AMERICAN ACADEMY OF OPHTHALMOLOGY®

Magnitude and Predictors of the Placebo Effects in the Dry Eye Assessment and Management Study

*Katherine Han, BS,[1] Aaron T. Zhao, BS,[2] Yinxi Yu, MS,[3] Penny Asbell, MD, MBA,[4] Gui-Shuang Ying, PhD,[5] The DREAM Research Group**

Purpose: To determine the magnitude and predictors of placebo effects on dry eye symptoms and signs in the Dry Eye Assessment and Management (DREAM) study.

Design: Secondary analysis of data from the DREAM study, a large-scale multicenter randomized clinical trial of patients with moderate to severe dry eye disease (DED).

Participants: One hundred sixty-four participants who were randomized to the placebo group (daily oral 1000 mg refined olive oil) and completed a 12-month follow-up in 27 United States centers.

Methods: At baseline, 3, 6, and 12 months, DED symptoms were evaluated using the Ocular Surface Disease Index (OSDI), and signs were assessed using conjunctival staining, corneal staining, tear break-up time (TBUT), Schirmer test, and meibomian gland dysfunction (MGD). Placebo effects were calculated as changes from baseline in DED symptoms and signs over 12 months. Univariable and multivariable models determined predictors for placebo effects.

Main Outcome Measures: Changes from baseline in DED symptoms and signs over 12 months after administration of the placebo.

Results: Among 164 participants (mean age 58 years, 82% female, 74% White) randomized to the placebo group, there were significant placebo effects that were evident by 3 months and remained until 12 months with improvement in OSDI total score (mean decline 10.4 points, $P < 0.001$), conjunctival staining score (mean decrease 0.5 points, $P < 0.001$), corneal staining score (mean decrease 0.9 points, $P < 0.001$), TBUT (mean increase 0.7 seconds, $P < 0.001$), and MGD score (mean decrease 0.3 points, $P = 0.01$). In multivariable analysis, a higher baseline OSDI total score ($P < 0.001$) and absence of rheumatoid arthritis ($P = 0.01$) predicted more improvement in OSDI total score ($R^2 = 0.25$). More severe DED in OSDI ($P = 0.005$), conjunctival staining ($P = 0.04$), and MGD ($P < 0.001$) at baseline predicted more improvement in MGD score ($R^2 = 0.25$).

Conclusions: The DREAM study revealed significant placebo effects on DED symptoms and signs, with more severe DED predicting larger placebo effects. Future DED trials should consider placebo effects in the trial design, statistical analysis, and result interpretation.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2025;5:100730*

Supplemental material available at www.ophthalmologyscience.org.

Dry eye disease (DED), a chronic condition affecting up to 50% of the global population,[1] is characterized by ocular discomfort, visual disturbances, and inflammatory damage to the cornea and conjunctiva.[1–3] In part due to the relatively common nature of the disease and in part due to the lack of an effective treatment for DED, many clinical trials have been conducted to advance therapeutic options for DED patients.[4] One of these trials was the Dry Eye Assessment and Management (DREAM) study, a multicenter, randomized, placebo-controlled clinical trial to evaluate the efficacy of ω-3 fatty acid supplements to treat patients with DED.[5,6] The DREAM study randomized participants with moderate-to-severe DED to either a daily oral dose of 3000 mg of eicosapentaenoic acids and docosahexaenoic acids or a daily oral dose of 1000 mg of a refined olive oil placebo. Although the DREAM study did not find a significant benefit of ω-3 fatty acid supplements in mitigating DED symptoms and signs when compared with the placebo, certain DED signs and symptoms were significantly improved over time in participants who were randomized to the placebo group, suggesting the existence of placebo effects.

The placebo effect, often observed in clinical trials, is a phenomenon characterized by physiological benefits experienced by patients when administered an inactive treatment instead of an active treatment.[7] Although the placebo effect is well-documented in clinical trials for the treatment of various diseases ranging from depression to surgery,[8] there

https://doi.org/10.1016/j.xops.2025.100730
ISSN 2666-9145/25

are limited studies that examine the placebo effect in DED clinical trials.[9,10] The presence of the placebo effect does not only cause difficulty in designing, conducting, and analyzing clinical trials, but it also poses challenges to the statistical validity and generalizability of the trial results. Understanding the placebo effect and its predictors may help mitigate the placebo effect in DED trials.

In this article, we aim to quantify the magnitude of placebo effects on the DED symptoms and signs that were comprehensively evaluated in the DREAM study following the standard protocol and to determine the predictive factors for placebo effects observed in the DREAM study. This analysis will provide insights into the potential determinants that influence placebo responses and advance our understanding of placebo effects in dry eye treatment, which will lead to the improved design of DED treatment clinical trials and the mitigation of unwanted placebo effects.

Methods

Study Participants

The DREAM study was a multicenter, randomized, placebo-controlled, double-masked, prospective clinical trial (Clinicaltrials.gov; Identifier NCT02128763) funded by the National Eye Institute of the National Institutes of Health, which assessed ω-3's efficacy in patients with moderate-to-severe DED. Each of the 27 clinical centers obtained their respective institutional review board approval and all abided by the Health Insurance Portability and Accountability Act. Investigators and study coordinators at each center were trained and certified to ensure that study protocols were followed. The DREAM study was conducted under the United States Food and Drug Administration as an investigational new drug application (IND 106 387). The study was approved by the institutional review board/ethics committee at each center, followed the tenets of the Declaration of Helsinki, and obtained written informed consent from all patients. The trial's design and primary results have been previously published.[11,12] Only the key trial features related to this study are described here.

