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Temporal Stability in the Perception of Dry Eye Ocular Discomfort Symptoms

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ABSTRACT

Purpose. A prospective longitudinal study was designed to investigate the ability of patients with tear deficiency to correctly recall their past symptoms. The ultimate goal of the study was to contribute to the ongoing research concerning the lack of association between dry eye symptomatology and clinical tests of tear film evaluation.

Methods. A total of 26 subjects with ages ranging from 29 to 61 years participated in the study. All subjects reported symptoms associated with tear deficiency, although none had been diagnosed with dry eye disease. Subjects were instructed to grade their symptoms on two different occasions, at the precise moment they were experiencing them, by means of a home questionnaire, and through a recall questionnaire, which was administered within a maximum interval of 10 days from the first questionnaire. Tear evaluation tests were performed at this second time. Non-parametric statistical analyses were used to investigate the relationship between present and recalled symptoms and between symptoms and signs, as well as between the different dry eye tests. The contributions of age, gender, and recall period were also evaluated.

Results. With the exception of irritation ($p = 0.029$) and scratchiness ($p = 0.025$), no statistically significant difference was encountered between home and recall questionnaires, although females were found to recall their symptoms slightly better than males ($p = 0.048$). An increase in the severity of the symptoms was associated with a better recollection ($p = 0.007$). Symptoms (home or recalled) and clinical signs were not correlated, although the recalled symptom of scratchiness presented moderately strong correlations with several dry eye tests.

Conclusions. Although the lack of correlation between dry eye tests and symptoms mirrored previous research, symptoms recall was found to follow certain interesting patterns, similar to those published in pain research literature.

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Key Words: clinical dry eye signs, dry eye, ocular irritation, pain, questionnaire, symptoms

The 2007 Report of the International Dry Eye Workshop[1] defines dry eye as a "[…] multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear instability with potential damage to the ocular surface […]." This description clearly requires both signs and symptoms to be present to ascertain a dry eye diagnosis. However, clinical experience repeatedly offers examples of asymptomatic patients with manifest ocular signs and symptomatic patients with clinical tests within the range of normality. The lack of agreement between symptoms and clinical signs is well documented in the literature.[2–12] Indeed, early studies on patients suffering from keratoconjunctivitis sicca[2–4] and Sjögrens[5] syndrome revealed limited, or at best, uncertain diagnostic values of classic tests such as tear break-up time (BUT), rose bengal staining and Schirmer test, with more advanced procedures like lactoferrin analysis, tear osmolarity assessment and antibody count also failing to mirror patients' self-reported symptoms. Similarly, Schiffman et al.[7] described a low correlation between a symptoms questionnaire and BUT, Schirmer I test and both lissamine green and fluorescein staining. Although some studies disclosed a good agreement between diagnostic tests and symptoms in patients with severe dry eye disease,[8,9] Schein et al.[10] revealed that symptoms are not a good diagnostic tool to assess disease progression. Similarly, Nichols et al.[11] demonstrated that dry eye clinical tests are not associated with ocular symptoms, even though the correlation between symptoms and both the phenol red thread test and rose bengal staining was found to approach statistical significance. These authors suggested the possibility that patients with aqueous deficiency dry eye may

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experience different symptoms frequencies and/or intensities than those with evaporative dry eye, thus speculating on an etiology dependent, and hence highly variable, symptomatology. In addition, Pult et al.,[12] in an exploration of the relationship between signs and symptoms in new contact lens wearers, reported that lid parallel conjunctival folds, non-invasive BUT, and Ocular Surface Disease Index score could be considered better predictors of contact lens-induced dry eye symptoms than hyperaemia, tear meniscus height, phenol red thread test, staining and lid wiper epitheliopathy, thus introducing the Contact-Lens-Predicting-Test as a combination of those factors.

With the sole exception of tear fluorescein clearance,[13,14] the fact that no other single diagnostic test for dry eye has been found to present abnormal results in all patients complaining of eye irritation,[15] often referred to as the lack of a "gold standard" test for dry eye,[16] has led clinicians to acknowledge patient's self-reported symptoms as the primary element in the diagnosis and treatment of dry eye.[17] The therapeutic approach to dry eye disease has often been prejudiced by the disagreement between signs and symptoms, as FDA protocols require a clinically and statistically significant improvement in at least one sign and one symptom to grant approval to any new drug formulation for dry eye.

