

# Techniques to Reduce the Placebo Effect in Glaucoma Clinical Trials

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## Key Words

Placebo effect · Glaucoma · Clinical trial · Trial design

## Abstract

**Aim:** To evaluate techniques used to reduce the placebo effect in prior well-controlled, single or double-masked placebo-controlled glaucoma trials. **Methods:** This study was a retrospective, non-patient-based, observational review of phase I–III trials with a placebo arm for glaucoma medicines available after 1977. **Results:** This study included 20 articles with 20 placebo control arms consisting of 458 patients evaluating 10 different glaucoma medications with 58 treatment arms. There was no statistical difference across the evaluated types of study designs to limit the placebo effect either for the morning trough or diurnal curve. The average reduction of the intraocular pressure in the placebo groups was  $1.6 \pm 1.5$  mm Hg for the morning trough and  $1.3 \pm 1.3$  mm Hg for the diurnal curve across all studies. **Conclusion:** The results of this study suggest that current design techniques described in the literature to limit the placebo effect appear ineffective compared to no additional techniques.

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## Introduction

Prior research has shown that a placebo effect (a measured reduction in intraocular pressure, IOP, from baseline in the placebo group) is common in well-controlled regulatory trials for glaucoma with an average decrease of  $2.3 \pm 1.6$  mm Hg from untreated baseline at 8 a.m. and a decrease of  $1.4 \pm 1.1$  mm Hg for the diurnal curve (PRN, internal data) [1–3]. All studies showed some placebo effect at 8 a.m., whereas all but one showed the effect for the diurnal curve.

A number of clinical trial designs have implemented techniques to help diminish the placebo effect. These have included: first, using a second qualifying day for untreated baseline to enter the study; second, using an afternoon IOP measurement as a second qualifying baseline; third, using a second masked reader apart from the person manipulating the IOP gauge on the tonometer, and lastly, using multiple IOP measures at the same time point.

These techniques are designed to limit the risk of entering a patient with a falsely high IOP into a study and thus theoretically inhibiting a placebo effect once the patient begins the masked treatment. Unfortunately, little information is available which analyzes these techniques. Such an analysis would be important because of the extra

**Table 1.** Summary of 8 a.m. morning trough and diurnal baseline and active treatment IOP values for eyes treated with placebo

	Treatment arms, n	Patients, n	Mean baseline IOP placebo, mm Hg	Mean ATV IOP placebo, mm Hg	IOP decrease from baseline to ATV, mm Hg	p value
<b>Trough</b>						
2 readers of the IOP	0	0	N/A	N/A	N/A	
Multiple IOP measures at one timepoint	2	33	26.4±1.6	25.1±2.2	1.3±0.6	
2 separate qualifying days	8	273	26.3±1.5	24.9±1.6	1.4±1.1	0.88
p.m. qualifying IOP	3	137	26.9±0.7	24.9±1.5	2.0±1.0	
No extra measures	10	170	26.1±2.1	24.4±3.2	1.8±1.8	
<b>Diurnal</b>						
2 readers of the IOP	0	0	N/A	N/A	N/A	
Multiple IOP measures at one timepoint	2	37	25.6±0.4	24.2±0.8	1.5±0.4	
2 separate qualifying days	5	163	25.7±2.1	23.7±1.3	2.0±1.1	0.27
p.m. qualifying IOP	3	137	25.4±0.5	23.5±1.0	1.9±0.6	
No extra measures	6	96	24.0±2.3	23.3±3.2	0.7±1.4	

ATV = Active treatment visi.

time and costs as well as the theoretical increased risk of corneal abrasion by the extra measures.

The purpose of this study was to evaluate techniques used to reduce the placebo effect in prior well-controlled, single or double-masked placebo-controlled glaucoma trials.

## Methods

### Study Criteria

Using published literature found on PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and medical reviews on the Food and Drug Administration's drug approval website (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>), we included in this study phase I–III trials with a placebo arm for commercially available glaucoma medicines that became commercially available after 1977.

The following search terms were used: primary open-angle glaucoma, ocular hypertension, IOP, diurnal, monotherapy, baseline, reduction as well as pharmaceutical class, and the brand and generic names of commercially available single and fixed combination agents. Only prospective, parallel, single- or double-masked clinical trials were included which measured either a three-point diurnal curve or morning trough IOP.

### Procedures

The available morning trough and diurnal curve IOP values were entered into a spreadsheet for both baseline and the last treatment visit. Quality assurance was performed on 10% of the entries.

### Statistics

PRN Pharmaceutical Research Network, LLC analyzed the data. The level to declare a significant difference between any groups being analyzed was 0.05 and all analyses were two-way [4].

The differences in reduction from baseline to the last treatment day for the various methods of IOP measurement were analyzed with a single-factor analysis of variance as is appropriate for continuous data. The diurnal curve represented the average of all the IOP time points throughout the day.

## Results

This study included 20 articles (1 phase I, 16 phase II and 3 phase III) with 20 placebo control arms consisting of 458 patients. The studies evaluated 10 different glaucoma medications with 58 treatment arms including: 3 prostaglandin analogs, 3 beta-blockers, 3 carbonic anhydrase inhibitors and 1 alpha-agonist.

The summary of the results is found in table 1. There was no statistical difference across the evaluated types of study designs to limit the placebo effect either for the morning trough or diurnal curve. The average reduction of the IOP in the placebo groups was  $1.6 \pm 1.5$  mm Hg for the morning trough and  $1.3 \pm 1.3$  mm Hg for the diurnal curve across all studies.

## Discussion

This study showed that design techniques to limit the placebo effect in glaucoma trials including multiple measures at one visit, a p.m. entry criterion, and a separate day entry criterion were no more effective in limiting a placebo effect than no design differences (one day entry

criterion with one reader and one IOP reading). Another design that has been utilized in some well-controlled trials has been a second masked reader. However, there were no trials available to evaluate with this design.

A placebo effect is important in the evaluation of regulatory trials because it may provide a different interpretation of the IOP data compared to the reduction in baseline from the active treatment itself. For example, if a medicine reduces IOP by 6 mm Hg from untreated baseline in the active control group but there is a 2 mm Hg placebo effect, this indicates there is only a 4 mm Hg IOP reduction with the medicine. When a start-up is attempting to license a new product to a larger pharmaceutical company a difference between 4 and 6 mm Hg in reduction can change the perceived commercial viability of the product. Consequently, techniques to limit the placebo effect would be useful. However, the results of this study are informative, but disappointing, in that no technique evaluated appeared effective in limiting the placebo effect.

Sharpe et al. [1] recently showed in prior phase II trials that the reduction from baseline was actually more predictive than the reduction from placebo for the IOP outcomes in future phase III and IV trials. However, the true extent of reduced IOP from commercialized products remains elusive since for ethical reasons phase III and IV trials typically include another active and not a placebo as the control.

Potential alternative techniques to limit the placebo effect might be investigator and technician education regarding awareness and importance of the placebo effect as well as the proper endpoint on the Goldmann tonometer, not allowing failed patients due to low baseline IOP to requalify (to avoid regression to the mean phenomenon), reviewing charts before study start to ensure patients have a prior history of untreated IOP >21 mm Hg, and limiting exercise and dietary habits which could falsely reduce the IOP on the morning of an active treatment visit.

This study suggests that current design techniques described in the literature to limit the placebo effect appear ineffective compared to no additional techniques.

This study was limited by the small number of trials available in each category to fully evaluate the placebo effect. Consequently more information would be useful to confirm these findings by evaluating a greater number of regulatory trials.

#### Disclosure Statement

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article. This study received no financial support from any private or government funding source.

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