

Association of cumulative topical anti glaucoma medication exposure with ocular surface disease severity in patients with primary open angle glaucoma : A cross sectional analytical study

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How to citation this article: Dr Suparna Jangra, Dr Shruti, Dr InderMohan Rustagi, “Association of cumulative topical anti glaucoma medication exposure with ocular surface disease severity in patients with primary open angle glaucoma : A cross sectional analytical study”, IJMACR– October– 2026, Volume – 9, Issue – 5, P. No. 609 – 622.

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Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Primary open-angle glaucoma (POAG) often requires prolonged topical therapy. Greater cumulative exposure to antiglaucoma medications and preservatives may be associated with ocular surface symptoms and tear-film abnormalities.

Aim: To assess the association between cumulative topical anti-glaucoma medication exposure and ocular surface disease severity among patients with POAG.

Materials and Methods: This hospital-based cross-sectional analytical study included 120 adults with POAG receiving topical medications. Lifetime per-eye instillations were estimated from medication history, daily instillation frequency and treatment duration.

Ocular surface assessment included the Ocular Surface Disease Index (OSDI), fluorescein tear break-up time (TBUT), Schirmer test and Oxford staining. Associations were evaluated using group comparisons, Spearman correlation and adjusted regression.

Results: OSDI-defined symptoms (score ≥ 13) were present in 89/120 patients (74.2%); 29 (24.2%) had severe symptoms. Mean OSDI increased from 13.9 ± 10.5 in the lowest exposure quartile to 38.3 ± 17.5 in the highest ($p < 0.001$). Cumulative instillations correlated positively with OSDI ($\rho = 0.586$, $p < 0.001$) and negatively with TBUT ($\rho = -0.323$, $p < 0.001$). After adjustment, each doubling of (1 + cumulative instillations) was associated with 7.28 higher OSDI points (95% CI 4.83–9.73;

p<0.001), 1.10 seconds shorter TBUT (p<0.001) and 1.20 mm/5 min lower Schirmer values (p=0.010).

Conclusion: Greater estimated cumulative topical medication exposure was associated with worse OSDI symptoms and selected objective ocular surface measures in POAG. The cross-sectional findings do not establish causation.

Keywords: Primary Open-Angle Glaucoma, Cumulative Medication Exposure, Ocular Surface Disease, OSDI, Tear Break-Up Time, Schirmer Test.

Introduction

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy that necessitates ongoing lowering of intraocular pressure, usually with long-term topical therapy.¹ Ocular surface disease (OSD) has been associated with duration of treatment, number of active agents and exposure to benzalkonium chloride (BAK).² Increased daily instillation frequency has also been associated with poorer ocular surface signs, with inconsistent findings for treatment duration.³ Topical hypotensive agents are frequently used by patients with dry eye symptoms.⁴

OSD assessment includes tear break-up time, Schirmer testing and ocular surface staining to document tear instability and epithelial injury.⁵ Indian POAG data indicate worse baseline tear parameters in medicated eyes than treatment-naïve eyes.⁶ Long-term users of preserved drops have more objective signs of ocular surface disease than untreated controls.⁷ Increased medication burden has also been linked to dryness, itching and ocular pain.⁸

Optical coherence tomography has demonstrated decreased corneal epithelial thickness in association with multiple topical agents.⁹ In Indian patients with glaucoma, OSDI and quality-of-life scores were worse

with BAK-preserved travoprost compared to BAK-free travoprost.¹⁰ A crossover trial also found that preserved latanoprost had a shorter tear break-up time and more conjunctival staining than preservative-free latanoprost.¹¹ Longitudinal data show worsening of dry eye symptoms and some visual activities with glaucoma therapy.¹² Overexpression of tear-film matrix metalloproteinase-9 indicates an inflammatory element to POAG OSD.¹³ Repeated exposure to BAK may be toxic to the corneal and conjunctival epithelium.¹⁴ Management reviews recommend ocular surface monitoring and less toxic formulations.¹⁵

Rationale

The number of drugs prescribed today does not fully reflect the changes in agents, frequency of instillation or duration of treatment in the past. Evaluation of cumulative exposure together with severity of OSD may help clarify clinically-relevant associations in POAG and guide surveillance of the ocular surface without implying causality.

Aim and Objectives

Aim: To evaluate the association between cumulative topical anti-glaucoma medication exposure and ocular surface disease severity in patients with primary open-angle glaucoma.

Primary Objectives

1. To assess the prevalence and severity of ocular surface disease among patients with primary open-angle glaucoma receiving topical anti-glaucoma medications.
2. To determine the association between cumulative topical anti-glaucoma medication exposure and ocular surface disease severity in patients with primary open-angle glaucoma.

Secondary Objectives

1. To evaluate the association of treatment duration, number of anti-glaucoma medications, and frequency of daily instillations with ocular surface disease severity.
2. To assess the relationship between cumulative topical anti-glaucoma medication exposure and objective ocular surface parameters, including tear break-up time, Schirmer's test, and ocular surface staining.

Materials and Methods

Study Design and Setting

This hospital-based, cross-sectional analytical study was conducted in the Department of Ophthalmology of a tertiary care teaching hospital in Haryana, India, during the specified study period.

Study Population

Adult patients aged ≥ 18 years with diagnosed primary open-angle glaucoma (POAG), receiving topical anti-glaucoma medications, were enrolled from rural and urban populations attending the ophthalmology outpatient department.

Sample Size and Sampling Technique

Approximately 120 patients were recruited through consecutive sampling, with the final sample size determined by statistical calculation and feasibility.

Inclusion Criteria

Patients aged ≥ 18 years with established POAG, receiving topical anti-glaucoma therapy and willing to provide written informed consent, were included.

Exclusion Criteria

Patients with active ocular infection, significant pre-existing corneal or conjunctival disease, recent ocular surgery, contact lens use, or other conditions affecting ocular surface assessment were excluded.

