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Neuropathic ocular pain due to dry eye is associated with multiple comorbid chronic pain syndromes

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ABSTRACT

Recent data demonstrate that dry eye (DE) susceptibility and other chronic pain syndromes (CPS) such as chronic widespread pain, irritable bowel syndrome and pelvic pain, may share common heritable factors. Previously, we showed that DE patients describing more severe symptoms tended to report features of neuropathic ocular pain (NOP). We hypothesize that patients with a greater number of CPS would have a different DE phenotype compared to those with fewer CPS. We recruited a cohort of 154 DE patients from the Miami Veterans Affairs Hospital and defined high and low CPS groups by cluster analysis. In addition to worse non-ocular pain complaints and higher PTSD and depression scores ($P<0.01$), we found that the high CPS group reported more severe neuropathic-type DE symptoms compared to the low CPS group, including worse ocular pain assessed via 3 different pain scales ($P<0.05$), with similar objective corneal DE signs. This is the first study to demonstrate DE patients who manifest a greater number of comorbid CPS report more severe DE symptoms and features of NOP. These findings provide further evidence that NOP may represent a central pain disorder, and that shared mechanistic factors may underlie vulnerability to some forms of DE and other comorbid CPS.

Perspective:

Dry eye (DE) patients reporting more frequent chronic pain syndromes (high CPS group) report worse DE symptoms and ocular and non-ocular pain scores. The high CPS group reports symptoms of neuropathic ocular pain (NOP) that share causal genetic factors with comorbid CPS. These results imply an NOP evaluation and treatment should be considered for DE patients.

Introduction

According to the Institute of Medicine Report on *Chronic Pain in America,* chronic pain conditions affect at least 116 million U.S. adults at a cost of $560–635 billion annually in direct medical treatment and lost productivity[8]. The Institute of Medicine report further concluded that, “Chronic pain has a distinct pathology, causing changes throughout the nervous system that often worsen over time.” Individuals suffering from one form of chronic pain often have other chronic pain conditions. These individuals will often describe mood disorders, disrupted sleep, decreased energy, difficulty concentrating, and report an overall decrease in their enjoyment of life [18, 42, 44, 56, 62, 64]. The phenomenon of a “chronic pain syndrome” (CPS) is somewhat poorly defined, but is essentially considered to be the persistence of pain past the point where resolution might reasonably be expected (often defined as 6 months or more). Such syndromes are thought to include functional disorders such as fibromyalgia, irritable bowel syndrome, temporomandibular pain, complex regional pain syndrome and chronic pelvic pain, as well as structural conditions such as diabetic neuropathy, osteoarthritis, and cancer pain, amongst others.

Dry eye is a common disorder that affects the quality-of-life of millions worldwide [58]. Dry eye is characterized by symptoms of ocular discomfort and visual disturbances, as well as variable signs including tear film and ocular surface disruption and inflammatory changes. [21, 41]. Damage or dysfunction in the corneal somatosensory pathway has also been postulated as a component of dry eye in some patients because of the high density and superficial location of the corneal nociceptors, making them vulnerable to repeated damage and injury [2, 22, 25]. Episodic or ongoing damage to

corneal nerves may result in permanent alteration of neuronal function, including reduced activation-thresholds and increased excitability [23, 24]. The abnormal corneal nerve morphology and sensitivity described in some patients with dry eye symptoms is consistent with this mechanism [3, 6, 50].

We previously reported that a subset of dry eye patients described their symptoms in terms consistent with neuropathic pain, including features of evoked pain to wind and temperature as well as increased sensitivity to light (photoallodynia or photophobia) [24]. In addition to dry eye symptoms of a specific neuropathic quality, the symptoms described by these patients also tended to be more severe and persistent than those of their "traditional" dry eye counterparts.[24] Furthermore, these symptoms were reported in the absence of objective ocular surface defects, and were more closely aligned to non-ocular or central neurologic mechanisms rather than to the presence of any ongoing peripheral pathology [19].

Additional evidence that some forms of dry eye represent a central disorder comes from work demonstrating increased forearm sensitivity to heat pain during objective quantitative sensory testing in dry eye patients.[56, 61] Similar to other CPS, dry eye is also strongly associated with depression, post-traumatic stress disorder, and sleep disruption [18, 20, 36]. Recent evidence suggests that both somatic and structural comorbid CPS, including dry eye, may share common genetic mechanistic factors [38, 62]. Collectively, these findings suggest that in at least some individuals, dry eye may actually represent a chronic neuropathic pain syndrome.

