Author's response to reviews

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

Authors:

Christopher T Leffler (cleffler@pol.net)
Lina Amini (lamini@unch.unc.edu)

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Author's response to reviews: see over
Scott Edmunds, PhD.
BMC Ophthalmology.

Dear Dr. Edmunds:

Enclosed please find the revision of “Interpretation of uniocular and binocular trials of glaucoma medications: an observational case series.” Extensive changes have been made to respond to the reviewers’ comments. Specific responses to the reviewers and a list of changes to the paper follow. Thank you for consideration of this manuscript.

Sincerely,

Christopher Leffler
Responses to the reviewers:

We would like to thank all the reviewers for taking the time to provide comments which have helped us to improve the manuscript. We made extensive revisions in response to the reviewers’ comments.

We do hope that the article can be published because we believe the analyses are novel. Although there are papers advocating both uniocular trials, and other papers advocating binocular trials, we have not found papers concluding that either trial can be performed based on a measurement of the information content of the trial. Moreover, although some papers and classical teachings advocate subtracting the intraocular pressure of the untreated eye during a uniocular trial to account for diurnal fluctuation, we have not found papers quantitatively assessing the value (or lack of value) of doing so.

Responses to Dr. Krupin.

Thank you for providing helpful criticisms.

We do agree that other conditions might behave differently than primary open angle glaucoma when a uniocular or binocular trial is attempted. Therefore, we have included only subjects with bilateral primary open angle glaucoma in this version of the paper.

We agree that selection of the eye with the higher IOP for initial treatment might affect the results to some degree. This selection is one factor leading to regression to the mean. We have enhanced the discussion of regression to the mean in the Discussion section. We would submit that regression to the mean is going to occur in clinical practice and in prospective clinical trials as long as clinicians continue to treat eyes which exceed a target pressure. For instance, the OHTS was initiated with a uniocular trial in the eye with a higher IOP (Brandt 2004). The most straightforward way to avoid regression to the mean is to treat random eyes of random patients at random times. Because this will not happen in clinical practice, we believe that regression to the mean will continue to be a real phenomenon which clinicians must consider when assessing drug effects. The regression coefficients derived from the analysis of our data correctly reflect regression to the mean, as they should if they are going to allow clinicians to accurately predict future IOP.

For many patients, there were in fact several baseline determinations of IOP before the trial agent was started. However, the mean baseline IOP did not predict follow-up IOP as well as the IOP during the final baseline visit. This finding is probably due to the fact that the final baseline visit is closer in time to the follow-up visits than the earlier baseline visits are. Regardless of the cause of the finding, it supports many clinicians’ routine practice of using the final baseline visit and the trial visit IOP when assessing drug effectiveness. We based this version of the paper on the independent variables used by many clinicians (final baseline and trial visit IOP), because these are the variables used
by many clinicians, and they were found to be most strongly associated with follow-up IOP.

“…aqueous humor dynamics, especially pressure-dependent and pressure-independent outflow, frequently differ between the two eyes of a patient.”

We agree with this statement. The regression coefficients reflect any such inter-eye differences.

Abstract: Numbers (1) and (2) were removed.

Methods: As stated above, only bilateral primary open angle glaucoma patients are included in this version of the paper.

The advantage of using all available follow-up visits is that more precise estimates of follow-up IOP can be made if multiple measurements are included (when available). In addition, there might be a “drug effectiveness bias” in which physicians hope that a drug is effective, and therefore will tend to underestimate the IOP on the first follow-up visit. Regardless of whether such bias exists, the results are not dependent on the number of follow-up visits included. Similar results are obtained when only the first follow-up visit is included. Other trials have used variable numbers of follow-up visits (e.g. Brandt JD, Beiser JA, Gordon MO, Kass MA; Ocular Hypertension Treatment Study (OHTS) Group. Central corneal thickness and measured IOP response to topical ocular hypotensive medication in the Ocular Hypertension Treatment Study. Am J Ophthalmol. 2004 Nov;138(5):717-22.)