The DREAM study enrolled and randomized 535 participants in a 2:1 ratio to receive either daily active supplements or placebo supplements for 12 months. The active group received 5 soft gelatin capsules per day, each containing 400 mg of eicosapentaenoic acid and 200 mg of docosahexaenoic acid, totaling a daily dose of 2000 mg of eicosapentaenoic acid and 1000 mg of docosahexaenoic acid. The placebo group received placebo capsules containing 1000 mg of refined olive oil. Refined olive oil was believed to serve as a true placebo due to the small quantity used and its lack of polyphenols (compared with extra virgin olive oil), making it unlikely to have an effect on DED.[5]

The trial aimed to include a broad spectrum of patients with symptomatic moderate-to-severe DED. The inclusion criteria required an Ocular Surface Disease Index (OSDI) score ranging from 25 to 80 at the screening visit and from 21 to 80 at the eligibility confirmation visit. Moreover, participants must have exhibited $\geq$2 of the following signs in $\geq$1 eye: conjunctival lissamine green staining score of $\geq$1, corneal fluorescein staining score of $\geq$4, tear break-up time (TBUT) of $\leq$7 seconds, and a result on Schirmer test with anesthesia of 1 to 7 mm in 5 minutes. The same qualifying signs had to be present in the same eye at both the screening visit and the eligibility confirmation visit.

Outcome Measures

The outcome measures included dry eye symptoms using the OSDI and eye-specific dry eye signs that included conjunctival staining score, corneal staining score, TBUT, Schirmer testing score, and meibomian gland dysfunction (MGD) score. These were measured at baseline, 3, 6, and 12 months.

Ocular Surface Disease Index total scores and 3 subscale scores ranged from 0 to 100, with a score of 0 indicating no ocular symptoms and higher scores indicating greater symptom severity. Conjunctival staining was assessed on a scale of 0 to 3 in the nasal and temporal areas for a total possible score of 0 to 6 per eye. Corneal staining was assessed in 5 areas of the cornea for a total possible score of 0 to 15 per eye. Higher conjunctival staining scores and corneal staining scores indicated more severe dry eye signs. Tear break-up time measures time (in seconds) from a blink to the appearance of gaps in the tear film, with shorter times indicating greater tear film instability. The Schirmer test measures the length of wetting of paper strips placed in the inferior cul-de-sac of the lower eyelid in millimeters/5 minutes, with shorter lengths indicating less tear production. Meibomian gland dysfunction was evaluated for plugging and lid secretion on a scale of 0 to 3 using the TearScience Meibomian Gland Evaluator at slit lamp examination. The total score (range from 0 to 6) using plugging and lid secretion was calculated, with a higher score indicating more severe MGD.

Statistical Analysis

The statistical analyses, aiming to evaluate the magnitude and predictors for the placebo effect, were performed using data from 164 of the 186 participants who were randomized to the placebo group and completed 12 months of follow-up. Placebo effects were calculated as changes from baseline in DED symptoms and signs over the 12-month follow-up period. We evaluated placebo effects over time by performing longitudinal analyses for dry eye symptoms and signs through generalized linear models with correlation from longitudinal measures and intereye correlation (for eye-specific signs only) adjusted by using generalized estimating equations. To assess the earlier and later changes in placebo effects, further statistical comparisons were made between baseline and 3 months and among 3-, 6-, and 12-month time points.

We performed univariable and multivariable regression analyses to determine predictors associated with placebo effects over 12 months (quantified as the change from baseline at 12 months in DED symptoms and signs). The baseline predictors evaluated included age, gender, race, cigarette smoking history, Sjögren syndrome status, depression, rosacea, self-reported rheumatoid arthritis, self-reported peripheral artery disease, the use of dry eye treatments, and their baseline values of DED symptoms and signs. The outcome variables for placebo effects at 12 months included change from baseline in OSDI overall score, OSDI ocular symptom subscale score, OSDI total score decline $\geq$10 points (e.g., dry eye symptoms improved by $\geq$10 points, which is clinically meaningful[13]), and change from baseline in each dry eye signs. Each predictor was evaluated for its association with each placebo effect of outcome measure using the univariable regression model for continuous measure and the univariable logistic regression model for categorical measure. The predictors associated with $P < 0.10$ from univariable analysis were included in multivariable regression models, which went through backward variable selection by only keeping predictors with $P < 0.05$ in the final multivariable model. All the statistical analyses were performed in SAS v9.4 (SAS Institute Inc), and 2-sided $P < 0.05$ was considered statistically significant.

Results

Demographics and Baseline Characteristics

The baseline demographic and clinical characteristics of 164 participants who were randomized to the placebo group and completed a 12-month follow-up are shown in Table 1. The mean age was 58 years, 82% were female, 74% were White, 12% had Sjögren syndrome, 6% had self-reported rheumatoid arthritis, 14% had depression, and 80% used artificial tears or gels for treating DED at baseline.

Table 1. Baseline Characteristics of Participants in the Placebo Group (N = 164)

Baseline Characteristics	
Age (yrs): mean (SD)	58.4 (12.1)
Gender: female (%)	134 (81.7%)
Race	
White	122 (74.4%)
Black or African American	20 (12.2%)
Asian	5 (3.0%)
American Indian or Alaskan Native	1 (0.6%)
>1 race	5 (3.0%)
Unable to answer	11 (6.7%)
Cigarette smoking	
Never	112 (68.3%)
Former	50 (30.5%)
Current	2 (1.2%)
Sjögren syndrome	
No	134 (81.7%)
Yes	19 (11.6%)
Unknown	11 (6.7%)
Depression (SF-36 mental component score ≤42)	
No	141 (86.0%)
Yes	23 (14.0%)
Rosacea (facial): yes (%)	36 (22.0%)
Self-reported rheumatoid arthritis: yes (%)	10 (6.1%)
Self-reported peripheral artery disease: yes (%)	11 (6.7%)
Dry eye treatments*	
Artificial tears or gel (%)	131 (79.9%)
Cyclosporine drops (%)	29 (17.7%)
Warm lid soaks (%)	29 (17.7%)
Lid scrubs or baby shampoo (%)	26 (15.9%)
Any other DED treatment (%)	59 (36.0%)

DED = dry eye disease; SD = standard deviation; SF-36 = 36-Item Short Form Survey.
*Participants can take >1 dry eye treatment.

