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Characteristics of ocular pain complaints in patients with idiopathic dry eye symptoms

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Abstract

Objective—The purpose of this study was to examine the severity and quality of ocular pain complaints in patients with dry eye symptoms.

Methods—Subjects with clinically-relevant dry eye symptoms (dryness, discomfort, tearing) of unknown origin seen in the Miami Veterans Affairs eye clinic were administered questionnaires for dry eye symptoms and ocular pain and underwent a standardized ocular examination. Qualities and severity ratings of ocular pain in subjects with idiopathic dry eye were compared to similar measures from published data in other chronic pain populations.

Results—The study sample consisted of 154 subjects, of which 91% were male and ranged in age from 27 to 89 (mean age = 61). Fifty-three percent of participants reported an average ocular pain of at least moderate intensity (numerical rating scale (NRS) ≥ 4), with specific characteristics (i.e., “burning” spontaneous pain) reported at frequencies comparable to prevalent chronic neuropathic pain syndromes as reported in the literature. Significant correlations were found between ocular pain metrics and dry eye symptom severity scores (r=0.57 to 0.66). Dry eye signs, however, did not generally correlate with ocular pain severity.

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Conclusions—A significant proportion of subjects with idiopathic dry eye symptoms reported moderate or greater ocular pain intensity, with the majority endorsing descriptors commonly used by patients with non-ocular neuropathic pain conditions. Identifying sub-groups of dry eye patients based on the presence and characteristics of ocular pain complaints may improve dry eye sub classification and better individualize treatment strategies.

Keywords

dry eye; ocular pain; neuropathic pain; neuronal dysfunction; sensitization

Introduction

Published estimates suggest that up to 30% of the population aged 50 years and older are affected by dry eye.[1] Dry eye's prevalence and morbidity combine to impart a significant financial burden, with an estimated indirect cost of $55 billion dollars annually in the U.S.[2] Studies using the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire have shown that dry eye negatively impacts daily activities, including reading, driving, and computer use.[3-5]

Historically, dry eye was thought of as a primary disorder of tear dysfunction leading to visual difficulties and classical symptoms of "dryness," "irritation," and "foreign body sensation."[6] However, dry eye signs, such as tear secretion (e.g. Schirmer test) and evaporation (e.g. tear break up time (TBUT)), often do not correlate well with dry eye symptoms.[7-10] Furthermore, there is a subset of patients with dry eye symptomology who have normal tear film parameters.[11] In recent years, several publications have suggested that dry eye likely results from multiple mechanisms, including pathology not only at the ocular surface, but also within the corneal peripheral and/or central somatosensory systems.[12-16] While the initial ocular insult may occur in the setting of a variety of conditions, including noxious environmental exposures, trauma (e.g. surgery), systemic autoimmune conditions, and chronic contact lens use; with persistent pathology, the postulated mechanism suggests neuroplasticity (peripheral and central sensitization) facilitating an acute-to-chronic pain transition. This hypothesis was very recently exemplified in an animal model of dry eye, where tear deficient rats exhibited conspicuous up-regulation of ocular responsive neural activity, characterized by central sensitization of trigeminal pathways at multiple levels in the brainstem.[17] Thus, for at least a subset of patients diagnosed with dry eye, the presence of physiologic dysfunction within the corneal somatosensory pathways, including peripheral and central neurons, (i.e. neuropathic ocular pain) may drive symptoms.

As such, it is likely that what is currently termed "dry eye" consists of a heterogeneous mix of syndromes, some of which may be more accurately defined as chronic pain conditions.[1,11] Symptoms typically associated with dry eye include descriptors that are synonymous with pain (defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[18]) Due to these wide phenotypic variations, it may be useful to subcategorize patients with dry eye symptoms into those with and without tear dysfunction, and those with and without chronic ocular pain symptoms. Characterizing pain-specific symptoms associated with dry

eye could potentially aid in identifying pertinent pathogenic mechanisms and facilitate the development of more targeted and effective treatment options.

