurate or incomplete.

Irritable bowel syndrome is a chronic gastrointestinal disorder characterized by abdominal pain associated with alterations in bowel habits (ie, diarrhea, constipation, or alternating between diarrhea and constipation). It affects approximately 5% to 10% of the adult population and is one of the most common reasons for healthcare consultations and absenteeism from work or school. As with other chronic pain conditions that involve central sensitization and hypersensitivity, effective treatment options for IBS are limited, and placebo response rates in RCTs are high.¹⁸ Although high placebo response rates have been an impediment in clinical trials, we hypothesize that it may be possible to ethically harness this placebo effect without deception for clinical benefit.¹⁹

In this RCT, we sought to extend the earlier, counterintuitive finding from our pilot trial that OLP is more effective than NPC in

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IBS by including a larger sample size, longer treatment duration, and concurrent comparison with double-blind placebo (DBP). In addition, we investigated whether the treatment efficacy of OLP differs from DBP. To the best of our knowledge, no such study has ever been performed. Based on our previous trial of OLP in IBS¹⁷ as well as OLP RCT studies in other conditions,^{6,14,16,20,22,24,27} we hypothesized that OLP would be superior to NPC for improving IBS symptoms.

2. Methods

2.1. Study design

We conducted a 6-week RCT in a single academic medical center from June 2016 to January 2019. Patients were randomly assigned in equal proportions to 3 groups: (1) OLP, (2) DBP, and (3) NPC, which controlled for natural history, regression to the mean, and Hawthorne effects. To create ethical conditions for DBP, half as many patients were randomized to a fourth group, double-blind peppermint oil (DBM).

As prospectively planned in our published protocol¹ and in our NIH grant application, our study focused only on placebo effects in IBS and, more particularly, on 2 primary questions: (1) Is open-label placebo superior to no treatment control? and (2) How does the efficacy of open-label placebo compare with the efficacy of double-blind placebo? From a purely *scientific* point of view, neither of these questions would require inclusion of an active treatment arm. However, from an *ethical* point of view, we needed to include an active treatment arm to establish double-blind conditions without deceiving patients and clinicians. The emphasis on placebo effects in our 2 primary aims is reflected in the fact that we randomized half as many patients to the peppermint oil arm, thus allocating more statistical power to our primary aims. Our a priori data analytic plan and our power analysis were both based on the planned 3-arm placebo study.¹ Consequently, outcomes from the double-blind assessment of peppermint oil group will be reported elsewhere.

Originally, the study was designed to include 280 participants in the 4 groups. However, because of a computer malfunction, primary outcome data on the first 26 patients were not collected. In collaboration with the NIH, our funding agency, we were given permission to restart the study from this point onward; moreover, we were also given approval to include an additional 60 participants to replace the lost data and to improve capacity for secondary analyses. Refer to **Figure 1** for details.

2.2. Eligibility and recruitment

Participants who were aged 18 to 80 years, met Rome IV criteria for IBS, and had at least moderately severe IBS symptoms (defined as a score of ≥ 175 on the IBS Symptom Severity Scale [IBS-SSS]) were eligible for an initial visit. Participants were eligible to participate if their IBS medication regimen (eg, fiber, tricyclic antidepressants, and antispasmodics) had been stable for at least 30 days and agreed not to change their IBS treatment for the duration of the study.

Participants were excluded from the study if they reported (1) unexplained or uninvestigated alarm features (eg, rectal bleeding, unintentional weight loss, iron deficiency anemia, and family history of colon cancer), (2) severe acid reflux (defined as an average of 3 or more episodes of heartburn or regurgitation per day over a week), (3) use of peppermint oil in the past 30 days, (4) a diagnosis, as judged by the investigators, that would interfere with the assessment of efficacy or the safety of the participant, or

(5) allergy to soybean oil (because the placebo contained soybean oil to match the appearance of the peppermint oil pills). See further and our published protocol study for additional details.¹

Participants were recruited from advertisements on public transportation, newspapers, direct mailings to patients, and referrals from healthcare professionals. When potential participants contacted the study staff, the study staff explained the entire trial transparently.

