Journal of the South East Asia Glaucoma Interest Group

Volume 10 Number 3 June 2008

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- to disseminate information that will improve the care of patients with all types of ophthalmological disorders, with a special focus on glaucoma
- to increase the understanding of such disorders through reporting of educational activities
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- to work closely with Asian and international researchers to achieve these aims
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Original Articles

Case Reports

Efficacy and Safety of Brimonidine/Timolol Fixed Combination for Open Angle Glaucoma or Ocular Hypertension

Andre K Theron,[1] Allan J Simpson[2]
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Aim: To assess the efficacy and safety of brimonidine/timolol fixed combination for open angle glaucoma or ocular hypertension in clinical practices throughout Australia and New Zealand.
Methods: In this 3-month multicentre open-label non-comparative observational study, 333 patients who were not responding adequately to ocular hypotensive monotherapy were prescribed 0.2% brimonidine/0.5% timolol fixed combination twice daily as replacement or adjunctive therapy. Patients were assessed at baseline, week 6, and month 3. Main outcome measures were the change in intraocular pressure compared with baseline, and the frequency and nature of adverse events.
Results: After 3 months, the mean intraocular pressure had decreased by 13.6% (mean reduction, 3.1 mm Hg) for patients using brimonidine/timolol replacement therapy and by 16.0% (mean reduction, 3.4 mm Hg) for those using brimonidine/timolol adjunctive therapy ($p < 0.0001$). Mean intraocular pressure decreased by 12.2% (mean reduction, 2.7 mm Hg; $p < 0.0005$) for patients who replaced dorzolamide/timolol fixed combination with brimonidine/timolol fixed combination as adjunctive therapy and by 10.5% (mean reduction, 2.9 mm Hg; $p < 0.01$) for patients with refractory high intraocular pressures. The most frequently reported adverse events were ocular hyperaemia (3.6%, 12 patients), ocular irritation (3.3%, 11 patients) and lid conditions (2.1%, 7 patients).
Conclusion: Brimonidine/timolol fixed combination was well tolerated and effective when used as adjunctive or replacement therapy for the treatment of glaucoma and ocular hypertension in clinical practice.

Key words: Brimonidine, Glaucoma, open-angle, Intraocular pressure, Ocular hypertension, Timolol

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Introduction

Elevated intraocular pressure (IOP) is a key risk factor underlying the irreversible vision loss associated with primary open angle glaucoma (POAG).[1,2] Typically, first-line treatment for lowering IOP is monotherapy with a topical prostaglandin analogue or a β-adrenergic antagonist (β-blocker).[3,4] Despite the proven efficacy of these hypotensive medications,[5] many patients eventually require adjunctive therapy to achieve their target IOP.[6] However, concurrent administration of multiple drugs can lead to inconvenient dosing regimens and is a major factor associated with poor patient compliance.[7]

Brimonidine/timolol fixed combination is the only α_2-agonist/timolol fixed combination eye drop to be approved for Australian and New Zealand patients with glaucoma or ocular hypertension (OH) who do not respond to monotherapy. Several randomised controlled clinical trials have shown brimonidine/timolol fixed combination to be as effective[8] or more effective[9,10] than either brimonidine monotherapy or timolol monotherapy. Moreover, patients treated with brimonidine/timolol fixed combination experience fewer side effects compared with brimonidine monotherapy.[9,10] While controlled clinical trials provide a robust assessment of the differences in efficacy and safety between treatments, they do not give an indication of the effectiveness and safety of treatments used in daily clinical practice.

Two studies, conducted over 2 months, have found brimonidine/timolol fixed combination to be effective and well tolerated when used in daily clinical practice in Canada.[11,12] To the authors' knowledge, no studies have assessed brimonidine/timolol fixed combination in Australian or New Zealand clinical practice. The aim of this 3-month observational study was to assess the efficacy and

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safety of brimonidine/timolol fixed combination therapy for POAG or OH in clinical practices throughout Australia and New Zealand.

Methods

This multicentre open-label non-comparative observational study involving 27 ophthalmologists from clinical sites in Australia (n = 14) and New Zealand (n = 9) was conducted from October 2005 to March 2007.

Patients

All patients provided voluntary written informed consent before participating in the study. Patients were eligible to participate if they were diagnosed with POAG or OH, and if their clinician considered that they were not responding adequately to ocular hypotensive monotherapy and required additional medications to reduce their elevated IOP to the desired target levels. Patients were not eligible to participate if they had any known hypersensitivity to the study medication or components within its formulation; were being treated with monoamine oxidase inhibitor therapy; had bronchospasm, bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease; or had sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, or cardiogenic shock.

Treatment Protocol

At baseline, eligible patients were prescribed 0.2% brimonidine/0.5% timolol fixed combination (Combigan®; Allergan Inc, Irvine, USA) as replacement or adjunctive therapy. Patients were instructed to instil 1 drop in each affected eye twice daily (approximately 12 hours apart). At each visit, patients received sufficient medication to last until the next visit.

Clinical Evaluation

Patients were evaluated according to each ophthalmologist's standard clinical practice at baseline, week 6, and month 3. One IOP measurement was taken at each visit and clinicians were requested to ensure that each visit was conducted at the same time of day to minimise diurnal variation. The frequency and nature of any adverse events were reported at each visit.

At baseline, clinicians were asked to subjectively assess how difficult each patient's IOP was to control (not difficult, somewhat difficult, difficult, very difficult). At the final visit, patients were asked to rate their satisfaction (unsatisfied, same satisfaction, more satisfied, very satisfied) with brimonidine/timolol compared with other hypotensive medications that they had used in the past and convenience (not easy, average, convenient, very convenient) of brimonidine/timolol. Clinicians were asked to rate overall performance (poor, fair, good, excellent) of brimonidine/timolol compared with other ocular hypotensive therapies that the patients had used in the past and to indicate whether brimonidine/timolol met their therapeutic expectations (did not meet, met, exceeded).

The efficacy outcomes were the mean change in IOP from baseline at each follow-up visit. The safety and tolerability outcomes were the frequency and nature of adverse events, and patients' and clinicians' subjective ratings of treatment at month 3.

Statistical Analysis

The efficacy analyses included all patients who received the study medication and had at least 1 valid IOP measurement. Safety and tolerability analyses included all patients who received study medication.

The Statistical Analysis Systems software (version 9.1; SAS Institute Inc, Cary, USA) was used for all statistical analyses. Data from the treated eye were included in the analyses; if both eyes were treated, the mean data from both eyes were used. Missing data were not included in the analyses. Differences between baseline and follow-up visits were analysed using a 1-sample Student *t* test for normally distributed data and Wilcoxon's signed-rank test for data that were not normally distributed. Differences were statistically significant at $p < 0.05$.

Results

Baseline Characteristics

333 patients were enrolled (242 from Australia and 91 from New Zealand). Most patients were aged 50 years or older, were Caucasian, and were diagnosed with POAG (Table 1). Clinicians considered that approximately one-third of patients had IOPs that were difficult or very difficult to control, and a similar proportion of patients were prescribed brimonidine/timolol as replacement or adjunctive therapy (Table 1). Eight patients were not using ocular hypotensive medication immediately before participating in the study. However, these patients were included as they required hypotensive medication and provided evaluable data.

Of the 62 patients (18.6%) who did not complete the study, 11.7% (39/333) withdrew because of an adverse event, 3.0% (10/333) withdrew because of lack of efficacy, 2.1% (7/333) were lost to follow-up, and 1.8% (6/333) withdrew for non-treatment–related reasons.

Efficacy

Brimonidine/timolol treatment was associated with a significant reduction in IOP, irrespective of whether patients were prescribed brimonidine/timolol as replacement or adjunctive therapy (Figure

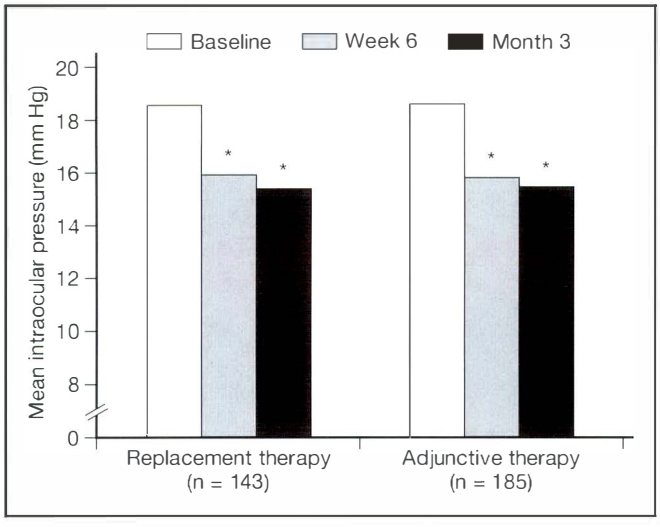
Table 1. Patient demographics and baseline characteristics.

Characteristic	Number of patients (%)*
Age (years)	330
<50	18 (5.5)
50-59	42 (12.7)
60-69	107 (32.4)
70-79	100 (30.3)
≥80	63 (19.1)
Sex	328
Male	158 (48.2)
Female	170 (51.8)
Ethnicity	329
Caucasian	276 (83.9)
Asian	45 (13.7)
Other	8 (2.4)
Diagnosis	328
Open angle glaucoma	311 (94.8)
Ocular hypertension	17 (5.2)
Control of intraocular pressure at enrolment†	322
Not difficult	101 (31.4)
Somewhat difficult	101 (31.4)
Difficult	86 (26.7)
Very difficult	22 (6.8)
Unknown	12 (3.7)
Prescribed treatment	332
Brimonidine/timolol monotherapy	143 (43.1)‡
Brimonidine/timolol adjunctive therapy	189 (56.9)§

* Missing data were not included in the percentage calculations.
† Control of intraocular pressure was assessed by clinicians and was based on patients' experiences with hypotensive medication before participating in the study.
‡ Includes 5 patients who were not using ocular hypotensive medication at baseline.
§ Includes 3 patients who were not using ocular hypotensive medication at baseline.

1). Clinically relevant and statistically significant reductions in IOP from baseline were observed at week 6 and were maintained up to month 3 (Figure 1). After 3 months, mean IOP decreased by 13.6% from baseline in patients prescribed brimonidine/timolol as replacement therapy (mean difference, -3.1 mm Hg; from 18.6 mm Hg [SD, 4.9 mm Hg] to 15.4 mm Hg [SD, 2.9 mm Hg];

Figure 1. Mean intraocular pressure achieved with brimonidine/timolol fixed combination as replacement or adjunctive therapy at each visit.
* $p < 0.0001$.



$p < 0.0001$) and by 16.0% in those who added brimonidine/timolol to their existing treatment regimen (mean difference, -3.4 mm Hg; from 18.7 mm Hg [SD, 5.1 mm Hg] to 15.5 mm Hg [SD, 5.0 mm Hg]; $p < 0.0001$). Of the 189 patients prescribed brimonidine/timolol as adjunctive therapy, 182 (96.3%) were treated with a prostaglandin analogue.

Significantly greater proportions of patients achieved low target IOPs after commencing brimonidine/timolol therapy compared with their previous treatment regimens (Figure 2). After 3 months of treatment, 81.3% of patients (226/278) achieved IOPs ≤18 mm Hg compared with 55.5% (182/328) at baseline ($p < 0.0001$). For 38 patients who replaced dorzolamide/timolol fixed combination with brimonidine/timolol fixed combination as adjunctive therapy, mean IOP decreased by 12.2% from baseline to month 3 (mean difference, -2.7 mm Hg; from 18.5 mm Hg [SD, 4.9 mm Hg] to 15.8 mm Hg [SD, 4.4 mm Hg]; $p < 0.0005$). On an individual level, IOP decreased for most patients, although a small number of patients experienced an increase in IOP (Figure 3).

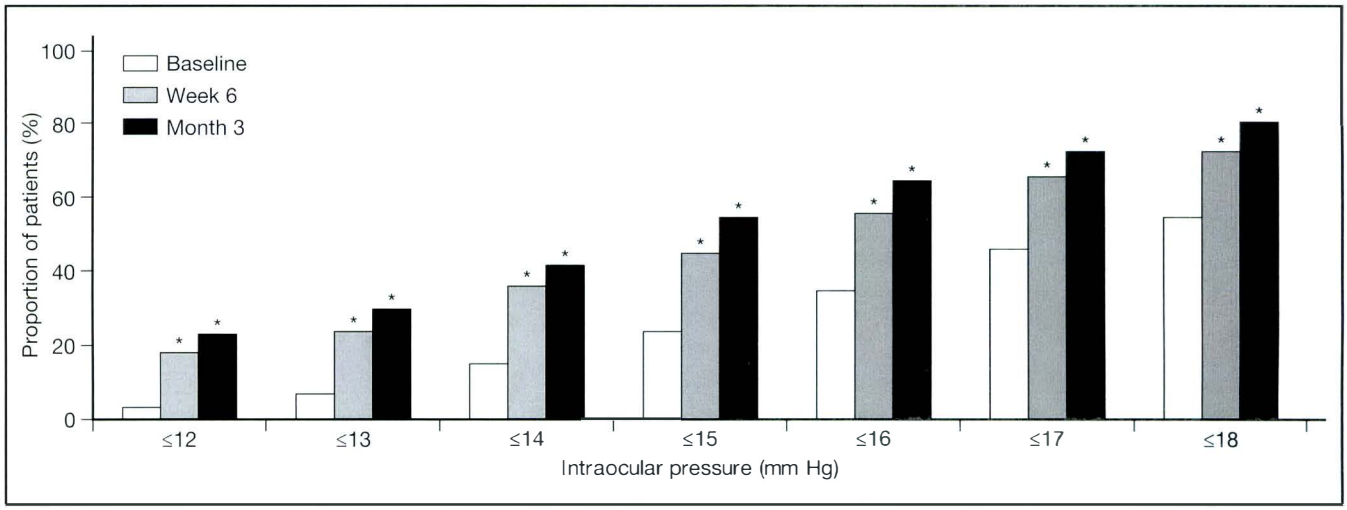
Clinically relevant and statistically significant reductions in IOP were evident in patients whose IOPs were considered by their clinicians to be difficult or very difficult to control. For patients with difficult to control IOPs (n = 86), mean IOP decreased from baseline by 14.8% after 3 months of treatment (-3.5 mm Hg; from 19.3 mm Hg [SD, 5.4 mm Hg] to 16.0 mm Hg [SD, 4.1 mm Hg]; $p < 0.0001$). For patients with very difficult to control IOPs (n = 22), mean IOP decreased from baseline by 10.5% after 3 months of treatment (mean difference, -2.9 mm Hg; from 20.1 mm Hg [SD, 4.5 mm Hg] to 17.2 mm Hg [SD, 4.1 mm Hg]; $p < 0.01$).

Reductions in IOP were observed irrespective of whether patients had lower or higher IOPs with their previous treatment regimens (Figure 4). After 3 months of treatment, mean IOP decreased a further 7.8% from baseline (mean difference, -1.3 mm Hg; from 15.1 mm Hg [SD, 1.7 mm Hg] to 13.8 mm Hg [SD, 2.9 mm Hg]; $p < 0.0001$) for patients who had already achieved low IOP (<18 mm Hg) with their previous treatment regimens.

Safety and Tolerability

After 3 months of treatment, brimonidine/timolol had a favourable safety and tolerability profile. Overall, the frequency of patients reporting at least 1 adverse event was 16.8% (56/333). The most frequently reported events were ocular hyperaemia (3.6%, 12/333), ocular irritation (3.3%, 11/333), and lid findings (2.1%, 7/333), with no serious adverse events reported. Most events were mild to moderate in severity (74.7%, 56/75). The most common reasons for patients withdrawing from the study because of an adverse event were ocular irritation (25.6%, 10/39), ocular hyperaemia (23.1%, 9/39) and lid findings (17.9%, 7/39).

Figure 2. Proportion of patients achieving target intraocular pressure at each visit.
* $p < 0.0001$.

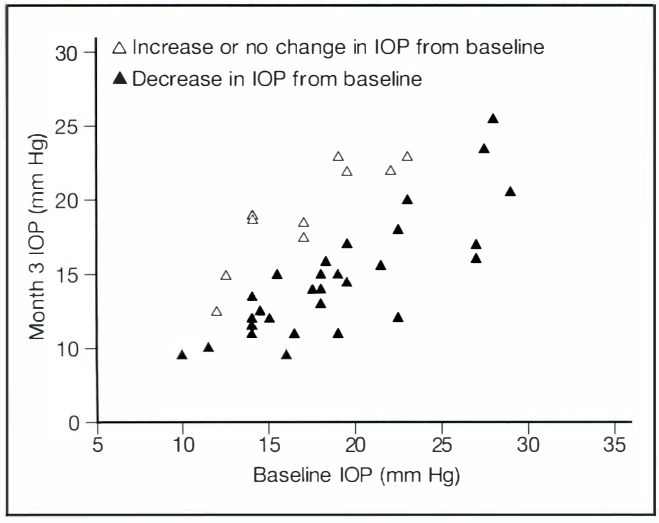


The subjective assessments of brimonidine/timolol were favourable. Most patients were satisfied or very satisfied (65.5%, 190/290) with brimonidine/timolol compared with their previous medications, and considered brimonidine/timolol to be convenient or very convenient (81.2%, 238/293). Most clinicians rated treatment with brimonidine/timolol as good or excellent (95.0%, 19/20) compared with patients' previous medications and indicated that brimonidine/timolol met or exceeded their therapeutic expectations.

Discussion

To the authors' knowledge, this is the first study to assess the effectiveness and tolerability of brimonidine/timolol fixed combination in Australian and New Zealand clinical practice. This study confirms evidence from randomised controlled clinical trials that fixed combination brimonidine/timolol is well tolerated and provides clinically relevant and statistically significant reductions in mean IOP when used alone or as adjunctive therapy.[8-10] This study adds to the findings of the 2 clinical practice studies conducted in Canada,[11,12] by showing that reductions in IOP were observed in patients who were not responding adequately to their previous hypotensive medication, irrespective of patients' IOP at enrolment or whether the glaucoma was considered to be difficult to treat.

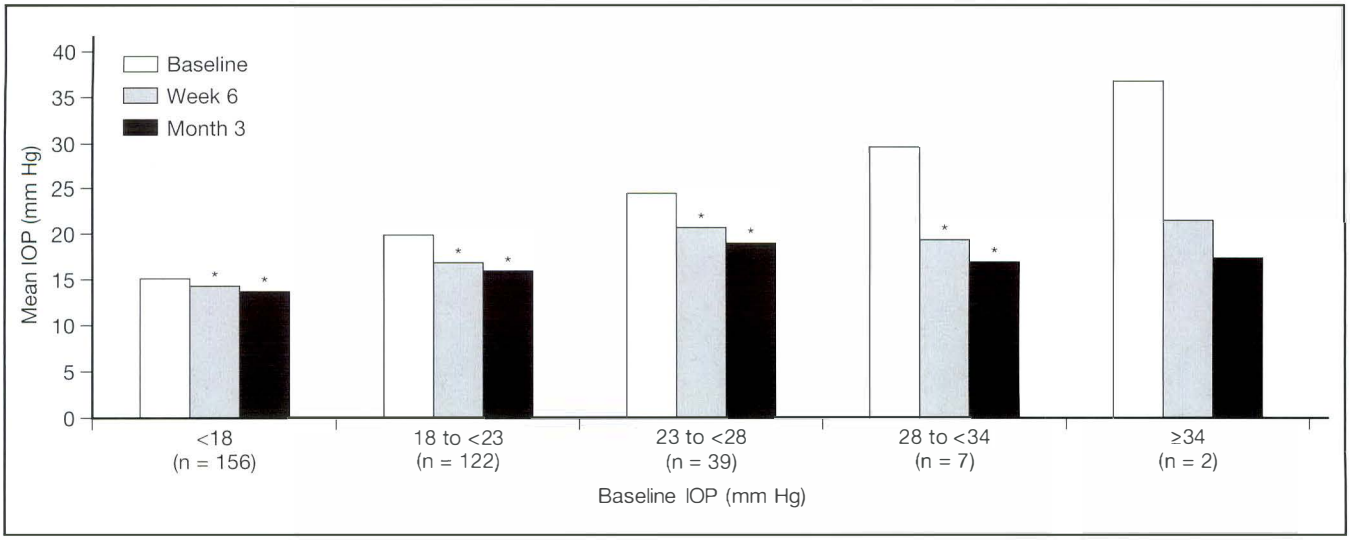
Figure 3. Intraocular pressure (IOP) at baseline and 3 months for patients who switched from dorzolamide/timolol fixed combination to brimonidine/timolol fixed combination as adjunctive therapy (n = 38).



The percentage reductions in IOP and mean reduction in IOP from baseline in this study were comparable to those observed in the clinical practice studies conducted in Canada with brimonidine/timolol.[11,12] In this study, IOP decreased by 13.6% and 16.0% after 3 months of brimonidine/timolol replacement and adjunctive therapy, respectively. Similarly, the studies from Canada reported a reduction in IOP of 17.8%[11] and 16.0%[12] after 2 months of brimonidine/timolol therapy. The proportion of patients in this study who achieved a reduction in IOP to ≤18 mm Hg from baseline is clinically relevant, as patients who continually meet this target IOP are less likely to progress to visual field loss compared with those who do not meet this target IOP.[13]

The findings that a further 12% reduction in IOP from baseline was achieved for patients who replaced dorzolamide/timolol with brimonidine/timolol as adjunctive therapy is comparable to the reductions observed in similar comparative groups in the clinical practice studies conducted in Canada. In contrast to these clinical practice studies, this study highlighted the variability in individual responses to a switch in hypotensive therapy and demonstrated that brimonidine/timolol can be considered as an effective alternative for most, but not all, patients who switch to fixed combination medications. Such variability in the reduction in IOP is to be

Figure 4. Mean intraocular pressure (IOP) achieved at each visit for patients with varying levels of baseline IOP.
* $p < 0.005$.



expected in clinical practice studies such as this because of the unrestricted selection criteria. Moreover, although these findings are encouraging, this study was not designed to compare efficacy between different treatment groups and additional studies that directly compare fixed combination dorzolamide/timolol and fixed combination brimonidine/timolol are needed to confirm these data.

