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Neuropathic Pain in the Eyes, Body, and Mouth: Insights from the Sjögren's International Collaborative Clinical Alliance

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Abstract

Objective: To evaluate how ocular, oral, and bodily neuropathic pain symptoms, which characterize small fiber neuropathies, are associated with Sjögren's syndrome (SS) classification based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria.

Methods: Participants enrolled in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry had ocular, rheumatologic, oral, and labial salivary gland (LSG) biopsy examinations, blood and saliva samples collected, and completed questionnaires at baseline. We used mixed effects modeling with age, country, gender, and depression being fixed effects and study site, a random effect, to determine if neuropathic pain indicators (assessed via questionnaires) were associated with being classified as SS.

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CONFLICT OF INTEREST

None declared.

Results: A total of 3,514 participants were enrolled into SICCA, with 1,541 (52.9%) meeting the 2016 ACR/EULAR classification criteria for SS. There was a negative association between being classified as SS and experiencing bodily neuropathic pain features of needle-like pain, prickling/tingling sensation, ocular neuropathic pain of constant burning, and constant light sensitivity, and having a presumptive diagnosis of neuropathic oral pain.

Conclusions: We found that those classified as SS had lower scores/reports of painful neuropathies compared with those classified as non-SS. Non-SS patients with dry eye disease or symptoms could benefit from pain assessment as they may experience painful small-fiber neuropathies (SFNs). Pain questionnaires may help identify pain associated with SFNs in patients with SS and non-SS dry eye. Future studies would be helpful to correlate self-reports of pain to objective measures of SFNs in those with SS, non-SS dry eye, and healthy controls.

Keywords

dry eye disease; neuropathic pain; Sjögren's syndrome

INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune disease characterized by exocrine gland inflammation and resultant damage manifesting most prominently as dry mouth and dry eyes. However, SS has widespread effects on the body, including vasculitis, dermatitis, and neurologic complications.[1]

Previous studies show that neuropathic mechanisms can contribute to dry eye symptoms,[2] suggesting overlap between dry eye and neuropathic pain symptoms. Neurologic complications associated with SS are highly variable.[3,4] Peripheral neuropathies are common neurological complication of SS.[5] Small-fiber neuropathies (SFNs) are the most common peripheral neuropathy in patients with SS.[5] Individuals affected by SFNs can experience pain that can be severe and debilitating.[6] Prior studies show that neuropathic pain intensity is more severe in patients with SFN than in patients with large or mixed fiber neuropathy.[7] Some patients with SFN may report having a cold-like pain, tingling, or pins and needles sensation, whereas more severe symptoms of pain are commonly described as burning, shooting, or prickly in quality.[6,8,9] Although questionnaires can be useful in identifying pain associated with SFNs, the gold standard for identifying such neuropathies consists of a biopsy of the affected region of the skin to demonstrate a reduction in the epidermal nerve fiber density.[8,10–12] Psychophysical assessment of warm and heat-pain thresholds have been found to correlate with skin biopsy results and can support diagnosis of SFN.[8] Additionally, previous studies have noted the possibility that unmyelinated nerve fibers may be useful as surrogate diagnostic markers for the presence of peripheral and autonomic neuropathies.[11] SFNs can also be identified in the cornea by in vivo confocal microscopy demonstrating a reduced density or altered morphology of small fibers.[13]

We sought to examine how bodily, ocular, and oral neuropathic pain symptoms in participants with dry eye enrolled in the Sjögren's International Collaborative Clinical Alliance (SICCA) might be associated with SS classification based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria.[14]

METHODS

Study Design and Population

The original study "International Research Registry Network for Sjögren's Syndrome" was approved by the University of California-San Francisco Institutional Review Board. The SICCA cohort represents a cross-sectional study of participants enrolled from nine international research sites in seven countries. Participants (≥21 years of age) met at least one of the following inclusion criteria: (1) complaint of dry eyes or dry mouth, (2) previous diagnosis of primary or secondary SS, (3) abnormal serology (positive anti-SSA, anti-SSB, or elevated ANA and RF), (4) bilateral parotid gland enlargement, or (5) multiple cervical/incisal dental caries. At the baseline SICCA visit, participants completed an interview and questionnaires and underwent ocular surface examinations in addition to oral and rheumatologic examinations.[14]