Data Collection

Demographic characteristics, glaucoma duration, medication history, drug classes, treatment duration, daily instillation frequency and preservative exposure were recorded using a structured proforma.

Assessment of Cumulative Medication Exposure

Cumulative medication exposure was estimated as lifetime per-eye instillation count by summing the daily instillation frequency multiplied by the corresponding duration of treatment in days for each formulation, accounting for reported treatment modifications. Historical BAK-containing instillations were estimated separately, these counts do not measure the actual quantity of instilled drug or preservative.

Ocular Surface Assessment

Ocular surface symptoms were assessed using the Ocular Surface Disease Index (OSDI). Unrounded OSDI scores were categorized as normal (<13), mild (13 to <23), moderate (23 to <33) or severe (≥ 33). OSDI ≥ 13 represented questionnaire-defined symptom positivity, not an independently confirmed clinical OSD diagnosis. Fluorescein tear break-up time, Schirmer testing and ocular surface staining using the Oxford grading scale assessed objective tear-film and epithelial parameters. One index eye per participant was represented in the eye-based analyses.

Statistical Analysis

Descriptive statistics included mean $\pm$ standard deviation, median and interquartile range, frequency and percentage. Group comparisons used the Mann–Whitney U and Kruskal–Wallis tests, and monotonic associations were examined using Spearman correlation. Multivariable analyses used robust linear regression with HC3 standard errors for OSDI, fluorescein tear break-up time and Schirmer results, and ordinal logistic regression

for Oxford staining grades. The predictor was $\log_2(1 + \text{cumulative instillations})$; models adjusted for age, sex, diabetes mellitus, ordinal glaucoma stage and current BAK-preserved therapy. Wilson 95% confidence intervals were reported for OSDI prevalence estimates. Two-sided p-values <0.05 were considered statistically

significant; secondary and exploratory analyses were not multiplicity-adjusted.

Ethical Considerations

Institutional Ethics Committee approval and written informed consent were obtained before recruitment.

Results

Table 1; Sociodemographic and baseline clinical profile of participants (N=120)

Characteristic	Category	n (%) / Mean $\pm$ SD
Age (years)	Mean $\pm$ SD	59.5 $\pm$ 11.0
Age group (years)	18–39	3 (2.5)
	40–49	20 (16.7)
	50–59	35 (29.2)
	60–69	36 (30.0)
	≥ 70	26 (21.7)
Sex	Male	65 (54.2)
	Female	55 (45.8)
Residence	Rural	41 (34.2)
	Urban/peri-urban	79 (65.8)
Education	No formal schooling	19 (15.8)
	Primary	21 (17.5)
	Middle	20 (16.7)
	High school	23 (19.2)
	Intermediate/diploma	18 (15.0)
	Graduate	15 (12.5)
	Postgraduate/professional	4 (3.3)
Glaucoma stage	Early	46 (38.3)
	Moderate	49 (40.8)
	Advanced	25 (20.8)
Diabetes mellitus	Yes	27 (22.5)
	No	93 (77.5)
Systemic hypertension	Yes	55 (45.8)
	No	65 (54.2)

Characteristic	Category	n (%) / Mean $\pm$ SD
Modified Kuppaswamy (urban/peri-urban, n=79)	Upper middle	18 (22.8)
	Lower middle	26 (32.9)
	Upper lower	35 (44.3)

Interpretation: Among the 120 analysed records, the mean age was 59.5 ± 11.0 years; 65 (54.2%) were male and 41 (34.2%) resided in rural areas. Patients aged 60–69 years constituted 36 (30.0%), while 26 (21.7%) were at least 70 years old. Early, moderate and advanced glaucoma affected 46 (38.3%), 49 (40.8%) and 25 (20.8%) participants, respectively. Among 79 urban/peri-urban participants, the upper-lower Kuppaswamy category included 35 (44.3%); the 41 rural patients were not assigned Kuppaswamy classes.

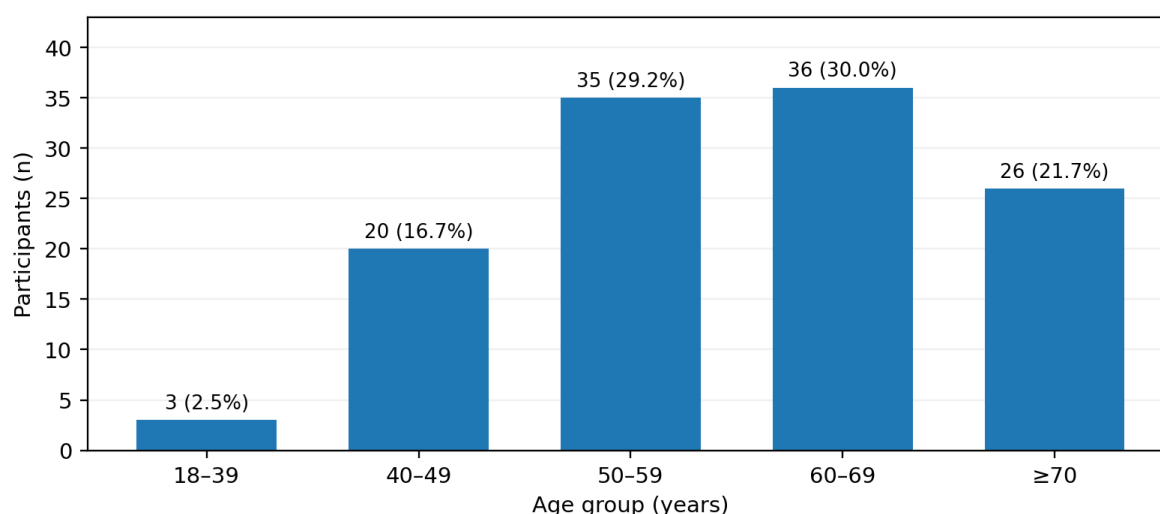


Figure 1: Age distribution of the study population.

