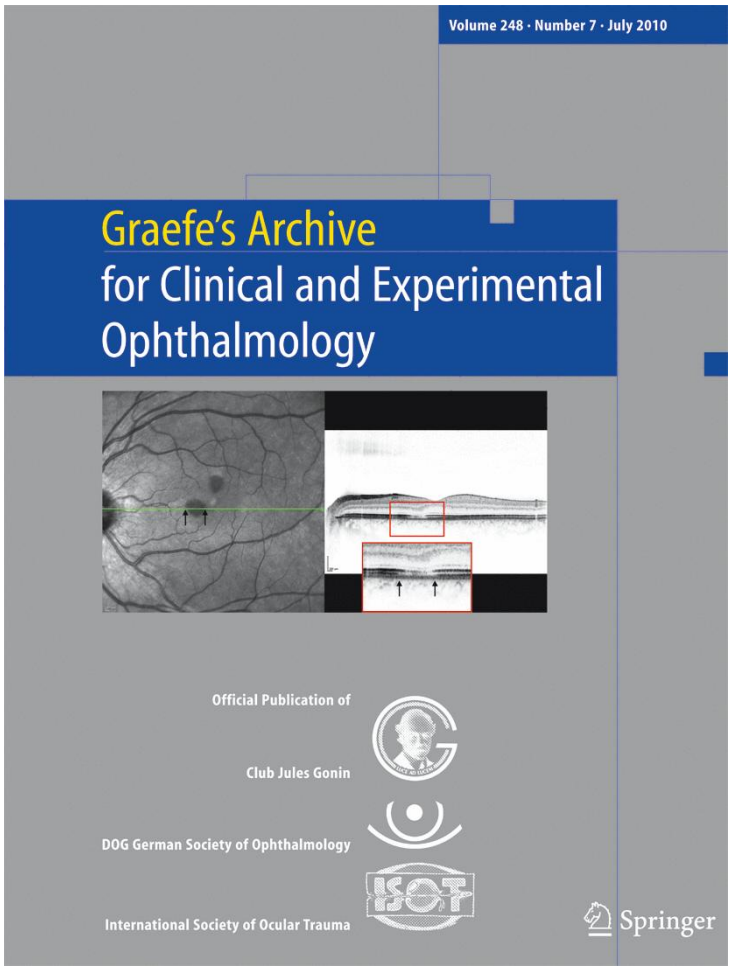
ISSN 0721-832X, Volume 248, Number 7



Graefes Arch Clin Exp Ophthalmol (2010) 248:1
DOI 10.1007/s00417-010-1339-4

GLAUCOMA

Risk factors for subject withdrawals in clinical trials evaluating glaucoma medications

William C. Stewart · Christina M. Demos · Meredith K. Turner · Jeanette A. Stewart

Received: 11 November 2009 / Revised: 6 February 2010 / Accepted: 14 February 2010 / Published online: 9 March 2010

Abstract
Background To evaluate risk factors for subject withdrawals from multicenter clinical trials evaluating glaucoma medications.
Methods An analysis of prospective, randomized, multicenter, parallel, active-controlled clinical trials with 70 subjects/treatment arm published from 1996–2008.
Results We analyzed 36 glaucoma studies including 17,511 subjects at 1,294 clinical sites. There were 2,060 (12%) subject withdrawals with 669 (32%) for administrative errors, 945 (46%) for adverse events (AEs), 197 (10%) for inadequate intraocular pressure (IOP) control and 249 (12%) for unknown reasons. By multilinear regression analysis, no positive risk factors for early subject withdrawals were observed following a Bonferroni correction ($p \geq 0.01$). A positive correlation was observed for medication errors and protocol violations to withdrawals due to ocular AEs and total administrative errors ($p < 0.0001$). Protocol violations alone were correlated to subject withdrawals for any AE (total/month) and systemic AEs ($p < 0.0001$). Females and Caucasians were correlated to medication errors ($p < 0$ .0001). Among medical therapies, alpha-agonists, beta-blockers, the carbonic anhydrase inhibitor/beta-blocker fixed combination and prostaglandins were correlated with systemic AEs ($p \leq 0.005$) while the alpha-agonists were correlated with withdrawals for poor IOP control ($p = 0.00056$).
Conclusions Subject withdrawals from clinical trials for total administrative errors or AEs potentially might be reduced by choosing sites with lower historical rates of protocol violations or medication dispensing errors. Drug class choice also may influence subject withdrawals for AEs and poor IOP control.