Given these results, in this study we hypothesize that dry eye patients with a greater number of chronic comorbid structural and functional pain syndromes (high CPS group) demonstrate a different phenotype than those with fewer comorbid conditions

(low CPS group). To study this question, we used cluster analysis to divide our population of symptomatic dry eye patients into these two groups according to their pain complaints. We then evaluated whether the high CPS group of dry eye patients reported symptoms of neuropathic ocular pain as compared to the low CPS group of dry eye patients.

Methods

Population Sample:

A cohort of 154 patients with dry eye symptoms, defined as a Dry Eye Questionnaire 5 score ≥6 and normal eyelid and corneal anatomy were prospectively recruited from the Miami Veterans Affair (VA) Healthcare System eye clinic between October 2013 and March 2015 and underwent a complete ocular surface examination. Patients were excluded from participation if they wore contact lenses, had ever undergone refractive, retinal, or glaucoma surgery or had undergone cataract surgery within the past 6 months, used ocular medications with the exception of artificial tears, had a history of HIV infection, sarcoidosis, graft-versus host disease or a collagen vascular disease, or acute ocular process such as conjunctivitis, infection, iritis. Miami VA Institutional Review Board (IRB) approval was granted (IRB number 3011.02) to allow the prospective evaluation of patients after informed consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki and Declaration of the World Medical Association.

Data collection:

For each individual, we collected data on demographics, past ocular and medical history, and current medications.

Binary CPS phenotype determination:

Patients were asked about the presence of the following chronic pain conditions, defined as any of the following for >3 months duration: arthritis, burn pain, headaches, diabetic neuropathy, tendonitis, central pain syndrome, muscle pain, complex regional pain syndrome/causalgia, back pain, cancer pain, trigeminal neuralgia, sciatica, shingles, surgical pain, temporomandibular pain, and fibromyalgia. Patients were also given a pain drawing in which they marked current locations of pain. The total number of pain locations was computed from these drawings as a summary score. Using a two-step cluster analysis based on number of reported chronic pain conditions and the pain locations summary score, the patient population was divided into two groups. Cluster group 1 (n=57) had a lower number of CPS (mean 2.5, SD 1.5) and a lower number of current pain locations (mean 1.1, SD 0.7). Cluster group 2 (n=97) had a higher number of CPS (mean 6.2, SD 3.5) and a higher number of current pain locations (mean 3.8, SD 1.1). The remaining analyses were performed evaluating for differences in DE status between these high and low CPS cluster groups.

Ocular surface evaluation:

All patients underwent a tear film assessment which included, in the order performed: (1) tear osmolarity (TearLAB, San Diego, CA), (2) tear breakup time (TBUT), (3) corneal staining, (4) Schirmer's strips with anesthesia, and (5) meibomian gland assessment. Tear osmolarity testing was performed once in each eye prior to instillation

of eye drops. The osmolarity hand-piece was held over the outer 1/3 of the inferior conjunctivae to sample the inferior tear meniscus. Patients were asked to look up and nasally. TBUT was measured through a slit-lamp biomicroscope with a cobalt blue filter and a beam approximately 4mm wide and 10mm high using the lowest level of illumination. Starting with the right eye, the patient looked down and nasally. The examiner gently retracted the upper lid and 5 µl of preservative free fluorescein was placed on the superior bulbar conjunctivae. The upper lid was released and the subject was allowed to blink normally for 15 seconds. The patient's head was positioned in the headrest of the slit-lamp instrument, making sure the patient was comfortably supported with their forehead in full contact with the headrest band. The patient was instructed to blink three times naturally, then stare and not blink. The investigator monitored the integrity of the tear film and, using a stopwatch, measured the time from the last blink until one or more black (dry) spots appeared in the precorneal tear film. After the 1st measurement, the patient was instructed to blink naturally 3 additional times and a 2nd measurement was taken. The procedure was then repeated a 3rd time. After a 60-second rest period, the entire procedure was repeated for the left eye. Corneal staining was assessed using the NEI standard scoring scale assessing 5 areas of the cornea. A grade was assigned to each section of the cornea (range 0 to 3) and a total score was generated by summing the 5 section scores[57]. After placement of 10 µl of proparacaine in each eye, Schirmer's strips were placed in the outer 1/3 of the lower conjunctivae and the length of wetting after 5 minutes was recorded in each eye. Meibomian gland assessment included an evaluation of lower eyelid vascularity, graded on a scale of 0 to 4 (0 none; 1 mild engorgement; 2 moderate engorgement; 3 severe engorgement) and

meibum quality (0 = clear; 1 = cloudy; 2 = granular; 3 = toothpaste; 4 = no meibum extracted).