Despite this hypothetical framework, little has been done to document the prevalence and characteristics of ocular pain associated with dry eye. In non-ocular pain conditions, validated self-report questionnaires are often used to identify the intensity and qualities of pain.[19-20] However, standardized pain questionnaires have not been used to assess the quality of pain related to dry eye. Therefore, in order to better understand ocular pain phenotypes within the context of dry eye, the present study was undertaken to investigate the prevalence, severity, and quality of pain complaints in patients with dry eye, using a numerical rating scale (NRS) for pain intensity, the short-form McGill Pain Questionnaire (SF-MPQ)[19], and the Neuropathic Pain Symptom Inventory (NPSI)[21], to compare these characteristics with published data from other chronic pain conditions, and to correlate these symptoms with ocular signs of dry eye.

Methods

A cross-sectional design was used to assess relationships between pain variables and dry eye metrics (symptom questionnaires and ocular surface examination). The research protocol was approved by the Miami VA Institutional Review Board and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population

Patients being seen in the eye clinic at the Miami VAMC were prospectively recruited by various practitioners between October 2013 and April 2015. The Miami VAMC eye clinic serves veterans in South Florida and evaluates and treats patients with a variety of ophthalmic conditions including refractive issues, cataracts, glaucoma, and retinal pathologies in addition to performing screening for eye pathology in patients with systemic conditions (diabetes, hypertension). As we wished to study “idiopathic” dry eye, that is dry eye symptoms not associated with well-established ocular or systemic conditions, patients were excluded from the potential participant pool if they had concomitant ocular or systemic processes that could confound their clinical presentation, such as anatomic abnormalities of their eyelids (e.g. ectropion), conjunctiva (e.g. pterygium), and/ or cornea (e.g. edema), history of glaucoma, history of refractive or retinal surgery, active external ocular process, cataract surgery within the last 6 months, use of contact lenses or ocular medications with the exception of artificial tears, HIV, sarcoidosis, graft-versus host disease, multiple sclerosis, stroke, or collagen vascular disease.

Procedures

Patients seen at the VA eye clinic who were interested in participating in the study were referred to the study coordinator who confirmed the absence of exclusion criteria. The study coordinator contacted the potential participant and scheduled the study session on a separate day. Informed consent procedures were completed, and questionnaires were administered to each subject by a member of the research team in the following order: 1) demographic information, past ocular, health, and medication history questionnaires (with co-morbidities

and medications being verified via medical record); 2) standardized questionnaires regarding dry eye symptoms (DEQ-5[22] and Ocular Surface Disease Index (OSDI)[23]); and 3) ocular pain questionnaires (NRS; SF-MPQ; a subset of questions taken from the NPSI). After questionnaires were completed, a standard examination of the ocular surface was performed.

The focus of the present paper includes data from a subgroup of subjects from this study. Only subjects who had at least mild clinically-significant dry eye symptoms, based on obtained DEQ-5 scores of greater than or equal to 6,[22] were included in the present data analysis.

Measures

Dry eye symptoms

DEQ-5[22]: The DEQ-5 is a validated[22], 5-item questionnaire that serves as a simple and rapid method for the diagnosis of dry eye. It combines patient responses regarding “eye discomfort” (frequency and intensity), “eye dryness” (frequency and intensity), and “watery eyes” (frequency) during the past month. DEQ-5 scores range from 0 to 22, with higher scores corresponding to greater severity of symptoms.

OSDI[23]: The OSDI is a validated tool for measuring the severity of dry eye[23] and was developed to evaluate the degree of disability associated with dry eye symptoms. It is scored on a 0 to 100 scale, with higher scores indicating greater disability associated with dry eye symptoms.

Ocular pain

NRS: Subjects were asked to rate the intensity of their average eye pain over a 1-week recall period using a numerical rating scale anchored at “0,” for “no pain sensation” and at “10,” for “the most intense eye pain imaginable.” This type of 0-10 NRS is recommended as the primary outcome measure in chronic pain clinical trials.[24]

SF-MPQ[19]: The SF-MPQ is a shortened form of the original MPQ[20], using the most commonly endorsed descriptors for sensory and affective dimensions across a number of pain patient groups. The SF-MPQ has been validated against the MPQ[19] and has been used by a number of groups across a variety of diagnoses.[25-27] Ratings of the severity (none, mild, moderate, or severe) of each of the 11 sensory descriptors (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, splitting) and 4 affective descriptors (tiring-exhausting, sickening, fearful, and punishing-cruel) from the SF-MPQ were collected. Subjects were asked to respond to all questions specifically in relation to their eye pain only. SF-MPQ subscores and total score were compared with published data from other pain patient groups.