Keywords Glaucoma · Risk factors · Withdrawals · Adverse events · Intraocular pressure

PRN Pharmaceutical Research Network, LLC, received no financial support from any private or government funding source. The authors do not have any proprietary interest to disclose.

Electronic supplementary material The online version of this article (doi:10.1007/s00417-010-1339-4) contains supplementary material, which is available to authorized users.

W. C. Stewart · J. A. Stewart
PRN Pharmaceutical Research Network, LLC,
Charleston, SC, USA

C. M. Demos · M. K. Turner
Charleston Research Company, LLC,
Charleston, SC, USA

W. C. Stewart (✉)
6296 Rivers Avenue,
Suite 309,
Charleston, SC 29406, USA
e-mail: info@prnorb.com

Introduction

Well-controlled clinical trials are the backbone for determining the efficacy and safety of medicines used in clinical practice [1]. However, such trials necessitate a large cost in human and financial resources. Consequently, careful pretrial planning may allow more efficient use of study resources.

One parameter that must be captured in well-controlled clinical trials is subject withdrawals from adverse events or administrative errors [2, 3]. The number of subject withdrawals in glaucoma clinical trials, regardless of reason (e.g., subject withdrawal of consent, adverse event, or administrative error), has been evaluated previously by

Stewart and associates who demonstrated dropout rates of between 1 and 39% from the intent to treat analysis. A statistically greater dropout rate existed with increasing length of study. However, they found no difference in percent withdrawals among the currently used glaucoma drug classes [1].

Nonetheless, to our knowledge, the specific reasons for subject withdrawals have been little studied in the ophthalmic or systemic literature. If factors associated with subject withdrawals due to study design, or site or subject errors could be identified, then pharmaceutical or government sponsors might be better able to develop studies or choose clinical sites to help limit subject withdrawals, with a subsequent potential increase in subject safety and reduced study costs.

The purpose of this study was to evaluate risk factors for (and associations of) subject withdrawals from multicenter clinical trials evaluating glaucoma medications.

Materials and methods

Sample population and procedures

We reviewed prospective, clinical trials of published glaucoma studies performed from 1996 to 2008. We identified these studies from PubMed (www.pubmed.gov) and the literature file of one of the authors (WCS). Search terms used were: "glaucoma", "parallel", "prospective", and "clinical trial". In addition, specific glaucoma medicines were searched including: "timolol", "timolol gel forming solution", "dorzolamide", "brinzolamide", "brimonidine", "latanoprost", "bimatoprost", and "travoprost". Both the brand and generic names of single agent preparations, and these same medicines combined into fixed combinations, were used as search terms.

To be included, studies must have contained at least 70 subjects per treatment arm and designed as randomized, multicenter, parallel, active-controlled, comparative trials. Subjects must have been diagnosed with common open-angle forms of elevated pressure including: ocular hypertension and primary open-angle, exfoliative or pigment dispersion glaucoma. In addition, articles must have included information regarding subject withdrawals both for adverse events and administrative and subject errors. All qualified available studies were included in this analysis. The complete list may be found as supplemental online material.

Excluded from this analysis were studies that failed to meet the above criteria. Each article was evaluated independently to assure they met inclusion criteria specified above by two of the authors (CMD, MKT). All data were extracted and entered into an Excel spreadsheet.

Data extracted from each article consisted of characteristics of the subjects and of the trial itself. In addition, we extracted information regarding the number of subject withdrawals from the study (i.e., those failing to complete per protocol) and the reason for the failure to complete, if known. Withdrawals were classified generally as those occurring due to an adverse event, administrative, or subject errors.

Administrative errors were defined as events occurring at the clinical site that lead to the loss of a randomized subject from the trial, including a medication dispensing error (e.g., incorrect study medicine dispensed) and protocol violations (e.g., enrolling a subject who failed to meet study inclusion/exclusion criteria). Also included in this category were 'other' and 'unknown' administrative errors.

Subject errors leading to withdrawal from the study were defined as failure to follow the protocol or becoming lost to follow-up. Data were evaluated both for total errors over the complete length of the study and errors per month. Only data available publicly within the published article were used in this analysis.