Table 2: Topical medication exposure and treatment burden by OSDI symptom status

Treatment exposure	Overall (N=120)	OSDI <13 (n=31)	OSDI $\geq$ 13 (n=89)	p-value
Topical treatment duration (months), mean $\pm$ SD	67.7 $\pm$ 39.0	41.9 $\pm$ 20.6	76.6 $\pm$ 40.0	<0.001
Current active drug classes, mean $\pm$ SD	1.9 $\pm$ 0.9	1.4 $\pm$ 0.6	2.1 $\pm$ 0.9	<0.001
Current formulations/bottles, mean $\pm$ SD	1.7 $\pm$ 0.9	1.3 $\pm$ 0.5	1.9 $\pm$ 0.9	0.002
Daily instillations per eye, median [IQR]	2.5 [1.0–3.2]	2.0 [1.0–3.0]	3.0 [2.0–4.0]	<0.001
Cumulative instillations, median [IQR]	4,155.0 [2,275.5–7,602.5]	1,766.0 [1,005.0–3,562.0]	5,128.0 [3,096.0–9,405.0]	<0.001

Treatment exposure	Overall (N=120)	OSDI <13 (n=31)	OSDI ≥13 (n=89)	p-value
Historical BAK instillations, median [IQR]	3,059.0 [1,005.0–5,776.5]	1,644.0 [944.0–2,740.5]	3,652.0 [1,857.0–7,550.0]	<0.001

Note: Mann–Whitney U comparisons for continuous/ordinal exposure variables. OSDI groups have been recalculated using unrounded score <13 versus ≥13. Cumulative exposure is estimated lifetime administration count, not an assay of actual dose or preservative mass.

Interpretation: The mean duration of topical anti-glaucoma therapy was 67.7 ± 39.0 months overall, compared with 41.9 ± 20.6 months in OSDI-negative and 76.6 ± 40.0 months in OSDI-positive participants ($p < 0.001$). Cumulative exposure was higher in the symptom-positive group (median 5,128.0 [3,096.0–9,405.0]) than in the symptom-negative group (1,766.0 [1,005.0–3,562.0]; $p < 0.001$). Current active drug classes averaged 2.1 ± 0.9 versus 1.4 ± 0.6 ($p < 0.001$).

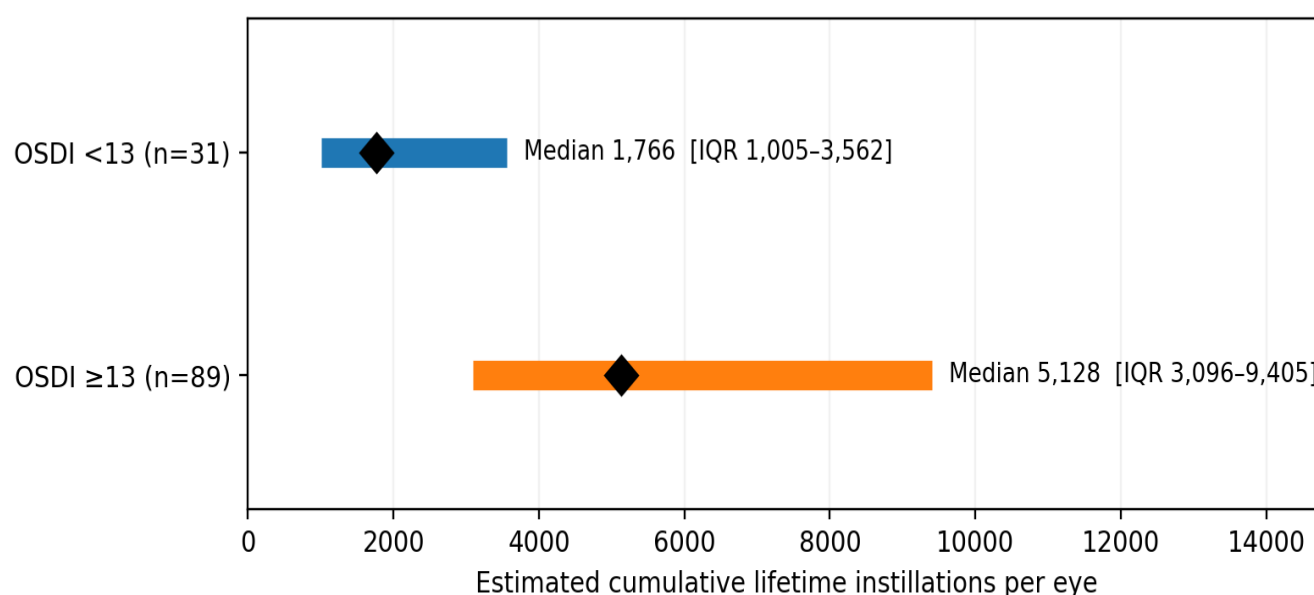


Figure 2: Estimated cumulative instillation count by OSDI-defined symptom category.

Table 3: Prevalence and severity of questionnaire-defined ocular surface symptoms

OSDI category	Unrounded score	n	Percentage (95% CI)	p-value
Normal	<13	31	25.8 (18.8–34.3)	Not applicable
Mild	13 to <23	34	28.3 (21.0–37.0)	
Moderate	23 to <33	26	21.7 (15.2–29.9)	
Severe	≥33	29	24.2 (17.4–32.6)	
OSDI symptom-positive	≥13	89	74.2 (65.7–81.2)	
Total	—	120	100.0	

Note: OSDI was classified using unrounded scores: normal <13, mild 13 to <23, moderate 23 to <33, and severe ≥ 33 . Percentages include Wilson 95% confidence intervals. Overall mean OSDI was 24.3 ± 15.6 . These are symptom categories, not independently confirmed clinical OSD diagnoses; no inferential p-value applies.