Brimonidine is frequently reserved for second-line or adjunctive therapy because it is associated with high rates of ocular allergy and inflammation and, consequently, low rates of persistence with therapy.[3,14-16] Findings from this 3-month study demonstrated that, although the most frequently observed adverse events were associated with symptoms of ocular allergy, the overall frequency of adverse events with fixed combination brimonidine/timolol was low. However, as ocular allergy with brimonidine can take between 1 and 2 years to eventuate,[16,17] studies with longer follow-up times are required to effectively assess the rate of this condition with brimonidine/timolol. Findings from a 12-month randomised controlled trial comparing fixed combination brimonidine/timolol with brimonidine or timolol monotherapy[10] suggest that fixed combination brimonidine/timolol is associated with a lower frequency of adverse events and discontinuation due to adverse events compared with brimonidine monotherapy.[10] Researchers speculate that the lower dosing frequency and reduced exposure to components within the eye drop formulations with fixed combination brimonidine/timolol are the main reasons for improved tolerability over brimonidine monotherapy.[10,16] However, it is also possible that the presence of the β-blocker, timolol, may confer a protective effect against brimonidine-induced allergy.[16]

The results from this study are clinically relevant because brimonidine/timolol was assessed in daily clinical practice, using clinicians' standard procedures, and included patients who were considered to be difficult to treat. The strengths of this study were that it was multicentre, prospective, had a relatively large sample size, and was conducted over 3 months. To meet the objective of assessing brimonidine/timolol in a clinical practice setting, the study was open label and patients were not monitored as frequently as patients enrolled in controlled clinical trials. The authors cannot exclude the possibility that the reductions in IOP in this study may have occurred, at least in part, because of an apparent spontaneous non-therapeutic reduction in IOP that can occur when patients switch medication.[18] However, the uniformity between findings from this clinical practice study and those in Canada provide confirmation of data from randomised controlled trials that fixed combination brimonidine/timolol is a useful option for patients who have refractory high IOPs.

In conclusion, brimonidine/timolol fixed combination is well tolerated and effective when used as adjunctive or replacement therapy for the treatment of glaucoma and OH in daily clinical practice.

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Central Tarsal Height of the Upper Eyelid of Asian Eyes Measured Prior to Eyelid Surgery

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Aim: *To determine the mean central tarsal height of the upper eyelid of Asian eyes.*
Methods: *In a cross-sectional observational study, the central tarsal height of 180 upper eyelids of 90 Asian patients was measured. The upper eyelid was everted, and the tarsus was measured directly using a surgical calliper prior to performing eyelid surgery. The measurements were tabulated and analysed using* t *test, analysis of variance, and Bonferroni test.*
Results: *The central tarsal height of the upper eyelid ranged from 5.0 mm to 9.0 mm (average, 7.49 mm; SD, 0.76 mm). Thirty two percent of the study population were Filipino, 30% were Chinese, 24% were Japanese, 11% were Vietnamese, and 3% were Korean. Fifty percent of patients were men and 50% were women. The mean age was 55.3 years (SD, 15.2 years). The men had an average tarsal height of 7.53 mm (SD, 0.52 mm) and the women had an average tarsal height of 7.27 mm (SD, 0.76 mm). There was no significant difference between the tarsal heights of men and women. There was a tendency for older people to have a decreased central tarsal height. Significant differences were found for the tarsal heights of the different races; Japanese people had the longest tarsal heights.*
Conclusion: *These findings further contribute to the increasing amount of research into the distinct anatomy of the Asian upper eyelid.*

Key words: *Asian continental ancestry group, Eyelids*

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Introduction

Several studies have been published detailing the differences between Asian and Caucasian upper eyelids.[1,2] The study by Reid et al noted that the upper eyelid crease in Caucasian people is high, while the upper eyelid crease in Asian people is low, or does not exist at all.[3] These researchers attributed this to the septum not reaching the superior tarsal border and, instead, inserting at a variable level on the levator aponeurosis.[2,3] A cadaveric study by Jeong et al found that the preaponeurotic fat pad descends antero-inferiorly to the tarsal plate in the Asian upper eyelid, but remains superior to the tarsal plate in Caucasian eyes.[4] Furthermore, these authors noted that there was more subcutaneous and suborbicularis fat in Asian upper eyelids than in Caucasian upper eyelids.[4]

Chen found that the upper tarsus in Asian eyes is often only 6.5 mm to 8.5 mm in vertical dimension compared with Caucasian eyes, for which the average is 10 mm, ranging from 9.5 mm upwards.[5] To the authors' knowledge, no study has been published presenting anthropometric data of the upper eyelid tarsus of Asian eyes. This study was performed to determine the mean central tarsal height of the upper eyelid in Asian eyes measured prior to eyelid surgery.

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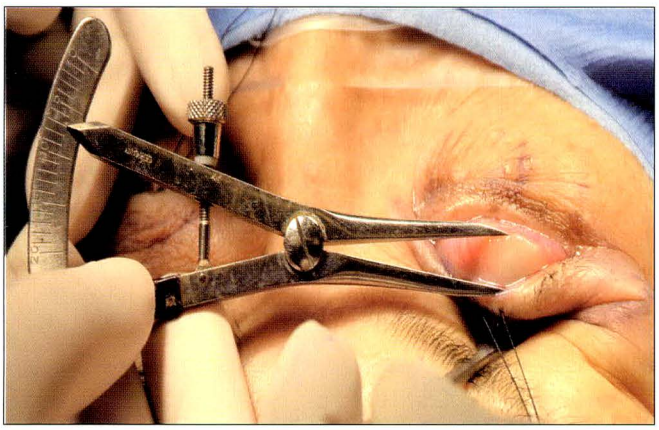
Methods

Patients

The upper eyelids of 90 Asian patients who were about to undergo eyelid surgery at the Division of Ophthalmology, Department of Surgery, University of Hawaii-John A Burns School of Medicine, Honolulu, Hawaii, were measured. Patients enrolled in the study had typical Asian eyelids, with an absent lid crease, or 'double eyelid'. Patients who had a Caucasian-like eyelid crease were excluded from the study. Patients with eyelid tumours, history of trauma to the eyelids, or disease processes that could potentially affect the tarsus, such as trachoma or Graves' ophthalmopathy, were also excluded. The eyelid procedures to be performed included upper eyelid entropion repair, blepharoplasty, and ptosis surgery.

Figure 1. Measurement of the central tarsal height using a surgical calliper.



Measurement Procedure

Prior to the surgical procedure and before infiltration of a local anaesthetic, 1 drop of topical proparacaine 0.5% sterile ophthalmic solution (Alcon Laboratories Inc, Houston, USA) was instilled in the inferior fornix. With the patient lying supine on the operating room table, both upper eyelids were everted using a Desmarres retractor. The central tarsal heights of the right and left upper eyelids were clearly identified. The same surgical calliper was used to measure the central tarsal height in mm, starting from the superior border of the lid margin to the superior edge of the tarsus in both eyes (Figure 1).

Statistical Analysis

All the measurements were taken by the same author. The data were tabulated and an independent *t* test was used for statistical analysis. Further analysis was done using analysis of variance to compare the mean tarsal heights among the different races, and a Bonferroni test to determine whether any race had significantly different tarsal heights. A p value of <0.05 was considered significant. A p value from 0.06 to 0.09 was considered marginally significant.

Results

The upper eyelid tarsal heights of 180 eyes of 90 patients were measured. The demographics of the study population are presented in Table 1. The racial distribution of the study population is shown in Figure 2. The mean age was 55.3 years (SD, 15.2 years).

Tabulation of the measurements revealed that the tarsal height ranged from 5.0 mm to 9.0 mm (mean, 7.49 mm; SD, 0.76 mm). Men had a taller central tarsal height (average, 7.53 mm; SD, 0.52 mm) than women (average, 7.27 mm; SD, 0.76 mm). Patients aged 60 years and older had a shorter mean central tarsal height than the younger age group. However, this observation was not statistically significant (Table 2).

Table 1. Demographics of the study population.

Characteristic	Number of patients (n = 90)
Number of eyes measured	180
Mean age (SD) [years]	55.3 (15.2)
Range (years)	20-85
20-59	46
≥60	44
Sex	
Male	45
Female	45
Race	
Filipino	29
Chinese	26
Japanese	22
Vitenamese	10
Korean	3

Figure 2. Racial distribution of the study population (n = 90).

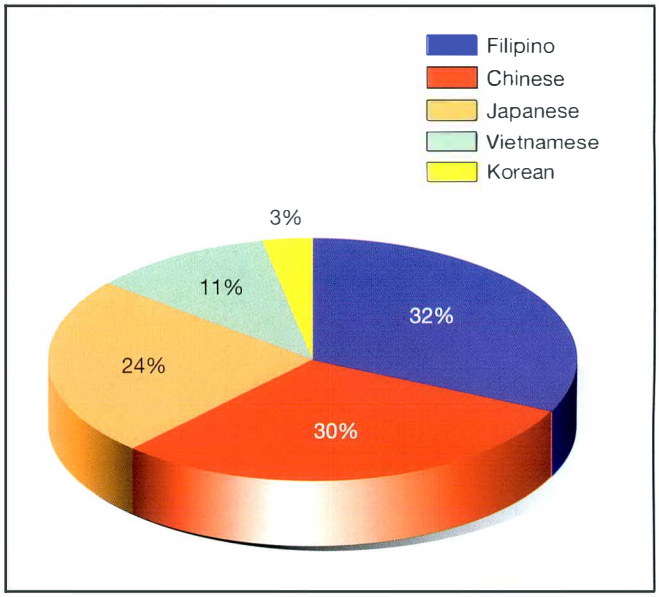


Table 2. Mean central tarsal height measurements.

Variable	Mean (SD) [mm]	*t* Value	p Value
Mean (n = 180)	7.49 (0.76)	NA	NA
Sex*			
Male	7.53 (0.52)	1.76	1.68
Female	7.27 (0.76)	1.76	1.68
Age (years)†			
20-59	7.79 (0.55)	3.62	3.40
60-85	7.42 (0.82)	3.62	3.40

* Non-directional 2-tailed *t* test for correlated samples ($p < 0.1$).
† Non-directional 2-tailed *t* test for independent samples ($p < 0.001$).
Abbreviation: NA = not applicable.

Table 3 shows the comparison of the mean tarsal heights according to race. The mean tarsal heights differed significantly according to race ($p = 0.013$). Pair-wise comparison shown in Table 4 indicates that the difference is only between the mean tarsal heights of Chinese and Japanese eyes; the mean tarsal height of Japanese eyes was significantly higher ($p = 0.01$).

Table 3. Mean tarsal height according to race.

Race	Number of patients	Tarsal height (mm) Mean (SD)	p Value
Filipino	29	7.62 (0.43)	
Chinese	26	7.22 (0.49)	
Japanese	22	7.73 (0.64)	0.013
Vietnamese	10	7.60 (0.52)	
Korean	3	7.17 (0.29)	

Table 4. Pair-wise comparison of mean tarsal height according to race.

Race	p Value	Significance
Filipino vs Chinese	0.08	Not significant
Filipino vs Japanese	>0.05	Not significant
Filipino vs Vietnamese	>0.05	Not significant
Filipino vs Korean	>0.05	Not significant
Chinese vs Japanese	0.01	Significant
Chinese vs Vietnamese	>0.05	Not significant
Chinese vs Korean	>0.05	Not significant
Japanese vs Vietnamese	>0.05	Not significant
Japanese vs Korean	>0.05	Not significant
Vietnamese vs Korean	>0.05	Not significant

Table 4 shows that there was a marginally significant difference in the mean tarsal heights between Filipino and Chinese eyes ($p = 0.08$). The number of Korean eyes was too small to show significance.

Discussion

The tarsus is the structural framework of the eyelids, composed of condensed fibrous and elastic tissues, and does not contain any cartilage.[6,7] The tarsus extends along the length of the upper and lower eyelids, measuring approximately 25 mm horizontally and 1 mm in width. The tarsus extends horizontally in a convex curve tapering medially and laterally. The superior tarsal plate has been known to be approximately 9 mm to 10 mm in vertical height in Caucasian eyes.[7]

In this study, the mean central tarsal height of Asian eyes was 7.49 mm (SD, 0.76 mm), 2.51 mm shorter than the accepted average tarsal height of 10 mm in Caucasian eyes. The finding that the male tarsal height was greater than the female tarsal height is consistent with every size-related measurement difference between male and female eyes.[8] Bashour stated that there are only 2 eyelid measurements that do not differ in size between men and women: the palpebral fissure height and the marginal reflex distance.[9] Yuzuhira et al found that the narrower palpebral fissure of Asian eyes was due to the lower transverse ligament compared with Caucasian eyes.[10] This structure restricted the vertical height of the palpebral fissure in Asian eyes.

A non-statistically significant decrease in the central tarsal height of patients aged 60 years and older was observed in this study. This is consistent with the findings of Huang et al who noted that the dimension of the lower tarsus diminishes with ageing.[11] These researchers attributed this factor to a decrease in the number and size of the meibomian glands and the change in character of intermingling fibro-connective tissues. Bashour and Harvey showed that there was a sharp decrease in the number and size of the glands, and an absence of collagen fibres with fragmentation of elastic fibres of the upper eyelid.[12] These authors also noticed that atrophy or shrinkage with age was more marked in women.

Camara et al described a physical finding often seen primarily in Asian eyes, called involutional lateral entropion.[13] This condition encompasses an inturning of only the lateral aspect of the upper eyelid margin, which is accompanied by tearing, eye redness, eye pain, and itchiness of the lateral canthal area. It was postulated in this study that Asians were more prone to this condition due to their shorter tarsal height.[13] The results of this study seems to verify this hypothesis.

In summary, in this study, the average central tarsal height of the upper eyelid in Asian patients was 7.49 mm (SD, 0.76 mm), with men having a central tarsal height of 7.53 mm (SD, 0.52 mm) and women having a central tarsal height of 7.27 mm (SD, 0.76 mm). These findings further contribute to the increasing amount of research into the distinct anatomy of the Asian upper eyelid.

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Knowledge of and Attitudes towards Eye Donation among Health Professionals in India

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Aim: *To describe the knowledge of and attitudes towards eye donation among health professionals in India between January and March 2005.*

Methods: *In this cross-sectional descriptive study, the staff, including general practitioners, medical students, nurses, and allied medical professionals, at 2 hospitals were interviewed. A close-ended questionnaire comprising 13 questions was used to collect information. The questionnaire was pre-tested and validated. Frequencies and percentage proportions were calculated. The responses related to knowledge of eye donation were grouped into excellent, good, and poor grades, and those related to attitude were grouped into positive and negative.*

Results: *206 staff members participated in the study. 102 participants had more than 2 years experience in the hospital. Twenty five participants (12.1%) had 'excellent' knowledge, and 'poor' knowledge was noted in 59 participants (28.6%). Knowledge varied according to staff type. 'Excellent' knowledge of eye donation was noted for 11 medical students (44%) and 9 postgraduate doctors (36%). 'Poor' knowledge was noted for 33 nurses (56%).*

Conclusion: *Awareness of eye donation among health professionals was low. Health promotion should target health professionals to improve their knowledge and alter their attitudes.*

Key words: *Attitude, Corneal transplantation, Knowledge, Tissue and organ procurement*

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Introduction

In India, 12 million people have visual impairment, which is the largest community of visually impaired people in any country.[1] 190,000 people are bilaterally blind and 590,000 have unilateral blindness. Corneal disorders are the principal cause of blindness among this population and could be treated by corneal transplant surgery; nearly 1 million people are in need of corneal transplant.[2] The annual donation of corneas in India has been reported to be as low as 12,746. In contrast, Sri Lanka, which has a smaller population, has more eye donation.[3] As the potential for eye donation in India is large, every effort should be made to identify the barriers to eye donation in the country. Health professionals could counsel and motivate relatives of deceased people to donate their relative's eyes.

HV Desai Eye Hospital in Pune, India, established an eye bank in 2004. The eye bank was supported by ORBIS, an international non-governmental organisation.[4] To increase corneal donation in the hospital catchment area, awareness campaigns were planned both for health professionals and for the community. Pune is a traditional religious society, so counselling for eye donation is important. Up-to-date information on the knowledge of and attitudes towards eye donation among health professionals could improve the impact of awareness campaigns. This study was performed to determine the knowledge of and attitudes towards eye donation of health professionals in India.

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Methods

This was a cross-sectional descriptive study of health professionals at 2 hospitals in Pune — HV Desai Eye Hospital and Ruby Hospital — performed from January to March 2005.

It was assumed that 15% of 2500 health professionals at the 2 hospitals would have an 'excellent' knowledge of eye donation. The study had an error margin of 5%, for which 182 randomly recruited staff were required. To compensate for any non-participation, the number of participants was increased by 10%.

Table 1. Questions asked of the participants and the number of correct responses.

	Number of correct responses (%)
1. Eye donation can be executed only after a person's death.	76 (36.9)
2. A young person who is bilaterally blind should be given priority as a recipient of a donated eye.	159 (77.2)
3. Only the cornea of the donated eye is used for transplant surgery.	95 (46.1)
4. A person's eye should be donated within 3 to 4 hours of death.	90 (43.7)
5. Only an eye doctor can collect the eyes from a dead person.	42 (20.4)
6. Blood grouping and cross matching is essential for eye transplantation.	103 (50.0)
7. Donated eyes are only used for transplant.	131 (63.6)
8. In case of death, if the relatives want to donate the eyes of a deceased person, they should contact the nearest eye bank.	164 (79.6)
9. Written consent of the person is mandatory before death for eye donation.	69 (33.5)
10. Are you willing to donate your eyes?	164 (79.6)
11. How did you come to know about eye donation?	69 (33.5)

Therefore, the minimum number of participants required was 200. Two technicians from the eye bank and a resident ophthalmologist were trained to administer the questionnaire. The close-ended questionnaire was prepared in the English and Marathi languages; Marathi is the regional language. The questionnaire in English was first translated into Marathi and then back-translated into English by different translators to ensure the validity. Questionnaires were tested by 10 staff members at the HV Desai Eye Hospital to compare 2 field investigator's methods of conducting the survey with those of a qualified counsellor experienced in the procedure. The overall agreement rate was >85%.

The respondents completed the form without any assistance from the investigators, taking approximately 20 minutes to complete the survey. The questionnaire sought demographic data of age, sex, education, and number of years working as a health professional, as well as information related to knowledge of and attitude towards eye donation (Table 1). The participants were asked 9 questions about the objectives of and procedures for eye donation. The questions were grouped into 3 key areas of eye donors and their relatives, eye transplantation surgery, and enucleation procedures at the eye bank. Two questions were open-ended to find out the knowledge-seeking attitude and motivation of participants towards eye donation. Four responses were possible for the knowledge-based questions: 'fully agree', 'agree', 'disagree', and 'fully disagree'. A correct response was awarded 2 points and a wrong response scored -2 points. The total possible score was divided into groups of >66%, 33% to 66%, and <33%. The knowledge of each health professional was graded as 'excellent', 'good', or 'poor' based on the total score. The responses to attitude-related questions were graded as 'positive' or 'negative'.

The data was computed using Microsoft Excel 2003. Frequencies and percentage proportions were calculated. Information about the procedures related to eye donation and eye banking were given to the participants after the study, and the importance of eye donation and its role in the Vision 2020 initiatives were discussed.

The study was approved by the research and ethics committee at HV Desai Eye Hospital.

Results

Of the 210 health professionals recruited to the study, 206 participated. Four staff members declined to participate due to pressure of time. The demographic characteristics of the participants are shown in Table 2.

Twenty five participants (12.1%; 95% confidence interval [CI], 7.68 to 16.60)] had 'excellent' knowledge of eye donation, 122 (59.2%; 95% CI, 22.47 to 34.81) had 'good' knowledge, and 59 (28.6%; 95% CI, 22.47 to 34.81) had 'poor' knowledge. Knowledge of eye donation was evaluated according to the participants' subgroup. Knowledge was poor among women compared with men (risk ratio, 1.68; 95% CI, 0.98 to 2.98). Medical students had significantly better knowledge than other health professionals ($\chi^2 = 15.5$, df = 3, p = 0.001). There was no association between knowledge and age or duration of work as a medical professional.

Table 2. Demographic characteristics of the participants.

Variable	Number of participants (%)
Sex	
Male	67 (32.5)
Female	139 (67.5)
Age group (years)	
<25	67 (32.5)
25-29	98 (47.6)
30-34	21 (10.2)
>35	20 (9.7)
Qualification	
Medical doctor	74 (35.9)
Postgraduate resident	32 (15.5)
Nurse	76 (36.9)
Doctor of alternative medicine	15 (7.3)
Other	9 (4.4)
Medical experience (years)	
<2	104 (50.5)
2-5	43 (20.9)
5-10	44 (21.4)
>10	15 (7.3)

Discussion

To the authors' knowledge, this is the first attempt to assess the knowledge of and attitudes towards eye donation among health professionals in western India. The results could be used as a baseline, and the impact of health education campaigns in the future could be assessed accordingly.

A study of medical students' perceptions of eye donation performed in Delhi suggested that more than 50% of the participants had sufficient knowledge about the procedures for eye donation.[5] In a study in Turkey, medical, nursing, and paramedical students were interviewed and knowledge of the procedures for organ donation was found to be insufficient for 63% of participants.[6] In this study, knowledge of the procedures was 'excellent' for only 12% of the participants. Thus, there is wide variation in the level of knowledge, which could be attributed to differences in the measurement tools and the study areas.

Poor knowledge of the importance and procedures for eye donation among health professionals is of concern. Health professionals are usually present when a person dies, especially in an urban context, where access to institutional care is available for people with terminal illness. Health professionals with sound knowledge of eye donation procedures could motivate the relatives of the deceased person to choose eye donation. They may also be able to protect the eyes before enucleation. A study performed in France showed that the rate of cornea donation increased from 6% to 20% following active intervention by health professionals.[7]

Level of knowledge of eye donation has been found to be associated with the characteristics of study participants. In a study conducted in urban areas of South India, 76% of participants had a satisfactory level of knowledge.[8] In another study, also conducted in South India, 50% of participants were aware of eye donation, although only a few participants knew details about the time of eye donation and its use for corneal transplant.[9] In contrast, awareness was as low as 30% in a rural population in South India.[10] Increased exposure of urban populations to media campaigns about eye donation and different educational levels among the various regions of India could be the reasons for these differences.