Change from Baseline in Dry Eye Symptoms and Signs

Scores of dry eye symptoms (OSDI total score and subscale scores) at baseline, 3, 6, and 12 months are reported in Table 2. Significant changes from baseline in OSDI total score and each subscale score were found in the first 3 months (all $P < 0.001$). However, these scores stabilized between 3 months and 12 months (all $P \geq 0.12$). The mean OSDI total score decreased from 42 at baseline to 33 at 3 months and remained in the range of 32 to 33 from 3 months to 12 months. There were statistically significant ($P < 0.001$) placebo effects on dry eye symptoms over 1 year as demonstrated by decline (e.g., symptoms improvement) in OSDI total score (mean decline 10.4 points, 95% confidence interval [CI]: 7.4−13.5 points), subscale scores of vision-related functions (mean decline 11.3 points, 95% CI: 7.9−14.6), ocular symptoms (mean decline 10.9 points, 95% CI: 7.7−14.2), and environmental triggers (mean decline 8.5 points, 95% CI: 3.6−13.4). The magnitude of change in OSDI overall score and subscale scores from baseline at 12 months was categorized into 5 groups: decline of ≥20, decline between 10 and 19, decline between 1 and 9, increase between 0 and 10, and increase of >10 (Fig 1, Table 3). The OSDI total score improved by ≥20 points in 27% of participants, improved by 10 to 19 points in 21% of participants, and worsened by ≥10 points only in 10% of participants (Table 3). Similarly, an improvement of ≥10 points in the OSDI score occurred in 51% of participants for the vision-related function subscale score, 46% of participants for the ocular symptom subscale score, and 43% of participants for the environmental trigger subscale score.

Change from Baseline in Dry Eye Signs

Regarding dry eye signs (Table 2), there was a significant decline over time (e.g., improvement of dry eye signs) in conjunctival staining score from baseline to 12 months ($P < 0.001$); the mean score changed from 2.9 at baseline to 2.7 at 3 months and 2.3 at 12 months. Similarly, there was a significant improvement in corneal staining score over time ($P < 0.001$), with a decrease in mean score from 3.8 at baseline to 3.3 at 3 months and 2.9 at 12 months. The TBUT showed improvement over time with a mean of 3.0 seconds at baseline, 3.4 at 3 months, and 3.7 at 12 months ($P < 0.001$). However, there was no significant improvement in the Schirmer test score ($P = 0.79$) and MGD score ($P = 0.08$) over the 1-year follow-up.

When the placebo effect on DED signs was quantified based on the change between baseline and 12 months, there were statistically significant improvements in conjunctival staining score (mean decrease of 0.5 points, $P < 0.001$), corneal staining score (mean decrease of 0.9 points, $P < 0.001$), TBUT (mean increase of 0.7 seconds, $P < 0.001$), and MGD score (mean decline of 0.3 points, $P = 0.01$). However, there was no statistically significant effect on the Schirmer test score ($P = 0.54$). When the sign change from baseline at 12 months was categorized into levels (Table 3), an improvement of ≥2 points in the conjunctival staining score occurred in 15% of participants, while a worsening of ≥2 points only occurred in 2% of participants. An improvement of ≥3 points in the corneal staining occurred in 17.7% of participants, while only 3.7% of participants experienced a ≥3-point worsening in their corneal staining score. Similarly, TBUT improved by >2 seconds in 13.4% of participants; only 2.4% of participants experienced a worsening of their TBUT by >2 seconds. For the MGD score, an improvement of ≥2 points occurred in 20% of participants, whereas only 10% of participants exhibited

Table 2. Dry Eye Symptoms and Signs at Baseline and Follow-Up Visits

Dry Eye Symptom Measures	Months				P Value		
	0	3	6	12	Overall	0 vs. 3	3, 6, 12
# of patients (n)	164	159	155	164			
OSDI score, mean (SD) (0–100, higher is worse)							
Total score	42.0 (16.0)	32.5 (18.8)	33.1 (19.4)	31.6 (18.7)	<0.001	<0.001	0.42
Vision-related function subscale	36.9 (18.8)	27.1 (21.1)	28.4 (21.5)	25.6 (20.3)	<0.001	<0.001	0.12
Ocular symptom subscale	44.0 (20.1)	34.1 (21.8)	34.5 (22.3)	33.1 (22.3)	<0.001	<0.001	0.58
Environmental trigger subscale	50.5 (28.2)	41.6 (28.2)	40.8 (31.1)	42.3 (30.7)	<0.001	<0.001	0.79
Dry eye signs							
Conjunctival staining score (0–6, higher is worse)	2.9 (1.4)	2.7 (1.4)	2.6 (1.3)	2.3 (1.5)	<0.001	0.003	0.001
Corneal staining score (0–15, higher is worse)	3.8 (2.6)	3.3 (2.4)	3.2 (2.4)	2.9 (2.4)	<0.001	0.001	0.02
Tear break-up time (sec, higher is better)	3.0 (1.5)	3.4 (2.4)	3.6 (2.2)	3.7 (2.4)	<0.001	0.055	0.25
Schirmer test score (mm/5 min, higher is better)	10.2 (7.1)	10.5 (6.8)	10.2 (7.0)	10.5 (6.7)	0.79	0.44	0.78
Meibomian gland dysfunction (0–6, higher is worse)	3.1 (1.7)	3.0 (1.8)	3.0 (1.8)	2.8 (1.9)	0.08	0.16	0.19
Use of dry eye treatments							
Artificial tears or gel	131 (79.9%)	108 (67.9%)	111 (71.6%)	104 (63.4%)	0.001	<0.001	0.08
Cyclosporine drops	29 (17.7%)	27 (17.0%)	28 (18.1%)	30 (18.3%)	0.80	0.44	0.67
Warm lid soaks	29 (17.7%)	25 (15.7%)	23 (14.8%)	24 (14.6%)	0.74	0.52	0.91
Lid scrubs or baby shampoo	26 (15.9%)	20 (12.6%)	21 (13.5%)	22 (13.4%)	0.67	0.21	0.92
Any other treatment	59 (36.0%)	35 (22.0%)	34 (21.9%)	31 (18.9%)	<0.001	<0.001	0.42