NPSI[21], questions 1 – 3, 5, 6, 11, and 12: The NPSI has been validated as an appropriate self-report instrument for assessing neuropathic pain,[21, 28-30], has been used to quantify different aspects of neuropathic pain,[21,29,30] and has been found to correlate with mechanical/ thermal allodynia and hyperalgesia assessed using quantitative sensory testing (QST).[30] However, it has not been validated specifically in samples of patients reporting

ocular pain. We utilized aspects of the NPSI that consist of 7 descriptors that are commonly associated with neuropathic pain. We omitted questions 4 and 7, which refer to temporal aspects of the pain condition, and questions 8, 9, and 10 from the analysis because they refer to pain evoked by stimuli that are not appropriate for the eye (i.e., brushing, pressure, or contact with cold in the painful area). Although these questions were omitted, responses from the remaining questions (1-3, 5, 6, 11, and 12) provide insight into specific neuropathic pain features when compared with published data from other pain patient groups specifically for responses to these overlapping questions. A total score was calculated from this subset of NPSI questions to use in analyses regarding relationships between neuropathic-like pain severity and dry eye characteristics.

Standardized ocular surface evaluation—All patients underwent tear film assessment, including measurement of (1) tear osmolarity (TearLAB, San Diego, CA) (once in each eye); (2) tear evaporation measured via tear breakup time (TBUT) (5 μl fluorescein placed, 3 measurements taken in each eye and averaged); (3) corneal epithelial cell disruption measured via corneal staining (National Eye Institute (NEI) scale[6], 5 areas of cornea assessed; score 0-3 for each area and total score 0-15); (4) tear production measured via Schirmer's strips with anesthesia; (5) meibomian gland assessment: eyelid vascularity was graded on a scale of 0 to 3 (0 none; 1 mild engorgement; 2 moderate engorgement; 3 severe engorgement) and meibum quality on a scale of 0 to 4 (0 = clear; 1 = cloudy; 2 = granular; 3 = toothpaste; 4 = no meibum extracted). *High* tear osmolarity, corneal staining, and meibomian gland scores, and *low* TBUT and Schirmer's scores are indicative of more severe dry eye.

Statistical Analysis

All statistical analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL) statistical package. Pearson and Spearman correlations were used to evaluate the strengths of association among ocular pain characteristics and standard assessments of dry eye symptoms and signs. Multi-variable linear regression analyses were performed to evaluate the contributions of ocular surface and tear film parameters, dry eye symptom severity, and health and medication variables to the severity of ocular pain, as measured by NRS and total scores on the SF-MPQ and the NPSI. A p-value of less than 0.05 was considered significant.

Results

Study sample

One hundred fifty-four patients met inclusion criteria, completed informed consent, questionnaires and ocular examination, and were included in data analysis. Demographic information, medical conditions, relevant systemic medications, and dry eye information for the study sample are summarized in Table 1.

Presence and intensity of ocular pain in dry eye subjects

The presence of ocular pain was examined using an 11-point NRS identifying the subject's "average" and "worst" intensity of eye pain over the past 1-week period. Based on previously defined cut-offs,[31] 11% (n = 17) of subjects reported no pain (NRS = 0) on

average over a 1-week recall period, 36% (n = 56) reported mild pain (NRS 1 - 3), 34% (n = 52) reported moderate pain (NRS 4 - 6), and 19% (n = 29) reported severe pain (NRS 7 – 10). A similar pattern was seen for worst pain over a 1 week recall period: 11% (n = 17) no pain, 25% (n = 39) mild pain, 26% (n = 40) moderate pain, and 38% (n = 58) severe pain.

Characteristics of ocular pain via the SF-MPQ

Eighty-two percent of dry eye subjects endorsed at least one sensory or one affective descriptor for their eye pain on the SF-MPQ. The frequencies of the different qualities of eye pain reported by subjects with dry eye symptoms are presented in Table 2. Subjects with dry eye most frequently described their ocular pain as “tiring-exhausting” (56%) and “aching” (56%), followed by “hot burning” (53%).