2.3. Study visits

2.3.1. Visit 1 (baseline)

After informed consent was obtained and baseline questionnaires were completed, participants were seen by a board-certified gastroenterologist (A.L., J.N., J.I., or V.R.), who performed a routine supportive GI-focused interview and physical examination, as would be performed in clinical practice, to verify eligibility. Physician assignment was quasi-randomized and based on availability. All participants received the same brief rationale describing the overall study. This rationale was semiscripted and emphasized 3 main points: (1) we know that placebos can produce clinically meaningful improvement in double-blind trials, (2) we do not know whether placebos work when honestly given (ie, unblinded or open label), and (3) it is not necessary to believe that placebos will work to experience benefit. For further details, see our previously published protocol study.¹ Although the bullet points were standardized, we allowed physicians to follow their usual therapeutic style. We did not train or direct the physicians to use any communication enhancements different from the regular practice. After this brief rationale, the physician opened a sealed, opaque envelope and informed the participant of their allocation to OLP, NPC, or double-blind (placebo or peppermint oil) groups. Given the complexity of the design, physicians then briefly reviewed the semiscripted information for the assigned arm (see Supplement for additional details, available at <http://links.lww.com/PAIN/B307>). For participants receiving pills (OLP, DBP, or DBM), it was emphasized that taking the pills as prescribed was critical and that any improvements could happen either rapidly or gradually. The scientific importance of the NPC was emphasized. Study physicians were trained in delivering the script transparently and with equipoise. Honesty was emphasized. If participants spontaneously expressed skepticism about OLP, physicians validated their doubts by discussing their own puzzlement and reflected on the unique design of this trial. Participants were encouraged to keep an open mind and “see what happens.” For patients on NPC, the scientific importance of this control group was emphasized, and it was repeated that they would receive advice on their IBS at the end of the study.

2.3.2. Visits 2 (midpoint) and 3 (end point)

During visit 2 (week 3) and visit 3 (week 6), all participants completed questionnaires, were verbally asked about adverse events, and briefly met with a study physician (A.L., J.N., J.I., or V.R. based on availability).

2.4. Placebo pills

Placebo pills contained 0.2 mL of soybean oil in enteric-coated softgels (~14 mm × 8 mm; manufactured by SoftGel Technologies Inc.; Los Angeles, CA) and were designed to match the peppermint oil pills (Pepogest; Greenbay, WI). All participants in the treatment arms received the same instructions to take 1 softgel, 3 times per day, 30 minutes before meals. All pills were

