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Citation of Previous Meta-analyses on the Same Topic:

A Clue to Perpetuation of Incorrect Methods?

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Abstract

Clinical relevance—Systematic reviews and meta-analyses serve as a basis for decision-making and clinical practice guidelines and should be carried out using appropriate methodology to avoid incorrect inferences.

Topic—We describe the characteristics, statistical methods used for meta-analyses, and citation patterns of all 21 glaucoma systematic reviews we identified pertaining to the effectiveness of prostaglandin analog eye drops in treating primary open-angle glaucoma, published between December 2000 and February 2012.

Methods—We abstracted data, assessed whether appropriate statistical methods were applied in meta-analyses, and examined citation patterns of included reviews.

Results—We identified two forms of problematic statistical analyses in 9 of the 21 systematic reviews examined. Except in 1 case, none of the 9 reviews that used incorrect statistical methods cited a previously published review that used appropriate methods. Reviews that used incorrect methods were cited 2.6 times more often than reviews that used appropriate statistical methods. We speculate that by emulating the statistical methodology of previous systematic reviews, systematic review authors may have perpetuated incorrect approaches to meta-analysis.

Conclusions—The use of incorrect statistical methods, perhaps through emulating methods described in previous research, calls conclusions of systematic reviews into question and may lead to inappropriate patient care. We urge systematic review authors and journal editors to seek the advice of experienced statisticians before undertaking or accepting for publication a systematic review and meta-analysis.

Meta-analysis adds value to a systematic review by providing a quantitative synthesis of all pertinent data from studies meeting minimum criteria for inclusion in the review. From meta-analysis, those using the systematic review learn not only whether a particular intervention works (or does not), but also are presented with an estimate of how well it

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works and the precision of that estimate. The value added, however, is dependent on the presumption that statistically correct methods are used for the meta-analysis.

As part of a study to develop and test a framework for prioritizing comparative effectiveness research, we identified, through comprehensive literature searches, systematic reviews that examined the effectiveness of interventions for primary open-angle glaucoma (POAG).^{1,2} We further assessed the methodologic quality of these systematic reviews and found 2 major types of problematic statistical analyses for meta-analysis.¹ We sought to understand better why more than one-third of systematic reviews of POAG management used incorrect statistical methods for meta-analysis.

The objective was to describe the characteristics, statistical methods used for meta-analyses, and citation patterns of systematic reviews on the effectiveness of prostaglandin analog eye drops in lowering intraocular pressure (IOP) in patients with POAG. We selected prostaglandin analog eye drops as a specific topic area because they are a widely used ocular hypotensive therapy and the topic is associated with the largest number of published systematic reviews.

Materials and Methods

The eligibility criteria and methods for identifying relevant systematic reviews have been described elsewhere.¹ Briefly, we included systematic reviews in which the comparison contained prostaglandin analog monotherapy and at least 1 meta-analysis was performed. We excluded papers describing methodological research or reanalysis of data from existing systematic reviews (e.g., using a different statistical method). We searched PubMed, EMBASE, and *The Cochrane Library* in September 2009 and then in March 2012 for published systematic reviews without any date or language restrictions. Two people independently assessed the titles and abstracts resulting from the search and afterward the full text of potentially qualifying reports for inclusion. All told, we identified 21 systematic reviews that examined the effectiveness of prostaglandin eye drops and met the eligibility criteria.^{3–23} These 21 reviews were published between December 2000 and February 2012.

We abstracted the name of the journal in which each review was published, sources of funding for the review, and number of studies and trial participants included in each review. We assessed whether the appropriate statistical methods had been applied in meta-analysis on the basis of the formulae the systematic review authors reported to calculate the variance for effect estimates of interest and the way they meta-analyzed results from multiple studies. We examined the reference lists of the included systematic reviews to determine whether they cited reviews published previously. We also searched the *Web of Science* database on April 5, 2012, to obtain the total number of times each review was cited and to obtain the 2011 impact factor of the journal in which the review was published. We plotted the citation patterns to the 21 reviews. Because of the small sample size, we did not conduct any formal statistical testing of the association between the journal impact factors, sources of funding, the size of the review, and the use of incorrect statistical methods and related citations.