In this study, undergraduate medical students had significantly better knowledge than participants in other categories. This was in contrast to the findings of an Italian study, in which medical and science students had similar rates of positive attitude towards organ donation when compared with art students.[11]

The participants in this study had the potential for good knowledge of eye donation and procedures. However, the low level of knowledge suggests that more effort is needed to increase awareness among health professionals. Inclusion of eye donation in the curriculum of medical and nursing studies and continuous medical education for doctors could improve the situation. A study in Korea identified that an effective educational programme was necessary for nursing students to improve their knowledge of brain death and organ donation.[12]

As the sample calculation aimed to represent health professionals at 2 hospitals, the subgroup outcomes will reveal trends only and should be compared with caution.

The level of knowledge of eye donation was low among health professionals in this study, especially among general practitioners and allied health professionals. The data could be used as baseline information and compared with similar studies after awareness campaigns. Organisations that plan to establish an eye bank and need corneas for transplant surgery should include awareness campaigns for health professionals as well as for the community.

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Compliance with Spectacle Wear and its Determinants in School Students in Central India

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Aim: To ascertain the magnitude and causes of compliance and non-compliance with spectacle wear.
Methods: In a cross-sectional qualitative study performed in a school, teachers trained in vision screening examined the students for their visual acuity. The refractionist evaluated their refractive status and prescribed spectacles. Seventy seven students were randomly selected to participate and were revisited in their schools in 2004. Their compliance with spectacle wear was noted and they were interviewed to identify the reasons for compliance or non-compliance. The data were analysed to calculate the frequency and percentage of non-compliance.
Results: Fifteen of 77 students who required spectacles were not wearing spectacles (19.5%; 95% confidence interval, 10.6-28.3). Sex, age, and geographical variation were not statistically significant for compliance. Among students who were compliant with spectacle wear, 75% were wearing spectacles at the time of the visit or had them in their pockets. Clarity of vision with spectacle wear was the main reason for compliance among 75% of the students. Reasons for not wearing spectacles were aversion, headache, breakage, or parents not allowing spectacles.
Conclusions: The refractive services should include follow-up of students with refractive error to ensure compliance with spectacle wear. Counselling of parents, repairing frames, and providing aesthetic frames could improve compliance. Analytical studies with a larger number of participants are recommended.

Key words: Compliance, Eyeglasses, Myopia, Refractive errors

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Introduction

Refractive error is a priority eye disease of the disease control strategy of 'Vision 2020 The Right to the Sight'.[1] Visual impairment and its effect on overall development, especially for children, is associated with compliance with spectacles. To ensure an effective refractive error service, the outcomes of the service need to be monitored, appropriate indicators framed, and operational research conducted.[2] It is therefore appropriate to study compliance with spectacle wear and to identify the underlying reasons for non-compliance.

Sadguru Netra Chikitsalaya (SNC), Chitrakoot, India, provides eye care services in a tribal belt of Central India.[3] SNC provides paediatric eye care to the adjoining districts of Uttar Pradesh and Madhya Pradesh. The residents in the catchment area are poor, and long distances between the villages and government eye hospitals in the state capitals are major barriers for access to eye care services.

Schoolchildren in 2 regions in Central India underwent vision screening in 2003. Qualified opticians re-examined the students with defective vision. The students in need were provided spectacles and the teachers were educated to advocate spectacle wear. Children with additional ocular pathology were referred to the ophthalmologist at SNC and were provided with spectacles. A study was then conducted to review the compliance with spectacle wear among the students with refractive error and to assess the reasons for non-compliance. Policies for improving vision screening and compliance with visual aids were also proposed.

Methods

Participants

This was a cross-sectional descriptive study. 20,993 children in Karwi in Manikpur Block in Uttar Pradesh and 30,542 children in Satna in Sohawal Block in Madhya Pradesh underwent vision screening in 2003. Students with refractive error were prescribed

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spectacles. A return visit to assess the rate of compliance with spectacle wear was done after 3 to 4 months. This study was performed between February and March 2004.

It was assumed that compliance with spectacle wear in students prescribed spectacles would be 70%. To calculate the compliance of spectacle wear with a 95% confidence interval (CI) and an accepted error margin of 10%, 64 randomly selected students were required to participate in the study. To compensate for absenteeism during the follow-up visit, the number of required participants was increased by 10%. At least 70 students were therefore required to participate in the study. The sample size was calculated by using the STATCALC model of EPI6 software.

To select students for follow-up, a list was made for each school and chits were used to identify the selected students. The teachers used the Snellen illiterate 'E' chart to conduct vision screening for 51,535 students. Students with low vision were referred to an optician who rescreened them. Any student with >0.75 D spherical myopia (unilateral or bilateral) was given spectacles free of charge to avoid amblyopia and asthnopia. 309 students were prescribed spectacles, and 77 were randomly selected to ascertain compliance.

Questionnaire

A pretested data collection form was used to collect the information. A data analyst with experience of retrieving health information from the case records was involved in compiling the information, using Microsoft Excel software. Demographic data included age, sex, and area of residence. The visual acuity, and spherical and cylindrical power of the spectacles for each eye were also noted. Field staff conducted the interviews with the students. Close-ended questions were used to collect the information. The students were asked for 7 reasons for using spectacles. More than one answer for any questions were noted.

Statistical Analysis

The data were analysed using the univariate analysis method with the help of the Statistical Package for Social Studies (version 11). The frequencies and the 95% CIs were calculated. To calculate the 95% CI for the non-compliance rate, the following formula was used:

$p \pm [\text{sqrt of } \{(p) \times (1-p)/n\} \times 1.96]$

where p is a fraction of the non-compliance rate and n is the number of students examined to assessing non-compliance.

To ensure the quality of the study, a standardisation workshop was conducted and the data collection forms and methods were piloted. The data were analysed with the help of an experienced epidemiologist and biostatistician.

Table 1. Characteristics of students with refractive error in Central India.

Variable	Students provided with spectacles (n = 309) Number (%)	Students followed up for compliance after 6 months (n = 77) Number (%)
Sex		
Male	178 (57.6)	39 (50.6)
Female	131 (42.3)	38 (49.4)
Age (years)		
<10	60 (19.4)	15 (19.5)
≥10	249 (80.6)	62 (80.5)
Area		
Karwi	105 (34.0)	35 (45.5)
Satna	204 (66.0)	42 (54.5)

The consent of the administrators of SNC to use the school screening records was obtained. The identities of the students were delinked while collecting the detailed information. The outcomes of the study and recommendations to improve compliance with spectacle wear among students with refractive error were discussed with the school authorities and the parents.

Results

The profile of the students with refractive error and those included in the study were compared (Table 1). The group with refractive error closely matched the study population.

Table 2 shows the non-compliance rate according to the demographics of the study population. Nearly 20% of the students who were prescribed spectacles were not wearing them at the time of the follow-up visit (Table 3). The variations in non-compliance between the subgroups were not significant.

Of the 15 students who were not wearing spectacles at the follow-up visit, 5 did not like wearing spectacles, 3 had spectacles with broken frames, 3 experienced headache when wearing spectacles, 1 was not allowed by the parents to wear spectacles, and 2 could not provide a reason. Five students had unilateral myopia of <1 D, 6 had <1 D cylinder, and 4 had a complex refractive error.

Among the 62 students who were wearing spectacles, 20 had refractive error of >0.75 D myopia or >0.5 D hypermetropia, 9 had combined spherical and high cylindrical refractive error in at least 1 eye, 25 had spherical refractive error of <1 D myopia, and the rest had mixed refractive errors.

Discussion

Disability due to not wearing appropriate spectacles could affect the daily activities of a child and can hamper the overall development. Therefore, eye care services that aim to improve the quality of life of children should provide vision screening and refractive services, and ensure that the students comply with the use of visual aids. This study was an attempt to initiate such a system, but it had the

Table 2. Non-compliance with spectacle wear among students in Central India.

Variable	Number of students examined	Number of students not wearing spectacles	Non-compliance rate (%)	95% Confidence interval
Sex				
Male	39	6	15.4	4.1-26.7
Female	38	9	23.7	10.2-37.2
Age (years)				
<10	15	1	6.7	-6.0-19.3
≥10	62	14	22.6	12.2-33.0
Area				
Karwi	35	6	17.1	4.7-29.6
Satna	42	9	21.4	9.0-33.8
Total	77	15	19.5	10.6-28.3

Table 3. Duration of spectacle wear and reasons for compliance among students in Central India.

	Compliant students (n = 61)* Number (%)	Non-compliant students (n = 15) Number (%)
Duration of spectacle wear (hours/day)		
1-2	1 (1.6)	0 (0)
2-4	3 (4.9)	0 (0)
4-6	13 (21.3)	0 (0)
6-8	1 (1.6)	0 (0)
>8	43 (70.5)	1 (6.7)
Missing information	0 (0)	14 (93.3)
Changes brought about by spectacle wear		
Clear vision	44 (72.1)	7 (46.7)
Relief from headache	7 (11.5)	2 (13.3)
Relief from tearing	0 (0)	0 (0)
Improved academic activities	2 (3.3)	0 (0)
Good performance in sports	0 (0)	0 (0)
Looking beautiful	4 (6.6)	0 (0)
No change	0 (0)	0 (0)
Others	0 (0)	0 (0)
Missing information	2 (3.3)	6 (40.0)

* One student could not complete the study due to illness.

limitations of a small number of participants and only 1 follow-up visit for observation 3 to 4 months after providing spectacles. The students, parents, and school authorities were given sufficient time to advocate spectacle wear, but some of the schools for which these services were carried out near to the end of the project might not have had sufficient time to procure spectacles and promote their use. However, as there was no clustering of non-compliant students in schools that received these services at the end of the project, this factor of variable advocacy could not be responsible for non-compliance. All students with refractive errors were given spectacles at no cost during the project. Therefore, cost was not a barrier to compliance with spectacle wear.

The compliance rate may have been low as this was the first time for this type of project in the area, and due to the poor socioeconomic and education status of the parents. The compliance rate was low when compared with the rate reported in studies in areas with better living standards and health awareness.[4,5] Provision of free spectacles in this study area might have led to better compliance. As unilateral myopia of 1 D without symptoms may not need spectacles, the policy of providing spectacles may have to change as compliance among these students might be lower than expected.

The small number of participants for subgroup trends did not permit comparison of compliance by sex, age, or area of residence. As the study area is a tribal belt and the average family income less than US$50 per month, analysing compliance by socioeconomic status was also not possible. Further study with a larger number of participants is suggested to identify high-risk groups. More follow-up and monitoring may improve compliance with spectacle wear.

Other studies have observed that over-prescribing of spectacles to schoolchildren is common.[6] This study confirmed these findings. Therefore, it is important to decide who should be given spectacles in school. Philosophically, it is recommended that spectacles should be provided to all children who need them.[7] However, for logistics and feasibility purposes, the vision screening polices recommended by the World Health Organization should be adopted — spectacles should be provided to people with myopic refractive error of more than 0.75 D and hypermetropic refractive error without symptoms

of more than +0.5 D.[2] Similar criteria for provision of spectacles should be applied in this study area. This would not only reduce the cost of the project but also increase compliance with spectacle wear. Students with high-power refractive error comply better than those with low-power refractive error, a unilateral problem, or astigmatic refractive error in 1 eye. Therefore, in addition to clinical judgment, the perception of spectacle use should be taken into account when evaluating compliance with spectacle wear.

How one looks when wearing spectacles was a major deciding factor for students to use spectacles. Providing wider choices of spectacle frames might reduce non-compliance for aesthetic reasons. This approach should be complimented with appropriate counselling of spectacle wearers. The aesthetic problem was mostly encountered among girls and their parents, who believed that by wearing spectacles, the girl's marriage prospects might be negatively affected. Changing such attitudes needs patience and counselling.

Maintaining the spectacles and arranging for mending after breakage should be part of the refractive services responsibilities.[8] This could improve the compliance rate among a community where distance and cost are barriers to using eye care facilities.

One study found that improvement in vision had little or no relationship with compliance.[9] This was also observed in this study, in that students with unilateral refractive error and astigmatism of <1 D were less compliant than students with high refractive error. However, the element of chance cannot be ruled out in this observation.

This was the first study of the provision of refractive services to this underprivileged population in Central India. It has enabled revision of the strategies of the service. Limiting provision of spectacles to students with >1 D myopia, >0.5 D hypermetropia, or symptoms of eye strain could further improve compliance with spectacle wear. The refractive services should be complemented by appropriate counselling of the students, and their teachers and parents. Follow-up of students prescribed spectacles should be an integral part of monitoring the refractive services in the future.

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Massager-induced Cataract

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This report is of a rare case of massager-induced traumatic cataract in a 21-year-old man presenting with complaints of bilateral blurred vision after using his parents' body massaging device on both eyes. His vision was 20/20 in both eyes, but he experienced significant glare. Slit-lamp examination revealed bilateral anterior capsular cataracts, which was worse in his right eye. The patient's vision remained stable during follow-up. However, he found the amount of glare and haloes debilitating and is considering cataract surgery. To prevent similar occurrences, massaging devices should always be accompanied by labels or instructions that warn consumers against their use on or around the eyes.

Key words: Cataract, Massager, Wounds and injuries

Asian J Ophthalmol. 2008;10:178-9

Introduction

Massager-induced cataract is a rare condition, with only 1 previous report in the literature.[1] This report is of a young man who developed bilateral cataracts after using his parents' body massaging device on both eyes.

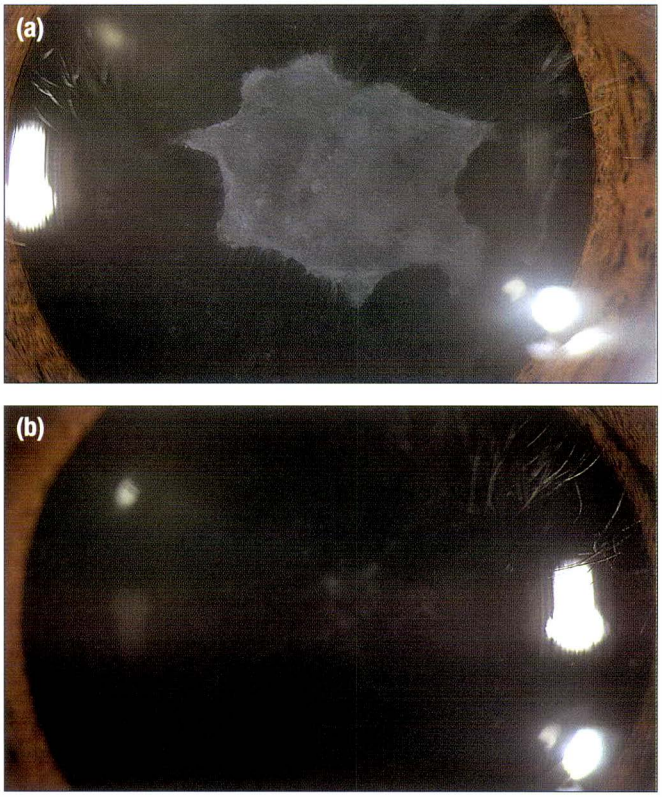
Case Report

A 21-year-old man with no significant medical or ophthalmic history presented in 2008 with bilateral blurred vision, which was worse in the right eye. He gave a history of using his parents' body massaging device on both his eyes after he had been playing computer games for more than 24 hours. This was done with the intent of relieving fatigue symptoms. He used it with considerable pressure on his eyes for a few minutes, with more force on his right eye. He immediately stopped using the device on his eyes after noticing that his vision was blurred and he attended the ophthalmology clinic 4 days later.

On examination, the patient's best-corrected visual acuity (BCVA) was 20/20 in both eyes. However, there was significant glare and he had difficulty focusing in bright light. Slit-lamp examination revealed bilateral anterior capsular cataracts, which was worse in his right eye (Figure 1a). Cataract was less significant in his left eye (Figure 1b). There was no evidence of lens dislocation or subluxation. With the exception of bilateral cataracts, the anterior and posterior segments of both his eyes appeared normal.

In subsequent follow-ups, his vision has remained stable with a BCVA of 20/20 in both eyes. However, the patient found the amount of glare and haloes debilitating and is considering cataract surgery.

Figure 1. Traumatic cataract in the (a) right eye; and (b) left eye.



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Discussion

To the best of the authors' knowledge, this is only the second reported case of massager-induced traumatic anterior subcapsular cataract.[1] Yet this case is unique in that it involved a young patient who presented early after onset of symptoms after using a massaging device not intended for use on the eyes.

The pathogenesis of such traumatic cataract may be explained using the contrecoup injury mechanism, previously described by Wolter.[2] The continuous and repetitive low-energy impact of the massaging device sends shockwaves along the plane of trajectory into the globe, which disrupt the anterior lens capsule and cause proliferation of lens epithelium in contusional cataract formation. This patient was fortunate in that he did not experience lens subluxation or dislocation as a result of zonular dehiscence secondary to simultaneous equatorial scleral stretching also caused by this mechanism.

Despite the good BCVA, this patient still has symptoms of glare and focusing difficulties. This is a possible indication for surgical intervention for traumatic cataract.[3]

To prevent similar occurrences, massaging devices should always be accompanied by labels or instructions that warn consumers against their use on or around the eyes. Such labels are still not commonplace due to the scarcity of the existing literature on this matter.

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Isolated Inferior Rectus Rupture and Inverse Knapp Procedure: a Rare Condition with an Uncommon Treatment

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This report is of a 35-year-old woman with isolated inferior rectus laceration presenting with pain and diplopia following an accidental injury to the left eye with a coat hanger hook. At surgical exploration, the inferior rectus was found to be subtotally lacerated and was eventually treated with the inverse Knapp procedure. Isolated laceration of the inferior rectus muscle, in the absence of significant injury to the globe and adnexa, is rare. The success of the inverse Knapp procedure for this patient shows an alternative way of treating vertical diplopia following inferior rectus injury.

Key words: *Bell palsy, Diplopia, Lacerations, Oculomotor muscles, Surgical procedures, operative*

Asian J Ophthalmol. 2008;10:180-1

Introduction

Isolated laceration of the extraocular muscles, in the absence of significant injury to the globe and adnexa, is uncommon.[1,2] This report is of a patient with direct traumatic laceration of the inferior rectus muscle causing vertical diplopia, which was eventually treated successfully by the inverse Knapp procedure.

Case Report

A 45-year-old woman presented to the eye casualty with pain and diplopia following an accidental injury to the left eye with a coat hanger hook in 2003.

Visual acuity was 6/5 in both eyes. Examination showed an inferior forniceal conjunctival laceration with subconjunctival haemorrhage in the left eye. Anterior segments and fundi were normal. The left eye was hypertropic and exotropic (Figure 1), with limited ocular motility in downgaze.

At surgical exploration, the inferior rectus was found to be subtotally lacerated 1 cm from its insertion, although a few fibres were still intact with no residual action (Figure 2). The distal end could not be identified and no muscle repair was possible. The conjunctiva was repaired. One week postoperatively, the

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Figure 1. At the time of presentation, the left eye was hypertropic and exotropic with inferior forniceal conjunctival laceration.

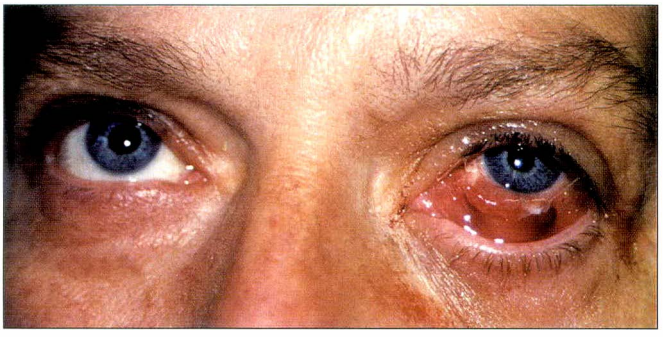


Figure 2. The left eye intraoperatively showing the subtotal lacerated proximal end of the inferior rectus muscle (black arrow) and the muscle hook under the residual attached inferior rectus fibres (white arrow).

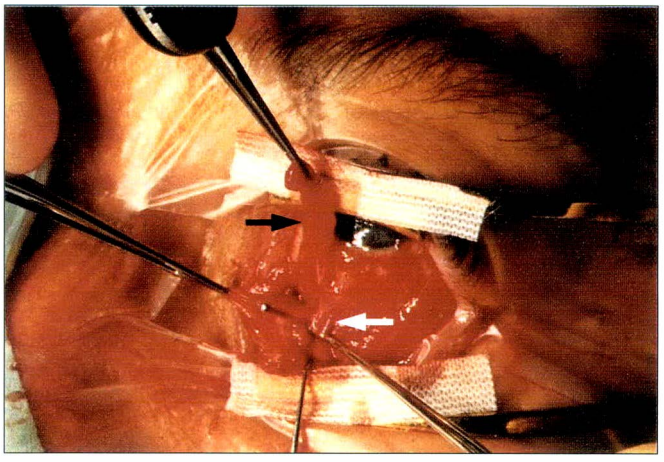
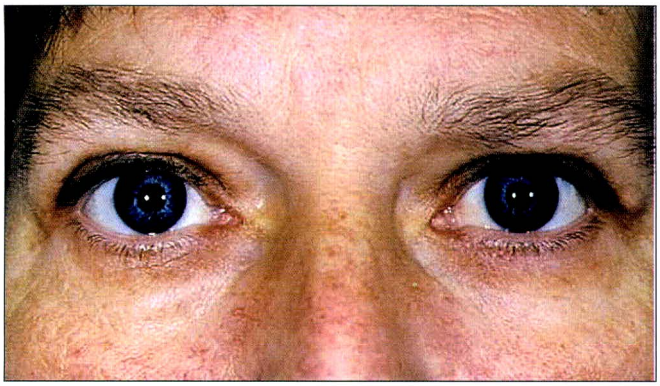


Figure 3. One year after the inverse Knapp procedure showing orthotropic eyes.



hypertropia measured 16 PD, with an exotropia of 12 PD in the primary position.