Characterization of pain syndromes

The following questionnaires were used to quantify the severity and characteristics of self-reported ocular and non-ocular pain, mental health, and quality of life.

Non-ocular pain severity: A numerical rating scale questionnaire (NRS) was used to assess concurrent non-ocular pain.[17] Scores ranged from 0 – 10 for the following questions: 1) How would you describe the overall intensity of your pain, on average during the last week? 2) How would you describe the overall intensity of your pain when it was at its worst, during the last 1 week?

Ocular symptoms: Patients were instructed to complete the following standardized questionnaires regarding their ocular complaints only: 1) Dry eye questionnaire 5 (DEQ5) (score 0-22); 2) Ocular surface disease index (OSDI) (score 0-100); 3) Numerical rating scale questionnaire (NRS) adapted for *ocular pain* ("How would you describe the overall intensity of your pain, on average during the last week? How would you describe the overall intensity of your pain when it was at its worst, during the last 1 week?"; score 0-10 for each question); (4) Neuropathic Pain Symptom Inventory (NPSI) applied to eye pain (score 0-100). In our modified version of the NPSI for neuropathic ocular pain we replaced 3 original descriptors (allodynia and hyperalgesia caused by brushing, pressure, or cold on the skin), with descriptors of ocular allodynia (eye pain caused or worsened by light and/or change in temperature) and ocular hyperalgesia (eye pain caused or worsened by wind); and (5) short form

McGill Pain Questionnaire (sf-MPQ) (score 0-45) to characterize eye pain (sensory and affective descriptors).

Mental health: Patients filled out standardized questionnaires to assess for the presence of depression using the Patient Health Questionnaire 9 (PHQ9) (score 0-27) and post traumatic stress disorder using the PTSD checklist – Military Version (PCL-M) (score 17-85).

Quality-of-Life: The Short Form Health Survey (SF-12) was used to obtain physical and mental health composite scores (PCS and MCS, score 0-100).

Analysis

Main outcome measures:

The main outcome measures were the frequency and severity of dry eye signs and symptoms (including neuropathic ocular pain), mental health indices, and quality-of-life measurements in high versus low CPS groups.

Statistical Methods:

All statistical analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL) statistical package. Frequencies and descriptive statistics were applied to data, as appropriate. Chi-squared, Fisher exact, Student's t-tests (for normally distributed variables), and Mann-Whitney tests (for non-normally distributed variables) were applied as appropriate to compare categorical and continuous variables between subjects.

Results

Demographics of Population Sample

Of the 149 subjects included in the study, 97 subjects were assigned to the high CPS group and 57 to the low CPS group based on cluster analysis. The high CPS group of DE patients were younger compared to the low CPS group (Table 1). Patients in the high CPS group also more frequently reported taking antidepressants and analgesic medication than their low CPS counterparts.

Non-ocular pain by group

Non-ocular pain was rated significantly greater in the high CPS versus low CPS group for mean and worst pain intensity during the past week (P<0.0005)(Table 2). Of the pain conditions reported, all were more frequent in the high CPS versus low CPS group (Table 3). This difference was not significant for fibromyalgia, post herpetic neuralgia, and cancer pain. The overall frequency of these CPS was also low (<10%), possibly due to our predominately male sample.

Ocular exam by group

Between the high CPS and low CPS group, no significant differences were seen in any objective ocular surface metrics (Table 4).

Ocular pain by group

The magnitude of all dry eye and ocular pain symptoms was greater in the high CPS versus low CPS group (Table 5). DE symptom scores were greater by both the DEQ5 and OSDI; and ocular pain scores were greater using all 3 instruments (NRS, NPSI, sf-MPQ)(P<0.05 for all). Furthermore, patients in the high CPS versus low CPS

group had significantly higher NPSI sub-scores for ocular burning spontaneous pain, pressing spontaneous pain, evoked pain, and paresthesias/dysesthesias.