Comparisons of SF-MPQ sensory and affective dimension scores from our sample were made with data from other chronic pain samples from the literature[32-35] (Table 3). In order to make data from the current dry eye sample comparable to these studies, only subjects who rated their average eye pain during the past week as at least 4 out of 10 on a NRS were included, as this was equivalent to the inclusion criteria for the previously published studies that were used for comparison.[32-35] Our patient cohort fell in the mid-range of scores compared to the other data taken from the literature, and appears most similar to the central neuropathic pain patients studied by Onouchi et al.[33]

Characteristics of ocular pain via NPSI

The frequency of positive responses and mean intensity scores to the NPSI questionnaire from the dry eye population are summarized in Table 4. For comparison, we also present data from Sommer et al[29] who used the NPSI-G (German validated version) to evaluate patients with chronic neuropathic pain conditions and those with pains that are primarily non-neuropathic in nature (osteoarthritis and headache). Specifically, burning was a frequent complaint in both our dry eye sample and in the chronic neuropathic pain conditions group but was less commonly seen in those with osteoarthritis and headache.

Correlation among questionnaires

Total scores on the SF-MPQ and the NPSI were highly correlated with each other (Pearson r = 0.72; Spearman rho 0.71, p <0.0005), and both were highly correlated with NRS ratings of eye pain (r = 0.61 (SF-MPQ vs. NRS); r = 0.66 (NPSI vs. NRS)). The DEQ5 and OSDI were also highly correlated with each other (Pearson r = 0.64; Spearman rho =0. 65, p<0.0005).

Correlation between ocular pain metrics and symptoms and signs of dry eye

Although pain metrics strongly correlated with the intensity of dry eye symptoms (DEQ-5, OSDI), similar associations were not observed between pain metrics and dry eye signs/ ocular surface measures (Table 5). Separate, forward, step-wise multi-variable linear regression analyses were performed to assess the factors that most strongly associated with each measure of ocular pain (NRS, total SF-MPQ score, and total NPSI score). Predictor variables included all ocular surface parameters (osmolarity, TBUT, corneal staining, Schirmer’s score, eyelid vascularity, eyelid quality), measures of dry eye symptom severity (DEQ-5, OSDI), and the demographic, health, and medication variables that were found to

be significantly associated with each pain measure separately. DEQ-5 scores and arthritis explained 42% of variability in NRS scores (R=0.65) and 39% of variability in NPSI scores (R=0.62), and DEQ-5 scores and the use of anxiolytics explained 37% of variability in total SF-MPQ scores (R=0.61). All other variables entered into the models did not significantly contribute to estimating ocular pain severity.

Discussion

The goal of this study was to delineate the frequency, severity, and quality of ocular pain in patients with dry eye symptoms and to compare these parameters with those of patients with non-ocular chronic pain conditions. The importance of pain as a prevalent symptom of dry eye is evidenced by our results demonstrating that many dry eye patients report ocular pain. Thus, a simple clinical tool such as the 11-point NRS can help guide the clinician in determining the extent of ocular pain present in the patient with dry eye symptoms. The NRS has been validated as a measure of pain intensity across multiple populations[34-38] and has been recommended for use as the primary outcome metric in clinical trials for chronic pain[24]. Further studies are needed, however, to validate the NRS specifically for ocular pain and to help define NRS cut-off values that can identify levels of ocular pain that are clinically significant. It is important to note that although the questionnaires utilized in the present study have not been directly validated for ocular pain, the strength in their use is our ability to compare pain complaints in patients with dry eye symptoms to those with various non-ocular pain conditions. In this regard, we found that “spontaneous burning pain” was a frequent complaint in both our dry eye sample and in chronic neuropathic pain conditions from the literature.[29] Unlike the skin, however, descriptors such as “burning”, in the setting of dry eye, may have a multifactorial etiology which could include both nerve dysfunction and/or evaporative stress. Despite this, in our previous work, we found that patients who reported “hot-burning” ocular pain had a more severe and persistent dry eye course[39] and were less likely to respond favorably to artificial tears[40], indicating that this descriptor may have clinical utility in identifying a more severe dry eye sub-type that is less related to tear film status. In fact, in pain conditions in areas outside the eye, “burning” has been shown to be more commonly used to describe neuropathic pain than other descriptors, and to substantially contribute to the differentiation between neuropathic and nociceptive pain patient groups.[41-42] More work needs to be done, however, to determine which, if any, descriptors can similarly help differentiate between different etiologies of pain in dry eye.