Statistics

All tests were performed on data from the intent to treat analysis, were unpaired, and two-way in design. We used a p value of 0.05 to declare significance. However, because of the multiple tests used evaluating subject withdrawals in this analysis we used a modified Bonferroni correction ($\alpha/10$) to adjust the p value to declare significance [4].

Comparisons of mean values were performed with an ANOVA test [5]. To analyze for risk factors for subject withdrawals we used multilinear regression analyses separately for subject and study characteristics as well as for site administrative and subject errors. Regression analyses were also performed for individual drug classes and ocular as well as systemic side-effects and intraocular pressure control.

A matrix correlation coefficient also was used to look for an association with administrative and subject errors with other characteristics of the study [6]. In contrast, subject and study characteristics were not statistically evaluated but were described. Statistical tests were performed using JMP software, Version 5.0.1 (SAS Institute, Cary, NC).

Results

Subject and study characteristics

The characteristics of the subjects and studies included in this analysis are shown in Table 1. For this analysis, 36 glaucoma studies met the entry criteria. Our initial review found 43 articles of which we excluded eight due to a lack of reporting of subject withdrawals or administrative errors.

Table 1 Study and subject characteristics

Variable	Number/mean ± standard deviation	Percent
Number of studies with withdrawal data	36	
Number of treatment arms	85	
Average number of treatment arms	2.2±0.7	
Average length of study (months)	8.0±9.9	
Total number of sites	1,294	
Average number of sites/study	32.4±43.5	
Average subjects/site	42.5±104.7	
Total intent to treat subjects	17,511	
Average subjects per study	364.8±302.7	
Subjects in United States	9,735	56
Subjects in Europe	5,639	32
Subjects in Asia	607	4
Nationality not able to be determined	1,530	8
Treatments arms per drug class (total 85)		
Beta-blocker	27	32
Prostaglandin	37	44
Alpha-agonist	3	4
Carbonic anhydrase inhibitor	11	13
Prostaglandin fixed combination	3	3
Alpha-agonist fixed combination	2	2
Carbonic anhydrase inhibitor fixed combination	2	2

Subject withdrawals

Subject withdrawals and the associated reasons are shown in Table 2. No positive risk factors for subject withdrawals were observed following the Bonferroni correction ($p \geq 0.01$). Withdrawals, however, were positively correlated to the number of treatment arms, total number of subjects and clinical sites ($p < 0.0001$).

Administrative errors

Administrative errors are detailed in Table 2 and the results of the regression analyses are presented in Table 3. No positive risk factors for administrative errors were observed following the Bonferroni correction ($p > 0.05$).

However, positive correlations were observed for medication errors and protocol violations to withdrawals due to ocular adverse events and total administrative errors ($p < 0.0001$). In addition, protocol violations alone were correlated to subject withdrawals from all adverse events (total as well as per month) and to systemic adverse events ($p < 0.0001$). Further, female gender and Caucasian race were correlated to medication errors ($p < 0.0001$).

Subject errors

Subject errors are shown in Table 2. Only failure to follow up had sufficient subjects to perform a regression analysis, which is shown in Table 3. Like total subject withdrawals, failure to follow up was a greater risk in larger trials ($p < 0.0001$). No other risk factors were noted following the Bonferroni correction ($p \geq 0.008$).

Treatment associations

The class of glaucoma medications and risks are shown in Table 4. No association with any currently used class of glaucoma medicine was found with ocular adverse events ($p > 0.05$). However, four separate medication classes were associated with systemic adverse events including: alpha-agonists were the most highly correlated but, beta-blockers, the carbonic anhydrase inhibitors/beta-blocker fixed combination and prostaglandins also had significant associations ($p \leq 0.005$). Further, the alpha-agonists were associated with withdrawals from the study due to poor pressure control ($p = 0.00056$).

Discussion

The purpose of this study was to evaluate risk factors for (and associations of) subject withdrawals from multicenter clinical trials evaluating glaucoma medications.