Mental health and quality-of-life by group

Consistent with our hypothesis, both psychiatric and quality-of-life measurements indicated significantly worse disease scores in the high CPS group compared to the low CPS group (Table 6). Specifically, the high CPS group reported greater PTSD scores on the PCL-M greater depression scores on the PHQ9, and lower SF-12 physical and mental composite scores compared to the low CPS group ($P<0.01$ for all).

Discussion

Neuropathic ocular pain is associated with comorbid chronic pain syndromes

The diagnosis of “dry eye” is applied to a heterogeneous collection of clinical syndromes characterized by ocular irritation and visual disturbance, often described in terms of a “foreign body sensation” or “dryness”. However, some commonly reported features of dry eye type discomfort parallel the symptoms characteristic of neuropathic pain commonly seen in CPS, including allodynia (in the case of the eye, seen in response to innocuous saline eye drops or light), hyperalgesia, burning, and pain evoked by touch, heat, or cold (as well as wind, in the case of the eye) [5, 59]. In addition, some patients with dry eye also develop secondary hyperalgesia within the distribution of the trigeminal nerve, consistent with altered central pain processing [10]. This secondary hyperalgesia can present as headaches, blepharospasm, or generalized discomfort around the orbit, face, and jaw [4, 47, 54]. In addition to these qualitative

similarities in the character of the pain experienced in dry eye and other CPS, there is a growing body of literature that describes 1) that dry eye tends to be comorbid with other CPS, and 2) that CPS and dry eye appear to share common underlying genetic mechanisms, which may explain this clustering.

Our results provide evidence for the existence of a subset of dry eye patients whose ocular symptoms may be the manifestation of an underlying central pain processing disorder. Patients of the high CPS group reliably described elements of neuropathic ocular pain, including paresthesias and evoked pain on NPSI scores, and more severe symptoms than the low CPS group, who we might consider to have "traditional" dry eye. These differences in pain quality and severity are noted without any significant differences in objective corneal pathology, again suggestive of a central disorder. In addition to dry eye symptomatology, we found that our high and low CPS groups also differed significantly in psychiatric indices and quality-of-life assessments, including significantly greater depression and PTSD scores, and lower SF-12 scores in the high CPS group. Furthermore, those in the high CPS group reported significant higher sf-MPQ sensory and affective subscores, as well as total MPQ scores. This is not surprising given the known strong association between chronic structural and functional pain disorders and these psychiatric measures and quality-of-life indices [1, 18, 32, 42].

Neuropathic ocular pain may represent a central sensitivity syndrome

While the comorbid tendencies of CPS (including dry eye) and common underlying heritable factors have been well described, the proposed mechanism for the diverse manifestations of what appears to be a central disorder remains an open

question. While there is increasing recognition that dysregulation of central neurocircutry contributes to a range of chronic comorbid functional and structural pain disorders, the specific mechanisms remain elusive. Recently, there has been a move towards conceptualizing some of these comorbid chronic pain disorders as "central sensitivity syndromes" [18, 42, 44, 56, 62, 64], characterized by central nervous system neuroplasticity resulting in increased resposiveness of nocipceptive neurons and altered descending pain modulation [10]. Central sensitivity has been postulated to underly a variety of commonly comorbid conditions, including the structural and functional CPS assessed in this study, such as osteoarthritis, burn pain, headaches, diabetic neuropathy, tendonitis, central pain syndrome, muscle pain, complex regional pain syndrome/causalgia, back pain, cancer pain, trigeminal neuralgia, sciatica, shingles, surgical pain, temporomandibular pain, and fibromyalgia. [11, 12, 18, 27, 29-33, 42, 44, 45, 48, 51, 55, 56, 62-64, 66, 67, 69-71]. As we again demonstrated, central sensitivity syndromes are often comorbid with depression, fatigue, anxiety, and sleep disturbance [1, 67-71].