OSDI = Ocular Surface Disease Index; SD = standard deviation.

worsening MGD score of ≥2 points. For Schirmer test, an improvement of ≥5 mm/5 minutes occurred in 21.1% of participants, whereas 15.5% of participants exhibited a decline of ≥5 mm/5 minutes.

Predictors for Placebo Effects on OSDI Total Score and Ocular Symptom Score

Univariable analysis results for predictors of placebo effects as assessed by OSDI total score and ocular symptom subscale score are shown in Table S4 (available at www.ophthalmologyscience.org). In univariable analysis, higher baseline OSDI total score ($P < 0.001$), non-White race ($P = 0.02$), and the absence of rheumatoid arthritis ($P = 0.009$) were significantly associated with more improvement in OSDI total score. Similarly, higher baseline ocular symptom subscale scores ($P < 0.001$), non-White race ($P = 0.02$), and the absence of rheumatoid arthritis ($P < 0.001$) were significantly associated with more improvement in OSDI ocular symptom subscale score. Higher baseline OSDI total score (odds ratio [OR] = 1.05, 95% CI: 1.03–1.07 for per point increase in baseline OSDI total score, $P < 0.001$) was significantly associated with a higher likelihood of OSDI total score improvement of ≥10 points, while higher baseline corneal staining score (OR = 0.87, 95% CI: 0.77–0.99 for per point of corneal staining score increase, $P = 0.03$), presence of Sjögren syndrome (OR = 0.24, 95% CI: 0.08–0.76, $P = 0.02$), and baseline use of cyclosporine drops (OR = 0.27, 95% CI: 0.11–0.67, $P = 0.005$) were significantly associated with a lower likelihood of OSDI score improvement of ≥10 points.

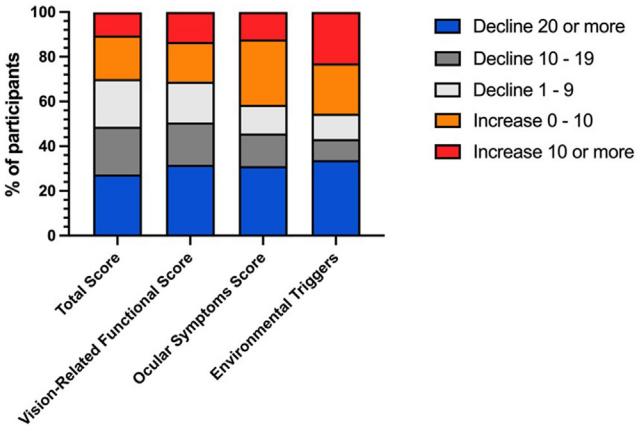

Figure 1. Stacked bar plot showing the magnitude of change from baseline at 12 months for OSDI total sore, OSDI vision-related function score, OSDI ocular symptom score, and OSDI environmental trigger score. The percentage of participants with a decline of ≥20 points, a decline of 10 to 19 points, a decline of 1 to 9 points, an increase of 0 to 10 points, and an increase of ≥10 points are shown for OSDI total score and each of subscale scores. OSDI = Ocular Surface Disease Index.

In multivariable analysis (Table 5), a higher baseline OSDI total score ($P < 0.001$) was associated with more improvement in OSDI total score, while self-reported rheumatoid arthritis ($P = 0.01$) was associated with less improvement in OSDI total score. These 2 factors predicted the placebo effect on the OSDI total score with an R^2 value of 0.25.

In the multivariable analysis for the placebo effect of the OSDI ocular symptom subscale score, higher baseline OSDI ocular symptom subscale score ($P < 0.001$) and non-White race ($P < 0.001$) were associated with greater improvement in the OSDI ocular symptom score. These factors predicted this placebo effect with an R^2 value of 0.31 (Table 5).

