Challenges in the clinical measurement of ocular surface disease in glaucoma patients

Stephen C Pflugfelder1
Christophe Baudouin2,3

1Ophthalmology-Ocular Surface Center, Baylor College of Medicine, Houston, TX, USA; 2Department of Ophthalmology, Quinze-Vingts Hospital, Paris, France; 3Vision Institute, Paris, France

Abstract: Ocular surface disease (OSD) is common among glaucoma patients. Clinical assessment of OSD can be challenging. This review focuses on some of the limitations relating to both subjective and objective measures of OSD, including dry eye. A survey of the literature was conducted to identify the caveats associated with different methods of assessing OSD. The effect of preservatives on the ocular surface, with respect to glaucoma patients in particular, was also reviewed. Objective methods for assessing ocular surface health and disease include the Schirmer test, tear break-up time, fluorescein turnover, corneal and conjunctival staining, tear osmolarity, and vital dyes. These measures all have limitations in terms of their ability to grade the severity of OSD. Previous studies using the OSD Index showed a mild-to-moderate correlation to dry eye disease severity. Other scoring systems for dry eye have shown a relationship to patient symptom scores or quality of life. Due to the challenges clinicians face concerning both subjective and objective ocular surface health assessments, discerning clinical improvement in ocular surface disease can be a challenge. Further research is needed in order to optimize existing clinical methods and/or identify alternative techniques for assessing OSD in the glaucoma population.

Keywords: dry eye, glaucoma, ocular surface disease, ocular surface disease index, preservatives, tear break-up time

Glaucoma and ocular surface disease (OSD)

Glaucoma is an optic neuropathy that is most often associated with elevated intraocular pressure (IOP). The most widely prescribed therapies are topical ocular drops. Prostaglandin analog (PGA) and beta-blockers are typically the initial medications of choice.1

Animal and human tissue studies have shown that pathologic changes to the ocular surface, conjunctiva, and trabecular meshwork can occur as a result of long-term exposure to preservatives in the topical medication formulation.2 The contribution of the active ingredients to these adverse effects cannot be ruled out. For example, even nonpreserved IOP-lowering medications, such as timolol, can increase the expression of immunoinflammatory markers and cytokines (human leukocyte antigen-DR region [HLA-DR], interleukin [IL]-6, and IL-8) in the conjunctival epithelium of glaucoma patients.3 Glaucoma patients often take multiple IOP-lowering drops in order to adequately control their IOP. Therapeutic regimens with multiple medications can increase patients’ potential exposure to preservatives even further.

Rossi et al investigated the presence of dry eye syndrome in 61 patients with ocular hypertension or glaucoma taking one to three drops of topical IOP-lowering medications
per day and 20 patients not taking medications (control group).4 Dry eye syndrome was defined as concomitant reduced tear break-up time (TBUT) and punctate keratitis. Approximately 40% of those taking two or three drops per day had dry eye syndrome, compared with 11% of those taking one drop per day and 5% of the control group. The OSD Index (OSDI) questionnaire, which will be discussed in more detail later, was used in this study. Moderate-to-severe OSD scores were observed for approximately 30% of glaucoma patients taking two or more drops per day. Because many IOP-lowering medications contain benzalkonium chloride (BAK), patients can be exposed to a considerable “BAK load” over their lifetimes.

Recent studies have examined the prevalence of OSD in glaucoma and ocular hypertensive patients. Leung et al conducted a study on 101 glaucoma patients in order to ascertain the prevalence of OSD.4 A majority of patients (59%) in this study reported symptoms of dry eye (via the OSDI). Schirmer tests showed 61% of the patients had a decrease in tear production. Positive results for corneal and conjunctival lissamine green staining were found in about 22% of the patients. Abnormal tear quality (reduced TBUT) was observed in 78% of patients.

Fechtner and colleagues also measured the prevalence of OSD in 630 patients from ten clinical sites.5 Their study found that 48.4% of the patients had some degree of OSD (mild, moderate, or severe). OSD symptom severity was positively correlated with the number of topical IOP-lowering medications administered. It is evident that the rates of OSD are higher for glaucoma patients treated with two or three medications than with monotherapy. Unfortunately, patients with pre-existing tear dysfunction may be even more susceptible to preservative toxicity.