This study found, not surprisingly, that the number of subject withdrawals was positively correlated to the number of treatment arms, total subjects, and clinical sites related to

Table 2 Subject withdrawals

Variable	Reason/type	Number/Mean	Percent
Total subject withdrawals		2,060	12
Total subject withdrawals/month		9.4±16.0	
Reasons for subject withdrawal	Drug adverse events	331	16
	Ocular reasons	516	25
	Systemic medical reasons	98	5
	Inadequate intraocular pressure control	197	10
	Other reasons (including non medical)	649	32
	Unknown	249	12
	Death	20	1
Total site/administrative errors		820	5
Total site/administrative errors/month		4.8±22.8	
Type of site/administrative errors	Protocol violations	232	28
	Medication error	503	62
	Other	74	9
	Unknown	11	1
Total subject/clinical errors		105	1
Total subject/clinical errors/month		0.5±1.0	
Type of subject/clinical error	Failure to follow protocol	5	5
	Failure to follow-up	67	64
	Lost data	33	31

study size. Importantly, the risk for a greater incidence of subject withdrawals was not greater in larger than smaller clinical trials by multilinear regression analysis.

However, to the authors' surprise, positive correlations were observed for medication errors and protocol violations to subject withdrawals due to ocular adverse events and total administrative errors ($p<0.0001$). In addition, protocol violations alone were correlated to subject withdrawals from all adverse events (total as well as per month) and to systemic adverse events ($p<0.0001$).

The reason for a positive correlation between medication errors or protocol violations to subject withdrawals due to side-effects was not clear by our data. There are several potential explanations. First, clinical sites more apt to enter subjects not meeting the inclusion and exclusion criteria, or to make medication errors, might be more likely to enroll subjects who would be at greater risk of suffering side-effects and who might have been excluded by a more careful clinical site. Second, a site more likely to commit enrollment or medication errors might not have carefully documented pre-study conditions. Once the subject was actually enrolled in the trial, however, observations made in the more careful research environment may have uncovered

Table 3 Regression analysis for subject withdrawals (p values)

	Subject withdrawal vs. study design	Subject withdrawal/ month vs. study design
Classes of medicine	0.08	0.2
Type of therapy	1.0	1.0
Number of treatment arms	0.1	0.2
Length of study	0.8	0.5
Total patients	0.7	0.6
Location	0.09	0.2
Number of sites	0.3	0.3
Average patients/site	0.09	0.2

Table 4 Class of glaucoma medication and risk

Variable	p value
Drug class vs. ocular adverse event	0.5
Alpha—agonist	0.07
Beta-blocker	0.2
Carbonic anhydrase inhibitor/beta-blocker	0.3
Prostaglandin	0.5
Drug class vs. systemic adverse event[a]	0.0001
Alpha—agonist[a]	<0.0001
Beta-blocker[a]	0.0007
Carbonic anhydrase inhibitor/beta-blocker[a]	0.005
Prostaglandin[a]	0.002
Drug class vs. inadequate intraocular pressure control	0.009
Alpha—agonist[a]	0.0006
Carbonic anhydrase inhibitor/beta-blocker	0.02

[a] Significant after the modified Bonferroni correction

pre-existing pathologies not previously noted, thus creating an adverse event. Consequently, this scenario, if true, would falsely inflate the incidence of side-effects related to the study medicines.

No individual class of medicine currently used in glaucoma practice was related to ocular side-effects. Nonetheless, four types of treatments were related to systemic side-effects including: alpha-agonists, beta-blockers, the carbonic anhydrase inhibitors/beta-blocker fixed combination, and prostaglandins. Alpha-agonists and beta-blockers have been noted previously to be associated with systemic side-effects [7–9]. However, only rarely have the prostaglandins been associated with systemic adverse events [10]. In addition, the alpha-agonists were more often related to subject withdrawal due to uncontrolled intraocular pressure. This may be because, as shown in previous literature, this class of medicine is less efficacious than the beta-blockers or prostaglandins and may produce less reduction from intraocular pressure baseline in the afternoon [11].

A further finding in this study was that females and Caucasians were correlated positively with medication errors. Again, the reason for this association was not apparent. However, prior research has indicated that women's report of bodily symptoms are more numerous, frequent, and intense than those of men [12, 13]. Also, women are more likely to complain of anxiety or depression. Consequently, if study personnel must discuss a greater number of complaints with female subjects, the corresponding increased workload to document such complaints within a clinical trial, potentially might become a distraction and lead to more medication errors [12, 13].

