

The DREAM Placebo - an Active Treatment for Dry Eye Disease?

The DREAM placebo was not an active treatment. Here are the reasons:

- **The dose of olive oil was very small - 5 gm or about 1 teaspoon per day.** The placebos were tested by an independent laboratory, that was not associated with the manufacturer of the capsules. The olive oil was 68% oleic acid, an omega-9 fatty acid considered neutral with respect to inflammation. Blood levels of oleic acid did not change over time in either the Active or Placebo group, and were typical of the general USA population.
- **The Mediterranean Diet includes olive oil, but at a much higher volume per day. 5 gm olive oil intake by the DREAM patients assigned to placebo was far lower than the olive oil intake associated with the Mediterranean Diet.** The DREAM olive oil was refined (low in polyphenols). The Mediterranean Diet daily dietary intake is typically at least 4 TB (about 60 gm) of olive oil, which is 12 times the daily amount in DREAM. In addition, **a Mediterranean Diet has several other key components including nuts, fresh fruits, vegetables, and fish.** Dietary intervention studies (Mediterranean Diet) with olive oil have used about 100gm, or **20 times** the amount used in DREAM placebos.
- The DREAM olive oil had a small amount of alpha-linolenic acid (ALA), a plant-based omega-3. The total dose in the 5 capsules was 30 mg. ALA conversion to EPA and DHA is not efficient; 30 mg of ALA provides about 3 mg of EPA +DHA. **Our active capsules had 3000mg, or 1000 times the EPA+DHA delivered by the placebo.** ALA, EPA, and DHA blood levels did not change in the placebo group.
- **Why did the “objective” signs improve in both groups? Improvement in signs was small in both groups.** (Table 2 in the paper:[mean change over time of -0.4 points for conjunctival staining (scored 0 to 6) , - 0.6 to -0.7 for corneal staining (scored 0 to 15) ,+0.6 to +0.7 sec in tear break-up time, and +0.3 to +0.4mm for Schirmer’s test]). **Whenever there is a threshold to be met, as for the DREAM eligibility criteria for signs, there is some degree of regression to the mean.** Finally, the change over time in the Active and in the Placebo group for the Schirmer test, which is the most objective of all the tests, was not statistically significant despite approximately 950 eyes studied for one year.
- **Several experts in the effects of fatty acids in humans agreed that the olive oil in the dose given in DREAM was an inactive treatment.** The DREAM protocol was reviewed by consultants during trial development (e.g., Artemis Simopoulos, MD, President of the Center for Genetics, Nutrition and Health), and by the DREAM Data and Safety Monitoring Committee (e.g., Thomas Brenna, PhD, Professor of Chemistry, UT Austin, previously Professor of Human Nutrition at Cornell).
- **“Placebo effects” have been observed in most clinical trials for dry eye disease.** Improvements in symptoms or in signs in the placebo group have been observed with use of vehicle eyedrops as well as with a variety of oils in low oral doses (safflower oil [omega-6], corn oil [omega-6 and omega-9], sunflower oil [omega-6], and olive oil [omega-9]).

¹ The Dry Eye Assessment and Management Study Research Group. n-3 fatty acid supplementation for treatment of dry eye disease. N Engl J Med. Epub Apr 13 2018. Available for free at http://www.nejm.org/doi/full/10.1056/NEJMoa1709691?query=main_nav_lg