For this study, we included all SICCA participants who were able to be classified as either SS or non-SS based on ACR/EULAR criteria.[14]

Variables and Measures

Neuropathic pain indicators analyzed included participant-reported symptoms of ocular pain (pain or burning in the middle of the night or upon waking in the morning, burning or stinging, and light sensitivity); and bodily pain (how much pain interfered with normal work including outside the home and house work during the past 4 weeks, continuous "prickling" or "tingling" feeling, sharp "jabbing" needle-like pain or pulses of pain, decrease (or inability) to feel surface features/size/shape/texture, decrease (or inability) to recognize hot from cold, and decrease (or inability) to feel pain/cuts/bruises/injuries). A presumptive diagnosis of neuropathic oral pain was made in participants who reported a burning sensation on the tongue or in other parts of the mouth in the absence of oral mucosal abnormalities – papillary atrophy, dorsal tongue erythema, fissured tongue, oral mucosal erythema – and/or oral candidiasis.

The independent variables, including presumptive neuropathic oral pain and bodily pain ("continuous 'prickling' or 'tingling', "sharp 'jabbing' needle-like pain or pulses of pain," decrease or inability to feel surface features/size/shape/texture, decrease or inability to recognize hot from cold, and decrease or inability to feel pain/cuts/bruises/injuries) were binary with responses "yes" or "no." The ocular pain symptoms "pain/burn at night," "burning or stinging," and "light sensitivity" were categorical with responses indicating the amount of time patients experienced pain and included "none of the time," "some of the time," "half of the time," "most of the time," and "all of the time." Pain interference with work, a bodily pain measure, was also categorical with responses "not at all," "a little bit," "moderately," "quite a bit," or "extremely."

The outcome variable in these analyses was classification as SS or non-SS based on the 2016 ACR/EULAR criteria. Fixed effects included age, country, gender, and depression (with responses "not at all," "a little bit," "moderately," "quite a bit," or "extremely"). Study site was a random effect.

In a secondary analysis, we created a composite pain score calculated by point assignment for each indicator of pain: presumptive neuropathic oral pain, bodily pain ("prickling or tingling," "sharp jabbing needle-like pain," and/or "pain interference with work"), and ocular pain ("pain/burning at night," "burning or stinging," and/or "light sensitivity"). For the binary responses, a score of 1 was assigned for response "yes." For the categorical responses, a score of 1 was assigned for feeling pain "most of the time" and "all of the time," a score of 0.5 assigned for feeling pain "half of time," and a score of 0 for feeling pain "some of the time" and "none of the time." Additionally, we looked at the correlation between being classified as SS and sum total of bodily pain score calculated based on how many positive responses participants provided to the "bodily discomfort" questions.

As additional analyses, we examined the association of weakness of hands, fingers, shoulder, thighs, inability to walk on heels, and inability to walk on toes with being classified as SS. Finally, we explored the correlation between total corneal staining of both eyes (as a measure of dry eye severity) and the three types of ocular pain (light sensitivity, burning or stinging, and pain/burn at night).

Statistical Analyses

Mixed effects modeling was performed to determine if neuropathic pain indicators were associated with being classified as having SS (Stata/SE version 15.0 software, StataCorp LP, College Station, TX). Multivariable linear regression was used to assess the association between total corneal staining and the three types of ocular pain controlling for age, country, gender, and depression.

RESULTS

Characteristics of the study population are presented in Table 1. A total of 3,514 participants were enrolled in the SICCA study. Less than half of the participants (1,541, 43.9%) were classified as SS, 1,857 (52.8%) were classified as non-SS, and 116 participants (3.3%) could not be classified and were therefore excluded from analysis. The majority of participants (90.6%) were women. The median age among participants was 54 years, with a minimum age of 21 years and maximum of 89 years. With respect to country of residence, 36.7% of participants were recruited from the United States, 12.6% from Argentina, 8.9% from the United Kingdom, 17.4% from Denmark, 4.6% from India, 9.5% from China, and 10.5% from Japan.