Interpretation: OSDI-defined symptoms (unrounded score ≥ 13) were present in 89 of 120 patients (74.2%; Wilson 95% CI 65.7–81.2%). Normal, mild, moderate and severe OSDI categories included 31 (25.8%), 34 (28.3%), 26 (21.7%) and 29 (24.2%), respectively. The overall OSDI score was 24.3 ± 15.6 ; the symptom-positive proportion should not be described as clinically confirmed OSD without a separate diagnostic definition.

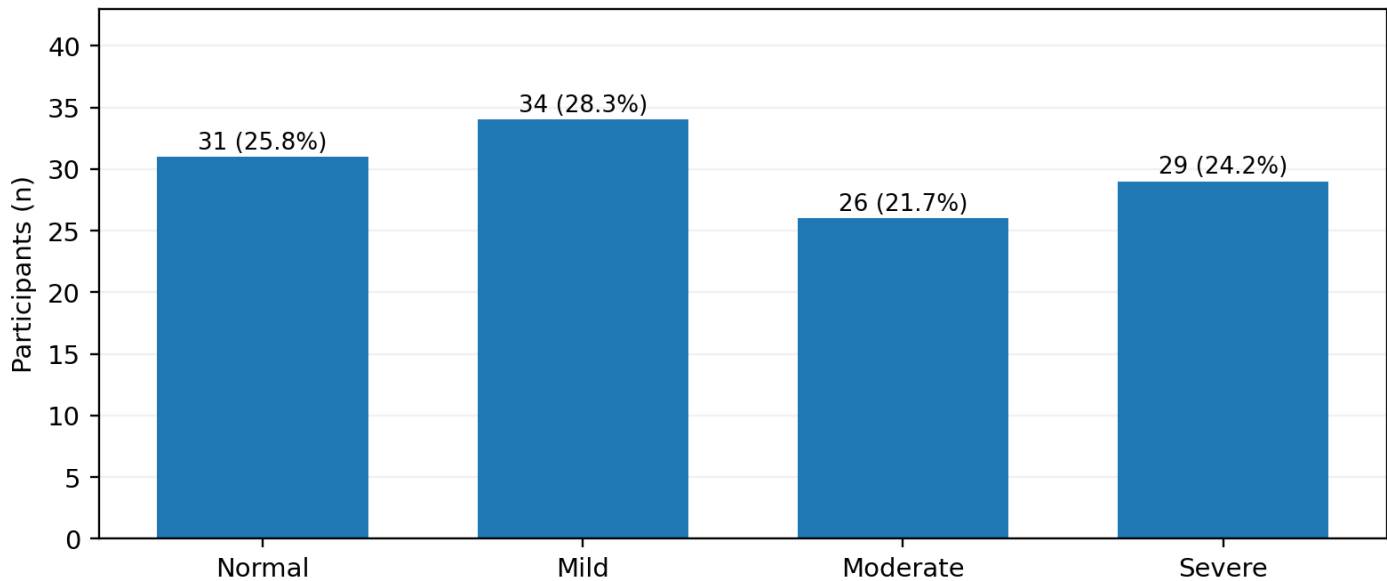


Figure 3: Distribution of OSDI-defined symptom severity.

Table 4: Primary analysis: cumulative medication exposure quartiles and OSDI severity

Exposure quartile	n	Cumulative instillations	OSDI (mean $\pm$ SD)	OSDI ≥ 13 n (%)	Severe n (%)	p-value
Q1	30	335–2,253	13.9 ± 10.5	12 (40.0)	2 (6.7)	<0.001
Q2	30	2,283–4,110	20.3 ± 11.6	23 (76.7)	4 (13.3)	
Q3	30	4,200–7,550	24.8 ± 10.8	24 (80.0)	5 (16.7)	
Q4	30	7,760–29,407	38.3 ± 17.5	30 (100.0)	18 (60.0)	

Note: Cumulative exposure quartiles are based on estimated lifetime per-eye instillations (n=30 each). The merged p-value represents the overall Kruskal–Wallis comparison of OSDI scores. It does not apply separately to the proportions in the two outcome columns.

Interpretation: Mean OSDI increased from 13.9 ± 10.5 in the lowest cumulative exposure quartile to 38.3 ± 17.5 in the highest quartile (overall Kruskal–Wallis $p < 0.001$). The proportions with OSDI ≥ 13 across Q1–Q4 were 12/30 (40.0%),

23/30 (76.7%), 24/30 (80.0%), 30/30 (100.0%) (overall categorical $p < 0.001$). Severe OSDI symptoms occurred in 2 (6.7%) of Q1 compared with 18 (60.0%) of Q4, consistent with an exposure-related gradient in these records.