A large-scale survey of 4107 patients measured the incidence of ocular toxicity caused by preservatives in IOP-lowering medications.7 Eighty-four percent of the patients used preserved eyedrops. All ocular symptoms were more prevalent in the patients who took preserved topical drops compared with those who only received preservative-free medications \( (P < 0.001) \). These symptoms included discomfort upon instillation, foreign body sensation, dry eye sensation, burning-stinging, tearing, and eyelid itching. Patients on preserved eyedrops had a more than twofold increased incidence of ocular signs. As one might expect, the prevalence of ocular signs and symptoms increased with the number of preserved drops in the therapeutic regimen.

Another multicenter epidemiologic survey conducted in Europe compared the prevalence of side effects between preserved and nonpreserved topical beta-blockers for a group of nearly 10,000 patients.3 Ocular side effects such as foreign body sensation, discomfort upon instillation, stinging-burning, and dry eye sensation were significantly more frequent in the preserved eyedrops group \( (P < 0.0001) \). BAK was the most commonly used preservative in topical IOP-lowering formulations at that time.9

A large retrospective analysis of over 20,000 patients found that glaucoma and ocular hypertension patients on a regimen of either latanoprost preserved with BAK or travoprost-Z preserved with SofZia® Preservative System (Alcon Laboratories, Inc, Fort Worth, TX) showed no significant difference in the rates of dry eye, ocular infection, or OSD over a 1-year period. Limitations of this claims-based study are its relatively short duration, lack of randomization, and inability to account for sample or over-the-counter use.10

A large-scale study from Germany, involving 20,506 patients, sought to analyze the links between glaucoma, dry eye, age, medication, and concomitant disease.11 Among individuals with glaucoma, more women than men were reported to develop dry eye (56.9% and 45.7%, respectively). The difference in the frequency of dry eye between men and women became more obvious after age 50 years. Hypertension, diabetes mellitus, and dry mouth, nose, and skin were the most frequent concomitant systemic diseases found in the survey. The incidence of dry eye increased with age, the number of IOP-lowering medications, and the duration of glaucoma.

The relatively high prevalence of OSD among glaucoma patients becomes apparent when one compares these rates to those in the general population. A cross-sectional survey among 25,444 men in the United States found that the prevalence of dry eye disease increased with age from about 3.9% among men aged 50–54 years to 7.7% among those aged 80 years.12 A survey of nearly 40,000 women in the United States reported that 5.7% of women <50 years old suffered from dry eye syndrome, compared with 9.8% of women ≥75 years of age.13 These rates are considerably lower than those previously mentioned for patients on IOP-lowering medications.

**The effect of preservatives on the ocular surface**

OSD and inflammation have long been associated with the chronic use of IOP-lowering medications and especially the preservatives contained in their formulations.7,4,15 A recent review suggested that long-term use of topical eyedrops can induce a host of ocular surface effects such as ocular...
discomfort, conjunctival inflammation, subconjunctival fibrosis, epithelial apoptosis, tear film instability, corneal surface impairment, and the increased risk of failure for glaucoma surgery.15

BAK is the most commonly used preservative in topical ocular medications.9,15,16 BAK has been shown to remain in corneal tissues for an extended period of time. In vivo rabbit studies found that BAK was detectable in the cornea and conjunctival tissues up to 7 days following instillation of a single 30 μL drop.17

BAK is known to disrupt tight junctions in the epithelial layer of the cornea.18 Pauly et al conducted studies with a human reconstituted corneal epithelial model to measure the effect of increasing concentrations (0.001%–0.5%) of BAK for 24 hours on the expression and distribution of the tight junction protein, occludin.19 BAK caused a disappearance of occludin in the superficial layers of the corneal epithelial model that was dose dependent.