Results

Table 1 presents the characteristics of these 21 reviews. Seven of the 21 reviews described within-class comparisons of different prostaglandins (i.e., one prostaglandin analog versus another),^{9,11,13,16,18,19,22} and the remaining 14 of 21 reviews described between-class comparisons or a combination of within-class and between-class comparisons.^{3–8,10,12,14,15,17,20,21,23} Some systematic reviews in the sample of 21 were published in well-regarded journals, including leading ophthalmology journals published in the United States and the United Kingdom. One-third of the reviews (7/21) were funded by the pharmaceutical industry.^{3,6,9,16–18,21} The reviews included a median of 13 studies (range, 6–93), with a median of 1959 participants in the included trials (range, 361–16 898).

One or more incorrect statistical methods were used in 9 of 21 systematic reviews. Four reviews summarized data by treatment group across trials, ignoring the randomized nature of trials and therefore resulting in nonrandomized comparisons.^{5,6,9,12} For example, instead of meta-analyzing the difference in IOP between the timolol and latanoprost groups from only those trials that randomized patients to either timolol or latanoprost, one review pooled mean IOP reduction in the timolol treatment groups from 21 trials and separately pooled mean IOP reduction in latanoprost treatment groups from 33 trials, and then compared the 2 pooled estimates to assess the comparative effectiveness of timolol and latanoprost.⁶ This analysis destroyed the randomized nature of trials because participants in the timolol group were no longer comparable with participants in the latanoprost group. The analysis therefore suffers from confounding and selection biases, and the conclusions drawn are unlikely to be valid. An illustrative example of the correct and incorrect methods is provided in Figure 1. The correct way to aggregate results from multiple studies is to meta-analyze the between-group summary estimates from each trial that describe the observed treatment effect.²⁴ Examples of summary estimates include difference between means for continuous data (e.g., mean IOP difference between the treatment and comparison groups) and risk ratio for dichotomous data (e.g., risk ratio comparing the proportion of individuals achieving a certain IOP level between the treatment and comparison groups).

In addition, 6 reviews that reported percentage change in IOP from baseline as the measure of effect reported wrong formulae to calculate the variance of the change (one review used both types of incorrect analyses).^{4,5,11,14,19,22} Examples of wrong formulae are shown in Appendix 2 of Li et al.¹ In brief, the wrong formulae ignored the correlation between the repeated IOP measurements from the same individual at baseline and the time point of interest. Furthermore, the wrong formulae equated the variance for percentage change in IOP from baseline to the variance for the change in IOP from baseline divided by the baseline mean IOP. The incorrect variance derived from the wrong formulae yields an incorrect estimate of the average treatment effect and 95% confidence interval. Importantly, percentage change in IOP from baseline to the time point of interest is a ratio of 2 quantities. Estimating the variance for a ratio is mathematically complex, and interested readers are referred to the statistical literature.²⁵ Alternatively, one could log transform the ratio and calculate variance on the log scale.

The 9 systematic reviews that used incorrect statistical methods were cited 24 times by subsequent reviews in this sample; this frequency of citation is in contrast to the 11 systematic reviews that used appropriate methods, which were cited 9 times (Fig 2). The 1 review that used unclear statistical methods was cited 3 times by subsequent reviews in this sample.

Except in 1 case,¹⁹ none of the reviews that used incorrect statistical methods cited a previously published review that used appropriate statistical methods. Reviews that used appropriate statistical methods cited a mix of reviews using appropriate and inappropriate methods. One review using appropriate statistical methods¹³ pointed out 1 of the 2 deficiencies in an earlier review⁵ to justify their study.