Dry eye in our high CPS group may more accurately be characterized as neuropathic ocular pain and considered a distinct entity from traditional dry eye. In these patients, whose high rate of manifestation of related chronic pain syndromes suggests a central disorder, perhaps with central sensitization as the underlying mechanism, it appears that their ocular symptoms are but another peripheral manifestation of their central disease. This is further supported by the greater magnitude of both ocular and non-ocular pain reported by high CPS patients in this study, a finding consistent with those recently reported by Vehof et al., showing a relationship between dry eye symptoms and higher forearm pain sensitivity (lower heat pain threshold) using quantitative sensory testing [61].

Review of mechanisms of central sensitivity linking comorbid pain conditions

The idea of a systemic predisposition to pain is plausible through multiple mechanisms, although the specifics of the development of central sensitivity have yet to be determined. The specific postulated mechanisms for the development of central sensitivity associated with dry eye include aberrations in pro-inflammatory cytokine signaling and glial cell-neuron interactions. In addition, there is a growing appreciation for the critical role of genetic mechanisms of vulnerability, which underlies these and other potential mechanisms.

A systemic inflammatory response may cause pain and other manifestations at varying sites via a mechanism that involves circulating pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL6) and IL1b [35]. Cytokine mediated mechanisms of pain sensitization may be particularly relevant in the case of neuropathic ocular pain, as recent data suggest that DNA polymorphisms in IL1 and IL6 may underlie susceptibility to dry eye [43]. These pro-inflammatory cytokines can mediate multiple pain syndromes, including neuropathic disorders, via complex mechanisms that include increased spontaneous firing of sensory neurons [46], enhanced excitatory neurotransmission and phenotypic alterations of the primary afferents [15]. Various pro-inflammatory cytokines can also cause fatigue and depression, disorders commonly found to be comorbid with CPS [52, 53, 60]. The presence of elevated plasma circulating pro-inflammatory cytokines in depression has been repeatedly documented, providing a common link between depression and chronic pain states [40].

Recently, the complex interactions between glial cells and neurons have received significant attention for their potential role in the pathophysiology of chronic pain [28, 49].

Substantial preclinical evidence has revealed that activated microglia and astrocytes mediate the generation and maintenance of several pain states [37] in a fashion that is determined by specific genetic polymorphisms and circulating pro-inflammatory cytokines [65]. Glial activation in the brain as a result of stress (e.g., traumatic brain injury, systemic inflammatory responses, xenobiotics, etc.) can induce the expression of pro-inflammatory cytokines that directly amplify spinal cord synaptic transmission and induce central sensitization to pain via signal amplification [28]. Although the causality remains unclear, there is evidence that peripheral and systemic inflammatory responses can lead to microglial activation and depression through interference with monoaminergic, glutamatergic, and neurotrophic systems [40]. Further research is warranted to determine if these factors represent a shared mechanism of susceptibility to neuropathic ocular pain and other CPS.

Finally, genetics play a large and increasingly well-defined role in conferring the clinical variability observed in nociception, pain processing, and therapeutic response [9, 10, 13, 14, 16, 34]. The recent results of Vehof et al., provide evidence of shared genetic mechanistic factors in multiple comorbid chronic pain conditions, including dry eye[62]. This group has also reported the heritability of chronic widespread pain, the primary symptom of fibromyalgia, at 58% in women, and suggests the presence of 2 latent traits underlying chronic widespread pain and various psychoaffective phenotypes, supporting the idea of a common genetic underpinning to functional pain syndromes, depression, and anxiety.[7] Genetic polymorphisms can significantly influence plasma levels of pro-inflammatory mediators, which may explain why certain individuals are prone to hypersensitivity and to a constellation of chronic pain states and depression [26]. Collectively, these findings suggest that future genomic studies should be helpful to

identify functional variants that are critical to disease susceptibility or resistance. These potential pharmaceutical targets should lead to the discovery of preventive approaches and mechanism-based therapies for dry eye and possibly other CPS.

Study limitations and conclusions

As with all studies, our findings need to be considered with our study limitations, which include: a cross-sectional study design, a unique dry eye population and the specific metrics used to capture neuropathic ocular pain features. In addition, despite our highly significant findings, the small sample size could make our study underpowered to reveal more subtle findings. Finally, our sample population was biased towards elderly, male veterans and was likely insufficient to assess some chronic pain syndromes like fibromyalgia and temporomandibular disorder, which are more prevalent in females.