Over half of the participants (51.3%) reported not feeling depressed at all, whereas 8.4% reported feeling depressed "more than half the days" and 7.1% "nearly every day." By SS status, 12% of the SS and 18% of the non-SS participants reported feeling depressed more than half the days or nearly every day. Less than a quarter of the total participants (16.9%) had a presumptive diagnosis of neuropathic oral pain. With respect to bodily pain, 42.0% of the participants reported prickling or tingling feeling, 37.4% reported sharp jabbing needle-like pain, 31.5% reported that pain interfered with their normal work quite a bit or extremely, 10.9% reported decrease in ability to feel texture, 5.2% reported decreased ability to recognize hot from cold, and 8.8% reported decrease in ability to feel pain. Ocular pain was reported in nearly 15% of the participants and described as pain/burn at night most or all

of the time, whereas 16.1% reported feeling burning or stinging most or all of the time, and 28.3% reported having light sensitivity most or all of the time in the last week. For questions related to weakness, 35.3% reported having weakness of hands, 38.1% had weakness of fingers, 33.4% had weakness of shoulder/upper arm, 29.0% had weakness of thighs, 15.4% "cannot walk on heels," and 14.4% "cannot walk on toes."

Bodily Pain

In multivariable models, indicators of bodily pain were significantly and negatively associated with being classified as SS (prickling or tingling feeling odds ratio [OR] = 0.80, sharp jabbing needle-like pain OR = 0.70, pain interference with work OR = 0.36, and inability to recognize hot from cold OR = 0.63; Table 2).

Ocular Pain

For ocular pain indicators, burning or stinging and light sensitivity, we found that there was a significant negative association between reporting higher levels of pain and being classified as SS. There were lower odds of being classified as having SS for those who reported feeling burning or stinging half of the time (OR = 0.61) and all of the time (OR = 0.64) compared with those who reported having burning or stinging none of the time. Similarly, compared with those who experienced light sensitivity none of the time, those with light sensitivity most and all of the time had significantly lower odds of being classified as SS (OR = 0.77 and OR = 0.78, respectively; Table 2). Pain/burn at night showed a significantly negative association with SS in unadjusted models.

Neuropathic Oral Pain

A presumptive diagnosis of neuropathic oral pain (burning in mouth in the absence of oral mucosal abnormalities) was found to have a significantly negative association with SS (OR = 0.52, 95% confidence interval [CI] = 0.43 to 0.63, $p < 0.001$).

Secondary Analyses

We found that there was a negative association between composite pain score (ocular, oral, and bodily pain) and classification as SS. For each 0.5 increase in composite pain score, the odds of being classified as SS decreased by 0.86 (OR = 0.86, 95% CI = 0.83 to 0.90, $p < 0.001$). Considering only bodily pain score, we found that the odds of being classified as SS decreased as sum total of bodily pain score increased (OR = 0.84, 95% CI = 0.79 to 0.89, $p < 0.001$).

We found that reporting weakness of hands was significantly associated with lower odds of being classified as SS (OR = 0.79, 95% CI = 0.67 to 0.92, $p < 0.01$). Weakness in other body parts (shoulder, thighs, and inability to walk on heels or toes), however, was not significantly associated with being classified as SS (Table 3).

For the association between corneal staining and reports of ocular pain, we found that total stain had positive association with burning/stinging and having pain/burn at night (Table 4). Having burning/stinging most of the time was significantly associated with 0.79 unit increase in total stain. Having pain/burn at night some of the time compared to none of the

time was significantly associated with a 0.38 unit increase in total corneal staining, while most of the time was significantly associated with 0.56 unit increase in total stain. Overall, more frequent ocular pain was associated with higher corneal stain scores.

DISCUSSION

Our findings indicate that in the SICCA cohort, experiencing bodily, ocular, and oral neuropathic pain was negatively associated with being classified as having SS. Additionally, those reporting neuropathic-quality bodily pain or having such pain interfere with their normal work and those with weakness of the hands had lower odds of being classified as having SS. Similarly, those with higher levels of neuropathic-quality ocular pain and a presumptive diagnosis of neuropathic oral pain had lower odds of being classified as having SS. In our secondary analyses, we found that an increase in composite pain score as well as total bodily pain score was associated with lower odds of being classified as having SS. These negative associations may be due to a number of reasons.