Qualitative descriptors of pain from the MPQ and the SF-MPQ have also been used by other researchers to distinguish pain types and to suggest potential mechanisms underlying different pain conditions.[41-42] The most common descriptors from the SF-MPQ chosen by our subjects with dry eye were: “tiring-exhausting”, “aching”, and “hot burning”. Similarly, burning mouth syndrome, traditionally described as a “discomfort’ condition,”[43] was later re-defined as a pain condition, with the MPQ adjectives “burning” and “tiring” among the five most frequently reported descriptors for this syndrome.[44] Thus, the overlap in symptom profile between dry eye and burning mouth syndrome, two pain conditions that manifest within the distribution of the trigeminal nerve, may suggest similar, overlapping mechanisms of pain.

Interestingly, despite the apparent convergence of ocular pain metrics and overall intensity of dry eye symptoms, such concordance was not observed when evaluating the relationship between pain and ocular surface parameters and tear film insufficiency. This again accentuates the potential engagement of underlying mechanisms attributed to nociceptive system dysfunction in some patients with chronic dry eye symptoms, which may be particularly relevant for those who present with dry eye symptoms but normal tear film and corneal surface parameters. Unfortunately, the structure of the eye does not currently allow for clinical use of the more commonly employed diagnostic studies, which can objectively evaluate for the presence of neuropathy, such as nerve conduction studies and quantitative sensory testing (QST). However, with the use of *in vivo* confocal imaging, Erdelyi et al., has demonstrated microneuroma formation in the corneal nerves of some dry eye patients, suggesting neuronal dysfunction.[45] Belmonte aesthesiometry testing has revealed differences in mechanical detection thresholds in dry eye patients, with some patients exhibiting decreased[46-48] and some increased thresholds[49,50] compared to controls. Furthermore, elevated levels of nerve growth factor (NGF) and other neuromediators have been reported in some patients with dry eye, once again, suggesting that neuroplasticity may be partly involved with pathogenesis.[51] Taken together, these findings suggest a link between chronic pain and dry eye that needs to be further explored.

The results of the present study now have systematically documented the characteristics of ocular pain in patients with “idiopathic” dry eye. These findings suggest that ocular pain is an important component of dry eye, and that corneal somatosensory dysfunction, including peripheral and central sensitization, may be a factor to consider when diagnosing and treating dry eye patients. Previous work in a large female cohort in England supports this assertion.[52, 53] Vehof et al. have documented a positive association between dry eye and other chronic pain conditions (i.e., pelvic pain, irritable bowel syndrome, and chronic widespread pain syndrome)[53], and have found that the group of subjects with dry eye had significantly heightened pain sensitivity to thermal stimuli presented on the forearm compared to subjects without a dry eye diagnosis.[52] These findings suggest that dry eye may be one “symptom” of a more centralized pain condition. Further elucidation of pain-relevant neural circuits implicated in the manifestation of dry eye may facilitate future development of directed therapies.

As with all studies, this work has limitations, which need to be considered when interpreting the results. Subjects in this study were volunteers from a population of older, mostly male, US veterans with a high frequency of comorbid conditions and as such, and thus making generalizations to other patient groups (i.e., non-veterans, women, younger patients) is limited. Furthermore, we excluded patients with ocular co-morbidities such as a history of refractive surgery and contact lens use so as to study pain complaints in patients with “idiopathic” dry eye. Repeating these questionnaires in other sub-groups of patients with dry eye symptoms will be an important avenue for further study. The order in which the questionnaires were administered might also produce biases with regards to self-report. Because the questionnaires were completed in the same order for all subjects, it was not possible to assess whether an order-affect may have influenced scores or the relationships among the metrics. In addition, the use of a cross-sectional questionnaire carries inherent response bias, subjectivity, or overestimation of self-reported symptoms. Also, we modified