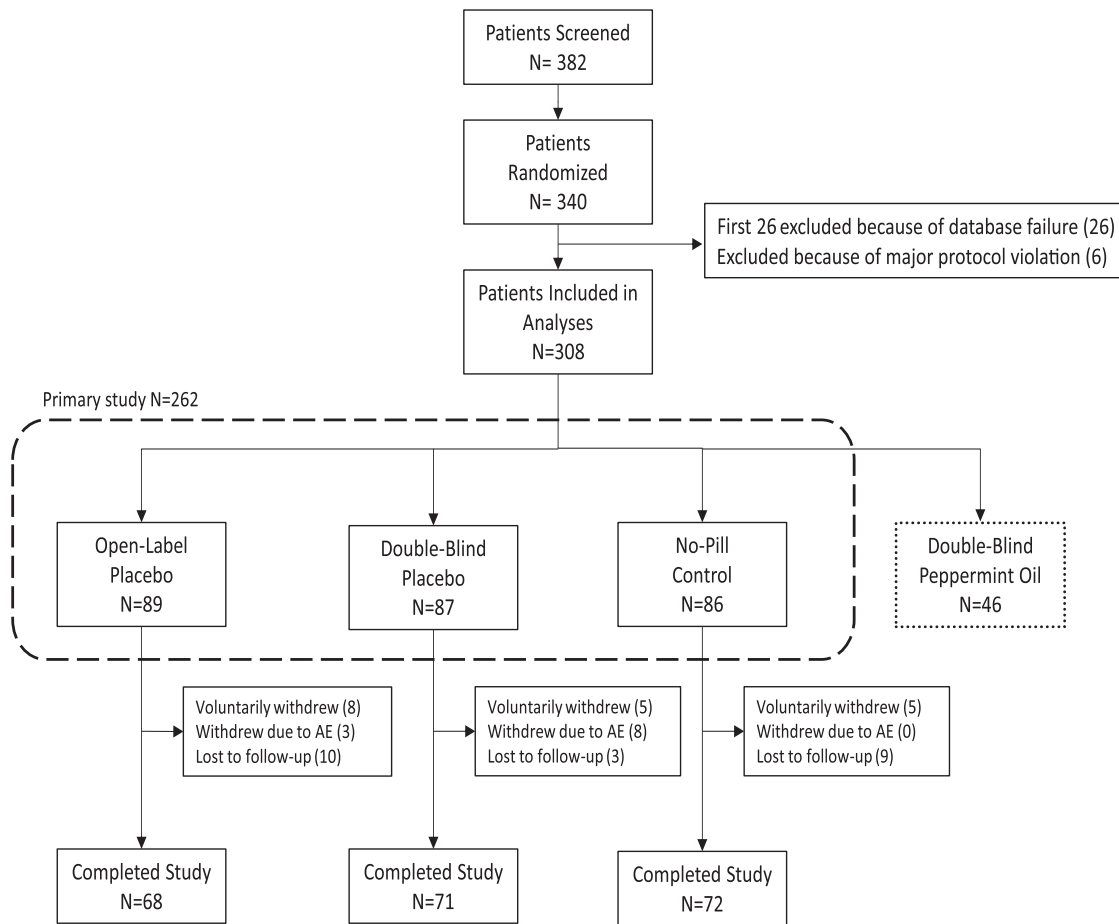


Figure 1. Patient flow diagram.

undisguisable. The bottles were labeled as “Open-Label Placebo” in the OLP arm and as “Double-Blind Placebo or Peppermint Oil” in the double-blind arm.

2.5. Randomization, stratification, and blinding

Treatment assignments were randomly generated by a program written by one of our biostatisticians (R.D.) using SAS statistical software (SAS Institute, Inc.; Cary, NC) and permuted block randomization with randomly varying block sizes. Randomization for the full study was performed in a 2:2:2:1 ratio (OLP, NPC, DBP, and DBM). Given that our placebo questions were primary and that peppermint oil was our foil, we randomized half as many participants to peppermint oil. We also stratified randomization based on IBS-SSS severity (<300 and ≥300) and sex, resulting in 4 strata. Furthermore, 34 participants were randomly assigned and completed a 30-minute qualitative interview after completing the study (these results will be published elsewhere).

All outcomes measures were administered by blinded research assistants. Participants in the DBP group were blinded to their treatment assignment (ie, they did not know whether their pills contained peppermint oil or not); however, participants in the OLP and NPC groups were not blinded.

2.6. Outcome assessments

The validated IBS Severity Scoring System (IBS-SSS) was the primary outcome measure. The IBS-SSS measures 5 items

(severity of abdominal pain, number of days with abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and interference with quality of life), each on a 0 to 100 scale. The IBS-SSS scores can range from 0 to 500, with higher scores indicating greater symptom severity. Irritable bowel syndrome symptoms can be categorized as mild (75-174), moderate (175-300), or severe (>300). A decrease of 50 points is considered a clinically meaningful improvement in symptoms.¹¹

We used 2 additional instruments as secondary IBS outcomes: (1) the IBS Global Improvement Scale (IBS-GIS),¹² which measures participants’ global improvement in the past 7 days on a scale that ranges from 1 (substantially worse) to 7 (substantially improved), and (2) the IBS adequate relief (IBS-AR) scale,²⁵ which is a single dichotomous question: “Have you had adequate relief of your IBS symptoms over the past week?” Unlike the IBS-SSS, the secondary outcomes are not measured at baseline.

To evaluate participants’ attitudes towards the treatments, participants were asked to rate their expectancy for improvement (0-100 visual analogue scale) if they received either placebo or peppermint oil. These questions were asked at baseline before learning randomization assignments.