In the multivariable analysis, higher baseline OSDI total score was associated with a higher likelihood of

Table 3. Change from Baseline at 12 Months in Dry Eye Symptoms and Signs

Dry Eye Symptoms and Signs	Change from Baseline at 12 Mos					
	Mean Change (95% CI)	*Improved by ≥20*	*Improved by 10–19*	*Improved by 1–9*	*Worsened by 0–9*	*Worsened by ≥10*
OSDI						
Total score	−10.4 (−13.5, −7.4)	45 (27.4%)	35 (21.3%)	35 (21.3%)	32 (19.5%)	17 (10.4%)
Vision-related function score	−11.3 (−14.6, −7.9)	52 (31.7%)	31 (18.9%)	30 (18.3%)	29 (17.7%)	22 (13.4%)
Ocular symptom score	−10.9 (−14.2, −7.7)	51 (31.1%)	24 (14.6%)	21 (12.8%)	48 (29.3%)	20 (12.2%)
Environmental triggers*	−8.5 (−13.4, −3.6)	54 (33.8%)	15 (9.4%)	18 (11.3%)	36 (22.5%)	37 (23.1%)
Dry eye signs		**Improved by ≥2 points**	**Improved by 1 point**	**Changed <1 point**	**Worsened by 1 point**	**Worsened by ≥2 points**
Conjunctival staining score (0–6, higher is worse)	−0.5 (−0.7, −0.4)	24 (14.6%)	41 (25.0%)	84 (51.2%)	11 (6.7%)	4 (2.4%)
Meibomian gland dysfunction (0–6, higher is worse)	−0.3 (−0.6, −0.1)	16 (9.8%)	14 (8.5%)	78 (47.6%)	23 (14.0%)	33 (20.1%)
		Improved >2 sec	**Improved by 1–2 sec**	**Changed <1 sec**	**Worsened by 1–2 sec**	**Worsened by >2 sec**
Tear break-up time (sec, higher is better)	0.7 (0.4, 1.0)	22 (13.4%)	26 (15.9%)	101 (61.6%)	11 (6.7%)	4 (2.4%)
		Improved by ≥3 points	**Improved by 1–2 points**	**Changed <1 point**	**Worsened by 1–2 points**	**Worsened by ≥3 points**
Corneal staining score (0–15, higher is worse)	−0.9 (−1.2, −0.6)	29 (17.7%)	60 (36.6%)	45 (27.4%)	24 (14.6%)	6 (3.7%)
		Improved by ≥ 5 mm/5 mins	**Improved by 2–4 mm/5 mins**	**Changed <2 mm/5 mins**	**Worsened by 2–4 mm/5 mins**	**Worsened by ≥5 mm/5 mins**
Schirmer test score† (mm/5 min, higher is better)	0.3 (−0.7, 1.2)	34 (21.1%)	26 (16.1%)	52 (32.3%)	24 (14.9%)	25 (15.5%)

CI = confidence interval; OSDI = Ocular Surface Disease Index.
*Four participants had missing values in the OSDI environmental trigger score at 12 months.
†Three participants had missing values in the Schirmer test score at 12 months.

Table 5. Multivariable Analysis of Baseline Factors Associated with a Change from Baseline in OSDI Total Score and Ocular Symptoms Subscale Score from Baseline at 12 Months

	Change in OSDI Total Score (12 Mos − Baseline)		Change in OSDI Ocular Symptoms Subscale Score (12 Mos − Baseline)		OSDI Total Score Declined ≥10 Points from the Baseline	
Baseline Predictor*	*Difference (95% CI)*	P *Value*	*Difference (95% CI)*	P *Value*	*Odds Ratio (95% CI)*	P *Value*
OSDI total score (per point increase)	−0.57 (−0.74, −0.41)	**<0.001**			1.06 (1.03, 1.08)	**<0.001**
OSDI ocular symptom subscale score (per point increase)			−0.48 (−0.62, −0.35)	**<0.001**		
Race				**<0.0001**		
Black vs. White			−11.5 (−19.9, −3.14)	**0.007**		
Other vs. White			−13.9 (−21.9, −5.88)	**<0.001**		
Self-reported rheumatoid arthritis (yes vs. no)	14.3 (3.34, 25.2)	**0.01**				
Sjögren syndrome (yes vs. no)					0.18 (0.05, 0.65)	**0.009**
Use of cyclosporine drops (yes vs. no)					0.26 (0.09, 0.72)	**0.01**
Model performance for prediction	$R^2 = 0.25$		$R^2 = 0.31$		AUC = 0.78 (95% CI: 0.70−0.85)	

AUC = area under the curve; CI = confidence interval; OSDI = Ocular Surface Disease Index.
Bold font indicates statistical significance with $P < 0.05$.
*Only significant baseline factors were included in the final multivariable model.

experiencing an improvement of ≥10 points in OSDI total score (adjusted OR = 1.06, 95% CI: 1.03−1.08 for per point increase in the baseline OSDI total score, $P < 0.001$), while the presence of Sjögren syndrome (OR = 0.18, 95% CI: 0.05−0.65, $P = 0.009$) and the use of cyclosporine drops at baseline (OR = 0.26, 95% CI: 0.09−0.72, $P = 0.01$) were associated with a lower likelihood of improving ≥10 points in OSDI total score (Table 5). These 2 factors predicted the improvement of ≥10 points in total OSDI score with an area under the curve of 0.78 (95% CI: 0.70−0.85).

Predictors of Placebo Effect on Dry Eye Signs

In the univariable analysis (Table S6, available at www.ophthalmologyscience.org), higher baseline Schirmer test scores were associated with a greater increase in the TBUT ($P = 0.03$); higher baseline corneal staining scores were significantly associated with a greater decline in the corneal staining score ($P < 0.001$); higher baseline conjunctival staining scores ($P < 0.001$), the female sex ($P = 0.03$), and identifying as "other race" ($P = 0.001$) were associated with a greater decline in the conjunctival staining score; higher baseline Schirmer test scores ($P < 0.001$) were associated with a greater decline in the Schirmer test score (Table S7, available at www.ophthalmologyscience.org.); and higher baseline OSDI total score ($P = 0.02$), higher conjunctival staining score ($P = 0.03$), higher MGD score ($P < 0.001$), and identifying as "other race" ($P = 0.006$) were factors associated with a greater decline in the MGD score (Table S7).