There was no improvement 4 months after the injury. As the patient still had troublesome diplopia, she underwent an inverse Knapp procedure with transfer of horizontal recti to the inferior rectus insertion under general anaesthesia, with minimal disruption of the scar tissue. Postoperatively, her eyes were orthotropic in primary gaze with no diplopia. There was minimal reduction of horizontal movements of the left eye with slight underaction in all elevated positions and diplopia only in upgaze. The patient was pleased with the results in terms of primary and downgaze positions. This satisfaction was maintained and the patient remained comfortable 1 year later (Figure 3).

Discussion

Extraocular muscle lacerations are rare.[1,2] The absence of any significant injury to the globe or the adnexa makes this case even more unusual. The 2 most frequently involved muscles in such trauma are the medial rectus and the inferior rectus.[2] This is due to their proximity to the corneoscleral limbus relative to the other muscles, and their increased visibility during the protective blink with associated upward and usually outward movement of the globe (Bell's phenomenon).[3]

The diagnosis of lacerated extraocular muscle requires a high index of suspicion and prompt surgical exploration. A transacted extraocular muscle retaining contractile function should be reanastomosed.[4] If the muscle function is permanently lost, muscle transfer may be indicated,[3,4] as for this patient for whom the inverse Knapp procedure was performed.

The common indications for the inverse Knapp procedure include congenital or acquired inferior rectus weakness, post-traumatic inferior rectus underaction, and residual large hypertropia in patients with poor binocular function.[5]

To the best of the authors' knowledge, there are no published reports of inferior rectus laceration being treated with this procedure. The success of the procedure for this patient suggests that the inverse Knapp procedure is a credible option for the treatment of vertical diplopia following inferior rectus injury.

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Bilateral Choroidal Metastases in a Patient with Lung Cancer

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This report is of bilateral choroidal metastases in a 62-year-old woman with non-small–cell lung carcinoma and metastases in the brain and left adrenal gland. The choroidal tumour in the right eye responded satisfactorily to chemotherapy, as shown by B-scan ultrasonographic measurements, with good maintenance of vision.

Key words: Carcinoma, non-small–cell lung, Choroid neoplasms, Drug therapy, Ultrasonography

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Introduction

Choroidal metastasis is the most common intraocular tumour in adults, and its occurrence in association with lung carcinoma (20.4%) is second only to breast cancer (52.6%).[1] The prevalence of choroidal metastasis in patients with disseminated lung cancer was reported to be 7.1%, and it is usually present only when at least 2 other organ systems are affected by metastasis.[2] The presence of choroidal metastasis may initiate the need for investigation of the primary malignant tumour. Lung cancer was detected in 64% of patients after the occurrence of choroidal metastasis.[3] This report is of a patient with bilateral choroidal metastases who had non-small–cell lung cancer and metastases in the brain and left adrenal gland.

Case Report

A 62-year-old non-smoking woman with histologically proven non-small–cell lung cancer since April 2002 underwent surgical excision of the lesion in the right lung and 4 cycles of chemotherapy (carboplatin and venorelbine). She had recurrence of the lesion in the right lung with metastasis to the brain and left adrenal gland in May 2004. She started 6 cycles of chemotherapy (carboplatin and gemcitabine) in the oncology unit. She presented to the eye clinic for painless blurred vision in the right eye on 21 June 2004, 2 weeks after the first cycle of chemotherapy was given.

The best-corrected visual acuity (BCVA) was 6/9 in the right eye and 6/6 in the left eye. The anterior segments and intraocular pressures were normal in both eyes. Slit-lamp biomicroscopic/binocular indirect ophthalmoscopic fundus examinations showed a large dome-shaped orange-coloured choroidal mass, with adjacent retinal detachment temporal to the macula in the right eye (Figure 1a), and a small flat yellowish choroidal mass temporal to the macula and a flat retina in the left eye (Figure 1b). B-scan ultrasonography of the right eye showed a large choroidal mass of maximum cross-sectional area (MCSA) of 123.62 mm^2 with adjacent retinal detachment and underlying choroidal thickening (Figure 1c). The patient also had a brain metastasis (Figure 1d).

Fundus photographs (Figure 2) and ultrasonic measurement of the tumour size in the right eye were taken at each follow-up visit. Towards the end of the chemotherapy regimen, the choroidal tumour in the right eye appeared smaller clinically with complete resolution of retinal detachment (Figure 3a), MCSA was 55.14 mm^2, and the BCVA in the right eye was stable. The tumour in the left eye remained static with good vision. The brain metastasis responded well to chemotherapy (Figure 3b). However, the tumour mass in the right eye started increasing in size (MCSA, 99.44 mm^2) 6 weeks after the completion of chemotherapy. External beam radiotherapy 2000 cGy divided into 5 doses was given in February 2005, following which there was a slight reduction in tumour size (MCSA, 95.8 mm^2). Two weeks after completion of radiotherapy, the tumour in the right eye had increased in size, which was confirmed by B-scan ultrasonography (MCSA, 101.66 mm^2).

Single-drug chemotherapy with docetaxel was given over 18 weeks. The tumour in the right eye did not respond and had eroded through the retina into the vitreous (Figure 3c). However, the retina was still flat, the macula appeared normal, and BCVA was good (6/9). Another chemotherapy course was offered to the patient, but she declined because of financial reasons. She was then treated palliatively and followed up every 3 months. The tumour in the right eye had reduced in size (MCSA, 78.20 mm^2; Figure 3d) at the

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Figure 1. Imaging showing (a) fundus photograph of the right eye at presentation showing a large dome-shaped orange-coloured choroidal mass with adjacent retinal detachment, temporal to the macula; (b) fundus photograph of the left eye at presentation showing a yellowish flat choroidal mass temporal to the macula and a flat retina; (c) B-scan ultrasonography of the right eye at presentation showing a large choroidal mass (white arrow) with adjacent retinal detachment, and choroidal thickening (black arrow); and (d) contrast computed tomography scan of the brain at presentation showing a metastatic lesion in the posterior horn of the left ventricle (white arrow).

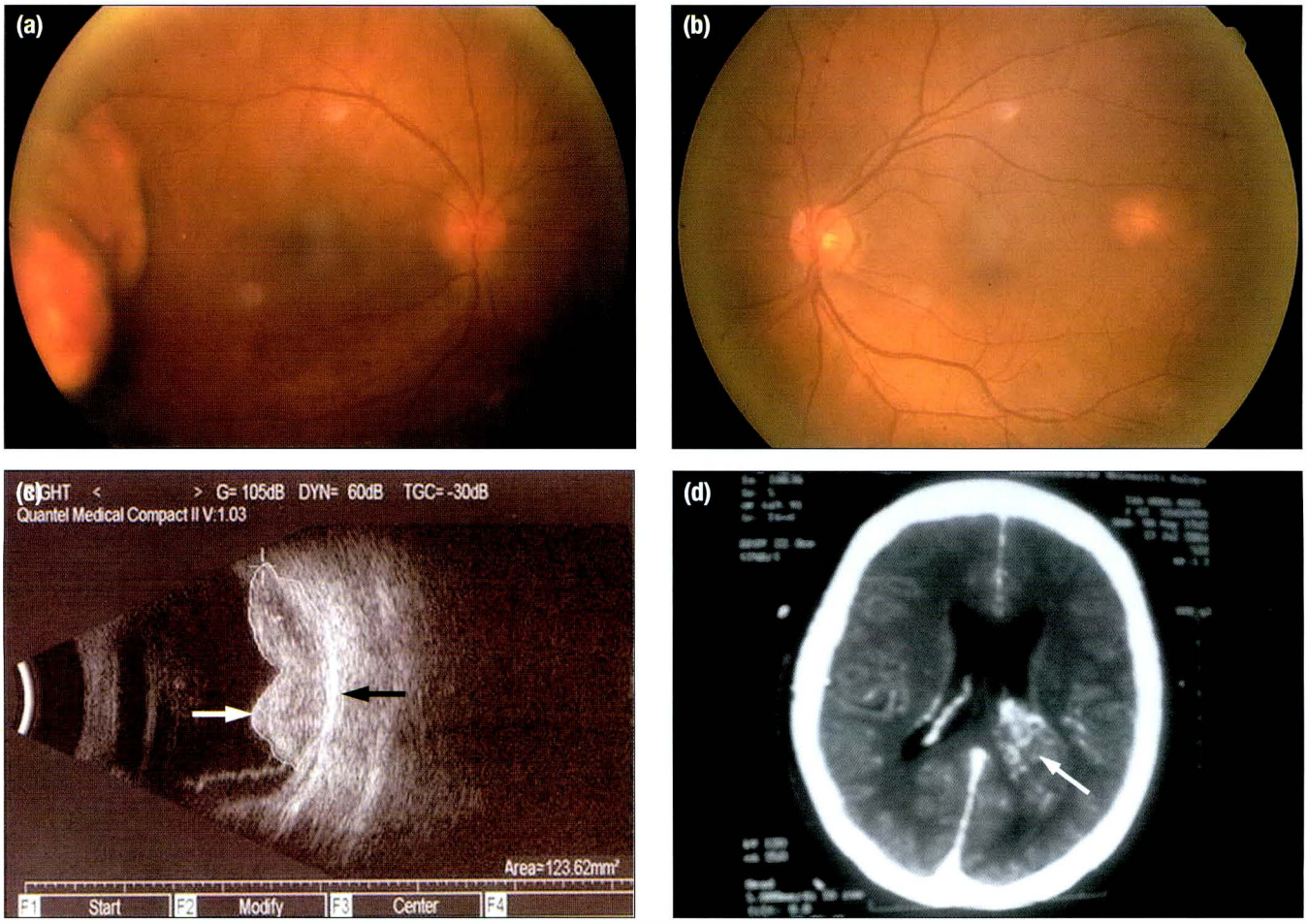
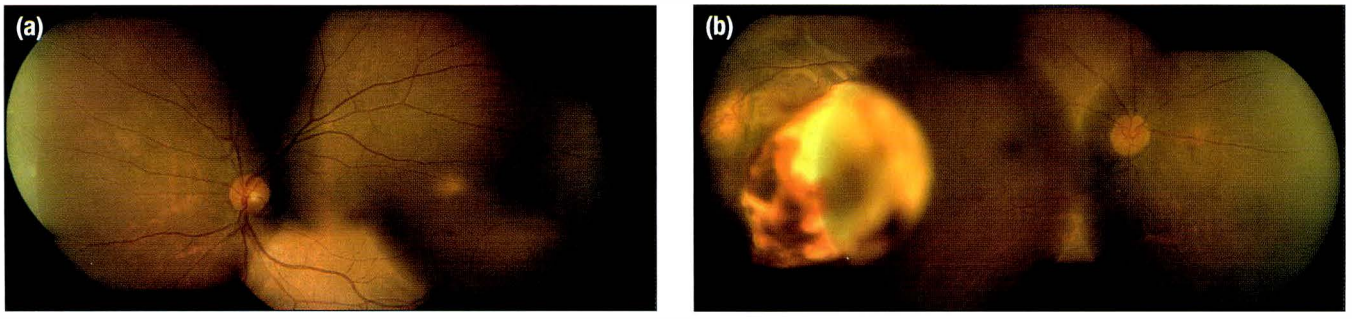


Figure 2. Composite fundus photographs of the (a) left eye; and (b) right eye.

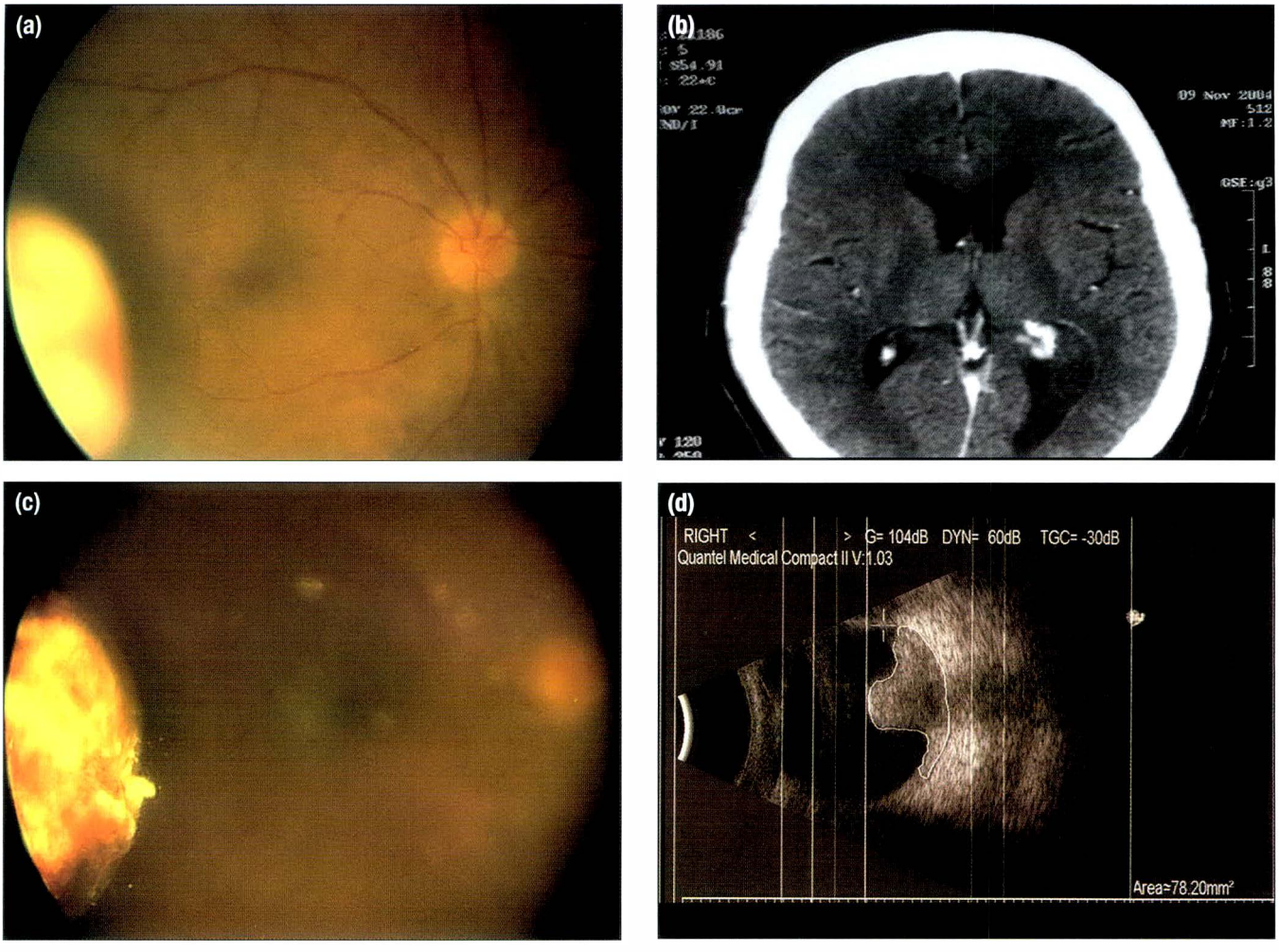


last follow-up visit in March 2006. The patient died in June 2006, 4 years after the diagnosis of lung cancer and 2 years after the diagnosis of choroidal metastases.

Discussion

The presence of choroidal metastasis indicates advanced dissemination, as further organ metastasis has been found in 70%[1] to 86%[3] of patients with choroidal metastasis from lung cancer. In this patient, metastasis was already present in the brain and left adrenal gland at the time of diagnosis of choroidal metastasis. In a study of 84 patients with metastatic lung cancer, brain metastasis was reported in 70.2% and adrenal metastasis in 17.8% of patients.[2] The choroid was the sixth site of organ metastasis. Treatment options for symptomatic choroidal metastasis

Figure 3. Imaging showing (a) fundus photograph of the right eye after 5 cycles of chemotherapy showing a choroidal mass temporal to the macula and complete resolution of retinal detachment; (b) contrast computed tomography scan of the brain at the same time as Figure 2a showing resolution of the metastatic lesion in the posterior horn of the left ventricle; (c) fundus photograph of the right eye 6 months after the second chemotherapy course showing erosion of the tumour into the vitreous; and (d) B-scan ultrasonography of the right eye at the last follow-up showing the reduction in size of the choroidal tumour.



include systemic chemotherapy,[1] external-beam radiotherapy,[4] transpupillary thermotherapy,[5] and photodynamic therapy.[6] Treatment regimens depend on the size and extent of the choroidal tumour, number of tumours, laterality, visual status of the affected and non-affected eyes, cancer stage, age, and general health of the patient. Preserving the patient's visual status may enhance the quality of life, while the prognosis is contingent on the response to therapy.[7] The decision to treat choroidal metastasis is usually made in consultation with the oncologist. The final reduction in choroidal metastasis size in the right eye from 123.62 mm^2 at the first visit to 78.20 mm^2 at last follow-up visit before death, and maintenance of good BCVA (6/9) in both eyes can be considered a satisfactory response to chemotherapy.

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Assessment of Comfort during Intravitreal Injections and Comparison of Anaesthetic Drops and Subconjunctival Anaesthesia

Dear Editor,

Intravitreal injections should be minimally painful and well tolerated by patients, as they may need to be administered repeatedly.[1-3] Previously, intravitreal injections were performed using peribulbar block, subconjunctival anaesthesia (SCA), or topical anaesthesia.[1-3] Peribulbar anaesthesia is now rarely used for routine intravitreal injections due to the inherent risks.[1-5] We performed an audit of patients' comfort during intravitreal injection given after SCA or topical anaesthetic eye drops.

Thirty patients undergoing intravitreal triamcinolone acetonide (IVTA) injection were randomised into 2 groups to receive either SCA or topical anaesthetic eye drops. None of the patients had received prior intravitreal injections. Table 1 shows the patients' demographic characteristics and the indications for IVTA.

The time delay between anaesthetic administration and IVTA injection was <5 minutes for all patients. Patients receiving topical anaesthesia had 3 instillations of 0.5% proxymetacaine 3 to 5 minutes apart and 1 drop immediately prior to IVTA injection, after the speculum was inserted. Patients receiving SCA had 2 applications of 0.5% proxymetacaine 5 minutes apart and subconjunctival injection of 2% lignocaine 1 to 2 mL to the inferotemporal quadrant adjacent to the site of IVTA injection. Lignocaine injection was followed by gentle ocular massage to facilitate the spread of the anaesthetic.

Using a universal eye speculum, IVTA 0.1 mL (4 mg) injection was administered to the inferotemporal site through the pars plana, using a 27 G needle. Following the procedure, 1 drop of 0.5% chloramphenicol was instilled into the conjunctival fornix and the eye was covered with a clear shield for 4 to 6 hours.

Subjective pain was assessed using a verbal score (0 = no pain and 10 = unbearable pain). Patients were asked to grade the level of pain experienced during administration of the dilating and anaesthetic drops, subconjunctival anaesthetic injection, IVTA injection, and 30 minutes postoperatively.

No intra- or postoperative complications occurred and no patients refused further injections because of pain or discomfort following IVTA. Table 2 shows the pain scores at all stages of the procedure. There were no differences in pain scores between the 2 groups at any stage of the procedure.

The safety and efficacy of topical and subconjunctival anaesthesia for intraocular procedures has been well documented.[2] Subconjunctival injections have been reported to cause subconjunctival haemorrhage, chemosis, pain, electrocardiographic abnormalities, and scleral perforation, particularly in patients with thin sclera and scarred conjunctiva.[3-5] The use of topical anaesthesia prevents these complications. Previous studies have found topical gel to be as effective as SCA.[1,3] Although Kaderli and Avci compared topical anaesthesia and SCA, they applied a lidocaine 4%–soaked sponge to the injection site for 5 minutes.[2] There have been no studies comparing topical anaesthetic drops and SCA for intravitreal injections.

Table 1. Demographic characteristics and indications for intravitreal triamcinolone acetonide injection according to anaesthetic type.

Variable	Topical anaesthetic	Subconjunctival anaesthetic
Age (SD) [years]	72 (6.2)	74 (7.5)
Eye		
Right	3	8
Left	2	7
Sex		
Male	7	2
Female	8	3
Indications for injection		
Age-related macular degeneration	2	3
Diabetic retinopathy	6	8
Vascular occlusions	6	3
Postoperative cystoid macular oedema	0	1
Telangiectasia	1	0

Table 2. Pain scores according to anaesthetic type.

Stage of procedure	Mean pain score (SD) [range, 0-10]		p Value
	Topical anaesthetic	Subconjunctival anaesthetic	
Dilating drop	0.73 (1.10)	0.80 (1.08)	0.87
Anaesthetic drop	0.60 (0.63)	0.60 (0.83)	1.00
Intravitreal injection	0.87 (0.83)	0.93 (0.96)	0.84
30 minutes postprocedure	0.47 (0.64)	0.27 (0.59)	0.38

Some ophthalmologists believe that topical anaesthetic drops are not effective for intravitreal injections.[3] This audit shows that topical anaesthesia provides satisfactory patient comfort for administration of IVTA injections. Clinically, patient comfort with topical anaesthesia was comparable with that achieved with SCA, and there were no statistical differences in pain scores for any of the stages assessed.

This audit was limited by the small number of patients and, therefore, the statistical power to detect small differences in subjective pain scores. There was no control group and the randomisation method of using the department waiting list was weak, although it was in keeping with the clinical situation in which the audit was performed.

There were no significant differences in pain scores for instillation of dilating or anaesthetic drops between the groups. These variables may be used as surrogate markers to suggest that patients in both groups had similar pain thresholds.

In our experience, both SCA and topical anaesthesia with proxymetacaine drops provide adequate anaesthesia for routine intravitreal injections. This audit demonstrates that topical anaesthesia is adequate for successful intravitreal injections and provides good patient comfort.

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Orbital Metastasis from Breast Carcinoma Simulating Orbital Cellulitis: a Misdiagnosis

Dear Editor,

Metastatic disease of the orbit accounts for 10% to 13% of all orbital tumours,[1] whereas the prevalence of ocular metastasis from breast carcinoma is approximately 27%.[2] The average age at diagnosis of ocular metastasis is 52 years, but the orbital involvement usually occurs 2 to 5 years after diagnosis of the primary tumour. Presentation of orbital metastasis at the age of 30 years without evidence of a primary tumour is rare.