2.7. Statistical analysis

To calculate power for our primary analysis, we used our previous pilot trial of OLP in IBS,¹⁷ in which the effect size for the standardized mean difference (Cohen *d*) between OLP and NPC

on IBS-SSS improvement was $d = 0.53$. We calculated that a total of 240 participants, with 80 participants in each of the 3 groups, were sufficient to achieve 90% power to detect such an effect size.

We conducted a modified intent-to-treat analysis that included all randomized patients who provided at least 1 postbaseline, primary outcome assessment, without any exclusions other than major protocol violations and database error (refer to **Fig. 1** for details). To address any potential bias due to missing data, we also planned to conduct a sensitivity analysis using multiple imputation by chained equations to replace missing data and allow for a full intent-to-treat analysis that would include all randomized participants with no exclusions.

To test whether 6 weeks of OLP, DBP, or NPC treatment resulted in different clinical outcomes in IBS, we conducted a 1-way analysis of covariance (ANCOVA) on IBS-SSS scores, with sex and baseline IBS-SSS scores as covariates and treatment condition (OLP vs DBP vs NPC) as the independent variable. If the omnibus ANCOVA was significant, we planned to conduct Fisher least significant difference (LSD) tests to make pairwise comparisons between the 3 groups. In the special case of 3 groups, it has been shown that this 2-step, Fisher LSD procedure controls type I family-wise error rate at the nominal alpha level, in this case 5%.¹³ For each contrast, we also planned to compute effect sizes in the form of Cohen d , the standardized mean difference between groups. By convention, a small effect size is $d = 0.20$, medium is $d = 0.50$, and large is $d = 0.80$.⁷

We also conducted a 1-way ANCOVA on IBS-GIS scores, with sex and initial severity (moderate vs severe), the factors used for stratifying the randomization, as covariates and treatment condition (OLP vs DBP vs NPC) as the independent variable. If the ANCOVA was significant, we planned to use Fisher LSD tests to make pairwise comparisons between the 3 groups. For each contrast, we also computed effect sizes in the form of Cohen d .

For IBS-AR, we conducted logistic regression analyses, with sex and initial severity (moderate vs severe) as covariates and treatment condition (OLP vs DBP vs NPC) as the independent variable. If the overall test for the 3 groups was significant, we planned to follow-up with pairwise post hoc tests.

Missing data minimization strategies included patient retention efforts and a modified intent-to-treat analysis. Patient-reported assessments were captured electronically at each visit, and the system prohibited participants from omitting items.

3. Results

3.1. Participants

A total of 340 participants were randomized to the 4 arms of the study. However, data from the first 26 participants were excluded because of a database failure. Six additional participants were excluded because of major protocol violations (eg, a patient assigned to DBP began taking over-the-counter peppermint oil). Only participants who were randomized to OLP ($n = 89$), DBP ($n = 87$), or NPC ($n = 86$) were included in this analyses ($n = 262$). For additional details, see the Methods section and **Figure 1**.

The demographic characteristics of the 3 groups are summarized in **Table 1**. The mean age was 42.0 years ($SD = 18.1$). Most participants were women (72.9%), and most reported their race as White (83.6%). Based on IBS-SSS (0–500), symptom severity at baseline was moderate (175–299) for 63.4% and severe (≥ 300) for 36.6% of participants. Overall, the mean baseline IBS-SSS

severity was 282.1 ($SD = 67.4$). Participants reported having consulted with a median of 2 physicians and 1 gastroenterologist for their IBS. Nearly half of the participants (47.7%) reported having had IBS for more than 10 years. There were no significant differences between the groups on any of the baseline characteristics reported in **Table 1**.

Because the study physicians may have differed in their communication styles, we examined whether the 4 gastroenterologists each saw roughly an equal number of patients in each of the 3 treatment arms. By chance, one would expect that 33.3% of each physician's clinical encounters should be in each of the 3 treatment groups. In fact, the lowest percentage was 27.8% and the highest was 37.5%, and the distribution of visits across treatment arms did not differ significantly from chance.