SS-related neuropathy may not necessarily be painful. For instance, a study of the clinical features of SFN related to SS versus idiopathic SFN found that patients with SS-related SFN had lower mean daily pain intensity and anxiety scores and less frequent and severe burning sensations compared with patients with idiopathic SFN.[15] Results showed that SFN in primary Sjögren's syndrome (pSS) may less specifically involve small sensory fibers and may be related to lower sensitization of small fibers compared to idiopathic SFN.[15] Furthermore, idiopathic SFN causes high morbidity due to pain.[16] Considering that those classified as non-SS were participants enrolled into the cohort by virtue of having complaints of dry mouth, dry eyes, or due to suspicion on the part of their physician of possibly having SS, it may be possible that compared with participants with SS, those classified as non-SS may have experienced more frequent and severe neuropathic pain unrelated to SS. Prior studies show that SFN remains idiopathic in a substantial proportion of patients[8,9,17] and that pSS may be present in only 9% to 30% of patients with SFNs.[18] In a cohort of patients with painful SFN, only a very low percentage (1.3%) had SS.[19] Additionally, neuropathic symptoms and pain may be frequent among people with dry eye disease.[2] Therefore, patients with dry eye who are not diagnosed with SS may experience painful neuropathies that may be important to assess and manage. Our finding also indicates that higher reports of pain were positively associated with an increase in corneal staining scores. Although peripheral neuropathies are reported in 2% to 10% of patients with SS, such neuropathies are not always necessarily painful.[4]

Additionally, pain may not be the most prominent symptom reported by patients with SS. A study of patients with pSS in the United Kingdom found that 45% ranked dryness as the symptom most in need of improvement, whereas only 15% ranked the pain symptom as most in need of improvement.[20] Moreover, because some patients with SS are seronegative for anti-SSA/B, the diagnosis of SS would rely on interpretation of the labial salivary gland biopsy. Misdiagnosis of SS may partly explain the high reported frequency of SFN in this disease when in fact only a small proportion of those with SS have SFN. A pure SFN is present in 3% to 9% of patients with pSS, although such SFNs have been identified primarily from intra-epidermal biopsies.[18]

Conversely, higher neuropathic pain intensity among those classified as non-SS may be a potential biomarker for underlying SS or future conversion to SS as classified by ACR/EULAR criteria. There is evidence that neurologic manifestations of pSS often precede the development of other diagnostic features of pSS.[21–24] Thus, those not meeting classification criteria for SS, but experiencing neuropathic pain may later convert to SS. Studies suggest that patients with idiopathic neuropathies but with clinical patterns suggestive of SS should be repeatedly queried about other symptoms of SS as the peripheral nervous system manifestations often precede glandular features of SS.[25] A long-term follow-up study found that a potential etiology could be determined in 25% of patients with a prior diagnosis of idiopathic SFN.[7] In addition, the state of SS disease activity (which was not captured at baseline in SICCA) may also play a role in the experience of pain.[26] Therefore, future studies should consider long-term follow-up of individuals not meeting SS classification criteria, but who report neuropathic pain, to assess conversion to SS.

Moreover, psychosocial problems, such as anxiety and depression, may contribute to the experience and perception of pain. Studies show that hypothalamic and limbic influences due to anxiety, depression, or psychosocial imbalances may interfere with circadian rhythm of basal tear production and contribute to neurologic dysfunction,[2,27] which is an important contributor to the development of dry eye.[27] Previous studies found that depression was associated with dry eye disease,[28] which can be correlated to increased experience and reports of pain. Similarly, one study showed that having symptoms of dry eyes in a non-SS setting was associated with higher scores of anxiety and depression, and lower sleep quality.[29] Therefore, there may be higher levels of stress, anxiety, depression, or other psychosocial problems, and unreported aspects of quality of life in those classified as non-SS that may contribute to increased experience or perception of pain. These phenomena may contribute to the experience and more frequent and severe reports of pain among our non-SS participants.

This study has some limitations. First, there was no neurological examination or nerve conduction study. Assessment of neuropathic pain was based on self-report. However, pain was evaluated using various questionnaires with specific questions as to body part and severity of pain. In addition, we found similar results in a sensitivity analysis in which we controlled for comorbidities that may be related to SFN, such as diabetes, HIV, and hepatitis C.[5] The role of fibromyalgia and autonomic dysfunction as it relates to neuropathic pain and dry eye symptoms may be useful to explore in future studies. Second, our results may not be entirely generalizable as our comparison group in the SICCA cohort were participants that had been referred into SICCA to determine if they might be classified as having SS. Future studies comparing patients with SS with non-SS dry eye patients and healthy controls could be informative. In addition, some of our diagnoses of neuropathic pain (eg, oral) were presumptive as they were derived from existing available variables, and no information regarding the history of the pain was available. However, it is not clear why this would skew the presumptive diagnosis as being more common among those not classified as having SS.