A 30-year-old woman with spontaneous proptosis of the right eye with associated restriction of extraocular movements for 2 weeks and rapid decrease in vision during the previous 4 days was referred to the clinic in 2006. A clinical diagnosis of orbital cellulitis had been made elsewhere and was treated with ciprofloxacin 750 mg twice daily for 6 days, but she did not respond. At presentation, her vision was light perception in the right eye and 6/6 in the left eye. Fundus photograph of the right eye showed evidence of optic disc infiltration with pallor, peripapillary retinal oedema, and splinter haemorrhages. There was no evidence of choroidal metastasis and the macula was healthy.

Systemic evaluation revealed palpable right submandibular and left axillary lymph nodes. The lymph nodes measured 2 x 3 cm, and were non-tender, firm, and freely mobile. There was no palpable breast mass. Computed tomography scan revealed a retrobulbar heterogeneous mass with diffuse infiltration of all the recti muscles and the optic nerve, extension into the preseptal area, and erosion of the superior orbital wall (Figure 1). Cytology from the orbital mass and enlarged lymph nodes revealed metastatic infiltrating breast carcinoma. Mammography revealed evidence of carcinomatous changes in the right breast (Figure 2). Cytological study of cerebrospinal fluid was normal. Blood investigation showed leukoerythroblastic pancytopenia. Systemic evaluation showed evidence of liver and lung metastases.

The patient was given systemic chemotherapy and external beam radiotherapy was started for the orbital metastasis. She died after 3 months of treatment.

Figure 1. Computed tomography scan showing a heterogeneous retrobulbar mass with optic nerve infiltration.

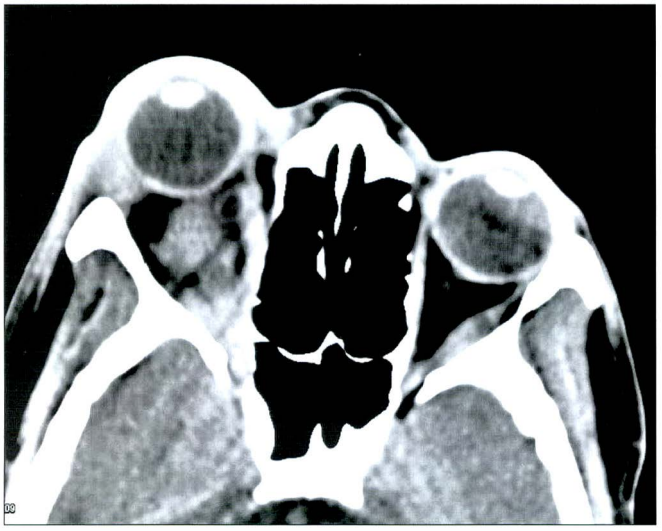
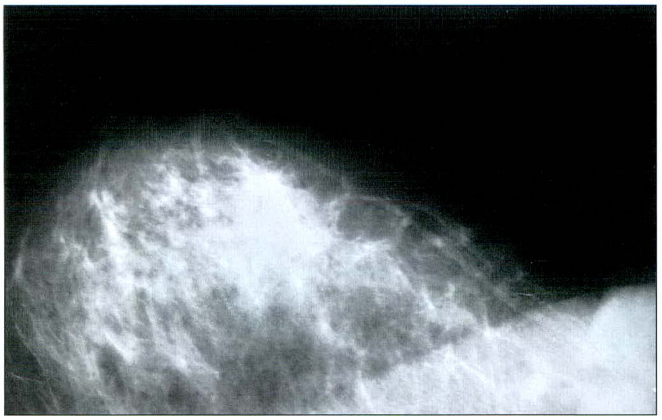


Figure 2. Mammography of the right breast showing an irregular mass with architectural distortion.



Orbital metastases most commonly occur in association with primary tumours of the breast, bronchus, kidney, or prostate. Orbital metastasis has varied presentation and can be misdiagnosed as orbital cellulitis, myositis, scleritis, or endophthalmitis.[3] The distinguishing features of orbital metastasis is the progressive course and lack of response to treatment.

The ocular structures most commonly involved are the highly vascular choroid, followed by the anterior segment and optic nerve.[4] Optic nerve involvement can be in the form of infiltrative or compressive optic neuropathy. In the presence of optic nerve infiltration, there is a high possibility of central nervous system (CNS) involvement, but in this case, the CNS was not involved.

Radiation therapy remains the cornerstone of the management of patients with orbital metastasis. The lesion usually regresses with radiotherapy and it is frequently effective for pain management. The prognosis for survival is poor, with a mean survival of 6 to 17 months.[5]

The misdiagnosis of orbital cellulitis for this woman might have been due to her young age and the absence of breast lumps. This patient underlines the consideration of orbital metastasis for all inflammatory orbital lesions not responding to treatment or with any evidence of an infiltrative lesion, and the need for thorough systemic evaluation.

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Alcon

Therapeutic Management Trends 2008

From the Alcon sponsored symposium *Therapeutic Management Trends 2008* held at the Inaugural Asia Cornea Society Scientific Meeting 2008 Singapore, 12 March 2008

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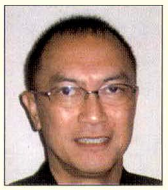

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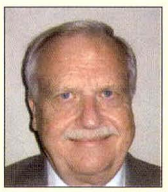

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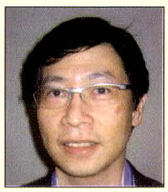

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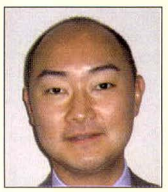

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Therapeutic Management Trends 2008

The Therapeutic Management Trends meeting was held at the recent Asia Cornea Society meeting in Singapore on 12 March 2008. Featuring a panel of distinguished speakers, the discussion focused on 3 key topics: ocular infection, ocular allergy, and dry eye. Dr Tat-Keong Chan introduced the concept of red eye, followed by presentations on surgical infections (Dr Cesar Espiritu), corneal infections (Prof Donald Tan), and fluoroquinolone resistance (Dr David Stroman). Dr Victor Caparas introduced the session on the ocular surface, and discussed allergic conjuntivitis, and Dr Francis Mah presented the treatment goals. Prof Liu Zuguo presented an Asian perspective of dry eye, and Dr Julian Theng discussed surgical-related dry eye. The meeting was sponsored by Alcon.

Ocular Infection

Red Eye — Differential Diagnosis

There are many causes of red eye, encompassing 3 main clinical entities of infectious conjunctivitis, allergic conjunctivitis, and dry eye (Table 1). The differential diagnosis is critical to the treatment for red eye, so a good clinical history and careful clinical examination are essential (Table 2).

Clinical Approach

Dr Chan explained that the consequences of inaccurate diagnosis are inappropriate treatment and the potential for complications — the wrong treatment is worse than no treatment. Incorrect treatment of bacterial conjunctivitis may mask the underlying condition, by alleviating symptoms, while the infection remains untreated. The appropriate treatment is topical antibiotics, which should be started as soon as possible. Microbial examination may be required, and systemic antibiotics prescribed, if necessary.

Table 1. Causes of red eye.

Bacterial infection
Viral infection
Fungal/parasitic infection
Allergic eye disease
Dry eye
Lid disease
Immune reaction
Intraocular inflammation
Acute glaucoma
Ocular trauma

"The wrong treatment is worse than no treatment"

In Asia, a lot of red eyes are being managed with steroids/antibiotic-steroid combinations. However, steroids are associated with serious ocular side effects of raised intraocular pressure, cataract, and microbial keratitis.

The first-line treatment for allergy is a combined antihistamine/mast-cell stabilizer to provide symptom relief. These agents have a rapid onset and long duration of action, and excellent safety and tolerability profiles.

Table 2. Points to note during history taking and clinical examination (slit-lamp biomicroscopy) for the differential diagnosis of red eye.

History	Clinical evaluation
Unilateral or bilateral	Localized or diffuse redness
Duration and nature of symptoms	Nature of discharge, if present
Discharge	Corneal clarity and thickness
Itching	Limbus
Foreign body sensation	Eyelids
Contact lens wear	Anterior chamber
Systemic illness	Pupils
Medication use	Posterior pole and optic nerve
Recent trauma or injury	

Table 3. Diagnostic clues.

- If the eyes itch — think of allergy
- If the eyes burn — think of dry eye
- If the eyes have purulent discharge — think of bacterial conjunctivitis

"Steroids are associated with serious ocular side effects of raised intraocular pressure, cataract, and microbial keratitis"

Clinical Examination

A critical component of the diagnosis of red eye is to distinguish between papillary and follicular conjunctivitis. Dr Chan recommended checking for follicular or papillary reaction, vesicles, meibomian gland orifices, and blepharitis on the lid margin. The cul-de-sac should be checked for pseudomembrane, scarring of the conjunctiva, or foreshortening of the fornix. Evaluation of the limbus will show neovascularization, marginal infiltrates, or Trantas' dots.

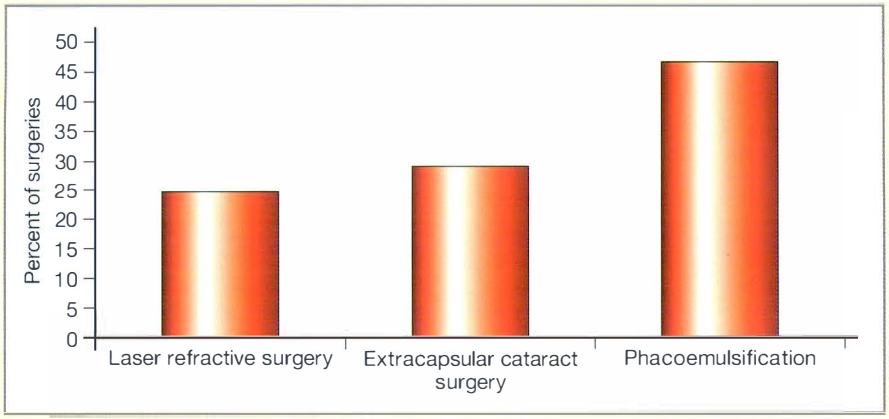
If discharge is present, the type may be a useful diagnostic indicator, for example, thick, stringy, ropey, or watery; plentiful or minimal; and clear or purulent. Some symptoms are more specific to a condition than are others, for example, purulent discharge is usually associated with bacterial conjunctivitis, itching with allergy, and burning with dry eye (Table 3).

Surgical Infections

All surgical procedures carry a risk for infection. The possibility and rate of infection of the ocular and intraocular structures depends on several factors:

- existing flora on the ocular surface and adjacent structures
- contamination of instruments, and other materials used during surgery
- level of virulence and contaminating load of the organism

Figure 1. Tissue contamination after laser refractive surgery and cataract surgery.



- patient factors of resistance and tissue clearance.

Tissue Contamination

Dr Espiritu described a recent study of 700 conjunctival smears, in which 76.6% were culture-positive — 69.4% were single species and 30.6% were multiple species. The majority of the organisms (41%) were gram-positive strains.

After laser refractive surgery, corneal interface contamination can be as high as 24.5% (Figure 1), with the most common organism being *Staphylococcus epidermidis* (87.7%). Anterior chamber contamination can occur with both extracapsular cataract surgery (up to 29%) and phacoemulsification (up to 46.5%) despite meticulous antiseptic techniques (Figure 1). The predominant organisms are coagulase-negative *Staphylococcus* spp and *Pseudomonas acnes*. Whether this contamination becomes an infection depends on the presence of opportunistic organisms and altered host defenses.

A survey of post-LASIK keratitis found that there was an increase in infections from 2001 to 2004 and a shift in the predominant organisms. Although gram-positive organisms increased, there was a decrease in atypical mycobacteria from 48% to 5%, possibly due to increased use of fourth-generation fluoroquinolones that cover for atypical mycobacteria.

Most isolates are introduced into the eye from the patient's conjunctival flora or from contamination of equipment. Table 4 shows the post-surgery endophthalmitis rates from various studies. Interestingly, clear corneal incisions increase the likelihood of endophthalmitis by 6- to 7-fold; this is likely to be related to postoperative hypotony and wound architecture/seal integrity.

Table 4. Post-surgical endophthalmitis rates.

Surgery	Infection rate (%)*
Cataract	0.07, 0.12, 0.34
Penetrating keratoplasty	0.11, 0.18
Secondary intraocular lens implantation	0.30, 0.37
Filtering surgery	0.06, 0.20
Pars plana vitrectomy	0.03, 0.07

* Rates given for more than 1 study.

Reducing the Risk

Dr Espiritu explained that reducing the risk of postoperative infection involves patient and operating theatre factors, antimicrobial prophylaxis, and surgical technique (Table 5).

Fourth-generation fluoroquinolones such as moxifloxacin (Vigamox) are the most appropriate class of antibiotics, and have sufficient broad-spectrum activity for use when local data on susceptibility patterns are not available. Surgeons should always consider an antibiotic with a broad spectrum of activity and good penetration.

Corneal Infections

Corneal infection is usually treated with highly effective antibiotics, of which the fourth-generation fluoroquinolones such as moxifloxacin are the most powerful class available. However, some corneal infections remain difficult to treat. Prof Tan described the recent experience of the Singapore National Eye Center (SNEC) in Singapore.

In 2006, there was an outbreak of *Fusarium* keratitis, associated with contact lens solution. In 2007, there was an outbreak of acanthameba keratitis, also associated with contact lens solution. A third emerging infectious keratitis, microsporidial kerato-conjunctivitis, was also observed in 2007.

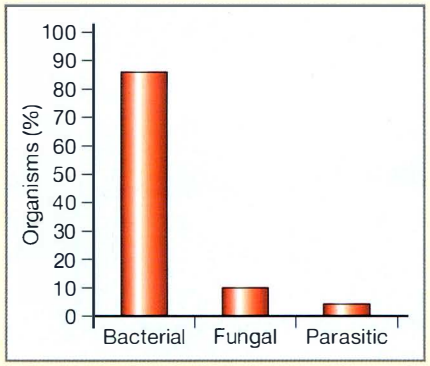
Fusarium *Keratitis*

Fusarium keratitis is always present at a baseline level, but during the 2006 outbreak, an unprecedented 13 cases linked to the same contact lens solution were noted at the SNEC during 1 week. In all, 68 culture-proven cases were detected during a 15-month period. In Singapore, natamycin was initially used

Table 5. Reducing the risk of postoperative infection.

Factor	Action
Patient	Treating all sources of infection preoperatively
	Effective preoperative, intraoperative, and postoperative antimicrobial prophylaxis
Operating theatre	Personnel asepsis, facility disinfection, instrument sterilization
	Surgical field asepsis, povidone iodine, draping
	Contamination-free disposables and consumables
Antimicrobial prophylaxis	Effective — bactericidal, broad-spectrum, high potency, no or minimal resistance
	Excellent bioavailability — high concentrations in target tissues
	Excellent biocompatibility — no or minimal toxicity
Surgical technique	Minimal manipulation and trauma to tissues
	Use of technology such as intraocular lens injection systems
	Good wound seal or tissue barrier, careful construction and solid architecture
Surgical team attitude	Patient-oriented, uncompromising, high-quality standards
	High index of suspicion and aggressiveness

Figure 2. Organisms cultured from microbial keratitis in Singapore.



for treatment, although fourth-generation fluoroquinolones were found to be effective in a similar outbreak in the USA.

Further investigation into *Fusarium* keratitis at the SNEC showed an increasing rate of microbial keratitis, from 79 cases in 1996 to 215 cases in 2006. Most of the organisms cultured were bacterial, but 15% were fungal or parasitic (Figure 2). The primary bacteria isolated were *P aeruginosa*, *S epidermidis*, and *S aureus*. Fourth-generation fluoroquinolones are active against these organisms, and may be given as first-line therapy for bacterial infectious keratitis.

"Fourth-generation fluoroquinolones may be given as first-line therapy for bacterial infectious keratitis"

Microsporidial Keratoconjunctivitis

More recently, an increase in parasitic keratitis has been emerging in Singapore. Microsporidial keratoconjunctivitis is a relatively new condition, first appearing in the mid-1990s. In Singapore, 1 case was recorded in 1999, increasing to 55 cases in 2007.

Microsporidial keratoconjunctivitis is generally mild and self-limiting, and may be unilateral or asymmetrically bilateral. The condition presents as a granular epithelial keratitis, and is commonly associated with red eye. In its more severe form, microsporidial keratoconjunctivitis presents as secondary uveitis, corneal stromal edema, or infiltrative stromal keratitis. Risk factors include trauma, contact lens wear, and topical steroid use.

Table 6. Treatment options for microsporidial keratoconjunctivitis.

Treatment	Drug
Classical therapy	Topical fumagillin Oral albendazole
Other therapies advocated	Fourth-generation fluoroquinolones — moxifloxacin Clindamycin Itraconazole Atovaquine Thalidomide
Possible role	Topical steroids in later stages

The current treatment options include classical therapies such as topical fumagillin or oral albendazole (Table 6). Other treatment options include fourth-generation fluoroquinolones such as moxifloxacin, and there may be a role for topical steroids in the later stages of the disease. Close interaction between clinicians, health care regulators, and the pharmaceutical industry is important to identify and treat these outbreaks of infection.

Fluoroquinolone Resistance

Early-generation fluoroquinolones target topoisomerase (gram-positive organisms) or DNA-gyrase (gram-negative organisms). However, fourth-generation fluoroquinolones act on both proteins in gram-positive organisms, thereby enhancing their activity.

Activity

Compared with ciprofloxacin and other second-generation fluoroquinolones, the fourth-generation fluoroquinolones are 8 to 16 times more active in vitro against many gram-positive organisms, including *Staphylococcus* spp and *Streptococcus* spp, and have similar activity against most gram-negative organisms. While moxifloxacin has less in vitro activity against *P aeruginosa* compared with ciprofloxacin, its increased penetration into the corneal tissues more than compensates for the reduced activity in vitro.

Resistance

Numerous studies have shown an increase in fluoroquinolone resistance of respiratory pathogens during the past 2 decades. However, there has not been a similar rise in fluoroquinolone resistance among community-acquired ocular isolates, except for outbreaks of methicillin-resistant *S aureus*. Dr Stroman described a study of otic infections that has shown no change in fluoroquinolone resistance of *P aeruginosa* between 2001 and 2006, despite the widespread use of topical fluoroquinolones. Fluoroquinolone resistance is driven by systemic use of antibiotics, rather than by acute short-term topical ophthalmic agents for localized infections.

In vitro testing is performed to identify strains 'resistant' to a particular antibiotic. A 'resistant' strain correlates with clinical failure if that antibiotic is used to treat the infection. However, the resistance definitions are specific for systemic infections and systemic treatment. There is no data correlating 'resistant' strains with clinical failure of topical therapy for ocular infections. Short-term therapy does not change the susceptibility of the pre-therapy pathogen, even in the case of treatment failure.

"The small amount of antibiotic in topical ophthalmic therapy does not contribute to the emergence of resistance"

A 1-week course of systemic moxifloxacin for respiratory infection introduces 2.8 g of the active drug into the body, while a course of topical moxifloxacin introduces only 0.025 g. There is therefore a >100-fold difference in the antibiotic load between

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Vigamox®
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Please see adjacent page for summary of product characteristics.

Vigamox®
(moxifloxacin HCl ophthalmic solution) 0.5% as base

VIGAMOX®(moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

DESCRIPTION: VIGAMOX® (moxifloxacin HCl ophthalmic solution) 0.5% is a sterile topical ophthalmic solution. Moxifloxacin is a fourth-generation fluoroquinolone antibacterial agent active against a broad spectrum of Gram-positive and Gram-negative ocular pathogens, atypical microorganisms and anaerobes.

Contains: Active: Moxifloxacin 0.5% (5 mg/mL); **Preservative:** None. Product is self-preserved. **Inactives:** sodium chloride, boric acid and purified water. May also contain hydrochloric acid/sodium hydroxide to adjust pH. VIGAMOX® Solution is isotonic and formulated at pH 6.8 with an osmolality of approximately 290 mOsm/kg.

CLINICAL PHARMACOLOGY:

Microbiology: Moxifloxacin has in vitro activity against a wide range of Gram-positive and Gram-negative microorganisms. Moxifloxacin inhibits the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. The C8-methoxy moiety of moxifloxacin also lessens the selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety found in older fluoroquinolones. Moxifloxacin's bulky C-7 substituent group interferes with the quinolone efflux pump mechanism of bacteria. In vitro resistance to moxifloxacin develops slowly via multiple-step mutations and occurs at a general frequency between 10-9 to 10-11 for Gram-positive bacteria. Moxifloxacin has been shown to be active in vitro against most strains of the following organisms; however, the clinical significance of these data is unknown.

Gram-positive bacteria:

Arthrobacter species, Bacillus cereus, Bacillus thuringensis, Corynebacterium accolens, Corynebacterium amycolatum, Corynebacterium bovis, Corynebacterium macginleyi, Corynebacterium propinquum, Corynebacterium pseudodiptheriticum, Enterococcus faecalis, Exiguobacterium species, Kocuria kristinae, Kocuria "lindaea", Kocuria rhizophila, Listeria monocytogenes, Microbacterium "harmaniae", Microbacterium "otitidis", Rothia mucilaginosus, Staphylococcus arlettae, Staphylococcus capitis, Staphylococcus caprae, Staphylococcus cohnii, Staphylococcus lugdunensis, Staphylococcus pasteuri, Staphylococcus saprophyticus, Staphylococcus sciuri, Streptococcus agalactiae, Streptococcus "conjunctiviae", Streptococcus cristatus, Streptococcus dysgalactiae, Streptococcus mitis, Streptococcus Groups C, G and F, Streptococcus "oculariS", Streptococcus oralis, Streptococcus parasanguinis, Streptococcus pyogenes, Streptococcus salivarius, Streptococcus sanguis, Streptococcus "schlechii"

Gram-negative bacteria:

Achromobacter xylosoxidans, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter johnsonii, Acinetobacter junii, Acinetobacter lwoffi, Acinetobacter "mumbaiae", Acinetobacter schindleri, Acinetobacter ursingii, Aeromonas caviae, Chryseobacterium indologenes, Chryseobacterium species, Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, Enterobacter cloacae, Enterobacter hormaechei, Escherichia coli, Klebsiella oxytoca, Moraxella osloensis, Morganella morganii, Neisseria gonorrhoeae, Pantoea agglomerans, Proteus mirabilis, Proteus vulgaris, Pseudomonas orzyihabitans, Pseudomonas stutzeri, Serratia liquefaciens, Serratia marcescens, Stenotrophomonas maltophilia

Anaerobic microorganisms:

Clostridium perfringens, Fusobacterium species, Porphyromonas species, Prevotella species, Propionibacterium acnes

Other Organisms:

Atypical Mycobacterium, Chlamydia pneumoniae, Legionella pneumophila, Mycobacterium avium, Mycobacterium marinum, Mycoplasma pneumoniae

Clinical Studies: VIGAMOX® Solution has been studied in patients from newborns to adults, including geriatric patients.