3.2. Primary outcome

The omnibus ANCOVA comparing OLP, DBP, and NPC on mean IBS-SSS improvement from baseline to 6-week end point was statistically significant ($P = 0.011$). The mean improvement in IBS-SSS from baseline to the 6-week end point, our primary outcome, was significantly greater in OLP compared with that in NPC (90.6 vs 52.3, $P = 0.031$). OLP and DBP did not differ significantly on IBS-SSS improvement ($P = 0.485$). The effect sizes were moderate for OLP vs NPC ($d = 0.43$) and small for OLP vs DBP ($d = 0.10$). These results are illustrated in **Figure 2** and summarized in **Table 2**. In addition, DBP was superior to NPC (100.3 vs 52.3, $P = 0.004$).

To provide some additional clinical data on response rates, we also performed a post hoc analysis of the percentage of participants who improved by 50 points on the IBS-SSS (considered a clinically significant response) and by 150 points (considered a very strong clinical response). As can be seen in **Table 2**, approximately 70% of OLP and DBP participants reported a 50-point reduction in IBS-SSS when compared with only 54% of NPC participants. Similarly, approximately 30% of OLP and DBP participants reported a 150-point reduction, as compared to only 12% of NPC participants.

3.3. Secondary outcomes

The omnibus ANCOVA comparing OLP, DBP, and NPC on mean global improvement scores (IBS-GIS) at the 6-week end point was statistically significant ($P = 0.021$). At the 6-week end point, OLP reported significantly higher mean IBS-GIS scores compared with NPC (4.37 vs 3.97, $P = 0.041$), as did DBP compared with NPC (4.48 vs 3.97, $P = 0.008$). OLP and DBP did not differ significantly from each other in mean IBS-GIS scores ($P = 0.562$). The observed effect sizes were from small to medium for OLP vs NPC ($d = 0.35$), medium for DBP vs NPC ($d = 0.46$), and small for OLP vs DBP ($d = 0.09$). In addition, the percentage of participants who reported moderate or substantial global improvement was significantly higher for OLP compared with that of NPC (18.1% vs 5.4%, $P = 0.019$, **Table 2** and **Fig. 2**).

To provide some additional clinical data on response rates, we also performed a post hoc analysis of percentage of participants who reported any global improvement (ie, slight, moderate, or substantial) as well as the percentage who reported moderate or substantial global improvement. These values are summarized in **Table 2**.

Although the rates of adequate relief reported at the 6-week end point by OLP (42.6%) and DBP (46.5%) were numerically higher than those of NPC (33.3%), the logistic regression testing for differences between the 3 groups was not statistically

Table 1

Demographics and baseline characteristics.

Demographics and baseline characteristics	Open-label placebo, n = 89	Double-blind placebo, n = 87	No-pill control, n = 86
Age	42.2 (17.8)	43.8 (19.2)	40.0 (17.0)
% Female	71.9	73.6	73.3
% African American	4.5	3.4	3.5
% Asian	3.4	4.6	10.5
% Caucasian	84.3	86.2	80.2
No. of doctors seen for IBS	2.5 (1.8)	2.3 (1.5)	2.9 (2.1)
Baseline severity (IBS-SSS)	286.0 (62.0)	285.8 (69.0)	274.4 (71.1)
% Moderate (IBS-SSS 175-299)	60.7	62.1	67.4
% Severe (IBS-SSS ≥ 300)	39.3	37.9	32.6
% IBS constipation	20.2	20.7	27.9
% IBS diarrhea	41.6	44.8	39.5
% IBS mixed	34.8	31.0	30.2
% IBS undefined	3.4	3.4	2.3
% IBS duration > 10 y	44.4	44.7	54.0
PHQ-8 depression	4.7 (4.2)	5.3 (4.9)	5.7 (5.3)
GAD-7 generalized anxiety	4.2 (4.2)	4.8 (4.5)	5.2 (5.6)

Values are means (SDs) unless otherwise specified.

GAD-7, Generalized Anxiety Disorder scale (range 0-21); IBS-SSS, IBS Severity Scoring System (range 0-500); IBS, irritable bowel syndrome; PHQ-8, Patient Health Questionnaire depression scale (range 0-24).

significant ($P = 0.258$); therefore, no follow-up tests were conducted (Table 2 and Fig. 2). To address any potential bias due to missing data, we also conducted a sensitivity analysis using multiple imputation by chained equations to replace missing data, thus producing a full intent-to-treat analysis that included all randomized participants without any exclusions. As detailed in the Supplement, these multiple imputation analyses produced a similar pattern of effects for all 3 outcome measures. Finally, outcomes at the 3-week midpoint were not statistically

significant but showed a similar pattern (see Supplement, available at <http://links.lww.com/PAIN/B307>).