In multivariable analysis (Table 8), higher OSDI total score ($P = 0.005$), higher TBUT ($P = 0.04$), higher conjunctival staining score ($P = 0.04$), higher MGD score ($P < 0.001$), and the presence of self-reported peripheral artery disease ($P = 0.003$) at baseline significantly predicted a greater improvement in MGD score at 1 year, with an R^2 value of 0.25.

There were no multivariable results for the predictors of placebo effect on TBUT, corneal staining score, conjunctival staining score, and Schirmer test score because no >1 predictor was statistically significant in the multivariable model.

Discussion

This study evaluated the magnitude and predictors of placebo effects on dry eye symptoms and signs among moderate-to-severe DED participants who received placebo treatment in the DREAM study. We found clinically relevant and statistically significant placebo effects on both DED symptoms and signs. These DED symptoms and signs are commonly used in the clinical care and clinical trials of DED. These reported placebo effects on dry eye symptoms and signs should be considered in clinical practice and clinical trials of patients with DED.

The issue of the placebo effect in DED has been well recognized,[9,10,14] but the magnitude of placebo effects on common dry eye symptoms and signs is not well quantified. By evaluating the change between baseline and 12 months in the DREAM participants randomized to the placebo group, we found significant improvement in dry eye symptoms and signs with a mean decline of 10.4 points in OSDI total score, 0.5 points in conjunctival staining score, 0.9 points in corneal staining score, and 0.3 points in MGD score and a mean increase of 0.7 seconds in the TBUT. These magnitudes of placebo effects on various DED symptoms and sign measures may provide useful information that should be considered for designing future DED clinical trials.

The placebo effect in dry eye treatment trials has been investigated in a recent meta-analysis of 56 placebo-controlled studies involving 12 205 participants. The meta-analysis found that placebo administration was not effective (based on the mean difference [MD] between baseline and last visit) in improving OSDI (MD = −8.1, $P = 0.2$), TBUT (MD = 0.4, $P = 0.3$), Schirmer test score (MD = −1.3, $P = 0.1$), and corneal staining (MD = −0.3,

Table 8. Multivariable Analysis of Baseline Factors Associated with a Change from Baseline in MGD at 12 Months

Baseline Factor*	Change in MGD Score (12 Mos − Baseline)	
	Difference (95% CI)	*P Value*
OSDI total score	−0.02 (−0.03, −0.004)	**0.005**
Conjunctival staining score*	−0.17 (−0.33, −0.004)	**0.04**
MGD score*	−0.41 (−0.54, −0.27)	**<0.001**
Self-reported peripheral artery disease (yes vs. no)	1.39 (0.49, 2.29)	**0.003**
Multivariable model performance for prediction	$R^2 = 0.25$	

CI = confidence interval; MGD = meibomian gland dysfunction; OSDI = Ocular Surface Disease Index.
Bold font indicates statistical significance with $P < 0.05$.
*For per unit increase.

$P = 0.1$).[10] Despite these nonstatistically significant placebo effects, the magnitudes of placebo effects reported in this meta-analysis are similar to placebo effects observed in our DREAM study in terms of OSDI, TBUT, and corneal staining scores. The large yet nonstatistically significant placebo effects observed in this meta-analysis may be due to the inherent variability associated with meta-analyses from including studies with variations in design, participant populations, dry eye severity, placebo interventions, and follow-up durations. In contrast, the DREAM study evaluated a relatively homogeneous cohort of moderate-to-severe DED participants randomized to the placebo group, allowing for a more precise assessment of placebo responses.

Our study's findings of improved dry eye symptoms as measured by OSDI in the placebo group are mostly consistent with previous placebo-controlled DED trials investigating the effect of ω-3 supplementation. A trial of 60 participants with 17 participants in the placebo group (1500 mg olive oil/day) found that the placebo group experienced a mean decrease of 10.5 points in OSDI total score by 3 months,[15] which was similar to the mean decline of approximately 10 points in OSDI by 3 months in the DREAM study. Another trial involving 51 participants in the placebo group (3136 mg linoleic acid/day) reported a mean decrease of 5.0 points in OSDI total score by week 6.[16] Since the OSDI is measured using a patient-oriented questionnaire comprising subjective questions, it is plausible that the psychological effect of the placebo effect (i.e., simply believing one received the active treatment) could have caused participants to select answers corresponding to improved dry eye symptoms.