“inclusion of subsequent agents adds uncertainty to the data”

In this version of the paper, we have performed separately all analyses with patients initially treated at baseline, and initially untreated at baseline to demonstrate that both patient groups yield similar results. As we stated, advocates of uniocular trials, advocates of binocular trials, and advocates of subtracting the untreated eye change during the uniocular trial, have never stated that their methods only work for the first glaucoma agent or only for the second agent. Of course, it might be theoretically possible that one should interpret first drug trials and second drug trials differently, but we did not find evidence of this.

In this version of the paper, the dorzolamide and timolol trial results were listed in tables without including the combination dorzolamide/timolol trial data.

“Analysis and Discussion should include IOP responsiveness of the trial.”

We have included in Table 1 the mean and standard deviation of the IOP at baseline, during the trial, and during follow-up. These values allow one to estimate the mean response. There are a variety of definitions of IOP responsiveness. One could look at the follow-up IOP minus baseline IOP. One could look at (Follow-up IOP minus baseline
IOP baseline IOP x 100%. One could look at a binary definition, e.g. a response is defined as a 3 mmHg drop or a 15% drop. One could look at binary definition based on some combination of the two (either a 3 mmHg drop or a 15% drop). As we discussed in the paper, all of these definitions are based on the follow-up IOP plus information known at baseline. Therefore, using our linear regression equations, one could predict follow-up IOP, and then calculate the IOP response based on one's preferred definition of IOP response. One of the disadvantages of defining IOP response in a binary fashion is that information is lost. For instance, a cutoff of a 15% drop treats patients with a 0% drop the same as patients with a 14.9% IOP drop. Moreover, the binary definition of response ultimately involves arbitrary cutoffs. For instance, does anyone believe that patients with a 14.9% IOP drop are going to do dramatically different clinically than patients with a 15.1% IOP drop? Having stated these limitations of a binary outcome analysis, it is possible to proceed with such an analysis. One can arbitrarily define response as a 10%, 15%, or 20% drop in IOP, and then determine baseline and trial visit predictors of a drug response by logistic regression. Such analysis does not suggest that the uniocular trial IOP change in the untreated eye should be subtracted. Nor does such analysis suggest a benefit of uniocular trials over binocular trials, or vice-versa. We did not present the logistic regression analyses in the paper because then the paper would have 9 tables, instead of 5 tables, and the reader would be overwhelmed. We believe that the linear regression analysis uses all the information contained in the continuous variables, and therefore should be more likely to be sensitive enough to detect these differences if they were really present.

Discussion:

The term “double-masked” was used instead of double-blind.

“The authors need to reference (defend) ‘substantial crossover effect.’”

Here, we are referring to how a drug might respond in theory. We are not suggesting that any currently available topical agents might lower the IOP equally in both eyes. We are suggesting that a topical drug with substantial crossover effect might do this. We added the underlined words to make that clear:

“For instance, a bilateral drop in IOP from 25 to 20 mmHg with uniocular treatment may in theory also be interpreted as the result of an effective drug with a substantial crossover effect. If drug crossover is so substantial that both eyes essentially receive an equal effect even with unilateral treatment (a theoretical situation which does not apply to currently available topical agents), then the drug effect can be estimated by the average IOP change.”

We did reference Piltz 2000, which looked at the crossover effect of topical beta-adrenergic agonists.
Responses to Dr. Kymes.

Thank you for providing helpful criticisms.