The effect of BAK on corneal barrier function has been assessed by measuring the change in transepithelial electric resistance (TER) of rabbit corneas in vivo.20,21 BAK (0.05%) caused an immediate decrease in TER.20 Later experiments using this model system reported dose-dependent decreases in TER upon exposure to concentrations ranging from 0.02%–0.005%.21 These BAK concentrations are comparable to those found in marketed IOP-lowering medications.9,16

Preclinical studies have examined the effect of BAK on the ocular surface. Detrimental effects on human conjunctival cell (Wong–Kilbourne derivative of Chang conjunctiva) viability and membrane integrity were observed upon exposure to PGA formulations containing BAK.22 In addition, apoptosis and necrosis increased upon exposure of the cells to BAK. In another set of experiments, growth arrest and apoptotic cell death occurred in a dose-dependent manner 24–72 hours after exposure.23 Debbsach et al, using this same conjunctival cell line, found that apoptosis occurred at lower concentrations of BAK while necrotic processes were observed at higher concentrations of this agent.24 They also demonstrated the production of reactive oxygen species following exposure of the cells to BAK. Ayaki and Iwasawa reported lower cell viability for human conjunctival, rabbit corneal, and bovine corneal cells exposed to varying dilutions of PGA formulations preserved with BAK.25

Another study showed a decrease in human corneal epithelial cell viability on exposure to a PGA topical formulation containing BAK.26 A dose-dependent decrease in cell survival was observed with treatment of human corneal and conjunctival cells of increasing BAK concentrations.27 Travoprost with 0.015% BAK was shown to have a higher proportion of viable cells compared to its vehicle, however. This cytoprotective effect was reported by Guenoun and colleagues with both travoprost and latanoprost.28 Epstein et al found elevated amounts of the inflammatory mediators such as tumor necrosis factor, C-reactive protein, IL-1, IL-10, and IL-12 in corneal and conjunctival epithelial cells exposed to BAK.29 BAK at 0.25% and 0.5% appeared to cause a loss of goblet cells, increases in corneal thickness, apoptosis, corneal inflammation, and neovascularization in another rat model.30 In addition, Kahook and Noecker reported that once-daily administration of latanoprost with 0.02% BAK caused a loss of corneal goblet cells in a rabbit model.31

The deleterious effects of BAK have been investigated in human clinical trials. Reductions in TBUT were observed both 3 hours and 3 days following dosing with BAK-preserved carteolol.32 Patients who received topical timolol preserved with BAK at 0.01% and 0.04% had lower Schirmer test values, shorter TBUTs, reduced goblet cell densities, and a greater amount of epithelial cell squamous metaplasia when compared with healthy age-matched patients in the control group.33 Arici and colleagues also observed deleterious effects of this preservative on Schirmer and tear break-up tests.34 Another clinical study found that chronic dosing of timolol maleate, preserved with BAK, caused damage to the ocular surface, most notably the mucus layer of the tear film.35

Martone et al evaluated the effects of chronic administration of preserved IOP-lowering medications on the ocular surface.36 Patients were divided into six groups based on their medication regimen. The preserved medication groups showed reductions in Schirmer I scores, esthesiometry, TBUT, superficial corneal epithelial cell density, and the number of subbasal nerves compared to the normal patients and those on preservative-free medications.

Several alternative preservatives have been developed in an attempt to minimize the toxic effects of BAK. Purite is an oxidative preservative that is used in brimonidine topical drops and artificial tears.37 A clinical study with brimonidine-purite 0.15% found that the majority of conjunctival hyperemia and allergic conjunctivitis adverse events were mild.38

Polyquad® (polyquarternium-1) is a polycationic preservative that is contained in formulations of contact lens disinfecting solutions39 and artificial tears.40 Labbe and colleagues showed that Polyquad induced considerably less toxicity than BAK in vivo.41 Polyquad produced similar
to the control for the tear production test, slit-lamp, fluorescein evaluation, and histology.

SofZia, mentioned previously, is a preservation system that is contained in the travoprost topical ophthalmic formulation, Travatan Z. In vitro studies using Chang conjunctival cells showed no significant effect on cellular viability and membrane integrity. No cytotoxicity was observed in cells incubated in travoprost with SofZia. Ayaki and Iwasawa reported that corneal and conjunctival cells exposed to varying dilutions (1x, 2x, and 10x) of travoprost preserved with SofZia (10, 30, and 60 minutes) had the highest viability of any of the PGA formulations tested. This formulation also did not increase apoptosis or necrosis. Lewis and colleagues reported that, during the course of a 3-month study, travoprost 0.004% with SofZia was well tolerated in glaucoma patients. Only one (1/344) patient experienced mild corneal staining. Ocular hyperemia occurred at an incidence of 6.4%. No treatment-related serious adverse events occurred during the study.