CONCLUSION

Participant-reported neuropathic pain was lower among participants classified as having SS compared with those classified as non-SS based on the ACR/EULAR criteria. Our findings suggest that people with SS may not necessarily experience painful neuropathies. Non-SS dry eye patients could benefit from pain assessment as they may have more painful idiopathic SFN. An investigation of the etiology of pain in non-SS patients with dry eye disease may be useful as symptoms, which are disproportionate to the signs of dry eye disease, could indicate a neuropathic basis.[2] Because painful neuropathies can be seen in non-SS patients, we recommend that pain be assessed for all new dry eye patient evaluations and in follow-up as painful neuropathies can evolve over time. Pain questionnaires can help identify pain associated with SFNs in patients with SS and non-SS dry eye. Incorporating objective measures of neuropathy, such as the evaluation of the corneal sub-basal nerve plexus using in vivo confocal corneal microscopy, would be useful for a more robust assessment of pain in future studies.

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SIGNIFICANCE AND INNOVATIONS

- Participant-reported neuropathic pain symptoms were lower among participants classified as Sjögren's syndrome (SS) compared with those classified as non-SS based on the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) criteria.
- Non-SS patients with dry eye disease or symptoms could benefit from pain assessment as they may experience painful small-fiber neuropathies (SFNs).
- We recommend pain be assessed for all new dry eye patient evaluations and in follow-up, as painful neuropathies can evolve over time.
- Pain questionnaires may help identify pain associated with SFNs in patients with SS and non-SS dry eye. Future studies would be helpful to correlate self-reports of pain to objective measures of SFNs in those with and without SS.

Table 1.

SICCA cohort demographics and pain reports

	Bodily pain			Ocular pain			Oral pain
	Pain interference with work quite a bit or extremely	**Sharp "jabbing" needle-like pain**	**"Prickling" or "tingling" feeling**	**Having light sensitivity most or all of the time**	**Burning or stinging most or all of the time**	**Having pain/burn at night most or all of the time**	**Presumptive neuropathic oral pain**
Classified as SS[1]	368 (23.9%)	467 (30.3%)	551 (35.8%)	386 (25.1%)	211 (13.7%)	194 (12.6%)	176 (11.4%)
Classified as non-SS[1]	705 (38.1%)	823 (44.3%)	898 (48.4%)	578 (31.2%)	332 (17.9%)	314 (17.0%)	409 (22.1%)
Sex							
Women	1006 (31.6%)	1215 (38.2%)	1359 (42.7%)	925 (29.1%)	525 (16.5%)	492 (15.5%)	549 (17.3%)
Men	100 (32.4%)	95 (30.7%)	110 (35.6%)	70 (22.7%)	42 (13.6%)	31 (10.0%)	40 (12.9%)
Race							
White	731 (36.3%)	906 (44.9%)	950 (47.1%)	633 (31.4%)	385 (19.1%)	351 (17.4%)	389 (19.3%)
Non-White	374 (25.4%)	402 (27.3%)	516 (35.0%)	361 (24.5%)	182 (12.3%)	171 (11.6%)	199 (13.6%)
Age group							
21 to 30 years	50 (25.4%)	60 (30.6%)	69 (35.2%)	47 (23.9%)	32 (16.2%)	29 (14.7%)	53 (17.0%)
31 to 45 years	238 (29.7%)	299 (37.2%)	353 (44.0%)	233 (29.1%)	133 (16.6%)	124 (15.4%)	132 (17.3%)
46 to 64 years	617 (34.5%)	719 (40.1%)	789 (44.1%)	515 (28.8%)	308 (17.2%)	291 (16.3%)	320 (18.8%)
65 years and older	200 (28.5%)	231 (33.0%)	257 (36.7%)	200 (28.5%)	94 (13.4%)	78 (11.1%)	84 (12.0%)
Site							
Argentina	135	175	293	140	77	97	108
China	38	34	33	36	9	1	23
Denmark	244	263	322	142	84	89	93
India	78	17	17	56	40	13	0
Johns	100	136	140	101	78	57	76
Hopkins (US)							
Japan	48	88	123	79	19	30	45
UCSF (US)	261	353	311	279	161	154	160
United Kingdom	103	118	106	74	42	35	35
UPenn (US)	99	129	131	88	57	47	49