In the DREAM study, we not only observed placebo effects on the subjective measure of DED symptoms, but we also found significant placebo effects on DED signs including the improvement in conjunctival staining score, corneal staining score, TBUT, and MGD score, which are objective measures determined by the clinician, so should not be affected by the psychological aspect of the placebo effect on the participant. This suggests that there is something beyond the control of the patient's conscious mind that caused placebo effects on DED signs. This finding suggested that objective clinical improvements in DED signs due to the administration of a placebo are not uncommon. Similarly, significant improvements in the measures of intraocular pressure were reported in patients randomized to placebo in the glaucoma treatment trials.[17] All of this suggests that the placebo effect is not simply limited to subjective patient-reported outcomes; it can manifest in clinical improvements evaluated by clinicians as well. The exact contributors to placebo effects on sign measures are unknown. One possible explanation is that although DED signs are described as "objective," they are still dependent on the observer and subject to bias, similar to evaluations of DED symptoms. Typically, both outcome assessors and patients enter a trial with the expectation of improvement in the DED, which can bias both groups toward reporting better outcomes, reflected in both DED symptoms and signs. Another frequently cited explanation for improvements seen in the placebo effect in DED signs is that the vehicle of the placebo could provide moisture to the eye and break down inflammatory molecules on the ocular surface.[4,18,19] However, since both the intervention and placebo for the DREAM study were administered as an oral capsule, this would not apply to our study. Another more relevant explanation posited by researchers is the increased adherence to prior DED treatment after enrollment in the trial.[14,20] However, we did not see an increase in the other dry eye treatments after randomization in DREAM participants; instead, we only observed a decrease in dry eye treatments including the use of artificial tears or gel from 79.9% at baseline to 63.4% at 12 months. Since the placebo effects were evaluated by comparing baseline and 12 months (i.e., approximately 1 year apart), the seasonal changes in environmental factors are unlikely causes of the placebo effects. One possible explanation for placebo effects is the phenomenon of "regression to the mean"[21] in that patients selected for the trial with moderate-to-severe DED will, on average, tend to improve. Another possible reason for observed placebo effects could be from the dry eye treatments used by participants at baseline. Topical medications such as cyclosporine drops are known to alleviate DED signs and symptoms that can take upward of 4 to 6 months to alleviate dry eye signs and symptoms.[22–24] Future research is needed to investigate the underlying mechanisms of the placebo effect on dry eye signs.

Although placebo effects in the dry eye treatment trials were well recognized, the predictors of placebo effects have not been well studied. The only study by Imanaka et al[9] on a total of 205 DED patients in the placebo arms of 3

randomized clinical trials found that baseline DED severity and age were predictive of placebo responses in frequently used end points of DED signs and symptoms. Specifically, patients >40 years of age exhibited stronger placebo responses in corneal fluorescein staining and dryness scores, and more severe dry eye signs and symptoms at baseline were predictive of larger placebo effects, which are consistent with our study findings. However, we did not find age was a significant predictor for placebo effects in our study, probably due to the difference in the characteristics of the study population in the Japanese study and the DREAM study.

The demonstrated placebo effects in the DED trials suggest the importance of including a placebo group in the randomized controlled trials for evaluating the efficacy of a new treatment for DED. With a placebo group, the determination of the efficacy of the new treatment should be through the comparison between the treatment group and the control group. The sole comparison between baseline and follow-up visits in dry eye symptoms and signs within the treatment group is invalid due to the inherent placebo effect observed in dry eye trials. The dependence of the placebo effect on the baseline dry eye severity implies the importance of balancing dry eye severity between the treatment group and the control group through randomization. The randomization stratified by dry eye severity may be considered to ensure the treatment group and the control group are balanced in their distribution of DED severity to yield a valid assessment of efficacy. The placebo effects also should be considered in the clinical care of DED patients. Cautions are needed in interpreting patient improvements as causal effects of active treatment in the context of possible placebo effects.

Despite our efforts to identify the predictors of the placebo effect to mitigate the placebo effects in future DED trials, we did not find many modifiable predictors of placebo effects except the baseline severity of DED symptoms and signs. As one can appreciate the magnitude and significant effects of placebo in our study as well as in other randomized trials, action should be taken to mitigate the placebo effect in future trials. One strategy to minimize the placebo effect in dry eye symptom (e.g., OSDI) reporting is making sure participants receive clear instructions and symptom reporting training before filling out questionnaires. A randomized study of patients with diabetic neuropathy found that patients who received pain reporting training before filling out their pain survey improved their reporting skills and resulted in more accurate evaluations of pain than patients who did not receive training.[25] The future study should also evaluate the validity of DED biomarkers, which may help establish the objective metrics to assess the severity and improvement of DED with treatment.[26]

The strengths of this study include the comprehensive evaluation of both the magnitude and predictors of placebo effects on several DED symptoms and signs that are commonly used in clinical care and clinical trials and the high-quality data collected from participants in 27 clinical centers following the standard trial protocol. However, this study also has several limitations. Firstly, the DREAM study only enrolled participants with moderate-to-severe dry eye and our findings may not be generalized to the dry eye patients with less severe dry eye because more severe DED is associated with larger placebo effects. Secondly, the DREAM study used olive oil capsules as a placebo; this limits the generalizability of our findings to other formulations or interventions of placebo. Future studies of the placebo effects of various placebo interventions in the broad dry eye population are needed to provide a better understanding of placebo effects and their predictors.

In summary, we observed significant and clinically meaningful placebo effects on both dry eye symptoms and signs of the DREAM participants randomized to placebo treatment using olive oil capsules. We found that more severe DED was associated with larger placebo effects. These findings have significant implications for the future clinical trials of DED. Given the high global prevalence of DED and the continuous search for effective treatment options for DED, international studies examining cultural, environmental, and genetic factors influencing placebo effects are needed to further refine our understanding and management of DED.

Footnotes and Disclosures

Originally received: December 14, 2024.
Final revision: January 29, 2025.
Accepted: January 30, 2025.
Available online: February 5, 2025. Manuscript no. XOPS-D-24-00561.

[1] School of Engineering and Applied Science, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania.

[3] Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[4] Bioengineering Department, University of Memphis, Memphis, Tennessee.

[5] Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

*The members of the DREAM Study Research Group at http://links.lww.com/ICL/A131.

Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures:

P.A.: Consultant — AbbVie, Amgen, Azura, Glia, Harrow, Iolyx, LinkBiologic, Premark, Regeneron, Santen, Trefoil, Horizon, Senju; Lecture honoraria — Vindico.

G.-s.Y.: Grants — NEI/NIH.

This study was supported by NEI Grants U10EY022879, U10EY022881, R21EY031338, and 2-P30-EY01583-26 and funds from the Research to Prevent Blindness.