In three randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX® Solution produced clinical cures in 80% to 94% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 85% to 97%. In one of these trials in pediatric patients from birth to one month of age, VIGAMOX® Solution produced clinical cure in 80% of patients with bacterial conjunctivitis. The microbiological success rate for the eradication of the baseline pathogens was 92%.

INDICATIONS AND USAGE: VIGAMOX® Solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Gram-positive bacteria:

Corynebacterium species, Microbacterium species, Micrococcus luteus*, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis*, Staphylococcus warneri*, Streptococcus mitis*, Streptococcus pneumoniae, Streptococcus viridans*

Gram-negative bacteria:

Acinetobacter species, Haemophilus "alconae", Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis*, Pseudomonas aeruginosa**

Other microorganisms:

Chlamydia trachomatis

*Efficacy for this organism was studied in fewer than 10 infections

CONTRAINDICATIONS: VIGAMOX® Solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS: In patients receiving systemically administered quinolones, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS:

General: As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Drug Interactions: While drug-drug interaction studies have not been conducted with VIGAMOX® Solution, they have been performed with the oral product at much higher systemic exposures than are achieved by the topical ocular route. Unlike some other fluoroquinolones, no clinically significant drug-drug interactions between systemically administered moxifloxacin and itraconazole, theophylline, warfarin, digoxin, oral contraceptives, probenicid, ranitidine or glyburide have been observed. In vitro studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Moxifloxacin was not mutagenic in four bacterial strains used in the Ames Salmonella reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity in vivo in a micronucleus test or a dominant lethal test in mice. Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose. Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic following up to 38 weeks of oral dosing at 500 mg/kg/day.

Pregnancy: Teratogenic Effects.

Pregnancy Category C: Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. Since there are no adequate and well-controlled studies in pregnant women VIGAMOX® Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when VIGAMOX® Solution is administered to a nursing mother. **Pediatric Use:** VIGAMOX® Solution has been shown to be safe and effective in pediatric patients including neonates. There is no evidence that the ophthalmic administration of VIGAMOX® Solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS: No serious ophthalmic or systemic adverse reactions related to VIGAMOX® Solution were reported. Adverse reactions were generally mild and occurred at an incidence similar to placebo (vehicle). The most frequently reported event was transient ocular discomfort (burning/stinging) reported at an incidence of 2.9%. Other reported events included headache, keratitis, ocular pain, ocular pruritus, ocular hyperemia, pharyngitis and subconjunctival hemorrhage which were reported at an incidence of 0.5% to 1.0%.

DOSAGE AND ADMINISTRATION: Instill one drop in the affected eye 3 times a day for 4 days.

Rx Only CAUTION: Federal (USA) law prohibits dispensing without prescription.

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Alcon Laboratories, Inc.
Fort Worth, Texas USA

References:

1. Kowalski RP, Yates KA, Romanowski EG, et al. An ophthalmologist's guide to understanding antibiotic susceptibility and minimum inhibitory concentration data. *Ophthalmology*. 2005;112:1987-1991.

2. Wagner RS, Abelson MB, Shapiro A, Torkildsen G. Evaluation of moxifloxacin, ciprofloxacin, gatifloxacin, ofloxacin, and levofloxacin concentrations in human conjunctival tissue. *Arch Ophthalmol*. 2005;123:1282-1283.

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Table 7. Limiting emergence of resistance.

- Appropriate antibiotic use:
  - Acute — not chronic — use
  - Short-term high-dose surgical prophylaxis
- Appropriate dosing schedule
  - Avoid antibiotic tapering
- Newer-generation fluoroquinolones
  - Less likely to select out resistant strains

systemic and topical therapy. Dr Stroman explained that the small amount of antibiotic in topical therapy does not contribute to the emergence of resistance.

Limiting Emergence of Resistance

To limit the emergence of resistance, antibiotic use should be appropriate, the correct dosing schedule adhered to, and appropriate antibiotics selected (Table 7). Topical therapy does not contribute to the emergence of resistance in and around the eye.

Ocular Allergy

Prevalence of Allergic Conjunctivitis

Ocular allergy is a common clinical condition. Patients present with conjunctival redness, associated with mild-to-moderate, occasional and transient, allergy-like symptoms of itching, burning, tearing, and photophobia. Patients exhibit the features of dry eye, but have no evidence of ocular disease.

The International Survey of Asthma and Allergy in Childhood found a clear pattern of increasing prevalence of allergy between 1995 and 2005. The greatest increase was for allergic rhinoconjunctivitis, which increased by approximately 0.3% per year in Asia. Environmental changes were implicated as a likely cause.

While data for allergic eye disease in Asian adults are available, Dr Caparas suggested that further information to better define the prevalence of allergy in the region is needed. Local studies suggest that the prevalence for allergic eye disease ranges from 3% to 27%. There appears to be an increasing prevalence of allergic conjunctivitis with increasing urbanization.

Causes of Increasing Allergy

Several hypotheses for the increase in allergy have been proposed (Table 8). One theory suggests that, by not exposing children to allergen triggers early in life, the T helper–cell response is favored in later life. There is some evidence that global warming and accumulation of carbon dioxide affects the production and distribution of pollen. There is also evidence that free radicals and oxidative stress are related to sustained periods of immune activation, leading to the production of free radicals.

Urban pollution can trigger an allergy-like condition. Immunoglobulin E (IgE) increases with exposure to air pollution, and the symptoms of rhinoconjunctivitis are more prominent in polluted areas of the world. This is particularly pertinent in the larger Asian cities, where diesel-burning vehicle pollution is widespread.

Allergic Response

The allergic response consists of an allergen being taken up by macrophages and presented by the antigen-presenting cell. This leads to a T helper-cell–type reaction, resulting in production of B cells, which become sensitized and produce IgE specific to the allergen. The IgE attaches to mast cells, which become sensitized. When exposed to the allergen, the mast cells destabilize and degranulate, which releases histamine, causing the symptoms of allergy.

Pollution causes a toxic or irritative type of conjunctivitis. There is evidence that diesel particulate matter acts as an adjuvant to the T helper cells to increase the immune response. The mucosal adjuvant hypothesis (Table 8) suggests that airborne pollutants stimulate an immune response by modifying the way that the antigen is presented to the immune system, thereby upregulating the molecules that lead to allergy and inflammation.

In addition, air pollution changes the way that an allergen is presented. Diesel emission particles alter the morphology of an allergen, resulting in reactive oxygen species that produce and intensify the allergic response. At a cellular level, air pollution causes changes in cell proliferation and elaboration of pro-inflammatory cytokines, as well as adaptive phenotypic changes in the conjunctiva.

Acute Allergic Conjunctivitis

Dr Mah explained that the causes of acute allergic conjunctivitis are typically environmental (Table 9), and occur in individuals with a genetic predisposition. The signs and symptoms include itching, redness, chemosis, lid swelling, and tearing. Ocular itching is the key to the diagnosis of allergic conjunctivitis.

Table 8. Causes of increasing allergy.

Hypothesis	Mechanism
Hygiene	Lack of triggers to T helper-type immune response in early life favors T helper-type response in later life
Global warming	Higher pollen production in urban, compared with rural, areas
Free radicals and oxidative stress	Sustained periods of T helper–type immune activation (chronic infection, pollution) lead to production of free radicals, causing oxidative stress to the tissues
Mucosal adjuvant hypothesis	Airborne pollutants function as mucosal adjuvants, stimulating an immune response through interaction with the immune system

Table 9. Types of allergic eye disease.

Category	Condition
Acute allergic conjunctivitis	Seasonal allergic conjunctivitis (hay fever) Perennial allergic conjunctivitis
Chronic allergic conjunctivitis	Vernal keratoconjunctivitis Atopic keratoconjunctivitis Giant papillary conjunctivitis

Then there's PATANOL® relief.

PATANOL® solution offers significantly greater efficacy compared to other anti-allergy eye drops, providing relief from itching, redness, tearing, chemosis, and lid swelling.[1] PATANOL® solution prevents ocular allergies from interfering with your patients' daily activities.[2]

Optimal relief for ocular allergies:
Wouldn't all your patients want that?

References:

1. Rosenwasser LJ, O'Brien T, Weyne J. Mast cell stabilization and anti-histamine effects of olopatadine ophthalmic solution: a review of pre-clinical and clinical research. *Curr Med Res Opin*. 2005;21:1377-1388.
2. Berger W, Abelson M, Gomes P, Beck M, Kimura S, Westbrook T, Storms W, Galant S. Effects of adjuvant therapy with 0.1% olopatadine hydrochloride ophthalmic solution on quality of life in patients with allergic rhinitis using systemic or nasal therapy. *Ann Allergy Asthma Immunol*. 2005;95:361-371.

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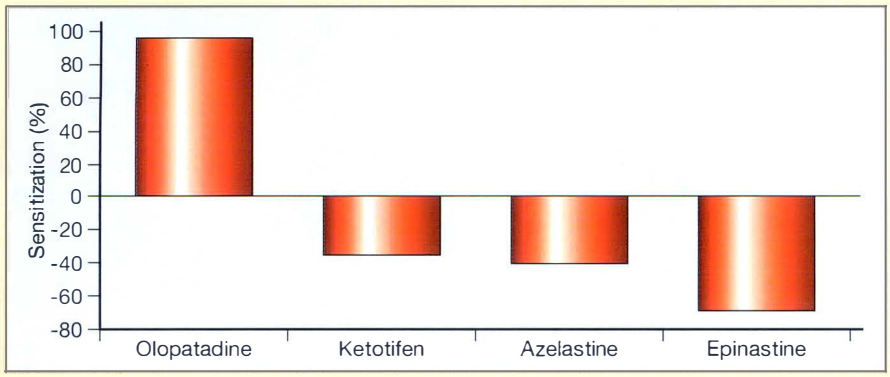
Patanol®
(olopatadine hydrochloride eye drops solution) 0.1%

Advanced solution for allergy eyes

Figure 3. Mast cell stabilization rates of ocular antiallergy therapies.



"Itching is the key to the diagnosis of ocular allergic conjunctivitis"

Perennial allergic conjunctivitis (PAC) is usually milder than seasonal allergic conjunctivitis, but it occurs throughout the year. PAC is associated with exposure to animals, with 70% to 80% of patients being allergic to dust mite feces.

Chronic Allergic Conjunctivitis

Atopic keratoconjunctivitis is a delayed hypersensitivity response. The condition is associated with atopic dermatitis and environmental antigens, it may be perennial, and there is a genetic predisposition. Vernal keratoconjunctivitis (VKC) is a potential cause of visual morbidity. VKC is associated with a genetic predisposition, history of atopy, and non-specific hypersensitivity. Giant papillary conjunctivitis is caused by repeated mechanical irritation, which may be aggravated by concomitant allergy.

Ocular Allergy Treatment Goals

The goals of treatment are to achieve optimum relief from symptoms. H_1-receptors play a significant role in ocular allergy. Therefore, affinity for the H_1-receptor is necessary for any treatment to be effective. Several agents have high affinity for the H_1-receptors, including olopatadine (Patanol), ketotifen, azelastine, and epinastine. However, as antihistaminic drugs do not stabilize mast cells, they do not curtail histamine release. Olopatadine stabilizes mast cells (Figure 3) and has an antihistaminic effect.

"Olopatadine stabilizes mast cells and has an antihistaminic effect."

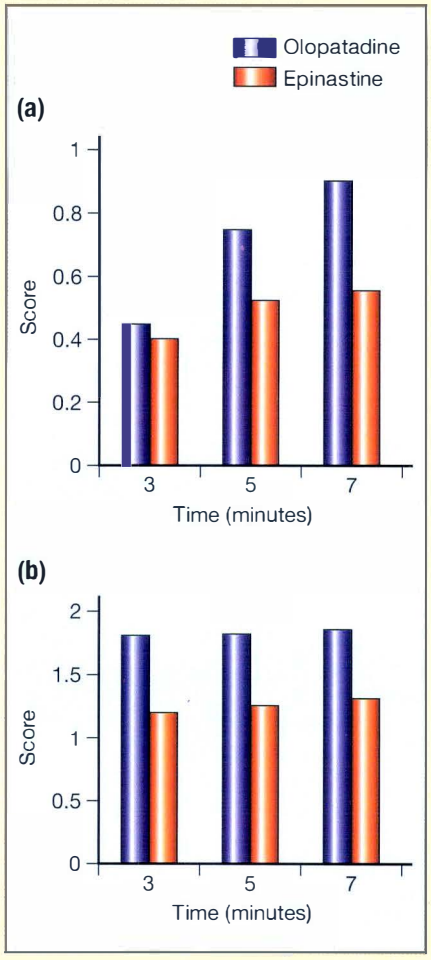
Ocular Allergy/Irritative Conjunctivitis in Urban Environments

- A subset of patients with chronic conjunctivitis do not have atopy or dry eye disorders.
- These individuals have a conjunctival hyper-reactivity to non-allergenic environmental stimuli.
- Airborne pollutants — particularly diesel emission particles — appear to play an important role.
- Recognition of changing patterns of ocular allergy may avoid unnecessary discomfort, especially in the light of advances in allergy-related pharmaceutical research and development.
- The increasing problem of air pollution and rapid growth of motor vehicle owners in the developing world make continued research a priority.

Several comparative studies of olopatadine have been performed to ascertain its efficacy for relief of itching and redness. Compared with ketotifen, olopatadine provided significantly reduced mean itching scores in an antigen challenge study, and patients preferred olopatadine to ketotifen. In an environmental model, more patients achieved significant control of itching and redness with olopatadine than with ketotifen.

Compared with azelastine, olopatadine provided significantly greater relief of itching in an antigen challenge study. Similarly, olopatadine provided significantly greater relief of ocular itching and redness than epinastine in an allergen challenge trial (Figure 4). Significantly more patients using olopatadine achieved complete relief of itching and redness.

Figure 4. Relief of (a) ocular itching; and (b) redness with olopatadine and epinastine.



Olopatadine in Summary

- Approximately 120 million people have ocular allergies in the USA.
- Itching and redness are the most prevalent signs and symptoms.
- The most effective therapy offers both antihistaminic and mast-cell stabilizing activity.
- Olopatadine consistently provides optimal relief of ocular allergies.
- Olopatadine's antihistaminic activity and mast-cell stabilizing properties offer:
  - superior efficacy for treating itching and redness
  - complete relief of allergy symptoms for an optimal number of people.
- Olopatadine solution has been shown to offer patients with ocular allergy the greatest likelihood of freedom from signs and symptoms.

Treatment for Irritative Conjunctivitis

Dr Caparas recommended the use of artificial tears, as they help to flush out the inflammatory mediators and stabilize the tear film, creating a barrier between the conjunctiva and the allergen or environmental pollutants.

In Summary

Itching and redness are the most prevalent signs and symptoms of ocular allergies. The most effective therapy offers both antihistaminic and mast-cell stabilizing activity.

Olopatadine consistently provides optimal relief of ocular allergies. Olopatadine's antihistaminic activity and mast-cell stabilizing properties offer superior efficacy for treating itching and redness, and complete relief of allergy symptoms in an optimal number of people. Olopatadine solution has been shown to offer patients with ocular allergy the greatest likelihood of freedom from signs and symptoms.

Dry Eye

Understanding Dry Eye

Dry eye is a common ocular surface disease. The functions of the ocular surface are to aid normal vision, and to provide comfort and a defensive barrier. The key factors are maintenance of a normal ocular surface and tear film stability.

The lacrimal gland functional unit (LFU) is an integrated system comprising the lacrimal glands, ocular surface and lids, and the sensory and motor nerves that connect them. This system controls the major components of the tear film. Damage or disease to any component of the LFU can destabilize the tear film, and lead to ocular surface disease, expressed as dry eye.

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability, with potential damage to the ocular surface. Dry eye is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

Dry Eye in Asia

The worldwide prevalence of dry eye ranges from 5% to 35%, with an estimated prevalence in Asia of 20.0% to 33.7%. Dr Liu explained that the prevalence may be higher in Asian than in Caucasian populations — more than 100 million people in China are affected — and Asians tend to have a more severe form of dry eye. The risk factors for dry eye are shown in Table 10.

"More than 100 million people in China have dry eye"

Dry eye may be classified as aqueous-deficient or evaporative. In China, dry eye is classified according to the composition and dynamics of the tear film as:

- aqueous deficiency
- lipid deficiency
- mucin deficiency
- abnormal tear dynamics
- combination.

The primary changes affect the tear film; lacrimal glands; ocular surface epithelia, cornea, and conjunctiva; meibomian glands; lacrimal duct system; and immune system. These primary changes are not always detectable by slit-lamp or other clinical examinations. Secondary changes occur on the ocular surface, and tend to be found in patients with more severe disease. These changes can be detected by clinical or laboratory tests. The core mechanisms of dry eye are tear hyperosmolarity and tear film instability (Table 11).

Future Challenges

Prof Liu mentioned that tremendous progress has been made in the understanding and treatment of dry eye, and new findings and information are emerging. However, several challenges to the treatment of dry eye remain.

Table 10. Risk factors for dry eye.

Known risk factors	Possible risk factors*
Low-humidity environments	Ethnic differences
Computer use	Nutrition
Contact lens wear	Environment
Refractive surgery	Genetics
Bone marrow transplantation and cancer	
Menopause and hormone replacement therapy	
Sex hormones	
Essential fatty acids	

* Need more evidence.

Table 11. Basis of dry eye symptoms.

- Tear film break-up during the interblink period
- Sheer-stress between the lids
- Response to reduced tear volume
- Reduced expression of mucins on the ocular surface
- Presence of inflammatory mediators on the ocular surface
- Hypersensitivity of the nociceptive sensory nerves

"Tremendous progress has been made in the understanding and treatment of dry eye"

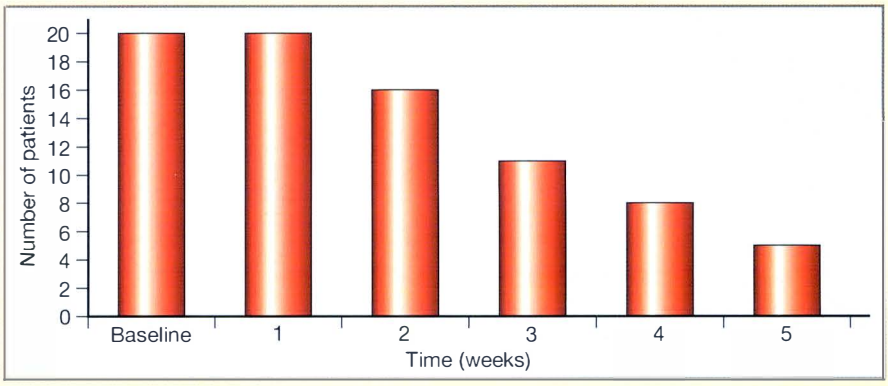
There is no gold standard for the diagnosis and monitoring of the condition, and no single clinical test is able to distinguish between people with and without dry eye. There is no consensus as to which combination of tests should be used to diagnose the disease. There is often a lack of correlation between patients' irritative ocular symptoms and clinical test results. The greatest challenges are how to diagnose mild dry eye and how to treat severe dry eye.

Surgical-related Dry Eye

Dry eye is very common after LASIK surgery. Approximately 15% of patients have dry eye before LASIK rising to 95% post-LASIK, with approximately 60% still experiencing dry eye after 1 month. After surgery, the tear film break-up time is reduced, lipid layer goblet–cell density is decreased, and Schirmer's test is decreased. This is probably because the number of sub-basal and superficial stromal nerves is decreased by 90% after LASIK surgery.

Denervation of the ocular surface leads to decreased corneal sensitivity, resulting in reduced blinking and an increased interblink interval, decreased aqueous tearing, reduced mucin and lipid production, and reduced mitosis. This mechanism leads to an unhealthy ocular surface and symptoms of dry eye.

Figure 5. Patients without dry eye symptoms after stopping Systane treatment.



Therapeutic Approaches

Although exposed damaged cells are constantly replaced, further damage will occur if the cells remain unprotected. An ideal therapy should therefore shield the ocular surface, integrate with the existing tear film, be long-lasting and comfortable, facilitate repair and replacement of damaged cells, maintain the health of the ocular surface, and prevent further damage.

The goals of artificial tears are to lubricate the eye, necessitating a long dwell time in the eye for lasting protection. Systane® lubricating eye drops are frequently used. Systane has a pH of 7.0 as a fluid in the bottle, but this increases to 7.5 to 7.8 when Systane meets the surface of the eye. The HP-guar cross-links with borate to form a soft gel (matrix) with bioadhesive properties, lubricating the eye and prolonging protection of the underlying epithelial cells.

A study to examine the duration of effect of Systane treatment over time enrolled 20 patients who had been successfully treated with Systane. Patients were requested to stop Systane treatment, and undergo standard tests for signs and symptoms at baseline and weekly for 5 weeks thereafter. Patients were free to discontinue the trial and return to Systane treatment at any time.

One week after stopping Systane therapy, all patients remained free of symptoms, and approximately half of the patients remained symptom-free after 3 weeks (Figure 5). The average time to return to Systane treatment was 3.5 weeks.

By the end of the study, the amount of corneal staining was significantly greater than at the start of the study ($p < 0.0001$). After 7 weeks without Systane, a patient survey on the symptoms of dry eye showed that there were significant changes from baseline in symptoms of burning ($p = 0.0004$), dryness ($p < 0.0001$), grittiness ($p = 0.0005$), and redness ($p = 0.0141$).

Dr Theng concluded that the effects of Systane persist for an average of 3.5 weeks after cessation of treatment. Systane is therefore associated with a sustained beneficial affect on the ocular surface. Dr Theng also related his satisfactory experience with Systane post-LASIK.

"Systane is associated with a sustained beneficial affect on the ocular surface"

In Summary

Systane has been shown to increase lubricity, stabilize the tear film, aid rapid ocular surface restoration, and promote rapid ocular surface healing in patients with dry eye symptoms.