Our findings support the concept that in a subgroup of dry eye patients, those describing symptoms of neuropathic ocular pain, their eye disease represents a central pain disorder that is heritable and may share causal genetic factors with other CPS. The clinical implications of our findings are great, as they suggest that dry eye patients with neuropathic ocular pain symptoms may need to be addressed differently than those without neuropathic ocular pain. Specifically, neuropathic pain symptoms are not currently evaluated during dry eye examinations focused on tear dysfunction and the ocular surface. Therefore, we propose based on our findings that dry eye patients also be screened for symptoms of neuropathic ocular pain. Those with neuropathic ocular pain may benefit from further screenings for comorbid pain conditions, depression and posttraumatic stress disorder. Dry eye patients demonstrating neuropathic ocular pain

with other CPS may also benefit from a multidisciplinary approach to their management, as recommended for other chronic pain states [39]. Once diagnosed, which can be achieved by the use of available questionnaires, [24] neuropathic ocular pain may prove difficult to treat. However, medications useful in treating other forms of CPS may eventually prove useful for this subtype of dry eye patients.

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Table 1. Demographics of Population Sample

	High CPS group* (N=97)	Low CPS group* (N=57)	P-value
Demograhic Data			
Age, mean (SD)	62 (11)	66 (11)	**0.03**
Gender, male, N (%)	88 (91%)	52 (91%)	0.92
Race, white, N (%)	43 (44%)	32 (56%)	0.34
Ethnicity, Hispanic, N (%)	32 (33%)	11 (19%)	0.07
Co-morbidities			
Hypertension, N (%)	70 (72%)	45 (79%)	0.35
Diabetes mellitus, N (%)	38 (39%)	19 (33%)	0.47
Sleep apnea, N (%)	23 (24%)	10 (18%)	0.37
BPH, N (%)	15 (16%)	11 (19%)	0.54
Medications			
Anxiolytic, N (%)	46 (47%)	19 (33%)	0.09
Antidepressant, N (%)	53 (55%)	14 (25%)	**<0.0005**
Anti-histamine, N (%)	22 (23%)	7 (12%)	0.11
Analgesics, N (%)	75 (77%)	27 (47%)	**<0.0005**

SD=standard deviation; N=number in each group; BPH=benign prostatic hypertrophy
* Determined by cluster analysis

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Table 2. Non-Ocular Pain Severity (by NRS) in Population Sample

	High CPS group* (N=97)	Low CPS group* (N=57)	P-value
	Mean (SD)	Mean (SD)	
Non-ocular pain intensity, averaged over past week (0-10)	6.0 (2.4)	3.9 (2.9)	**<0.00005**
Non-ocular pain intensity, worst during past week (0-10)	7.0 (2.4)	4.6 (3.4)	**<0.00005**

* Determined by cluster analysis

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Table 3. Frequency of Comorbid Chronic Pain Conditions** in Population Sample

Condition	High CPS group* (N=97)	Low CPS group* (N=57)	P-value
Primary Central Sensitization	Number (%)	Number (%)	
Back Pain	81 (84%)	29 (51%)	**<0.0005**
Muscle Pain	71 (73%)	18 (32%)	**<0.0005**
Headaches	52 (54%)	20 (35%)	**0.03**
Tendonitis	39 (40%)	7 (12%)	**<0.0005**
Central Pain Syndrome	16 (17%)	0 (0%)	**0.001**
Trigeminal Neuralgia	11 (11%)	0 (0%)	**0.007**
TMD Pain	9 (9%)	0 (0%)	**0.03**
Fibromyalgia	1 (1%)	0 (0%)	1.00
Secondary Central Sensitization	Number (%)	Number (%)	
Arthritis	79 (81%)	22 (39%)	**<0.0005**
Chronic Post-Surgical Pain	33 (34%)	5 (9%)	**<0.0005**
Diabetic Neuropathy	29 (30%)	8 (14%)	**0.03**
Sciatica	33 (34%)	4 (7%)	**<0.0005**
Burn Pain	26 (27%)	5 (9%)	**0.007**
Post-Herpetic Neuralgia	11 (11%)	5 (9%)	0.61
Cancer Pain	4 (4%)	0 (0%)	0.30
Individual Central Sensitivity	Number (%)	Number (%)	
CRPS/Causalgia	16 (17%)	0 (0%)	**0.001**

TMD=Temporomandibular joint disorder; CRPS=complex regional pain syndrome;
* Determined by cluster analysis
** Classification from Yunus 2015 [71].