3.4. Expectancy

Before learning their randomization assignment, patients were asked to rate their expectancy for improvement (0-100 visual analogue scale) if they received placebo or peppermint oil. Open-label placebo and DBP participants reported nearly identical

Table 2

Outcomes at 6-week end point.

IBS-SSS improvement from baseline to 6-wk end point				<i>P</i>			
	Open-label placebo (n = 68)	Double-blind placebo (n = 71)	No-pill control (n = 72)	Global test	OLP vs NPC	DBP vs NPC	OLP vs DBP
Primary outcome							
Mean (SD)	90.6 (89.5)	100.3 (99.6)	52.3 (87.0)	0.015	0.038	0.005	0.485
95% CI	68.6–112.6	78.7–121.8	30.8–73.7				
IBS-SSS reduction from baseline to 6-wk end point				<i>P</i>			
	Open-label placebo	Double-blind placebo	No-pill control	Global test	OLP vs NPC	DBP vs NPC	OLP vs DBP
Secondary outcomes							
50-point reduction*	69.1%	70.4%	54.2%	0.083	—	—	—
150-point reduction*	29.4%	29.6%	12.5%	0.018	0.021	0.014	0.999
Global improvement (IBS-GIS) at 6-week end point				<i>P</i>			
	Open-label placebo	Double-blind placebo	No-pill control	Global test	OLP vs. NPC	DBP vs. NPC	OLP vs. DBP
Mean (SD)	4.37	4.48	3.97	0.021	0.041	0.008	0.562
Slight, moderate, or substantial*	41.7%	44.6%	24.3%	0.019	0.047	0.008	0.607
Moderate or substantial*	18.1%	20.3%	5.4%	0.012	0.019	0.007	0.834
Adequate relief (IBS-AR) at 6-week end point				<i>P</i>			
	Open-label placebo	Double-blind placebo	No-pill control	Global test	OLP vs. NPC	DBP vs. NPC	OLP vs. DBP
Percentage	42.6%	46.5%	33.3%	0.258	—	—	—

* Post hoc analyses.

IBS-SSS, IBS Severity Scoring System; IBS-GIS, IBS Global Improvement Scale; IBS-AR, IBS adequate relief.

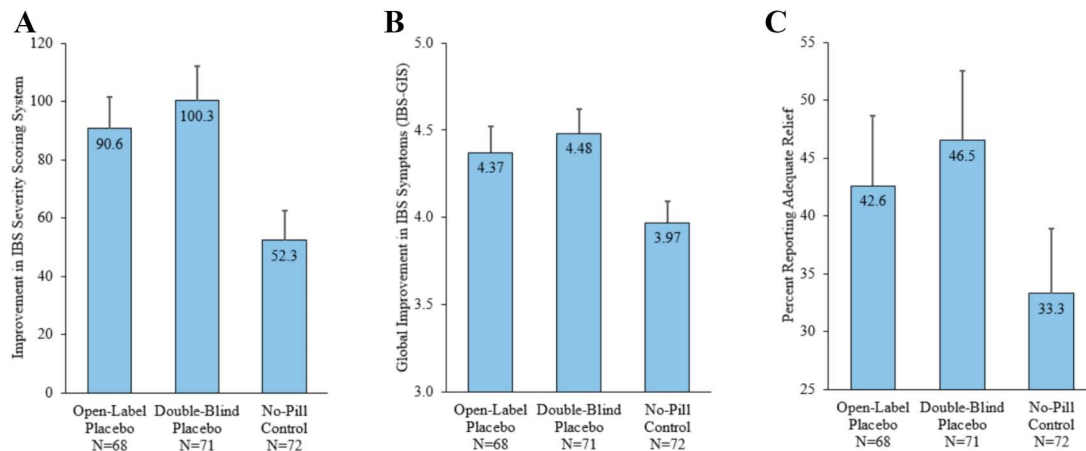


Figure 2. Outcomes at 6-week end point. (A) Primary outcome: Improvement on the IBS Severity Scoring System (IBS-SSS). (B) Secondary outcome: Global improvement in IBS symptoms (IBS-GIS). (C) Secondary outcome: Percentage of participants reporting adequate relief of symptoms (IBS-AR). Error bars depict standard errors. IBS, irritable bowel syndrome.