The *Web of Science* search indicated that the most frequently cited review (99 times) was one that used both an incorrect method to conduct the meta-analysis by pooling the treatment effect for each individual treatment arm separately and an incorrect formula to calculate the variance of the effect estimate.⁵ It was published in the journal with the highest impact factor among the journals in which our sample of 21 reviews were published.

Discussion

Systematic reviews aim to provide distilled evidence for clinical decision making and support the development of clinical practice guidelines. This study examined the evidence base consisting of all systematic reviews published before March 2012 on prostaglandin analog eye drops in treating POAG. We identified 2 forms of problematic statistical analyses in more than 40% of the systematic reviews examined. Except in 1 case, none of the 9 reviews that used incorrect statistical methods cited a previously published review using appropriate methods, but they had been cited 2.6 times more often than reviews using appropriate statistical methods. We are not aware of any literature or statistics textbooks that recommend the incorrect statistical methods we observed. After examining the systematic reviews included in this study and citation patterns (Fig 2), we speculate that by emulating the statistical methodology of previous systematic reviews, systematic review authors may have perpetuated incorrect approaches to meta-analysis.

The methodological literature increasingly has been concerned with use of citations to measure an article's and journal's impact, without considering how information from the cited work was used.^{26–30} Our study used citation analysis to examine one possible use of previously published articles and led us to speculate that systematic review authors using data analysis methods that are new to them may rely on articles from similar studies for statistical guidance rather than consulting a statistician or the statistical literature. This conclusion is supported by the high prevalence and similarity of the problem across systematic reviews and the observation that, although some authors cited references for meta-analysis that recommend correct methods, such as *The Cochrane Handbook for Systematic Reviews of Interventions*, they still reported analyses that used incorrect formulae.¹⁴

The potential hazard of basing clinical decisions and recommendations on findings from systematic reviews using incorrect methods for meta-analysis is concerning. It is likely that highly cited papers have a greater impact on patient care than those cited less frequently. If those highly cited papers report invalid estimates of effect that differ meaningfully from what would have been obtained using appropriate analyses (e.g., reverse the direction of effect), those estimates could lead to harm of patients or waste of health care resources.

We attempted to assess the potential impact of the incorrect analyses by reconstructing analyses. However, we could not verify some data in the meta-analyses when we compared the data in the review with the original articles from which the data were abstracted. In addition, we did not have access to individual patient data, making it impossible to calculate percentage change in IOP from baseline to the time point of interest and its variance. Reviews comparing the same interventions sometimes included a different set of trials. If one wishes to compare findings from these different meta-analyses, the first step would be to consolidate all trials on prostaglandin analog eye drops in lowering IOP, critically appraise their quality critically, and perform meta-analyses using statistically sound methodology. Findings from such meta-analysis then can be compared against findings from reviews included in our sample to identify discrepancies and contributing factors.

In all reviews that incorrectly pooled treatment arms, the reviews examined at least 3 treatment methods involving prostaglandin analogs for lowering IOP in patients with POAG, even when most original randomized controlled trials compared only 2 treatments. Pooling treatment arms without preserving the original randomized comparison has been described as the “naïve method” for drawing inferences about the comparative effectiveness of 3 or more competing interventions.³¹ Referring to publications as “meta-analyses of randomized controlled trials” consequently is misleading. To synthesize results from a plethora of trials on multiple competing interventions, network meta-analysis is the approach that preserves the randomized nature of the trial.^{31–34} Methods for comparing multiple interventions are developing rapidly. Interested researchers are advised to refer to the statistical literature and to consult a statistician before embarking on such analyses.³⁴

We discourage researchers from conducting meta-analysis using percentage change in IOP from baseline unless all required data are available, that is, all trials reported summary estimates of effect as well as some form of precision measure (e.g., variance, standard deviation, standard error, or confidence intervals) or the researchers have access to individual patient data. In reality, such data are available rarely and attempts to derive them are error prone. Our findings suggest that readers and users of systematic reviews should be cautious when percentage of change in IOP has been used in a meta-analysis to gauge the treatment effect.