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Table 4. Ocular Surface Examination in Population Sample

	High CPS group* (N=97)	Low CPS group* (N=57)	P-value
	Mean (SD)	Mean (SD)	
Tear osmolarity, mOsm/L	305 (17)	303 (17)	0.63
Tear film breakup time, seconds, (less time indicates more rapid tear evaporation)	8.9 (3.8)	9.4 (3.6)	0.39
Corneal staining, (0-15) (higher value indicates more surface disruption)	2.2 (2.8)	2.2 (2.3)	0.85
Schirmer's test, mm of moisture (lower value indicates lower tear production)	13.8 (6.6)	14.0 (6.2)	0.87
Eye lid vascularity, (0-3) (higher value indicates more abnormal vascularity)	0.57 (0.71)	0.79 (0.84)	0.10
Meibum quality, (0-4) (higher value indicates more abnormal meibum)	2.0 (1.2)	1.8 (1.2)	0.47

All numbers represent the more severe value in either eye

* Determined by cluster analysis

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Table 5. Dry Eye and Ocular Pain Symptoms in Population Sample

	High CPS group* (N=97)	Low CPS group* (N=57)	P-value
	Mean (SD)	Mean (SD)	
DEQ5 (0-22)	13.6 (3.7)	11.7 (3.9)	**0.004**
OSDI (0-100)	44 (25)	29 (22)	**<0.0005**
Ocular pain intensity, averaged over past week (0-10)	4.5 (2.5)	2.9 (2.4)	**<0.0005**
Ocular pain intensity, worst during past week (0-10)	5.5 (3.0)	3.9 (3.0)	**0.002**
NPSI total (0-100)	29 (23)	19 (19)	**0.006**
NPSI subscale 1 (burning spontaneous pain) (0-10)	3.7 (3.2)	2.7 (3.0)	**0.047**
NPSI subscale 2 (pressing spontaneous pain) (0-10)	2.8 (2.7)	1.9 (2.6)	**0.03**
NPSI subscale 3 (paroxysmal pain) (0-10)	1.9 (2.6)	1.5 (2.2)	0.34
NPSI subscale 4 (evoked pain) (0-10)	3.5 (2.9)	2.1 (2.4)	**0.003**
NPSI subscale 5 (paresthesia/dysesthesia) (0-10)	2.6 (2.8)	1.6 (2.3)	**0.01**
sf-MPQ sensory (0-33)	7.7 (7.3)	4.1 (5.0)	**0.001**
sf-MPQ affective (0-12)	2.8 (3.0)	1.3 (1.9)	**0.01**
sf-MPQ total (0-45)	10.4 (9.7)	5.5 (6.6)	**0.001**

NPSI=Neuropathic Pain Symptom Inventory questionnaire modified to refer to ocular complaints; DEQ5=Dry Eye Questionnaire; OSDI=Ocular Surface Disease Index questionnaire; sf-MPQ=McGill Short Form questionnaire

* Determined by cluster analysis

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Table 6. Psychiatric Complaints and Quality-of-Life in Population Sample

	High CPS group* (N=97)	Low CPS group* (N=57)	P-value
	Mean (SD)	Mean (SD)	
PTSD checklist Military Version (17-85)	45 (20)	36 (19)	**0.005**
Depression score via PHQ9 (0-27)	10.8 (8.0)	6.9 (7.5)	**0.004**
SF-12, Physical composite score (0-100)	35 (11)	47 (10)	**<0.0005**
SF-12, Mental composite score (0-100)	43 (14)	48 (12)	**0.01**

PTSD= post traumatic stress disease; PHQ9=Patient Health questionnaire; SF12=Short Form Health Survey questionnaire.
* Determined by cluster analysis

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- **Dry eye patients reporting more structural and functional chronic pain syndromes (high CPS group) also report symptoms of neuropathic ocular pain**
- **The high CPS group also reports worse dry eye symptoms, depression, quality-of-life indices, ocular and non-ocular pain**
- **Neuropathic ocular pain may share causal genetic factors with other overlapping chronic pain conditions**
- **These clinical results imply dry eye exams should include an evaluation of neuropathic ocular pain**
- **A multidisciplinary approach used for chronic pain treatment may also benefit dry eye patients with neuropathic ocular pain**

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