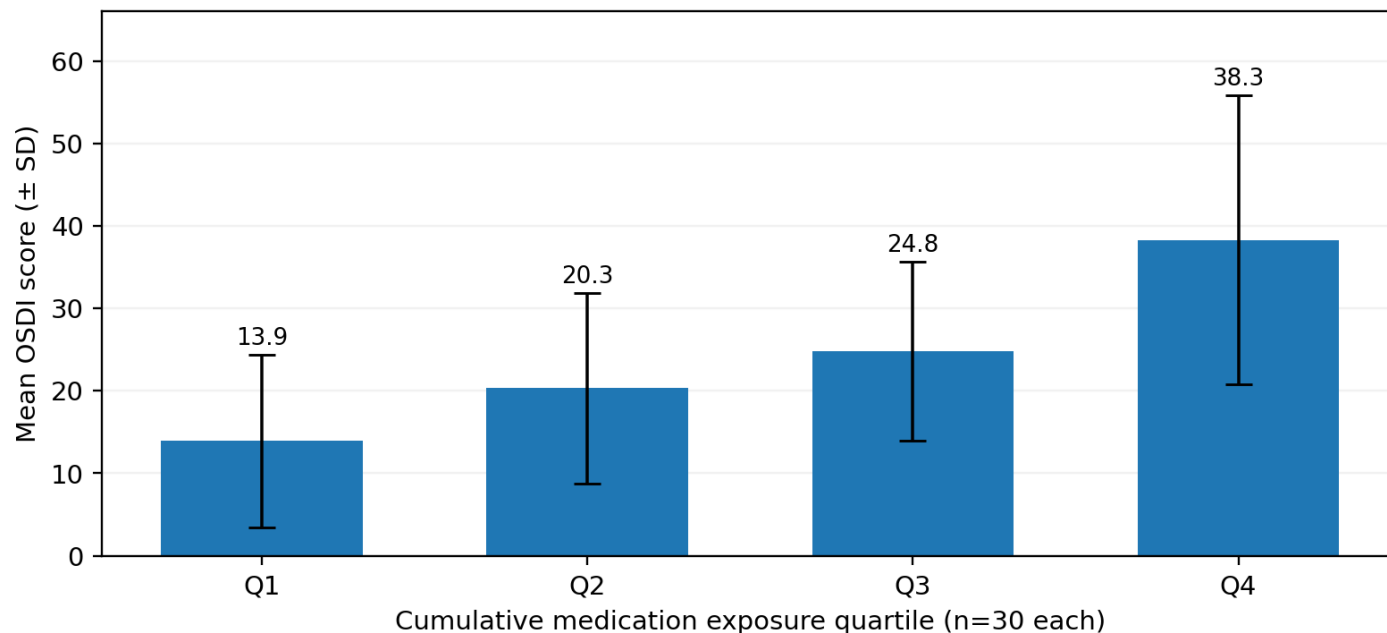


Figure 4: Mean $\pm$ SD OSDI score across quartiles of cumulative topical exposure.

Table 5: Treatment duration, drug-class count and instillation frequency versus OSDI

Treatment factor	Category	n	OSDI (mean $\pm$ SD)	OSDI ≥ 13 n (%)	p-value
Duration of therapy	<3 years	30	15.3 $\pm$ 10.4	15 (50.0)	<0.001
	3 to <6 years	43	23.1 $\pm$ 13.1	30 (69.8)	
	≥ 6 years	47	31.3 $\pm$ 17.3	44 (93.6)	
Number of drug classes	1	46	17.4 $\pm$ 10.9	27 (58.7)	<0.001
	2	45	24.7 $\pm$ 15.4	34 (75.6)	
	≥ 3	29	34.7 $\pm$ 16.8	28 (96.6)	
Daily instillations / eye	1–2	60	18.7 $\pm$ 11.6	38 (63.3)	<0.001
	3–4	39	26.8 $\pm$ 15.8	30 (76.9)	
	≥ 5	21	35.8 $\pm$ 18.1	21 (100.0)	

Note: Each displayed p-value is the overall Kruskal–Wallis comparison of OSDI scores across the three levels of that treatment characteristic. Categorical symptom associations are exploratory: duration $p < 0.001$, drug classes $p = 0.001$, frequency $p = 0.004$. Medication classes are not identical to bottles because fixed combinations exist.

Interpretation: Mean OSDI rose from 15.3 $\pm$ 10.4 among patients treated for <3 years to 31.3 $\pm$ 17.3 among those treated for ≥ 6 years ($p < 0.001$). Patients receiving one active drug class had a mean OSDI of 17.4 $\pm$ 10.9 versus 34.7 $\pm$ 16.8 for three or more classes ($p < 0.001$). Mean scores similarly increased from 18.7 $\pm$ 11.6 for 1–2 daily instillations to 35.8 $\pm$ 18.1 for ≥ 5 daily instillations ($p < 0.001$), supporting the secondary treatment-burden objective.

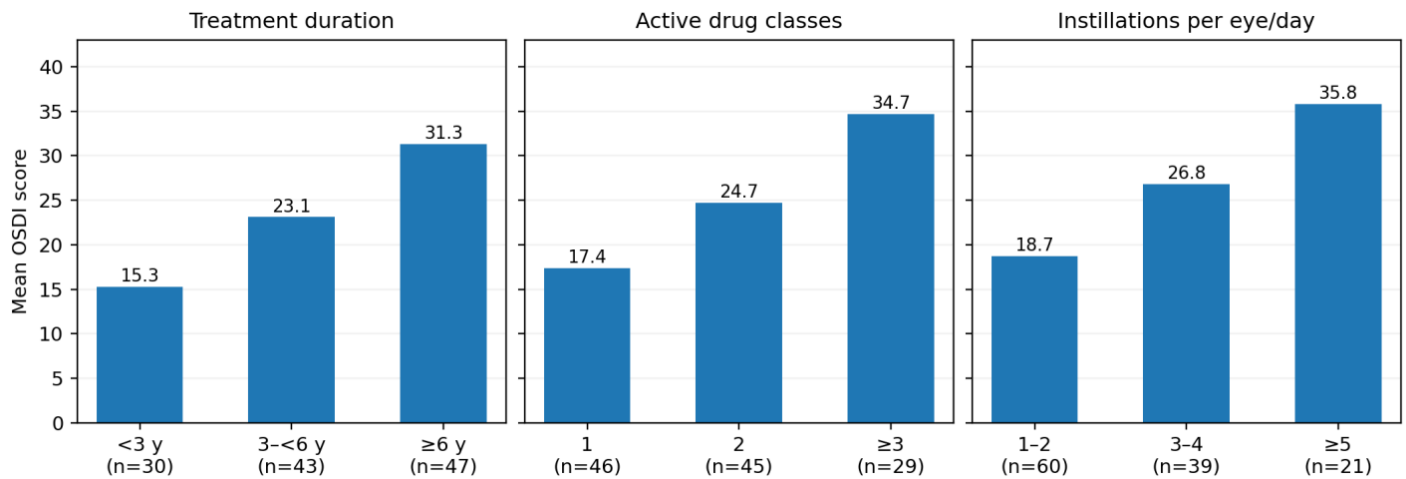


Figure 5: Mean OSDI scores by treatment duration, active drug-class count and daily instillation frequency.