Challenges of measuring OSD in glaucoma patients

Objective measures

Clinical methods of assessing physiologic functions that contribute to ongoing ocular surface health as well as disease have been developed over the past decades. Schirmer I (without anesthesia; Schirmer II is performed with anesthesia) consists of placing a filter paper strip on the lower lid margin in the temporal position of an unanesthetized patient. This continues to be a useful test for the clinician; however, the length of time required for the procedure is a disadvantage as it causes discomfort to the patient often resulting in reflex tearing which impacts the variability of the data.

Several diagnostic tests evaluate the quantity and quality of the tear film. The measurement of TBUT following the instillation of a fluorescein dye is a widely used clinical technique. Nichols et al found the TBUT analysis to be more reproducible than the Schirmer test. A number of factors can reduce the utility of this test in the clinical trial setting. These confounding factors can include: heterogeneous populations, variations in measurements and scoring, and environmental influences. These techniques have limitations, as they tend to measure the extent of ocular surface damage from dry eye and are relatively insensitive in the early stages of dry eye disease.

Clinicians often rely on the presence of ocular irritation symptoms, the Schirmer test, TBUT, and ocular surface vital dyes to diagnose tear dysfunction. More sophisticated clinical tests are currently available, which may have greater sensitivity for detecting OSD in glaucoma patients, but they are currently not widely available. One such technique for evaluating the health of the ocular surface (such as dry eye) is computerized videokeratoscopy. This diagnostic tool utilizes computer algorithms for analyzing Placido rings that reflect off the surface of the cornea. Other noninvasive techniques, such as aberrometry, have proven to be useful for assessing ocular surface health.

Confocal microscopy has been used in recent years for evaluating ocular surface health. Using this technique, mean individual epithelial cell area and nucleocytoplasmic ratios were found to be worse in dry eye patients. Benitez-del-Castillo et al reported that dry eye patients had a reduced density of corneal epithelial cells and a decrease in the number of subbasal nerves. Another study using confocal
microscopy reported that the clinical scores were significantly lower in the preserved medication group ($P < 0.05$) compared to those for the nonpreserved group. Superficial corneal epithelial cell density was reduced in all patients on IOP-lowering medications (except for the preservative-free group [$P > 0.05$]) compared to control subjects ($P < 0.001$).

Impression cytology, a method to sample the conjunctival epithelium, has been used to study the underlying causes of OSD. The expression of inflammatory markers such as HLA-DR was measured in patients taking topical IOP-lowering medications using this technique. HLA-DR was higher in these patients than in either allergic patients or normal volunteers.

Sullivan and colleagues recently conducted a prospective study of 299 patients across 10 sites in the United States and European Union that examined the clinical value of tear osmolarity and several other tests for evaluating the severity of dry eye disease. The rank order of correlation coefficients to disease severity, from highest to lowest, was osmolarity ($r^2 = 0.55$), conjunctival staining ($r^2 = 0.47$), corneal staining ($r^2 = 0.43$), meibomian score ($r^2 = 0.37$), TBUT ($r^2 = 0.30$), and Schirmer test ($r^2 = 0.17$). Interestingly, disease severity was poorly classified using a combination of clinical thresholds for about 63% of patients with mild-to-moderate dry eye.

Subjective measures

Several survey instruments have been developed for assessing ocular surface health. The McMonnies Dry Eye Questionnaire is a subjective method of assessing ocular health from the patient’s perspective. This patient-reported outcome instrument was designed to differentiate dry eye patients from those with a normal ocular surface.

An OSD-specific questionnaire has been developed (OSD-QoL) to evaluate health-related quality of life. This instrument was developed in France and consists of a diagnostic aid and a subjective section that relates to treatment, perception of treatment, and quality of life.

The OSDI

Another subjective measurement tool for assessing symptoms of OSD is the OSDI. The instrument consists of 12 questions that are designed to provide a quick assessment of ocular irritation symptoms related to dry eye disease and their effect on vision-related functioning. The 12 items of the OSDI questionnaire are graded on a scale of 0–4 as follows: 0 = none of the time; 1 = some of the time; 2 = half of the time; 3 = most of the time; and 4 = all of the time. The total OSDI score is calculated according to the following formula:

$$\text{OSDI} = \left(\frac{\sum \text{of scores for all questions answered}}{\text{total number of questions answered}} \times 100\right)$$

The overall OSDI score is based on a scale from 0–100, which is defined as follows: 0–12 = normal; 13–22 = mild OSD; 23–32 = moderate OSD; 33–100 = severe OSD.