Our data are important because they indicate that the most common clinical trial design or logistical features do not adversely influence subject withdrawals because of site or subject errors including: geographic location, or subject or study characteristics (except obviously study size). However, sponsors of a clinical trial might potentially reduce the number of subject withdrawals by choosing clinical sites that have proven previously that they are attentive to study details which might limit protocol violations and medication errors. However, limiting females and Caucasians from studies to reduce medication errors does not seem inherently fruitful in adequately evaluating medication efficacy and safety. Sponsors should realize, in addition, that the class of glaucoma medicine they choose to evaluate may influence subject withdrawals from side-effects or inadequate pressure control.

Reducing the factors associated with subject withdrawals due to administrative errors potentially may not only enhance subject safety but also reduce study costs. The cost of lost subjects from the intent to treat analysis has never been adequately studied in ophthalmology to our knowledge. Generally, subject withdrawals are accounted for in the study design by over-enrolling subjects by 10–20% [1]. If a phase III program required 320 subjects then a sponsor might enroll an extra 60 subjects, in approximately five sites, to account for subject withdrawals. To open and maintain five sites over a 12-month study (with an added 3 months recruiting time) would cost about $226,000. Added an approximate $4,000/subject investigator fee, the cost of over-enrolling is about $446,000 (internal data, PRN). Despite over-enrolling, if the dropout estimate is missed and the study must be extended to open new sites and enroll more subjects, the cost would be even greater. These additional expenses would be accompanied by a delay in submitting the new drug application to the FDA and the associated lost revenue from an approved medication.

This study suggests that subject withdrawals from clinical trials for total administrative errors or adverse events potentially might be reduced by choosing sites with a historical low rate of protocol violations or medication errors. Drug class choice also may influence subject withdrawals for adverse events and poor intraocular pressure control.

This study evaluated neither the specific causes for the risks and associations identified nor whether the actual incidence of subject withdrawals could be reduced by taking corrective measures. Future research might be useful to more fully understand the reasons for administrative clinical site errors and subject withdrawals during clinical trials and how to correct these factors. In addition, further research is needed to confirm or disprove the association of the various glaucoma preparations to systemic adverse events observed in this study. Limiting clinical site errors and subject withdrawals may enhance subject safety as well as reduce cost and time lines for clinical trials.

References

1. Silverman SL (2009) From randomized controlled trials to observational studies. Am J Med 122:114–120
2. Lai TY, Wong VW, Lam RF, Cheng AC, Lam DS, Leung GM (2007) Quality of reporting of key methodological items of randomized controlled trials in clinical ophthalmic journals. Ophthalmic Epidemiol 14:390–398
3. Lumley J, Bastian H (1996) Competing or complementary? Ethical considerations and the quality of randomized trials. Int J Technol Assess Health Care 12:247–263
4. Siegel S (1956) Nonparametric Statistics for the Behavioral Sciences. McGraw-Hill, Inc, New York
5. Miller RG 91998) Beyond ANOVA: Basics of Applied Statistics. Chapman & Hall/CRC, Boca Raton, pp 1–36
6. Book SA (1978) Essentials of Statistics. McGraw-Hill, Inc, New York
7. Stewart WC, Castelli WP (1996) Systemic side effects of topical β-adrenergic blockers. Clin Cardiol 19:691–697

8. Stewart WC, Garrison PM (1998) ß-blocker-induced complications and the glaucoma subject: newer treatments to help reduce systemic side effects. Arch Intern Med 158:221–226
9. Stewart WC, Stewart JA, Jackson AL (2002) Cardiovascular effects of timolol maleate, brimonidine or brimonidine/timolol maleate in concomitant therapy. Acta Ophthalmol Scand 80:277–281
10. Alm A, Grierson I, Shields MB (2008) Side effects associated with prostaglandin analog therapy. Surv Ophthalmol 53(Suppl1): S93–105
11. Stewart WC, Day DG, Stewart JA, Schuhr J, Latham KE (2001) The efficacy and safety of latanoprost 0.005% once daily versus brimonidine 0.2% twice daily in open-angle glaucoma or ocular hypertension. Am J Ophthalmol 131:631–635
12. Barsky AJ, Peekna HM, Borus JF (2001) Somatic symptom reporting in women and men. J Gen Intern Med 16:266–275
13. Kroenke K, Spitzer RL (1998) Gender differences in the reporting of physical and somatoform symptoms. Psychosom Med 60:150–155