Table 6: Objective tear-film and staining parameters across cumulative exposure quartiles

Objective measure	Q1 (n=30)	Q2 (n=30)	Q3 (n=30)	Q4 (n=30)	p-value
Fluorescein TBUT (seconds)	11.5 ± 3.1	9.2 ± 3.6	9.6 ± 3.6	7.5 ± 3.8	0.001
Schirmer (mm/5 min)	18.9 ± 5.2	16.2 ± 5.9	15.5 ± 3.7	14.5 ± 7.2	0.044
Oxford staining grade (0–5)	0.6 ± 1.0	1.0 ± 1.1	0.8 ± 1.1	1.6 ± 1.7	0.098

Note: Values are mean ± SD; row-specific p-values are Kruskal–Wallis tests. Oxford grades are ordinal, so means are descriptive. Only one index-eye measurement per patient is represented.

Interpretation: TBUT declined from 11.5 ± 3.1 seconds in Q1 to 7.5 ± 3.8 seconds in Q4 (p=0.001); Schirmer values were 18.9 ± 5.2 and 14.5 ± 7.2 mm/5 min in those groups, respectively (p=0.044). Oxford staining increased from 0.6 ± 1.0 to 1.6 ± 1.7, but the four-group comparison did not reach conventional significance (p=0.098).

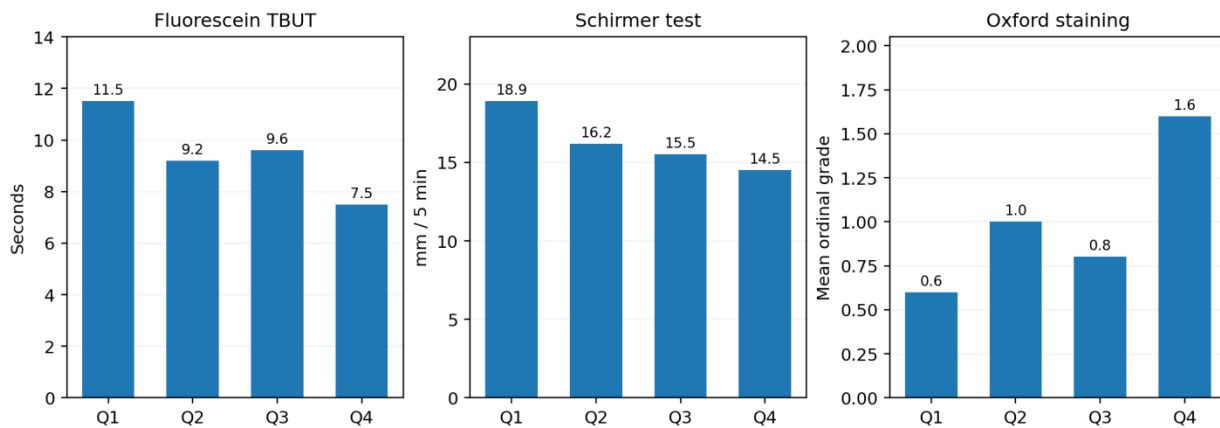


Figure 6. Mean TBUT, Schirmer and Oxford staining results across cumulative exposure quartiles.

Table 7: Spearman correlations between topical treatment exposure and ocular surface outcomes

Exposure variable	Outcome variable	Spearman ρ	p-value
Total cumulative instillations	OSDI score	+0.586	<0.001
Topical treatment duration	OSDI score	+0.427	<0.001
Current active drug classes	OSDI score	+0.430	<0.001
Daily instillation frequency	OSDI score	+0.403	<0.001
Total cumulative instillations	TBUT	-0.323	<0.001
Total cumulative instillations	Schirmer	-0.269	0.003
Total cumulative instillations	Oxford grade	+0.191	0.037

Note: All correlations are unadjusted and two-sided (N=120). The primary prespecified exposure–OSDI correlation is the first row; other tests are exploratory and have not been corrected for multiplicity. Clinical relevance should be judged using effect sizes and confidence intervals, not p-values alone.

Interpretation: Cumulative instillations showed a positive correlation with OSDI score (Spearman ρ =+0.586, p <0.001). Treatment duration, drug-class count and instillation frequency were also positively correlated with OSDI (ρ =+0.427, +0.430 and +0.403, respectively; all p <0.001). Higher cumulative exposure was associated with shorter TBUT (ρ =-0.323, p <0.001) and lower Schirmer values (ρ =-0.269, p =0.003); the staining correlation was comparatively weak (ρ =+0.191, p =0.037).