Abbreviations: SICCA, Sjögren's International Collaborative Clinical Alliance; SS, Sjögren's syndrome; UCSF, University of California – San Francisco; UPenn, University of Pennsylvania.

Table 2.

Multivariable analyses – association between indicators of pain and being classified as SS

	Independent variable	Responses	OR	95% CI	*p* value
Bodily pain	Pain interference with work (Not at all = reference)	A little bit	0.73	0.59 to 0.90	<0.01
		Moderately	0.63	0.51 to 0.78	<0.001
		Quite a bit	0.51	0.41 to 0.64	<0.001
		Extremely	0.36	0.26 to 0.49	<0.001
	Sharp jabbing needle-like pain (No = reference)	Yes	0.70	0.60 to 0.82	<0.001
	Prickling or tingling feeling (No = reference)	Yes	0.80	0.68 to 0.93	<0.01
	Decrease (or inability) to feel to feel surface features, size, shape or texture	Yes	0.77	0.61 to 0.98	0.03
	Decrease (or inability) to recognize hot from cold	Yes	0.63	0.45 to 0.88	<0.01
	Decrease (or inability) to feel pain, cuts,bruises, or injuries	Yes	0.74	0.57 to 0.95	0.02
Ocular pain	Light sensitivity (None of the time = reference)	Some of the time	0.93	0.78 to 1.13	0.48
		Half of the time	0.88	0.65 to 1.20	0.43
		Most of the time	0.77	0.61 to 0.97	<0.05
		All of the time	0.78	0.61 to 0.99	<0.05
	Burning or stinging (None of the time = reference)	Some of the time	0.95	0.80 to 1.13	0.58
		Half of the time	0.61	0.46 to 0.81	<0.001
		Most of the time	0.81	0.63 to 1.04	0.09
		All of the time	0.64	0.44 to 0.91	<0.05
	Pain/burn at night (None of the time = reference)	Some of the time	0.96	0.79 to 1.16	0.65
		Half of the time	0.77	0.53 to 1.12	0.18
		Most of the time	0.77	0.59 to 1.01	0.06
		All of the time	1.00	0.73 to 1.35	0.98
Oral Pain	Presumptive neuropathic oral pain	Yes	0.52	0.43 to 0.63	<0.001
Composite pain score		-	0.86	0.83 to 0.90	<0.001
Total bodily pain score		-	0.84	0.79 to 0.89	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio; SS, Sjögren's syndrome.

Table 3.

Multivariable analyses –association between indicators of weakness and being classified as SS

Independent variable	Responses	OR	95% CI	*p* value
Weakness of hands	Yes	0.79	0.67 to 0.92	<0.01
Weakness of fingers	Yes	0.85	0.73 to 0.99	0.04
Weakness of shoulder/upper arms	Yes	0.86	0.73 to 1.01	0.07
Weakness of thighs	Yes	0.85	0.72 to 1.01	0.06
Cannot walk on heels	Yes	0.83	0.67 to 1.03	0.09
Cannot walk on toes	Yes	0.83	0.67 to 1.04	0.10

Abbreviations: CI, confidence interval; OR, odds ratio; SS, Sjögren's syndrome.

Table 4.

Multivariable linear regression – association between reports of ocular pain and corneal staining

Independent variable	Responses	Coefficient	95% CI	*p* value
Light sensitivity (None of the time = reference)	Some of the time	0.45	0.16 to 0.74	0.03
Burning or stinging (None of the time = reference)	Some of the time	0.29	0.15 to 0.57	0.04
	Most of the time	0.79	0.39 to 1.18	<0.01
Pain/burn at night (None of the time = reference)	Some of the time	0.38	0.08 to 0.67	0.01
	Most of the time	0.56	0.16 to 0.97	<0.01

Abbreviation: CI, confidence interval.