HUMAN SUBJECTS: Human subjects were included in this study. The study was approved by the institutional review board/ethics committee at each center, followed the tenets of the Declaration of Helsinki, and obtained written informed consent from all patients.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Han, Zhao, Asbell, Ying

Data collection: Ying, Asbell

Analysis and interpretation: Han, Zhao, Yu, Asbell, Ying

Obtained funding: Ying, Asbell

Overall responsibility: Han, Zhao, Yu, Asbell, Ying

Abbreviations and Acronyms:
CI = confidence interval; **DED** = dry eye disease; **DREAM** = Dry Eye Assessment and Management; **MD** = mean difference; **MGD** = meibomian gland dysfunction; **OR** = odds ratio; **OSDI** = Ocular Surface Disease Index; **TBUT** = tear break-up time.

Keywords:
Dry eye disease, Placebo effect, Dry eye symptoms, Dry eye signs, Predictors.

Correspondence:
Gui-Shuang Ying, PhD, Center for Preventive Ophthalmology and Biostatistics, Department of Ophthalmology, Perelman School of Medicine at University of Pennsylvania, 51 North, 39th Street, Philadelphia, PA 19104. E-mail: gsying@pennmedicine.upenn.edu.

References

1. Farrand KF, Fridman M, Stillman IO, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 Years and older. *Am J Ophthalmol*. 2017;182:90−98.
2. Nelson JD, Craig JP, Akpek EK, et al. TFOS DEWS II introduction. *Ocul Surf*. 2017;15:269−275.
3. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15:334−365.
4. Nichols KK, Evans DG, Karpecki PM. A comprehensive review of the clinical trials conducted for dry eye disease and the impact of the vehicle comparators in these trials. *Curr Eye Res*. 2021;46:609−614.
5. Asbell PA, Maguire MG, Peskin E, et al. Dry eye assessment and management (DREAM©) study: study design and baseline characteristics. *Contemp Clin Trials*. 2018;71:70−79.
6. Dry Eye A, Management Study Research G, Asbell PA, et al. n-3 fatty acid supplementation for the treatment of dry eye disease. *N Engl J Med*. 2018;378:1681−1690.
7. Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: illness and interpersonal healing. *Perspect Biol Med*. 2009;52:518−539.
8. Hafliethadottir SH, Juhl CB, Nielsen SM, et al. Placebo response and effect in randomized clinical trials: meta-research with focus on contextual effects. *Trials*. 2021;22:493.
9. Imanaka T, Sato I, Tanaka S, Kawakami K. Predictive factors for the placebo effect in clinical trials for dry eye: a pooled analysis of three clinical trials. *Br J Ophthalmol*. 2017;101:1471−1474.
10. Prinz J, Maffulli N, Fuest M, et al. Placebo administration for dry eye disease: a level I evidence based systematic review and meta-analysis. *Int J Clin Pharm*. 2022;44:1087−1101.
11. Asbell PA, Maguire MG, Peskin E, et al. Dry eye assessment and management (DREAM(C)) study: study design and baseline characteristics. *Contemp Clin Trials*. 2018;71:70−79.
12. Asbell PA, Maguire MG, Peskin E, et al. Dry eye assessment and management (DREAM(c)) study: study design and baseline characteristics. *Contemp Clin Trials*. 2018;71:70−79.
13. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol*. 2010;128:94−101.
14. Novack GD. Compared to what? The placebo effect in dry eye therapy. *Ocul Surf*. 2018;16:265−269.
15. Deinema LA, Vingrys AJ, Wong CY, et al. A randomized, double-masked, placebo-controlled clinical trial of two forms of omega-3 supplements for treating dry eye disease. *Ophthalmology*. 2017;124:43−52.
16. Epitropoulos AT, Donnenfeld ED, Shah ZA, et al. Effect of oral Re-esterified omega-3 nutritional supplementation on dry eyes. *Cornea*. 2016;35:1185−1191.
17. Choe S, Kim YK, Chung W, et al. Placebo effect and its determinants in ocular hypotensive therapy: meta-analysis and multiple meta-regression analysis. *Ophthalmology*. 2023;130:1149−1161.
18. Margo CE. The placebo effect. *Surv Ophthalmol*. 1999;44:31−44.
19. Montecchi-Palmer M, Wu M, Rolando M, et al. Possible strategies to mitigate placebo or vehicle response in dry eye disease trials: a narrative review. *Ophthalmol Ther*. 2023;12:1827−1849.
20. Foulks GN. Challenges and pitfalls in clinical trials of treatments for dry eye. *Ocul Surf*. 2003;1:20−30.
21. McDonald CJ, Mazzuca SA, McCabe Jr GP. How much of the placebo 'effect' is really statistical regression? *Stat Med*. 1983;2:417−427.
22. Ames P, Galor A. Cyclosporine ophthalmic emulsions for the treatment of dry eye: a review of the clinical evidence. *Clin Invest (Lond)*. 2015;5:267−285.
23. de Oliveira RC, Wilson SE. Practical guidance for the use of cyclosporine ophthalmic solutions in the management of dry eye disease. *Clin Ophthalmol*. 2019;13:1115−1122.
24. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. *Ophthalmology*. 2000;107:631−639.
25. Treister R, Lawal OD, Shecter JD, et al. Accurate pain reporting training diminishes the placebo response: results from a randomised, double-blind, crossover trial. *PLoS One*. 2018;13:e0197844.
26. Roy NS, Wei Y, Kuklinski E, Asbell PA. The growing need for validated biomarkers and endpoints for dry eye clinical research. *Invest Ophthalmol Vis Sci*. 2017;58:BIO1−BIO19.