Reviewer's report

Title: Interpretation of uniocular and binocular trials of glaucoma medications: an observational case series.

Version: 1 Date: 26 May 2007

Reviewer: Steven Kymes

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General

The authors have used an observational case series to construct a linear regression model that seeks to estimate the response of the fellow in the one-eyed trial. The approach seems to be somewhat creative; however, we believe that some of their methods would benefit from additional explanation, and more rigorous implementation.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The authors have relied on linear regression techniques to attempt to account for uncontrolled confounding factors that are inherent in a case series design. Whether this approach sufficiently addresses confounding between the pre-treatment IOP and post-treatment is unclear, but the technique does rely on certain assumptions to construct a valid model.

In general, OLS regression (the method employed) requires that the outcome variable be normally distributed to yield a valid result. In the current report, this would imply that the post-treatment IOP measure in the fellow eye would have a normal distribution. This is an assumption that should be investigated before using OLS for these analyses. On occasion, you can assume that the sample size is large enough to make this less relevant. But in the case of IOP, we would expect that there would be a significantly skewed distribution that would potentially lead to a biased estimate. At minimum, the investigators should check the residuals of their results to insure there that there is not correlation in the error term that indicates some unaccounted for confounding factor.

If it is determined that the biased outcome measure is problematic, the next step would be to employ an alternative method of regression, or some transformation of the variables that allow the investigators to account for the skewed distribution.

While I may simply not be familiar with the terminology employed, it seems to an additional issue that would need to be addressed was the inclusion of people with currently on and IOP lowering agent in the sample. The authors make a somewhat weak argument for inclusion of this group (page 6, lines 9-11). But they fail to realize that there is sufficient potential for confounding due to inclusion of this group to put them in the position of justifying its inclusion. While they did some analyses of this question, what they should have done is conduct a separate analysis with this group, and determine if the results were significantly different to justify a stratified analysis or to report the results separately. If the results are not substantially different, than this will provide evidence that the results can be pooled without fear of bias.

The use of the simulation to help “tease out” the regression to the mean effect is novel and interesting, but it is not clear how it was incorporated into the analyses, at least to this reviewer. In addition, if they are going to do this, it is essential that the results of the simulation be anchored to some external source of data. Say a longitudinal study of IOP fluctuation in an untreated population. By not doing so, the authors are leaving themselves open criticism that they are adjusting their analyses using “smoke and mirrors” or even worse, mathematical gimmicks.

The use of stepwise regression (backwards or forwards) is not optimal. The inclusion of variables in the model should have a theoretical basis, and all should be included and reported. If it is found that some of the variables included are not significant and the authors choose to exclude for parsimony that should be explained in the paper.

Is there a reason to believe that the inclusion of so many types of glaucoma is also a potential source of
confounding? It is not clear that this was addressed in the regression model. If it is known that response to treatment differs by type of disease, then it should be justified why they other conditions should be included in the analysis at all.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The author’s apology on p. 18, line 5-6 for their low R-squared is unnecessary. They have explained in their models 45-50% of the variance (assuming that violation of the assumptions of normalcy did not create a problem). It is nearly impossible in nature to explain greater variation than that using baseline variables.

Table 1 is confusing. They should provide a single clean table providing the baseline data for the sample, without including the “group difference” columns.

Tables 4 on, as well as the figures seem to be providing a fully unnecessary and very confusing level of detail. These should be consolidated to make the author’s point clearly and succinctly.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I receive grant support and consultation fees from Allergan and Pfizer.