This study has limitations. We included a small sample of systematic reviews published before March 2012 on a single topic. The findings may not apply to other systematic reviews or topic areas. However, we continue to read recent ophthalmology publications that have used the same wrong formula for variance^{35–38} and that have pooled data by treatment group incorrectly.³⁸ Systematic review authors publishing more than 1 systematic review have repeated the same errors with each publication. Thus, we believe that there is lack of

awareness of the problem by authors, peer reviewers, and journal editors. In addition, this study is exploratory and did not attempt to determine the context in which a reference was cited or whether the authorship of the citing and cited references overlapped. Research is needed to explore the explanation for and consequences of the citation patterns we observed. Finally, reviews using incorrect methods were published on average earlier than reviews using appropriate methods, which may have led to more citations.

Systematic reviews and meta-analyses are complex research endeavors; it is important that they are carried out appropriately because they serve as a basis for decision-making and clinical practice guidelines.³⁹ In keeping with the Institute of Medicine standards for performing systematic reviews and meta-analysis,⁴⁰ systematic review teams should include at least 1 methodologist trained in performing systematic reviews. Ideally the review team should be connected to a support system, such as the Cochrane Collaboration's Eyes and Vision Group, for performing the review. The use of Preferred Reporting Items for Systematic Reviews and Meta-Analyses⁴¹ as a checklist for the reporting of systematic reviews also may help to prevent the errors found in our study. We urge systematic review authors and journal editors to seek the advice of experienced statisticians before undertaking or accepting for publication a systematic review and meta-analysis. Simply emulating methods described in previous research is not a reliable approach for achieving valid answers to the question of what works best.

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Treatment	A	B	C	D
RCT 1	✓	✓		
RCT 2	✓	✓	✓	
RCT 3	✓		✓	
RCT 4	✓			✓
RCT 5		✓	✓

Correct method
Incorrect method

Figure 1.

A hypothetical example of correct and incorrect methods for comparing interventions in a meta-analysis. In this hypothetical example, there are 5 randomized controlled trials (RCTs) that each compared a pair of interventions for a given condition. If A versus B is the comparison of interest, only A and B data from RCT 1 and RCT 2 should be meta-analyzed because they are the only trials that randomized participants to treatment A versus B. Yet with the incorrect method, data from the 4 trials that compared treatment A versus any other treatment (RCT 1, RCT 2, RCT 3, and RCT 4) are pooled, and separately, data from 3 trials that compared treatment B versus any other treatment (RCT 1, RCT 2, and RCT 5) are pooled. The 2 separately pooled estimates then are compared incorrectly to assess the relative effectiveness of A and B. The incorrect method of analysis destroys the randomized nature of trials because participants randomized to treatment A in RCT 3 and RCT 4 are not comparable with participants randomized to treatment B in RCT 5. Inferences drawn from such incorrect analysis are unlikely to be valid because they suffer from confounding and selection bias.

Figure 2. Graph showing citations of systematic reviews of prostaglandin analog eye drops in patients with primary open-angle glaucoma.

Characteristics of Systematic Reviews of Prostaglandin Analog Eye Drops in Patients with Primary Open-Angle Glaucoma