Systane for Dry Eye

- Increases lubricity.
- Stabilizes the tear film.
- Aids rapid ocular surface restoration.
- Promotes rapid ocular surface healing.

2008 SEAGIG/ AACGC Joint Congress

Seoul, Korea, 25-27 September 2008

SEAGIG 2008 Seoul, Korea

AACGC

The 5th Congress of the South East Asia Glaucoma Interest Group (SEAGIG 2008) and the 6th Meeting of the Asian Angle-Closure Glaucoma Club (AACGC) will take place in Seoul, Korea, from 25-27 September 2008. SEAGIG was established to facilitate contact between glaucoma specialists in the region, to encourage collaborative research and service projects, to increase the opportunities for exchange of skills and knowledge in this rapidly advancing field, and to assist comprehensive ophthalmological colleagues and other eye care workers (whether medically trained or not) to keep up to date with advances in all aspects of glaucoma diagnosis and management. The aim of the AACGC is to establish a scientific network for Asian glaucomatologists who are interested in exchange of knowledge about angle closure glaucoma.

The conference organising committee plans to introduce an educational and scientific programme that will cover cutting-edge basic and clinical research topics in the field of glaucoma. You are invited to make the scientific programme more dynamic and stimulating by submitting abstracts and registering for the conference.

Symposium Themes

- Normal-Tension Glaucoma
- Glaucoma Screening and Awareness in Asia
- Medical Treatment
- Surgical and Laser Treatment
- Imaging and Diagnosis
- Controversies/Future Trends
- Neuroprotection in Glaucoma
- Angle-Closure Glaucoma

Important Dates

Abstract submission deadline	6 June 2008
Early registration	30 June 2008
Abstract acceptance notice	11 July 2008

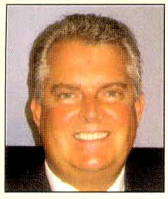
For further details, contact the website at:

www.seagig2008seoul.org

Enquiries should be directed to:

info@seagig-aacgc.org

Dry Eye Disease and Restasis



Steven Wilson
Cole Eye Institute
The Cleveland Clinic Foundation
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Ohio, USA

Dry eye disease is a real condition that needs more than a palliative solution. The condition is a disorder of the tear film caused by tear deficiency or excessive tear evaporation, which can cause damage to the interpalpebral ocular surface. Artificial tears provide transient relief, but they do not treat the underlying inflammation associated with the pathophysiology of dry eye. Restasis® ophthalmic emulsion is the only therapy that has been proven to help patients produce more of their own tears.

Dry eye disease is an inflammatory condition,[1] resulting from activated T cells in the lacrimal glands that subsequently cause ocular surface tissue damage. Diminished tear production and altered tear quality is caused by ocular inflammation associated with keratoconjunctivitis sicca. Restasis contains the immunomodulator cyclosporine and, unlike artificial tears, Restasis is believed to treat inflammation by inhibiting T-cell activation.

The International Task Force Delphi Panel on Dry Eye[2] and the International Dry Eye WorkShop[3] have established guidelines for the treatment of dry eye disease. Both guidelines recommend Restasis as an important part of the treatment of patients with level 2 to level 4 dry eye.

Phase 3 Trials

Pivotal phase 3 clinical trial results show that Restasis:[4]

- increases tear production
- reduces corneal staining
- increases goblet cell density
- reduces reliance on artificial tears.

Fifteen percent of patients using Restasis had improved Schirmer scores of ≥10 mm from a baseline of <5 mm compared with 4% of patients in the control group ($p < 0.001$); 65% to 70% of patients in the Restasis group had an improved Schirmer score of ≥1 mm. Corneal staining improved by 84% for patients using Restasis ($p = 0.005$). Conjunctival biopsy showed decreased T-cell activation after 6 months from baseline; importantly, this effect of Restasis was observed for patients both with and without Sjögren's syndrome (Table 1). Patients treated with Restasis had a 191% increase in goblet cells ($p = 0.13$), while patients treated with the control solution had no significant change from baseline. The reduction in patient reliance on artificial tears was significant between the 2 groups after 6 months ($p < 0.05$ versus vehicle).

Further study by Pflugfelder et al showed that Restasis significantly increased goblet cell density after 12 weeks ($p < 0.001$) compared with baseline and artificial tears.[5]

Diagnosis and Treatment

The Delphi panel criteria for diagnosis and treatment divide dry eye into 4 levels of severity, as follows:[2]

- level 1 may be symptomatic, with slightly increased conjunctival staining, and is usually situational (seasonal or computer-based)
- level 2 is associated with conjunctival staining, punctate corneal staining, and blurred vision
- level 3 is associated with greater symptom severity, significant conjunctival staining, marked punctate corneal staining, including central corneal staining, and filamentary keratitis
- level 4 is associated with severe symptoms, heavy conjunctival staining, which may include scarring, and severe corneal staining.

Treatment for level 1 dry eye is usually artificial tears to manage symptoms (Table 2). Treatment for level 2 disease incorporates preservative-free artificial tears, gels and ointments at night, and Restasis to treat the underlying cause of the disease. The treatment options for level 3 disease include Restasis

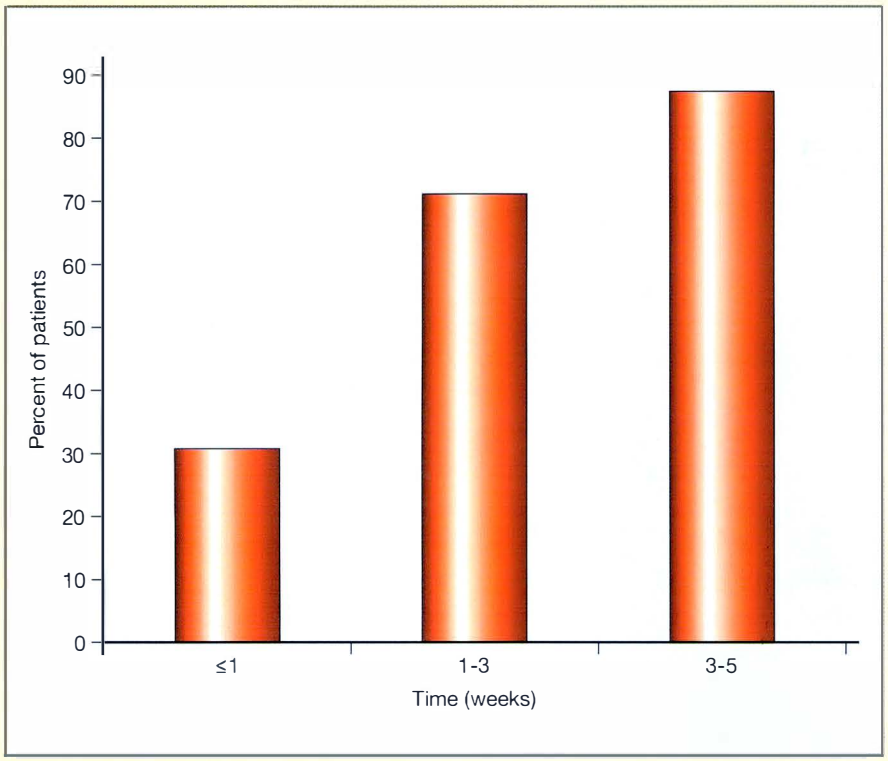
Table 1. Effect of Restasis on CD3-stained T lymphocytes in the conjunctiva.

	CD3-stained T lymphocytes (cells/mm²)	
	Sjögren's syndrome	Non-Sjögren's syndrome
Baseline	3965	2291
6 months	819	762

Table 2. Delphi panel criteria for diagnosis and treatment of dry eye.

Disease severity	Diagnostic criteria	Treatment
Level 1	May be symptomatic Slightly increased conjunctival staining Usually situational (seasonal or computer-based)	Artificial tears to manage symptoms
Level 2	Conjunctival staining Punctate corneal staining Blurred vision	Preservative-free artificial tears Gels and ointments at night Restasis to treat the underlying cause of the disease
Level 3	Increased symptom severity Substantial conjunctival staining Marked punctate corneal staining, including central corneal staining Filamentary keratitis	Restasis to treat the underlying cause of the disease Topical short-term corticosteroids Anti-inflammatory agents Punctal occlusion
Level 4	Severe symptoms Heavy conjunctival staining, which may include scarring Severe corneal staining	Moisture goggles Tarsorrhaphy Serum-based therapies

Figure 1. Patients' perceptions of the benefits of Restasis.



and topical short-term corticosteroids; if patients do not respond, anti-inflammatory agents may be added, and punctal plugs may be inserted. Patients with level 4 disease do not always respond well to treatment, so early treatment to avoid progression is important. Treatment options include moisture goggles, tarsorrhaphy, and serum-based therapies. Restasis is used to greatest effect for patients with levels 2 and 3 disease.

Patient Satisfaction

A study of 14,927 patients with dry eye who were treated with Restasis assessed their perception of therapy. Thirty one percent of patients experienced a benefit within 1 week of starting treatment, 71% reported a benefit within 3 weeks and 87% noted a benefit within 5 weeks (Figure 1). In terms of patient satisfaction, 78% would recommend Restasis, and 75% and 19% of patients would or may continue to use the treatment, respectively.

To manage patients' expectations during treatment, many patients will experience a benefit during the first month. However, approximately 30% to 40% of patients will require longer term treatment (≥1 month) before they experience a substantial benefit. Therefore, a 6-month course of treatment is recommended to ensure that the full benefit is experienced.

Safety Profile

Restasis has a favourable safety profile. The safety parameters monitored include adverse events, blood chemistry, intraocular pressure, visual acuity, biomicroscopy, conjunctival microscopy, conjunctival microbiology, and cyclosporine blood levels. Some patients notice stinging on instillation of Restasis, but this usually occurs in patients with more severe disease and stops after a few weeks of treatment.

Dosing Regimen

Restasis should be used regularly rather than on an 'as needed' basis. The recommended dosing regimen is 1 drop in each eye every 12 hours. If artificial tears are used concomitantly, a gap of 15 minutes should be left between instillations. Similarly, if contact lenses are worn, a gap of 15 minutes should be left between administration of Restasis and insertion of the lenses.

Response to Early Treatment

Early treatment of dry eye disease is important, as patients have a better response to Restasis if they have moderate disease.[6] Restasis may therefore be started for any patient with level 2 or greater disease.

The patients' response should be the determining factor for stopping treatment. Most patients will experience a return of the signs and symptoms at some stage after stopping treatment, but a subgroup of patients will experience complete resolution of all signs and symptoms after discontinuing long-term treatment (6 to 12 months). This finding suggests that Restasis can halt the progression of the disease, although monitoring for recurrence is recommended. Further study is indicated to ascertain this long-term beneficial effect of Restasis.

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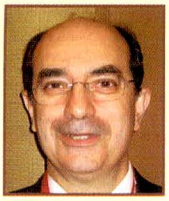
ALLERGAN

Dry Eye in Clinical Practice



Minas Coroneo
The University of New South Wales
Sydney
Australia

Treatment in 1949

In 1949, Shipton and D'Ombrain published a case report of a 56-year-old woman who presented with poor vision in artificial light and continuous ocular irritation.[1] D'Ombrain suspected Sjögren's syndrome and applied a litmus paper test, which resulted in 1 mm of the paper being wet after 5 minutes. The patient was prescribed artificial tears to treat the symptoms of dry eye.

Despite this report, the concept of dry eye affecting vision has only recently generated interest. However, Ishida et al have shown that functional visual acuity is significantly lower in patients with dry eye than in control patients, and that visual acuity improves significantly after punctal occlusion.[2]

Shipton and D'Ombrain found that their patient's mouth was dry and her tongue was bright red, suggesting inflammation of the mucosal surface.[1] Other symptoms of dryness included thin brittle fingernails, dry hair, and absence of sweat, suggestive of Sjögren's syndrome. The authors then referred to possible inheritance of Sjögren's syndrome. Interestingly, Sjögren's syndrome has since been found to be associated with an abnormality in interferon regulatory factor-5.[3]

Shipton and D'Ombrain prescribed vitamin B in tablet form, Vegemite (a yeast extract that is rich in vitamin B), and campolon (a crude extract from the fresh liver of Antarctic whales that is rich in omega 3 fatty acids).[1] In effect, Shipton and D'Ombrain were prescribing modern treatment for dry eye.

Multivitamins have been shown to increase tear film stability in patients with dry eye.[4] Polyunsaturated fatty acids such as fish and flaxseed oils have anti-inflammatory effects. A high dietary intake of n-3 fatty acids is associated with a decreased incidence of dry eye among women.[5]

Shipton and D'Ombrain also noted that their patient was depressed. Today, it is known that dry eye has a negative impact on quality of life. When compared with other disease states such as angina, the impact on quality of life of moderate dry eye is comparable to that of moderate angina (Figure 2).[6]

Treatment in 2008

In 2007, a 30-year-old woman presented with a 4-year history of sore red eyes. She worked in an air-conditioned office and regularly used a computer. She was otherwise in good health and did not smoke. Her visual acuity was 6/9 in both eyes, with no significant refraction error. She had a rapid tear film break-up time, mild inferior punctate staining, and blepharitis.

Various treatment approaches were tried, including preservative-free lubricants, autologous serum, lid scrubs, doxycycline 50 mg daily, slow-release fish oil supplementation, testosterone cream 1%, Restasis, and punctal occlusion. The patient slowly improved with Restasis over 6 months, and punctal plugs were inserted.

The patient's visual acuity increased to 6/6 in both eyes after treatment with Restasis, and her Ocular Surface Disease Index scores improved.

Treatment Advances

Improvements in the management of dry eye between 1949 and 2008 include the development of preservative-free lubricants, treatment for blepharitis and rosacea, systemic

Figure 2. Quality of life trade-off scores for dry eye and angina.

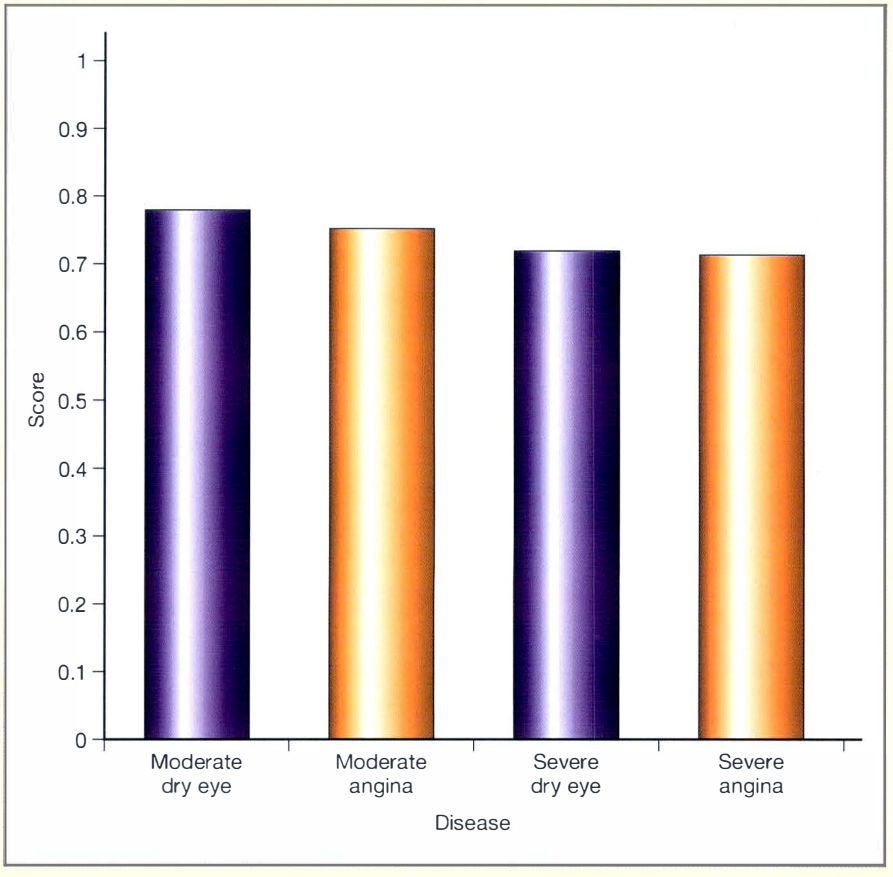
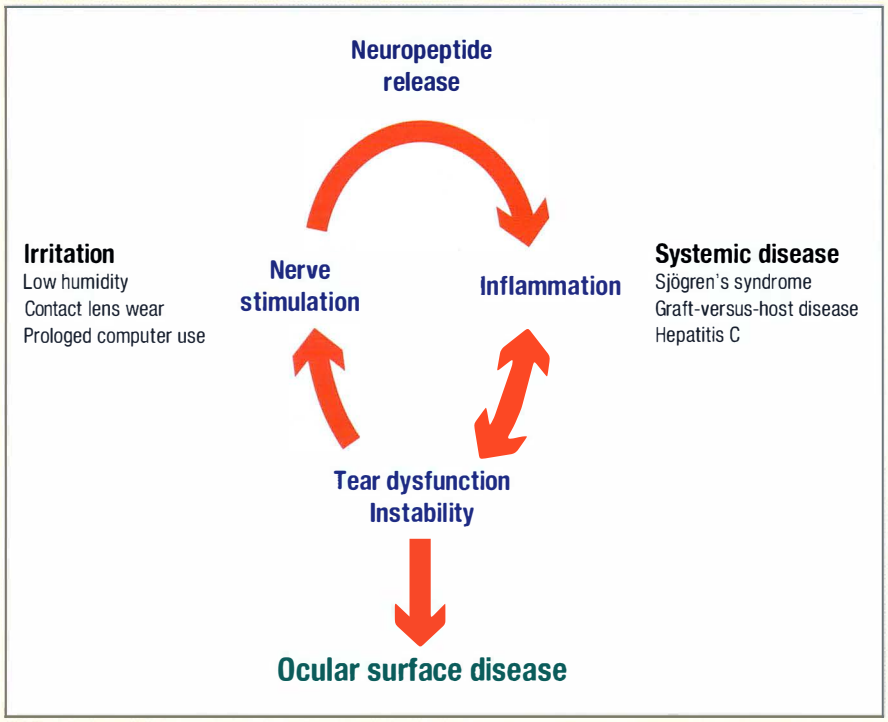


Figure 3. Dry eye cycle of inflammation.



evaluation (immune, endocrine, and cardiac systems), punctal occlusion, autologous serum eye drops, and cyclosporine.

Clinical Pearls

Compliance with treatment is an important issue for resolution of symptoms. In a practice setting, there is an association between patient-reported compliance with medication and more rapid onset of the effects of increased tear production.[7] Barriers to compliance include prolonged treatment duration and cost.

Inflammation in dry eye disease is not simply 'red eye' but a condition of altered tear film composition. Many factors play a role in inflammation (Figure 3), which can result in a vicious cycle of nerve stimulation, inflammation, and tear dysfunction or instability.

Signs of dry eye do not always correlate with symptoms,[8] and both signs and symptoms can fluctuate. Corneal sensation can be affected by innervation damage due to ocular surface disease[9] or altered corneal epithelial barrier function.[10] Neuropathic pain may be present and some patients respond well to antidepressant medication.

Punctal occlusion is associated with complications of watery eye, inflammation, infection, pyogenic granuloma, and extrusion. However, for patients with refractory dry eye, the combined effects of punctal occlusion and Restasis may be additive. Restasis appears to promote the long-term health of the ocular surface, while punctal occlusion increases wetness initially.[11]

Restasis has been used as treatment for a range of conditions other than dry eye, including atopic allergy and vernal keratoconjunctivitis, corneal allograft rejection, contact lens–induced dry eye, blepharitis and ocular rosacea, LASIK-associated dry eye, and graft-versus-host disease.[12] Interestingly, there is a 2-fold increased risk for dry eye among patients with pterygium, but cyclosporine is effective for treating pterygium-induced ocular surface disease.

In Summary

The 2 major advances that have been made since 1949 are the recognition of the critical role of ocular surface inflammation in dysfunctional tear syndrome and its management with Restasis, which has improved quality of life for many patients.

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From the Allergan satellite symposium **Inflammation and Dry Eye** *held at the Asia Cornea Society meeting, Singapore, 13 March 2008.*

2008 SEAGIG/ AACGC Joint Congress

Seoul, Korea, 25-27 September 2008

SEAGIG 2008 Seoul, Korea

AACGC

The 5th Congress of the South East Asia Glaucoma Interest Group (SEAGIG 2008) and the 6th Meeting of the Asian Angle-Closure Glaucoma Club (AACGC) will take place in Seoul, Korea, from 25-27 September 2008. SEAGIG was established to facilitate contact between glaucoma specialists in the region, to encourage collaborative research and service projects, to increase the opportunities for exchange of skills and knowledge in this rapidly advancing field, and to assist comprehensive ophthalmological colleagues and other eye care workers (whether medically trained or not) to keep up to date with advances in all aspects of glaucoma diagnosis and management. The aim of the AACGC is to establish a scientific network for Asian glaucomatologists who are interested in exchange of knowledge about angle closure glaucoma.

The conference organising committee plans to introduce an educational and scientific programme that will cover cutting-edge basic and clinical research topics in the field of glaucoma. You are invited to make the scientific programme more dynamic and stimulating by submitting abstracts and registering for the conference.