A factor analysis of the OSDI indicated that there were three different subscales within the questionnaire including: ocular symptoms, environmental triggers, and vision-related function. A Cronbach $\alpha$ analysis indicated a high degree of internal consistency in all three of the subscales as well as the OSDI total score overall. The OSDI scores have been shown to correlate with McMonnies questionnaire and the National Eye Institute Visual Functioning Questionnaire-25. Some differences do exist between these measures due to the fact that the OSDI is specific for dry eye disease. This instrument was previously validated in a dry eye patient population. To the authors’ knowledge, the OSDI is yet to be validated for use specifically with glaucoma patients.

Some investigators have examined the correlation between the OSDI and symptoms of dry eye and OSD. Versura et al reported significant correlations between the OSDI subjective symptoms and tear osmolarity for patients with mild ($r = 0.313$) and moderate ($r = 0.462$) OSD. However, the correlation was not significant for patients with severe OSD ($r = 0.09$). Within normal-to-moderate dry eye cohorts, Sullivan et al found the following correlation coefficient to disease severity: osmolarity ($r^2 = 0.55$), conjunctival staining ($r^2 = 0.47$), corneal staining ($r^2 = 0.43$), OSDI ($r^2 = 0.41$), meibomian score ($r^2 = 0.37$), TBUT ($r^2 = 0.30$), and Schirmer result ($r^2 = 0.17$).

Valente and colleagues measured the signs and symptoms of tear film dysfunction using the OSDI in patients on ocular hypotensive drops containing BAK. Approximately half (26/50, 52%) of the patients on an ocular hypotensive regimen containing BAK showed symptoms of tear film dysfunction. Signs of OSD appeared to be greater in patients on more than two topical medications. Signs and symptoms of OSD were correlated for patients on monotherapy consisting of $\beta$-adrenergic antagonists.

Some caveats to consider with the OSDI are the natural fluctuations in dry eye symptoms. Walker et al found significant differences in study participants’ reporting of visual function in the OSDI depending on the time of day. They found more visual function limitations relating to dry eye symptoms (eg, working on the computer, driving, watching television) in the evening than in the morning.
Another factor that may complicate the assessment of dry eye using the OSDI is corneal hypoesthesia. Bourrier and colleagues have shown that corneal sensitivity tends to decrease with age.65 Furthermore, patients with dry eye were shown to have higher thresholds for thermal, chemical, and mechanical stimulation than their normal counterparts. Benitez-del-Castillo confirmed that sensitivity to these stimuli was reduced, which was attributed to a decreased number of subbasal corneal nerves.55 Martone and colleagues showed that the reduction in the number of subbasal nerves was associated with a decrease in corneal sensitivity for patients on IOP-lowering therapies preserved with BAK.36 This decrease in corneal sensitivity may interfere with a patient's perception of dry eye symptoms and therefore confound the interpretation of results from the OSDI.

Miller and colleagues recently conducted a study with 310 patients to determine the minimal clinically important difference for the OSDI.43 A subject global assessment and a clinician global impression served as the basis for estimating the minimal clinically important difference for the overall OSDI scores (range 0–100). The subject global assessment and clinician global impression correlated with the change in OSDI score for all categories except for the normal category. The range of minimal clinically important difference values was 4.5–7.3 for mild and moderate disease, and 7.3–13.4 for severe disease.

Several confounding factors may cause measurements, using the OSDI in large-scale clinical trials that are well controlled, randomized parallel groups masked with prospectively-stated statistical objectives, to be problematic. The studies often consist of heterogeneous populations from disparate study sites. There are individual variations in each patient's response to their dry eye symptoms. Concomitant medications or comorbid diseases can also affect the ocular surface health. This is particularly true of patients with glaucoma, who are usually elderly and on multiple chronic topical ocular drops. Longer treatment periods are often needed in order to see improvements in their ocular surface health. Differences in climate across study sites can also affect the outcome. The positive placebo effect can confound the evaluation of the patient response to treatment. Since the OSDI measures ocular surface symptoms, it may not be able to show improvements in OSD per se.