the NPSI questionnaire in our study by omitting questions that appeared inappropriate for the eye; this may also limit our findings. However, we felt that our goal of providing descriptive information on ocular pain complaints, and the comparison of dry-eye related pain to other chronic pain conditions was still accomplished with the use of data obtained from the individual questions that were administered from the modified NPSI. The moderate-high correlations between the modified total NPSI score and the SF-MPQ and the NRS, suggests this NPSI total score is valid for the analyses presented here. Further studies will be needed to more adequately validate pain questionnaires that can be used specifically to characterize and quantify ocular pain. Continued exploration will be critical to extend our findings to more directly assess the natural history of dry eye and the relationships among neuronal dysfunction, neuropathic pain-like symptoms, ocular signs, and other chronic pain syndromes.

With these limitations in mind, this study highlights the prevalence of ocular pain, with frequent neuropathic-like qualities, in a significant subgroup of patients with dry eye. The therapeutic implications of assessing the characteristics of eye pain, including its qualities, temporal patterns, and exacerbating and alleviating factors, should be further explored. The importance of eventually defining endophenotypes in patients with dry eye is that mechanism-based treatments may be used to better target subtypes of patients most likely to benefit from these interventions.

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Table 1

Demographic information and clinical features of the studied population.

Characteristic	Mean (SD)	Range
Age, years	64 (11)	27-89
	Number	**Percent**
Gender, male	140	91%
Race, white	75	49%
black	71	46%
Ethnicity, Hispanic	43	28%
Co-morbidities		
Current Smoking	45	29%
Hypertension	115	75%
Hypercholesterolemia	97	63%
Diabetes	57	37%
Post traumatic stress disorder	40	26%
Depression	92	60%
Arthritis	65	42%
Sleep apnea	33	21%
Medications		
Anti-depressants	67	44%
Anxiolytics	65	42%
Analgesics	102	66%
Anti-histamine	29	19%
Gabapentin/ Pregabalin	37	25%
Duloxetine/ Venlafaxine	4	3%
Dry eye symptoms	**Mean (SD)**	**range**
DEQ-5	12.9 (3.9)	6-22
OSDI	39 (25)	0-100
Dry eye signs		
Tear osmolarity, mOsm/L	304 (17)	277-371
Tear film breakup time, seconds	9.1 (3.7)	2.6-25
Corneal staining, (0-15)	2.2 (2.6)	0-14
Schirmer’s test, mm of moisture	13.9 (6.4)	0-32
Eyelid vascularity, (0-2)	1.9 (1.2)	0-2
Meibum quality, (0-4)	0.65 (0.76)	0-4

DEQ-5=Dry Eye Questionnaire 5; OSDI=Ocular Surface Disease Index; SD=standard deviation.

Table 2

SF-MPQ responses in subjects with mild or greater dry eye symptoms (DEQ-5≥6).

	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Aching	68 (44%)	44 (29%)	25 (16%)	15 (10%)
Tiring-exhausting	67 (44%)	46 (30%)	21 (14%)	18 (12%)
Hot-burning	72 (47%)	42 (27%)	24 (16%)	14 (9%)
Sharp	89 (58%)	38 (25%)	13 (8%)	12 (8%)
Tender	89 (58%)	35 (23%)	22 (14%)	6 (4%)
Throbbing	92 (60%)	35 (23%)	15 (10%)	10 (7%)
Heavy	92 (60%)	34 (22%)	18 (12%)	8 (5%)
Stabbing	101 (66%)	31 (20%)	10 (6.5%)	10 (6.5%)
Gnawing	105 (68%)	30 (20%)	13 (8%)	4 (3%)
Sickening	105 (68%)	31 (20%)	12 (8%)	4 (3%)
Splitting	110 (71%)	29 (19%)	9 (6%)	4 (3%)
Punishing-cruel	110 (71%)	21 (14%)	14 (9%)	7 (5%)
Fearful	111 (72%)	24 (16%)	13 (8%)	4 (3%)
Shooting	117 (76%)	19 (12%)	9 (6%)	7 (5%)
Cramping	119 (77%)	25 (16%)	5 (3%)	3 (2%)

SF-MPQ=short-form McGill Pain Questionnaire; DEQ-5=Dry Eye Questionnaire 5.