mean baseline expectancies for both questions (55.9 vs 55.3, respectively, for peppermint oil; and 40.1 vs 41.9, respectively, for placebo). These small differences between OLP and DBP were not significant ($P > 0.65$ for both tests). Combining OLP and DBP together, a paired t test showed that expectancies were significantly higher for peppermint oil as compared to those for placebo (55.6 vs 41.0, respectively, $P < 0.001$). Interestingly, expectancy for the DBP group was significantly correlated with improvement in IBS-SSS scores from baseline to the 6-week end point ($P = 0.01$) with a medium effect size ($r = 0.30$). By contrast, expectancy for the placebo treatment was not significantly correlated with outcome in the OLP group ($P = 0.25$), and the observed effect size was negative and of small magnitude ($r = -0.14$). The difference between these 2 correlations (ie, $r = 0.25$ vs $r = -0.14$) was statistically significant ($P = 0.01$).

3.5. Adverse events

Significantly more participants in the DBP group reported adverse events (31.0%) as compared to participants in both OLP (15.7%, $P = 0.008$) and NPC (9.3%, $P < 0.001$) groups. The proportion of participants in the OLP and DBP groups reporting adverse events did not differ significantly ($P = 0.27$). There were a total of 22 adverse events reported in OLP compared with 44 in DBP and only 11 in NPC. Adverse events reported by 2 or more participants overall are summarized in **Table 3**, most of which were gastrointestinal.

4. Discussion

This is the first study to directly compare the effects of OLP and DBP in any medical condition. We found that OLP was significantly better than NPC in improving IBS symptoms as measured by our primary outcome (IBS-SSS), as well as by one of our secondary outcomes, global improvement (IBS-GIS). We also found that improvement in IBS symptoms (IBS-SSS) and global improvement (IBS-GIS) in participants receiving OLP was similar to those receiving DBP. This study confirms our previous finding in IBS that OLP is superior to usual care (ie, NPC)² and challenges the widely held assumption that blinding is necessary for participants to improve with placebo.

Although the test for the other secondary outcome, adequate relief (IBS-AR), was not statistically significant, a numerically

higher percentage of participants in the OLP group reported adequate relief as compared to that of NPC (42.6% vs 33.3%). Our study is consistent with previous studies showing that OLP is superior to usual care (ie, NPC).^{6,14,16,17,20,22,24,26,27} To the best of our knowledge, this study had the largest sample size and longest duration of any OLP trial to date.

It is notable that there were twice as many adverse events reported in DBP when compared with OLP. This is likely due to the “nocebo” effect, in which participants receiving DBP sometimes report side effects due to their knowledge that they might be receiving an active medication. Indeed, in clinical trials, reported side effects to placebo often match the typical side effects associated with the investigational treatment (presumably because participants are given information about possible side effects of the investigational treatment).³¹ We accurately informed participants that side effects were rarely reported in published RCTs of peppermint oil and that those side effects were typically mild and related to reflux/heartburn.¹⁰ Nonetheless, we observed higher reports of reflux in the DBP group compared with OLP and NPC groups.

The clinical response to OLP in this trial was high with a 69.1% of participants receiving OLP reporting a clinically meaningful improvement in symptoms (ie, improvement in IBS-SSS ≥ 50 points).¹¹ The finding that openly prescribed placebo may be as effective as blinded placebo has implications for clinical practice and for future OLP research, especially in chronic visceral and somatic pain conditions.¹⁹ It has been well documented that many physicians admit to prescribing medicines that they believe will not have any pharmacological effects in the hope of inducing a placebo effect (sometimes referred to as “impure” placebos).^{9,21,23} For example, in a national survey of 1200 randomly selected U.S. physicians, approximately 50% reported having regularly prescribed impure placebos.²⁸ This practice is most often observed in the treatment of patients with chronic functional conditions.⁵ The results of this study suggest, however, that deception may not be necessary and that, at least in some conditions, patients may still show improvement even when prescribed OLPs.