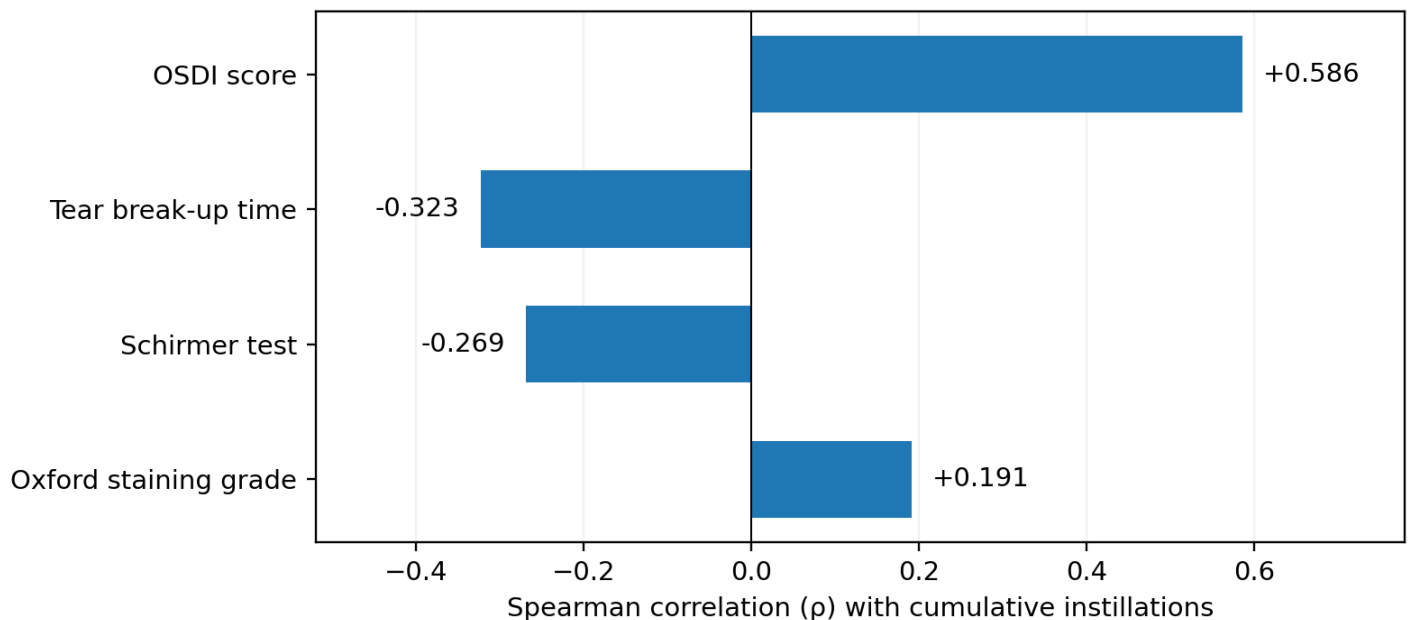


Figure 7; Spearman correlations between cumulative instillation count and ocular surface outcome measures.

Note: Correlation coefficients are plotted from Table 7; individual-level data are not available for a scatter plot.

Table 8: Adjusted cumulative exposure associations with symptomatic and objective outcomes

Outcome	Model	Adjusted estimate	95% CI	p-value
OSDI score	Robust linear	+7.28 points	+4.83 to +9.73	<0.001
Fluorescein TBUT	Robust linear	-1.10 seconds	-1.61 to -0.59	<0.001
Schirmer test	Robust linear	-1.20 mm/5 min	-2.13 to -0.28	0.010
Oxford staining grade (0–5)	Ordinal logistic	OR 1.37	1.03–1.82	0.032

Note: Principal predictor in every model: $\log_2(1 + \text{cumulative instillations})$, so one unit is a doubling of (1 + estimated instillations). Covariates: age, sex, diabetes, ordinal glaucoma stage and current BAK-preserved therapy. Robust HC3 OLS intervals for OSDI, TBUT and Schirmer; Adjusted proportional-odds model for Oxford staining (ordinal grades 0–5). Models describe statistical associations rather than causal effects.

Interpretation: After adjustment for age, sex, diabetes mellitus, glaucoma stage and current BAK-containing treatment, each doubling of (1 + estimated cumulative instillations) was associated with a +7.28-point difference in OSDI (95% CI +4.83 to +9.73; $p < 0.001$). The corresponding adjusted associations were -1.10 seconds for TBUT ($p < 0.001$) and -1.20 mm for Schirmer ($p = 0.010$). For Oxford staining, the ordinal model estimated an adjusted common OR of 1.37 (95% CI 1.03–1.82; $p = 0.032$). These are observational association estimates and do not demonstrate medication-induced ocular surface damage.