One could expect that the likelihood of showing a difference for glaucoma patients with the OSDI between treatment groups might be higher if certain factors were considered in the study design. For example, study patients would be on therapy for extended treatment periods. The study populations could be limited to mild and moderate dry eye patients. No concomitant medications should be allowed. The studies could exclude other ocular disease states that can affect/exacerbate OSD. More sensitive parameters such as impression cytology could be used. Although difficult to incorporate all of these criteria, some study designs have attempted to mitigate confounding outcomes.47,68

Clinical results with the OSDI

Several investigators have been able to show differences with regard to the ocular surface health of patients with glaucoma by using the OSDI. Henry and colleagues conducted a multicenter study using the OSDI with patients who changed from their previous prostaglandin therapy to travoprost with SofZia.64 Glaucoma and ocular hypertensive patients included in this study were originally taking latanoprost or bimatoprost monotherapy and demonstrated a need for an alternative therapy due to tolerability issues. Overall OSDI scores were 12.0 for latanoprost, 13.2 for bimatoprost, and 8.7 for travoprost (after 8 weeks of travoprost treatment; \( P < 0.0001 \) vs latanoprost; \( P < 0.0001 \) vs bimatoprost). About 70% of the 253 patients with OSD symptoms at baseline had a decrease in symptom severity by at least one level (ie, a shift in symptom severity from moderate to mild) on the OSDI scale. It was possible to discern these differences successfully with the OSDI most likely due to the fact that the patients were experiencing some adverse effects with respect to tolerability at the baseline visit.

Horsley and Kahook evaluated glaucoma patients with the OSDI 8 weeks after they made a transition from latanoprost with 0.02% BAK to travoprost with SofZia.57 Patients were required to have a baseline TBUT <6 seconds and they were instructed to avoid using other topical drops during the study. At the 8-week time point they found that there were decreases in mean inferior corneal staining from 2.40 to 1.38 (\( P < 0.001 \)) and mean OSDI scores from 26.31 to 16.56 (\( P < 0.001 \)). In this trial, the ability of the OSDI to discriminate between the two groups was improved by a careful design of the protocol that attempted to minimize confounding factors (such as other topical medications).

Katz and colleagues measured the symptoms of OSD in patients with ocular hypertension or open-angle glaucoma that had been on BAK-preserved latanoprost 0.005% monotherapy for at least 1 month.49 The patients had baseline scores of \( \geq 13 \) on the OSDI. They were then randomly assigned to either continue with latanoprost therapy or transition to
travoprost without BAK (preserved with SofZia). OSDI evaluations were repeated at 6 and 12 weeks. Mean OSDI scores at 12 weeks were significantly lower for patients with mild OSD in the travoprost (11.6 ± 10.8) group than in the latanoprost (14.4 ± 11.9) group (P = 0.04). Patients who had previously been treated with BAK-preserved latanoprost for > 24 months were more likely to improve to a normal OSDI score after 12 weeks if they were transitioned to travoprost preserved without BAK (P = 0.03).

These clinical studies demonstrate, despite aforementioned issues with the application of the OSDI to differing patient populations and OSDI instrument caveats, that clinically significant differences in OSD symptoms can be identified with the OSDI. This tool continues to be used in clinical trials in an attempt to discern clinical improvement in OSD can be a difficult task. Further work needs to be done to optimize existing clinical methods and/or identify alternative methods for assessing OSD in glaucoma patients.

Conclusion
Due to challenges that clinicians face with both subjective and objective ocular surface health assessments, discerning clinical improvement in OSD can be a difficult task. Further work needs to be done to optimize existing clinical methods and/or identify alternative methods for assessing OSD in glaucoma patients.

Acknowledgment
Julie Crider provided medical writing assistance that was funded by Alcon Laboratories, Inc.

Disclosures
SCP received consulting fees from Alcon, Allergan, Bausch and Lomb, and GlaxoSmithKline and research grants from Allergan and GlaxoSmithKline. CB received consulting fees and research grants from Alcon, Allergan, MSD, Pfizer, Santen, and Thea.

References

26. Yee RW, Norcom EG, Zhao XC. Comparison of the relative toxicity of travoprost 0.004% without benzalkonium chloride and latanoprost 0.005% in an immortalized human cornea epithelial cell culture system. Adv Ther. 2006;23(4):511–519.