Symposium Themes

- Normal-Tension Glaucoma
- Glaucoma Screening and Awareness in Asia
- Medical Treatment
- Surgical and Laser Treatment
- Imaging and Diagnosis
- Controversies/Future Trends
- Neuroprotection in Glaucoma
- Angle-Closure Glaucoma

Important Dates

Abstract submission deadline	6 June 2008
Early registration	30 June 2008
Abstract acceptance notice	11 July 2008

For further details, contact the website at:

www.seagig2008seoul.org

Enquiries should be directed to:

info@seagig-aacgc.org

SEPTEMBER 2008

4-6
IXth Bienial Conference of SAARC Academy of Ophthalmology
New Delhi, India
Contact: Dr Namrata Sharma
Tel: (91 1) 126 953 144
Fax: (91 1) 126 588 919
E-mail: sao2008@gmail.com

26-28
Ophthalmic Anesthesia Society (OAS) 22nd Annual Meeting
Chicago, Ilinois, USA
Contact: Karen S Morgan
Tel: (1 805) 534 0300
Fax: (1 805) 534 9030
E-mail: info@eyeanesthesia.org

OCTOBER 2008

16-19
Laser Congress Korea 2008
Seoul, Korea
Contact: Joung OK Lee
Tel: (82 25) 113 713
Fax: (82 25) 173 713
E-mail: khg000@unitel.co.kr

18-19
Glaucoma Meeting Basel 2008 — 'Glaucoma Therapy: State of the Art'
Basel, Switzerland
Contact: Daniela Hauenstein
Tel: (41 612) 658 718
Fax: (41 612) 658 652
E-mail: info@glaucoma-meeting.ch

18-20
Annual Conference of Strabismological Society of India
New Delhi, India
Contact: Dr Subhash Dadeya
Tel: (91 11 2323 4622, ext 292
Fax: (91 11) 2323 5574
E-mail: dadeyassi@gmail.com/dadeya86@hotmail.com

NOVEMBER 2008

15-16
Hong Kong Academy of Medicine 15th Anniversary Congress
Hong Kong
Contact: Justin Ng/Daniel Chok
Tel: (852) 2871 8896/(852) 2871 8815
Fax: (852) 2871 8898
E-mail: hkam15@hkam.org.hk

Note to Readers
This section is intended to highlight activities of interest to glaucoma specialists and ophthalmologists in Asia. Please let us know of any forthcoming activities that you may be organising or wish to feature on this section.

1. NAME OF THE MEDICINAL PRODUCT

DUOTRAV™

40 micrograms + 5 mg/ml eye drops solution (travoprost/timolol)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate). For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (see Section 5.1).

4.2 Posology and method of administration

Use in adults, including the elderly

The dose is one drop of DuoTrav™ eye drops, solution in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. It should be administered at the same time each day. Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions. If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart (see section 4.5).

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

When substituting another ophthalmic antiglaucoma agent with DuoTrav™, the other agent should be discontinued and DuoTrav™ should be started the following day.

Paediatric patients

The efficacy and safety of DuoTrav™ eye drops, solution in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

Use in hepatic and renal impairment

No studies have been conducted with DuoTrav™ eye drops, solution or with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment. Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment was necessary in these patients.

For ocular use.

The patient should remove the protective overwrap immediately prior to initial use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

4.3 Contraindications

Hypersensitivity to travoprost, timolol, or to any of the excipients. Bronchial asthma, a history of bronchial asthma or severe chronic obstructive pulmonary disease. Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock. Severe allergic rhinitis and bronchial hyperreactivity; corneal dystrophies; hypersensitivity to other beta-blockers.

4.4 Special warnings and precautions for use

Systemic effects

Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta adrenergic blocking agents may occur. Cardiac failure should be adequately controlled before beginning therapy with timolol. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of timolol maleate. Beta adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia. They may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension.

Anaphylactic reactions

While taking beta adrenergic blocking agents, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant therapy

Timolol may interact with other medicinal products (see section 4.5).

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when DuoTrav™ eye drops, solution is given to patients already receiving an oral beta-blocking agent. The use of two local beta adrenergic blocking agents or two local prostaglandins is not recommended.

Ocular effects

Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. The long-term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed. In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported.

Travoprost may gradually change eyelashes in the treated eye(s); these changes were observed in about half of the patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes. The mechanism of eyelash changes and their long term consequences are currently unknown.

Travoprost has been shown to cause slight enlargement of the palpebral fissure in studies in the monkey. However, this effect was not observed during the clinical trials and is considered to be species specific. There is no experience of DuoTrav™ eye drops, solution in inflammatory ocular conditions; nor in neovascular, angle-closure, narrow-angle or congenital glaucoma and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma.

Caution is recommended when using DuoTrav™ in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema. In patients with known predisposing risk factors for iritis/uveitis, DuoTrav™ can be used with caution.

DuoTrav™ contains benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to application of DuoTrav™ and wait 15 minutes after instillation of the dose before reinsertion. DuoTrav™ contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers, guanethidine or beta-blocking agents, antiarrhythmics, digitalis glycosides or parasympathomimetics. The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers. Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

4.6 Pregnancy and lactation

Women of childbearing potential/contraception

DuoTrav™ eye drops, solution must not be used in women who may become pregnant unless adequate contraceptive measures are in place (see section 5.3).

Pregnancy

There are no adequate data from the use of travoprost in eye drops in pregnant women. Animal studies with travoprost have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Well controlled epidemiological studies with systemic use of beta-blockers did not indicate malformative effects, but some pharmacological effects such as bradycardia have been observed in foetuses or neonates. Data on a limited number of exposed pregnancies indicate no adverse effects of timolol in eye drops on pregnancy or on the health of the foetus/newborn child but bradycardia and arrhythmia have been reported in one case in the foetus of a woman treated with timolol eye drops. To date, no other relevant epidemiological data are available.

DuoTrav™ eye drops, solution should not be used during pregnancy unless clearly necessary.

Lactation

It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. Timolol is excreted in breast milk. However, at therapeutic doses of timolol in eye drops the calculated dose of timolol for the infant would be too low to produce clinical beta-blockade. The use of DuoTrav™ eye drops, solution by breast-feeding women is not recommended.

4.7 Effects on ability to drive and use machines

As with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

In clinical studies involving 721 patients, DuoTrav™ eye drops, solution was administered once-daily. No serious ophthalmic or systemic undesirable effects related to DuoTrav™ were reported. The most frequently reported treatment-related undesirable effect was ocular hyperaemia (15.0%). Almost all patients (98%) who experienced ocular hyperaemia did not discontinue therapy as a result of this event.

The following undesirable effects were assessed to be treatment-related and are classified according to the following convention:

very common (≥ 1/10), common (> 1/100 to < 1/10), uncommon (> 1/1000 to ≤ 1/100), rare (> 1/10,000 to ≤ 1/1000), or very rare (≤ 1/10,000). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness.

Psychiatric disorders: *Common:* nervousness

Nervous system disorders: *Common:* dizziness, headache

Eye disorders: *Very common:* eye irritation, ocular hyperaemia – *Common:* punctate keratitis, anterior chamber cells, anterior chamber flare, eye pain, photophobia, eye swelling, conjunctival haemorrhage, corneal staining, ocular discomfort, abnormal sensation in eye, visual acuity reduced, visual disturbance, vision blurred, dry eye, eye pruritus, conjunctivitis allergic, lacrimation increased, eyelid irritation, erythema of eyelid, dermatitis eyelid, asthenopia, growth of eyelashes – *Uncommon:* eyelid pain, eye allergy, conjunctival oedema, blepharitis, eyelid oedema, eyelids pruritus

Vascular disorders: *Common:* heart rate irregular, blood pressure increased, heart rate decreased, blood pressure decreased

Respiratory, thoracic and mediastinal disorders: *Common:* bronchospasm - *Uncommon:* dyspnoea, cough, throat irritation, postnasal drip Hepatobiliary disorders: *Uncommon:* alanine aminotransferase increased, aspartate aminotransferase increased

Skin and subcutaneous tissue disorders: *Common:* urticaria, skin hyperpigmentation (periocular) -*Uncommon:* dermatitis cotact

Musculoskeletal, connective tissue, and bone disorders: *Common:* pain in extremity

Renal and urinary disorders: *Uncommon:* chromaturia

General disorders and administration site conditions: *Uncommon:* thirst

Travoprost: Additional undesirable treatment-related effects reported in clinical trials with concomitant therapy (travoprost and timolol) or with monotherapy with travoprost, or post marketing events reported for travoprost that have not been reported with DuoTrav™ eye drops, solution include the following presented in decreasing order of seriousness within each SOC (bodysystem):

Eye disorders: macular oedema, uveitis, iritis, conjunctival disorder, conjunctivitis, conjunctival follicles, eyelid margin crusting, iris hyperpigmentation

Respiratory, thoracic and mediastinal disorders: asthma

Skin and subcutaneous tissue disorders: skin desquamation

Timolol: Additional undesirable treatment-related effects reported in clinical trials with concomitant therapy (travoprost and timolol) or monotherapy with timolol, or events reported for timolol that have not been reported with DuoTrav™ eye drops, solution include the following presented in decreasing order of seriousness within each SOC (bodysystem):

Metabolism and nutritional disorders: hypoglycaemia

Psychiatric disorders: depression

Nervous system disorders: cerebrovascular accident, cerebral ischaemia, syncope, myasthenia gravis, paresthesia

Eye disorders: corneal disorder, diplopia, conjunctivitis, eyelid ptosis

Cardiac disorders: cardiac arrest, arrhythmia, cardiac failure, atrioventricular block, palpitations

Respiratory, thoracic and mediastinal disorders: respiratory failure, nasal congestion

Gastrointestinal disorders: diarrhoea, nausea

Skin and subcutaneous tissue disorders: rash, alopecia

General disorders and administration site conditions: chest pain, asthenia

4.9 Overdose

If overdose with DuoTrav™ eye drops, solution occurs, treatment should be symptomatic. Timolol does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals – antiglaucoma preparations and miotics – beta-blocking agents – timolol, combinations.

ATC code: S01ED51

Mechanism of action

DuoTrav™ eye drops, solution contains two active substances: travoprost and timolol maleate. These two components lower intraocular pressure by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone. Travoprost, a prostaglandin $F2_{\alpha}$ analogue, is a full agonist which is highly selective and has a high affinity for the prostaglandin FP receptor, and reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in man starts within approximately 2 hours after administration and maximum effect is reached after 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24 hours with a single dose.

Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Secondary pharmacology

Travoprost significantly increased optic nerve head blood flow in rabbits following 7 days of topical ocular administration (1.4 micrograms once-daily).

Pharmacodynamic effects

Clinical effects

In a twelve-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of DuoTrav™ eye drops, solution dosed once-daily in the morning was 8 to 10 mmHg. The non-inferiority of DuoTrav™ as compared to latanoprost 50 micrograms/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all visits. In a three-month, controlled clinical study in patients with open angle glaucoma or ocular hypertension and baseline mean IOP of 27 to 30 mmHg, the mean IOP-lowering effect of DuoTrav™ dosed once-daily in the morning was 9 to 12 mmHg, and was up to 2 mmHg greater than that of travoprost 40 micrograms/ml dosed once-daily in the evening and 2 to 3 mmHg greater than that of timolol 5 mg/ml dosed twice daily. A statistically superior reduction in morning mean IOP (8AM – 24 hours after the last dose of DuoTrav™) was observed compared to travoprost at all visits throughout the study. In two three-month, controlled clinical studies in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 23 to 26 mmHg, the mean IOP-lowering effect of DuoTrav™ dosed once-daily in the morning was 7 to 9 mmHg. Mean IOP reductions were non-inferior, although numerically lower, to those achieved by concomitant therapy with travoprost 40 micrograms/ml dosed once-daily in the evening and timolol 5 mg/ml dosed once-daily in the morning. Inclusion criteria were common across the studies, with the exception of the IOP entry criteria and response to previous IOP therapy. The clinical development of DuoTrav™ included both patients naive and on therapy. Insufficient responsiveness to monotherapy was not an inclusion criterion. Existing data suggest that evening dosing might have some advantages in the mean IOP reduction. Consideration should be given to patient convenience and their likely compliance when recommending morning vs. evening dosing.

5.2 Pharmacokinetic properties

Absorption

Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes rapid ester hydrolysis in the cornea to the active free acid. Following once-daily administration of DuoTrav™ eye drops, solution in healthy subjects (N=15) for 3 days, travoprost free acid was not quantifiable in plasma samples from the majority of subjects (80%) and was not detectable in any samples one hour after dosing. When measurable (≥ 0.01 ng/ml, the assay limit of quantitation), concentrations ranged from 0.011 to 0.020 ng/ml. The mean timolol steady-state Cmax was 0.692 ng/ml and Tmax was approximately 1 hour after once-daily administration of DuoTrav™.

Distribution:

Travoprost free acid can be measured in the aqueous humour during the first few hours in animals and in human plasma only during the first hour after ocular administration of DuoTrav™ eye drops, solution. Timolol can be measured in human aqueous humour after ocular administration of timolol and in plasma for up to hours after ocular administration of DuoTrav™.

Metabolism

Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin $F2_{\alpha}$ which are characterised by reduction of the 13-14 double bond, oxidation of the 15- hydroxyl and β-oxidative cleavages of the upper side chain.

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma t1/2 of timolol is 4 hours after ocular administration of DuoTrav™ eye drops, solution.

Excretion

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Less than 2% of an ocular dose of travoprost was recovered in urine as free acid. Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites.

5.3 Preclinical safety data

In monkeys, administration of DuoTrav™ eye drops, solution twice-daily was shown to induce increased palpebral fissure and to increase iris pigmentation similar that observed with ocular administration of prostanoids.

Travoprost

Topical ocular administration of travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity. Reproduction toxicity studies with travoprost have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered ^{3}H-travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml).

Timolol

Non-clinical data revealed no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (7000 times the clinical dose) and increased foetal resorption in rabbits (14000 times the clinical dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients Benzalkonium chloride, mannitol, trometamol, polyoxy-ethylene hydrogenated castor oil 40 (HCO-40), boric acid, disodium edetate, trometar and/or hydrochloric acid (for pH adjustment), purified water.

6.2 Incompatibilities Not applicable.

6.3 Shelf life 3 years. Discard 4 weeks after first opening.

6.4 Special precautions for storage Store at 2°- 25°C.

6.5 Nature and contents of container 2.5 ml oval bottle with dispensing plug and screw cap, presented in an overwrap.

6.6 Special precautions for disposal No special requirements.

Alcon®
ALCON-COUVREUR
B-2870 Puurs (Belgium)

DUOTRAV™ Solution combines two powerful agents into one single bottle. As they work together, you'll see IOP levels decrease dramatically – up to 12 mm Hg from baseline.[1] Combining this level of efficacy with once-daily dosing enhances patient compliance. Successfully managing glaucoma is now easier than before. **THE RIGHT CHOICE FOR SUCCESS.**

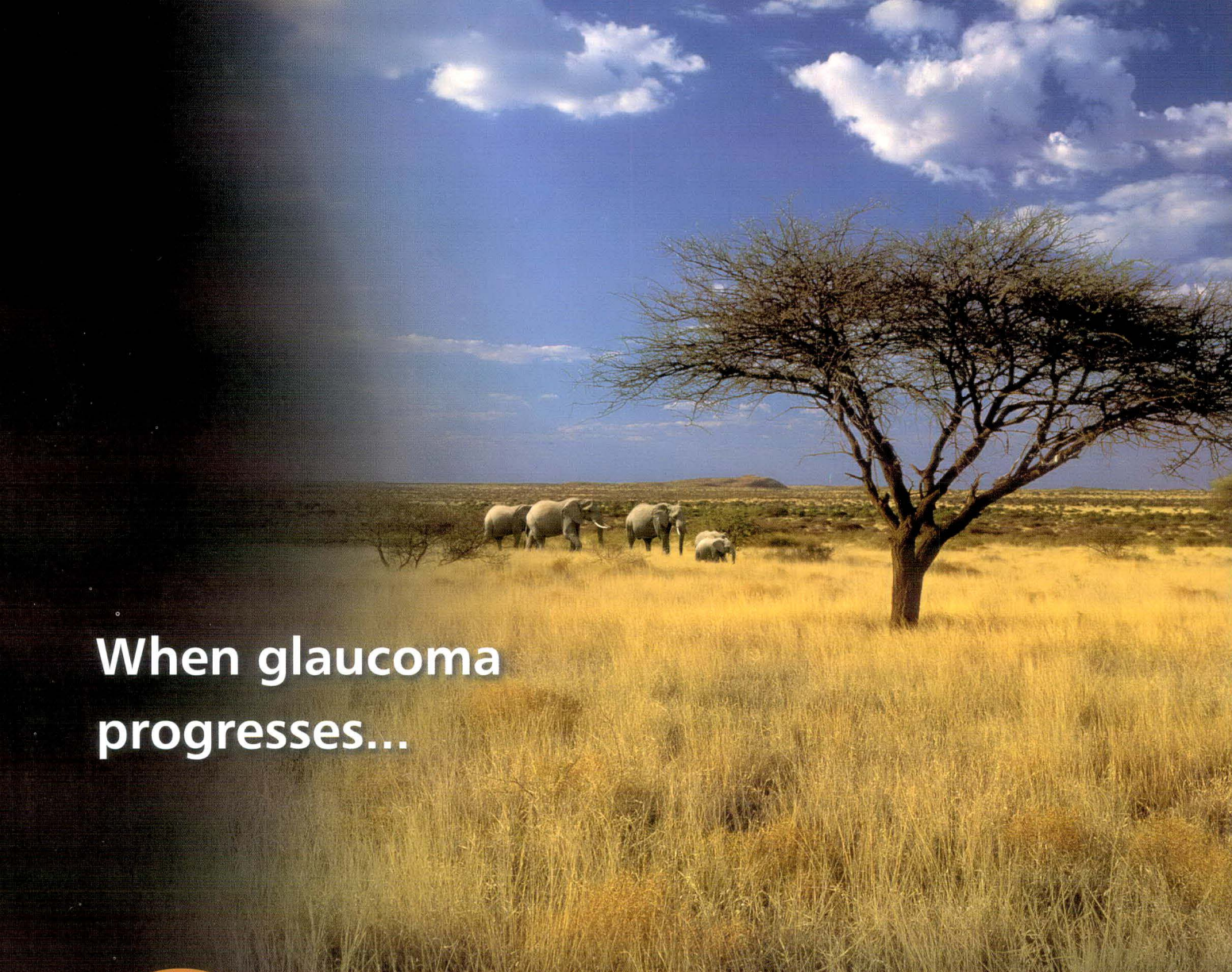
DUOTRAV™
40 micrograms + 5 mg/ml eye drops solution (travoprost;timolol)

Alcon

Please see adjacent page for prescribing information.

Reference:
1. Barnebey HS, Orengo-Nania S, Flowers BE, et al. The safety and efficacy of travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution. *Am J Ophthalmol.* 2005;140:1-7.

DUOTRAV® Solution is indicated for the decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.



When glaucoma progresses...

Xala Control

...Progress to Once Daily Xalacom® latanoprost/timolol maleate for proven efficacy[1-6]

REFERENCES: 1. Larsson L-I, *et al*. The effect on diurnal intraocular pressure of the fixed-combination of latanoprost 0.005% and timolol 0.5% in patients with ocular hypertension. *Acta Ophthalmol Scand*. 2001;79:125–8. 2. Konstas AGP, *et al*. Twenty-four hour control with latanoprost-timolol-fixed combination therapy vs latanoprost therapy.*Arch Ophthalmol*. 2005;123:898–902. 3. Diestelhorst M and Larsson L-I, for the European-Canadian Latanoprost Fixed Combination Study Group. A 12-week, randomized, double-masked, multicenter, study of the fixed combination of latanoprost and timolol in the evening versus the individual components. Ophthalmology. 2006;113:70–6. 4. Shin DH, *et al*. Efficacy and safety of the fixed combinations latanoprost/timolol versus dorzolamide/ timolol in patients with elevated intraocular pressure. Ophthalmology. 2004 Feb;111:276–82. 5. Topouzis F, *et al*. A 1-year study to compare the efficacy and safety of once-daily travoprost 0.004%/ timolol 0.5% to once-daily latanoprost 0.005%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. *Eur J Ophthalmol*. 2007;17:183–90. 6. Martinez A and Sanchez M. A comparison of the safety and intraocular pressure lowering of bimatoprost/timolol fixed combination versus latanoprost/timolol fixed combination in patients with open-angle glaucoma. *Curr Med Res Opin*. 2007;23:1025–32.

In the 6-month registration trials, the most frequent adverse events were eye irritation, including stinging, burning, and itching (12.0%); eye hyperemia (7.4%); corneal disorders (3.0%); conjunctivitis (3.0%); blepharitis (2.5%); eye pain (2.3%); headache (2.3%); and skin rash (1.3%)[1].

Summary of Prescribing Information

Composition: Bottles containing 2.5 ml ophthalmic solution, 1 ml contains 50 mcg of latanoprost and 6.8 mg of timolol maleate equivalent to 5 mg timolol. **Indications:** Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension insufficiently responsive to topical beta blockers and PG analogues **Contraindications:** Reactive airway disease including bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease, sinus bradycardia, second or third-degree atrioventricular block, overt cardiac failure, or cardiogenic shock, known hypersensitivity to latanoprost, timolol maleate, or any other component of the product. **Adverse Reactions:** Adverse events observed in 1% of the patients treated with Xalacom during clinical development were: abnormal vision, blepharitis, cataract, conjunctival disorder, conjunctivitis, corneal disorder, errors of refraction, eye hyperemia, eye irritation, eye pain, increased iris pigmentation, keratitis, photophobia, and vision field defect. Other systemic reactions include infection, sinusitis, and upper respiratory tract infection,diabetes mellitus, hypercholesterolemia, depression, headache, hypertension, hypertrichosis, rash, and skin disorder and arthritis **Warnings and Precautions:** Latanoprost: increased brown pigmentation of iris, reversible eye lid skin darkening. May gradually change eyelashes and vellus hair in the treated eye, heterochromia, and macular edema, including cystoid macular edema. Limited experience in the treatment of inflammatory neovascular or congenital glaucoma. No adequate and well-controlled studies in pregnant women, use with caution in nursing women. Timolol: Monitor patients with severe heart disease for signs of cardiac failure. Aggravation of Prinzmetal's angina, aggravation of peripheral and central circulatory disorders, hypotension, fatal cardiac failure, severe respiratory reactions such as fatal bronchospasm in patients with asthma and bradycardia may occur. Consider gradual withdrawl prior to major surgery. Used with caution in patients with spontaneous hypoglycemia or diabetes, may mask certain signs and symptoms of hyperthyroidism. Patients with h/o atopy/ severe anaphylactic reaction to allergens may be more reactive to repeated challenge with such allergens. May increase muscle weakness in patients with myasthenia gravis/ myasthenic symptoms; choroidal detachment after filtration procedures. Patients should not drive or use machines while on Xalacom. **Dosage:** One drop in the affected eye(s) once daily. Dose should not exceed once daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. Safety and effectiveness not established in children.

Please refer to the SmPC before prescribing Xalacom® (Latanoprost and Timolol maleate)

Pfizer Ophthalmics

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