Table 1

Study ID and Author	Publication Date	Journal	2011 Journal Impact Factor	Sources of Funding	No. of Included Studies (Participants)	Types of Interventions the Review Examined	Correct Methods for Meta-analysis
1. Einarson et al ³	December 2000	Clinical Therapeutics	2.321	Pharmacia & Upjohn	9 (2152)	Latanoprost vs. brimonidine	Cannot tell
2. Zhang et al ⁴	August 2001	British Journal of Ophthalmology	2.902	Not reported	11 (1256)	Latanoprost vs. timolol	No *
3. van der Valk et al ⁵	July 2005	Ophthalmology	5.454	Dutch Health Care Insurance Council	27 (6953)	Timolol, betaxolol, brimonidine, dorzolamide, brinzolamide, latanoprost, travoprost, bimatoprost (between each other or vs. placebo)	No * [†]
4. Holmstrom et al ⁶	November 2005	Current Medical Research and Opinion	2.380	Allergan	42 (not reported)	Travoprost, latanoprost, or bimatoprost as monotherapy, or used in combination with timolol or brimonidine vs. another active drug or placebo	No [†]
5. Li et al ⁷	November 2006	Clinical and Experimental Ophthalmology	1.977	Chinese Medical Board Grant	12 (3048)	Travoprost vs. other prostaglandin analogs or timolol	Yes
6. Fung et al ⁸	January 2007	British Journal of Ophthalmology	2.902	None	15 (1824)	Latanoprost vs. brimonidine	Yes
7. Denis et al ⁹	March 2007	Current Medical Research Opinion	2.380	Alcon	9 (1318)	Latanoprost, bimatoprost, and travoprost	No [†]
8. Hodge et al ¹⁰	January 2008	British Journal of Ophthalmology	2.902	None	8 (1131)	Prostaglandin analogs vs. brimonidine or dorzolamide	Yes
9. Cheng and Wei ¹¹	April 2008	Clinical Therapeutics	2.321	None	13 (1302)	Bimatoprost vs. latanoprost	No *
10. Stewart et al ¹²	July 2008	European Journal of Ophthalmology	0.965	None	11 (386)	Betaxolol, timolol, timolol gel-forming solution, dorzolamide, brinzolamide, brimonidine, latanoprost, bimatoprost, and travoprost	No [†]
11. Aptel et al ¹³	December 2008	Journal of Glaucoma	1.776	None	8 (1610)	Latanoprost, bimatoprost, and travoprost	Yes
12. Cheng et al ¹⁴	February 2009	Journal of Ocular Pharmacology and Therapeutics	1.509	Not reported	14 (2149)	Latanoprost vs. combination of dorzolamide and timolol	No *
13. Mei Li Ke Mu and Ju Er Ti ¹⁵	March 2009	Chinese Journal of Evidence-Based Medicine	Not available	Not reported	6 (361)	Latanoprost vs. dorzolamide and timolol combination	Yes
14. Honrubia et al ¹⁶	March 2009	British Journal of Ophthalmology	2.902	Pfizer	13 (2222)	Latanoprost vs. travoprost or bimatoprost	Yes

Study ID and Author	Publication Date	Journal	2011 Journal Impact Factor	Sources of Funding	No. of Included Studies (Participants)	Types of Interventions the Review Examined	Correct Methods for Meta-analysis
15. Vinuesa-Silva et al ¹⁷	April 2009	Archivos de la Sociedad Española de Oftalmología	Not available	Pfizer	8 (2600)	Latanoprost and timolol fixed combination vs. any active control	Yes
16. Eyawo et al ¹⁸	August 2009	Clinical Ophthalmology	Not available	Pfizer	16 (2669)	Latanoprost, bimatoprost, and travoprost	Yes
17. Cheng et al ¹⁹	August 2009	Current Therapeutic Research—Clinical and Experimental	0.333	Not reported	17 (1491)	Latanoprost vs. travoprost	No*
18. Ge et al ²⁰	December 2009	Chinese Ophthalmic Research	Not available	Not reported	6 (2094)	Bimatoprost vs. timolol	Yes
19. Orme et al ²¹	March 2010	Current Medical Research and Opinion	2.380	Pfizer	93 (16,898)	Prostaglandin analog vs. any other topical hypotensive drug	Yes
20. Qian et al ²²	August 2011	Chinese Journal of Evidence-Based Medicine	Not available	Not reported	13 (1433)	Latanoprost vs. travoprost	No*
21. Aptel et al ²³	February 2012	European Journal of Ophthalmology	0.965	Not reported	20 (4684)	Latanoprost and timolol fixed combination, bimatoprost and timolol fixed combination, travoprost and timolol fixed combination compared against each other or with their individual components	Yes

* Wrong variance calculation.

[†]Treatment arms pooled incorrectly.