We would argue that treatment with OLP fulfills the American Medical Association’s ethical standards of informed consent, transparency, and respect for person.^{4,30} Survey and focus group evidence suggests that patients are willing to try OLP. For example, a survey of 853 U.S. patients indicated that 62% would “probably” or “definitely” take OLP if recommended by a doctor.¹⁵

Table 3**Adverse events.**

Adverse events (AEs)	Open-label placebo n = 89	Double-blind placebo n = 87	No-pill control n = 86
Total number of AEs	22	44	11
Reflux/heartburn, n (%)	1 (1.1)	10 (11.5%)	0 (0.0%)
Diarrhea	5 (5.6%)	5 (5.7%)	0 (0.0%)
Belching	1 (1.1%)	2 (2.3%)	0 (0.0%)
Nausea	0 (0.0%)	3 (3.4%)	2 (2.3%)
Abdominal pain	2 (2.2%)	2 (2.2%)	1 (1.2%)
Gas	1 (1.1%)	4 (4.6%)	0 (0.0%)
Constipation	0 (0.0%)	2 (2.3%)	1 (1.2%)
Bloating	2 (2.2%)	1 (1.1%)	0 (0.0%)
Epigastric pain	0 (0.0%)	1 (1.1%)	1 (1.2%)
Fatigue	0 (0.0%)	2 (2.3%)	0 (0.0%)
Bronchitis	0 (0.0%)	1 (1.1%)	1 (1.2%)
Cold-like symptoms	0 (0.0%)	1 (1.1%)	1 (1.2%)

Only adverse events that occurred in 2 or more participants are listed. Therefore, the total number of adverse events is greater than the sum of the individual events listed.

This finding was replicated in a focus group in the United Kingdom (n = 58).³ In this study, we only assessed participants' expectancies for placebo, in general. In future studies, it would be helpful to also assess participants' expectancies for OLP specifically. There are no data on physicians' attitudes, but we speculate that OLP may not as be as acceptable to physicians because their professional identity is tied to "medications that are not placebos." More confirmatory data, engaged discussion, and critical self-examination may be required before physicians would be willing to prescribe OLPs.

This study has several strengths, including its relatively large sample size, rigorous end points, and innovative design. However, there are also some limitations to consider. Participants in this study may not be representative of the general population of patients with IBS because they were individuals who were willing to try OLP and/or herbal medicine (ie, peppermint oil) as a treatment for IBS. However, we would note that the same limitation applies to all RCTs. For example, an RCT testing a new medication would only be generalizable to patients who are willing try a pharmaceutical for their disorder, thus excluding those who are skeptical about drug treatments. In addition, because no objective markers have been definitively associated with IBS, our results necessarily relied on the standard measures of self-reported symptoms used by IBS researchers and clinicians. That said, we deliberately chose a functional illness defined by patient self-appraisal because previous research and theoretical models suggest that these conditions reliably have robust placebo responses.¹⁸ Finally, despite the positive results for OLP from our 2 initial RCTs in IBS, we believe that these findings should be independently replicated by a large multicentered trial of longer duration.

It is important to emphasize that the findings presented in this study should not be interpreted as meaning that OLPs should be considered as a substitute for DBPs in pharmaceutical RCTs. Double-blind placebos not only control for placebo effects but also reduce potential biases involving allocation, attention, detection, performance, and attrition.^{8,29}

5. Conclusion

It seems that, in some conditions, concealment or deception is not necessary for patients to benefit from placebo treatment. Moreover, our data suggest that OLP has comparable efficacy to DBP in IBS. Despite these conclusions, more research is required to harness OLP as an ethical and effective treatment for IBS and, perhaps, other chronic functional disorders.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Ethics approval: This study was approved by the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center. Data sharing: Deidentified data will be made available with formal request with ethics approval.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/B307>.

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