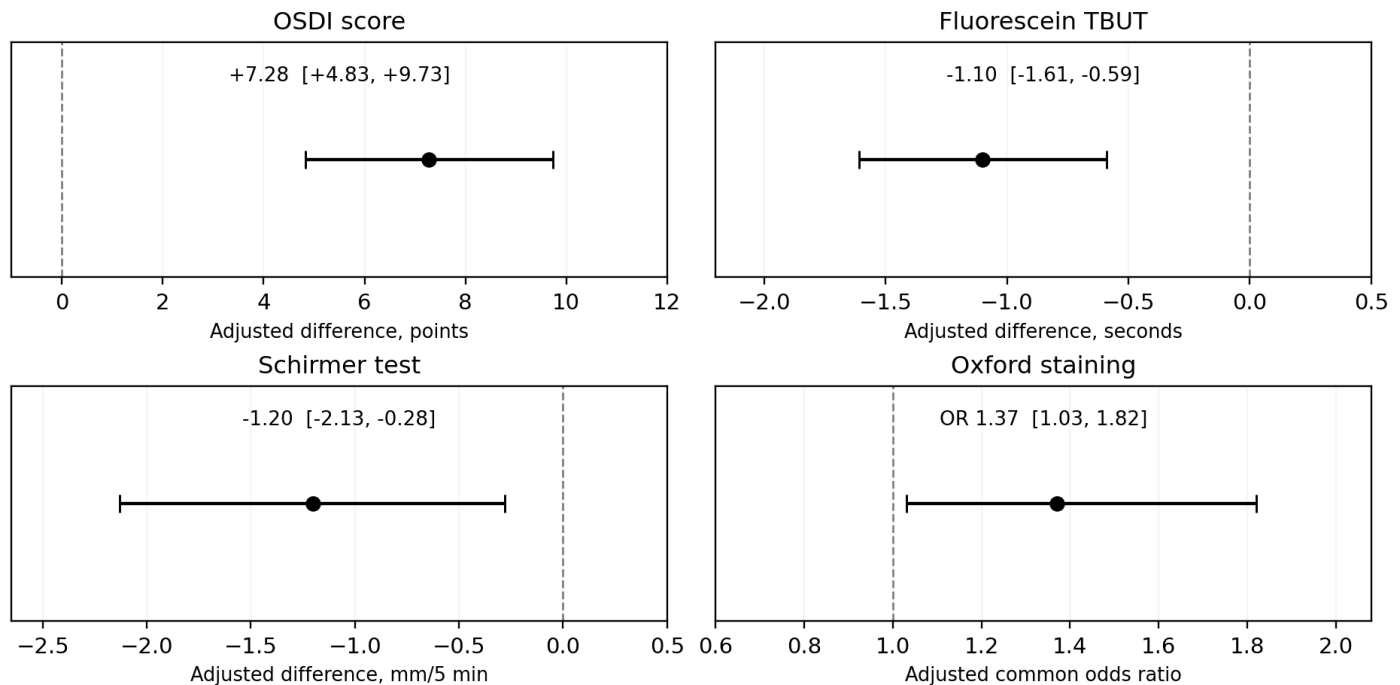


Figure 8: Adjusted exposure coefficient plots with 95% confidence intervals; each panel uses its own measurement scale.

Discussion

In this cross-sectional analysis of 120 adults with primary open-angle glaucoma, increasing cumulative topical medication exposure was associated with greater

questionnaire-defined ocular surface symptom severity. OSDI scores rose across the exposure quartiles, from 13.9 ± 10.5 in Q1 to 38.3 ± 17.5 in Q4, while the prevalence of OSDI scores ≥ 13 increased from 40.0% to

100.0%. The positive correlation between cumulative instillations and OSDI ($p=0.586$, $p<0.001$) was supported by an adjusted difference of 7.28 OSDI points for each doubling of (1 + cumulative instillations). Samico et al.¹ also found higher OSDI scores among patients using three or four antiglaucoma medications than among those using one or two. Lajmi et al.² identified treatment duration, medication number and preservative exposure as factors associated with ocular surface disease. Similarly, OSDI increased with therapy duration and active drug-class count in the current analysis; however, Parkkari et al.³ associated daily drop burden, but not treatment duration, with ocular surface abnormalities, indicating that duration-related findings may differ across populations.

OSDI-defined symptoms were present in 74.2% of the analysed participants, including severe symptom scores in 24.2%; these figures indicate questionnaire positivity rather than independently confirmed clinical ocular surface disease. Sahlu and Giorgis⁴ reported a substantial burden of dry eye symptoms among glaucoma patients receiving topical treatment. Anghel-Timaru et al.⁵ emphasized objective tear-film and staining assessments in medicated patients. Srivastava et al.⁶ observed impaired ocular surface parameters in treated Indian patients with POAG compared with treatment-naïve patients. In the current analysis, TBUT and Schirmer results were lower with higher cumulative exposure, consistent with the poorer tear-film findings reported by Awe et al.⁷ among medicated patients compared with controls. Tirpack et al.⁸ also linked topical polytherapy with dryness and ocular pain. Miklaszewski et al.⁹ described corneal epithelial thinning with increasing medication number, although corneal epithelial thickness was not assessed in these 120 records.

Historical BAK-containing instillation counts were higher among OSDI-positive participants, but these counts are estimates of administration frequency rather than measurements of preservative dose. Kumar et al.¹⁰ reported higher OSDI scores with BAK-preserved than with BAK-free travoprost in Indian patients, while Lee et al.¹¹ reported better ocular tolerability with preservative-free latanoprost. Maeng et al.¹² documented worsening dry eye symptoms during glaucoma treatment, providing further context for patient-reported morbidity. Kim et al.¹³ identified tear-film matrix metalloproteinase-9 expression in glaucoma-related ocular surface abnormalities, suggesting a possible inflammatory contribution. Goldstein et al.¹⁴ discussed epithelial toxicity associated with benzalkonium chloride, and Kemer et al.¹⁵ emphasized ocular surface monitoring and preservative-sparing treatment strategies. The adjusted associations with cumulative exposure persisted after accounting for current BAK-preserved therapy, but the design does not isolate a causal effect of preservatives or any particular drug class.

With increasing cumulative exposure, fluorescein TBUT and Schirmer values showed statistically significant differences across quartiles, whereas the unadjusted four-group comparison for Oxford staining was not significant ($p=0.098$). The adjusted ordinal model suggested a modest association with higher staining grades (odds ratio 1.37, 95% CI 1.03–1.82), which should be interpreted cautiously alongside the weak unadjusted staining correlation ($p=0.191$). Limitations include the cross-sectional design, the reliance on reconstructed treatment histories rather than directly measured administered doses, possible confounding by glaucoma severity and other ocular surface risk factors, and multiple exploratory tests. The study therefore

supports an association between cumulative treatment burden and ocular surface morbidity, not medication-induced damage or a temporal causal relationship.

Conclusion

Among the 120 analysed POAG records, higher estimated cumulative topical anti-glaucoma medication exposure was associated with more severe OSDI-defined symptoms and poorer tear-film measures. Symptom-positive patients had substantially higher cumulative instillation counts, and mean OSDI scores increased across exposure quartiles. Cumulative exposure remained associated with higher OSDI scores, shorter TBUT and lower Schirmer values after adjustment for measured clinical factors. These findings support systematic ocular surface assessment alongside long-term glaucoma management and consideration of treatment burden when selecting suitable regimens. Because the analysis was cross-sectional and based on estimated exposure, causality cannot be established; further prospective research is needed.

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