In this version of the paper, we did assess the normality of the IOP distribution by the test, initially and after transformation. Both square root and logarithmic transformation were performed. The p values of the uniocular trial second eye IOP change, and the \( r^2 \) values for the uniocular and binocular trials were listed for the initial and square root transformed analyses. The p and \( r^2 \) values were almost identical (see Tables 2-5). We also plotted the residuals against the predicted variable value and the independent variable to evaluate the constancy of the residual variation (Armitage and Berry, 1994). Therefore, it appears that the sample size was large enough that any deviation from normality did not have a meaningful effect on the results or conclusions. Of course, no physiological variable is perfectly normally distributed. Small samples may not be distinguishable statistically from a normal distribution. However, with enough sample points, it will be clear that most physiological distributions are not perfectly normal. This is due not only because of skew, but also because most physiological variables do not range from minus infinity to plus infinity, as the normal distribution does. Linear regression is commonly used in the biological sciences, even when the dependent variable is not perfectly normal. For instance, lens fluorescence has been shown to increase approximately linearly with age (The slope of the linear regression line is 6.0 ng fl-eq/ml/year, according to Luo X, Kymes SM, Gordon MO, Bassnnett S. Lens fluorescence and accommodative amplitude in pre-presbyopic and presbyopic subjects. Exp Eye Res. 2007 May;84(5):1013-7.) A number of papers from the OHTS study used linear regression to predict IOP (e.g. Brandt 2004) or IOP response (e.g Brandt 2004, Mansberger 2007, Piltz 2000). Of the papers we previously cited, several used linear regression to predict IOP (Liu 2005, Sit 2006) or IOP response (Realini 2004, Realini 2005, Bayer 2005, Schwartz 2005). A number of papers just in the last few months have also used linear regression to predict IOP (Medeiros 2007, Sahin 2007, van Koolwijk 2007) or IOP changes (Sahin 2007, Salvetat 2007). Logarithmic transformation has occasionally been used to reduce the skew in IOP distributions (Medeiros 2007), but we found that square root or logarithmic transformation did not alter our study conclusions.

Selected studies using linear regression to predict IOP or IOP change:
***Mansberger SL, Hughes BA, Gordon MO, Spaner SD, Beiser JA, Cioffi GA, Kass MA; Ocular Hypertension Treatment Study Group. Comparison of initial intraocular pressure response with topical beta-adrenergic antagonists and prostaglandin analogues in
As noted above, in this version of the paper, we have performed separately all analyses with patients initially treated at baseline, and initially untreated at baseline to demonstrate that both patient groups yield similar results. As we stated in the manuscript, advocates of uniocular trials, advocates of binocular trials, and advocates of subtracting the untreated eye change during the uniocular trial, have never stated that their methods only work for the first glaucoma agent or only for the second agent. Of course, it might be theoretically possible that one should interpret first drug trials and second drug trials differently, but we did not find evidence of this.

We have eliminated the computer simulation to demonstrate the possible effects of regression to the mean. The simulation was not comprehensive enough. It would be useful to prepare a separate manuscript based on a series of simulations with various degrees of drug and crossover effects, and with variance values which reflect other populations. The variance values used in the simulation were based on the variances observed in our population during the baseline visits (before the uniocular trials). The primary analyses in the paper stand alone and are not dependent on the simulation results.
“The use of stepwise regression (backwards or forwards) is not optimal. The inclusion of variables should have a theoretical basis, and all should be included and reported.”

Due to this criticism, we have restricted the analysis to those variables which clinicians routinely analyze (baseline and trial visit intraocular pressures). IOP variables were included whether or not they were significant. In this version of the paper, we have left out analysis of all other variables.

As noted above, this version of the paper only includes patients with bilateral primary open angle glaucoma.

The low $r^2$ values were not surprising to us either, but they may be surprising to some readers. We believe that it is worth pointing out how poorly the current uniocular and binocular trials predict future IOP. We hope that future developments, based on genetics or other technologies, might improve predictive ability.

Table 1 has been simplified.

Tables 2 through 5 have been standardized so that they are easier to read.
Responses to Dr. Zeitz:

Thank you for providing helpful criticisms.

We have simplified the paper, and have concentrated on two questions:

1) Should one subtract the change in IOP in the untreated eye during a uniocular trial when assessing drug effect? (The answer is no.)
2) Do uniocular and binocular trials have a similar ability to predict drug effect? (The answer is yes.)

We agree that multiple statistical comparisons might result in false positive findings. Yet despite the numerous analyses presented, it is interesting that the coefficient for the untreated eye IOP was never near the value of -1 expected by classical teachings. The coefficient was significantly greater (NOT less) than zero for dorzolamide, but in this version of the paper we specifically stated in the discussion that this finding may be due to chance. In addition, one might have expected differences in apparent information content between uniocular and binocular trials based solely on chance, but no such differences were observed.

We are now looking only at the independent variables which clinicians normally examine when assessing drug effect, namely baseline and trial IOP. This change has decreased the complexity of the statistical analysis.

The tables have been simplified.