Table 3

The mean intensity of dimensions of the SF-MPQ (mean(SD)) in the dry eye sample compared with common etiologies of neuropathic pain.

SF-MPQ dimension score	Dry eye sample (mean (SD))	Central neuropathic pain conditions (mean(SD))		Diabetic neuropathic pain (mean(SD))	Post-herpetic neuralgia pain (mean(SD))
	(n=81 *)	Siddall et al. (n=136)[32]	Onouchi et al. (n=103)[33]	Satoh et al. (n=123)[34]	Rowbotham et al. (n=110)[35]
Total	13.0 (9.7)	17.9 (9.1) †	12.2 (9.1)	9.4 (7.5) †	18.7 (8.5) †
Sensory	9.7 (7.1)	13.7 (6.6) †	9.5 (7.1)	7.4 (5.5) †	14.5 (6.4) †
Affective	3.2 (3.1)	4.3 (3.2) †	2.7 (2.6)	2.0 (2.5) †	4.1 (3.2)

SF-MPQ=short-form McGill Pain Questionnaire; SD=standard deviation.

Siddall et al. study[32] included patients with central neuropathic pain conditions from spinal cord injury.

Onouchi et al. study[33] included patients with central neuropathic pain conditions from spinal cord injury (37%), cerebral stroke (58%), and multiple sclerosis (5%).

* In order to make data from the current dry eye sample comparable to those from the literature, only subjects who rated their average eye pain during the past week at least 4 out of 10 on a NRS were included.

† P value comparison of means between non-ocular pain population and dry eye population <0.05 (2 tailed independent t test).

Table 4

Proportion of patients reporting neuropathic pain symptoms (NPSI score ≥ 1) compared to other chronic neuropathic conditions, osteoarthritis, and headache.

NPSI Item	Dry Eye (n=154)	Chronic neuropathic pain conditions* (n=68)	Osteoarthritis* (n=93)	Headache* (n=76)
	%	%	%	%
Burning	70.1	73.4	31.9†	30.8†
Squeezing	46.8	50.8	24.3†	53.1
Pressure	63.0	64.4	67.0	87.5†
Electric	34.4	42.6	21.9†	42.2
Stabbing	44.2	68.8†	68.9†	61.6†
Pins/needles	43.5	77.7†	26.1	35.6
Tingling	56.5	52.3	26.4†	30.5†

NPSI: Neuropathic Pain Symptom Inventory, modified for dry eye, questions 8-10 on evoked pain not used as these are not appropriate for the eye.

*Neuropathic pain (central pain – 12%, nerve injury pain – 15%, peripheral neuropathy – 73%), osteoarthritis, and headache patient samples, data adapted from Sommer et al.[29]

†P value comparison of frequencies between non-ocular pain population and dry eye population <0.05.

Table 5

Correlation coefficients examining the strength of association between pain metrics and dry eye symptoms and signs

Dry eye symptoms and signs	NRS Pearson r/ Spearman rho	SF-MPQ Pearson r/ Spearman rho	NPSI Pearson r/ Spearman rho
DEQ-5	0.66†/0.66†	0.59†/0.63†	0.61†/0.63†
OSDI	0.63†/0.61†	0.60†/0.59†	0.57†/0.57†
Osmolarity	0.05/0.06	0.04/0.05	0.110.13
Tear break up time	−0.08/−0.10	−0.09/−0.04	−0.08/−0.13
Corneal staining	0.06/0.03	0.05/0.06	0.08/0.11
Schirmer's score	−0.02/−0.05	−0.03/−0.06	−0.07/−0.13
Eyelid vascularity	−0.008/−0.01	0.00/−0.01	−0.09/−0.12
Eyelid quality	0.16/0.17*	0.06/0.03	0.08/0.08

NRS=Rating of average ocular pain intensity over a one week recall period on a numerical rating scale.

SF-MPQ=short form McGill Pain Questionnaire; NPSI=Neuropathic Pain Symptom Inventory, modified for dry eye, questions 8-10 on evoked pain not used as these are not appropriate for the eye.

DEQ-5=Dry Eye Questionnaire 5; OSDI=Ocular Surface Disease Index;

*p value<0.05;

†p value<0.00005.