The lack of association between clinical signs and symptoms has been investigated from two different perspectives. On the one hand, many authors have informed of the low repeatability of many of the most commonly used clinical tests[18–20] and of the low to moderate correlation between the various tests.[21–23] On the other hand, symptoms have been found to offer a better repeatability than objective tests,[8] but to present a short or diurnal variability and a longer cycle throughout the progression of the disease. Indeed, Begley et al.[24] reported that the percentage of patients with non-Sjögren dry eye who experienced moderate to severe symptoms increased from 32% in the morning to 60% in the evening. A similar trend was discovered by Nichols et al.[25] in a group of contact lens wearers, as opposed to spectacle wearers and clinical emmetropes, although diurnal variations across refractive modalities were highly dependent on the symptom under evaluation. Long-term symptoms variability has been attributed to anatomical changes to the ocular surface.[26–28] Thus, injured corneal nerve endings have been observed to develop microneuromas that may alter transducing signals leading to hypesthesia and dysaesthesias, which may account to earlier symptoms being out of proportion to tissue damage.[29] Similarly, later stages of the disease have been associated with decreased nerve sensitivity, resulting in reduced symptoms in contrast to a higher prevalence of ocular signs such as corneal and conjunctival staining.[30,31]

Several normalized dry eye questionnaires have been developed over the last decades to facilitate symptoms reporting and scoring. However, accurate interpretation of the results and comparison between the various questionnaires are being challenged by their heterogeneous length, intended use, population in which they were tested, mode of administration, and extent of validation. For instance, although the Ocular Surface Disease Index has been found to exhibit a good to excellent test-retest reliability, the McMonnies Dry Eye Index, which was developed as an screening tool, is considered as a less consistent example of dry eye questionnaire.[7,24,32,33]

It is interesting to note that in some dry eye questionnaires, subjects are asked to recall the symptoms they experienced during the previous days, up to the previous 2 weeks,[34] whereas in others, the recall period is not specified, thus allowing the patient to decide whether to report current symptoms or recalled symptoms from previous episodes of ocular discomfort. Given the above mentioned short-term and long-term variability of ocular symptomatology, it could be speculated that the mental process required for symptom recollection may involve the integration of significantly heterogeneous levels of discomfort to reach some sort of "symptoms average" which, when reported, will probably differ from the symptoms that are actually present at the time of the patient's examination.

Studies on pain perception and appraisal reveal that reports on pain intensity or level of unpleasantness show a high degree of variability among individuals and depend on factors such as patient's psychological state, past pain experiences, pain present at recall, and developed pain coping mechanisms.[35–39] Therefore, it could be assumed that the perception of ocular discomfort follows a similar behavior, further influencing the report of present and recalled symptoms and contributing to the discrepancies between clinical signs and symptoms in dry eye.

The aim of this study was to examine the difference between present and recalled dry eye symptoms and to determine whether the correlation between clinical signs and symptoms was dependent on when these symptoms were reported. For this purpose, patients were asked to report symptoms at the time they were actually experiencing them and, again, a few days later, based on the sole recollection of the experienced symptoms. Factors associated with symptoms recall were also investigated, as well as the relationship between the various clinical dry eye tests.

METHODS

Subjects

Thirty-two patients attending an optometric practice located in the city of Zaragoza (Spain) were recruited for this study, which took place between the months of September and November, 2009. Patients were both contact lens wearers and non-wearers with a history of reported ocular discomfort symptoms, although none of the patients had been diagnosed with dry eye disease. Exclusion criteria were existing ocular pathology, ongoing ocular treatment, and history of ocular or refractive surgery. All participants provided written informed consent after the nature of the study was explained to them. The study was conducted in accord with the Declaration of Helsinki tenets of 1975 (as revised in Tokyo in 2004).

Questionnaire Design

Ocular discomfort symptoms were assessed through a self-administered *ad hoc* questionnaire. The two versions of this questionnaire were very similar, except that the home questionnaire (Q1) included two demographic questions (age and gender) and also inquired about contact lens usage. The second or recollection questionnaire (Q2) also queried subjects about the time interval between Q1 and Q2.

Both questionnaires addressed the same symptoms: irritation, dryness, scratchiness, grittiness, soreness, changeable vision, and

light sensitivity. These symptoms have been reported to be the most frequent symptoms in mild to moderate dry eye and in contact lens wearers.[40,41] Subjects used a vertical visual analog scale (VVAS) to grade each of their symptoms. This scale consisted of a vertical straight line without any markings anywhere on its 100 mm of length. The top of the scale was labeled as "very intense" and the bottom as "I don't experience this symptom." This type of scale has been validated as an instrument for the quantification and reporting of pain.[42–44]

Procedure

Qualified subjects were scheduled for two visits. At the first, or baseline visit, informed consent was obtained and all subjects were handed the first questionnaire to take home with them, with instructions to report their symptoms at the precise moment they were experiencing them. Subjects were also urged to return for a second visit within a maximum of 10 days after the first questionnaire was filled out. During the second visit, subjects were asked to complete the second questionnaire by recalling the experienced symptoms that prompted them to answer the home questionnaire. The second visit, which took place at the same time of day for all subjects, also included a battery of standard clinical tests of tear film evaluation. These testing procedures, which are well described in published literature, were performed in the following order: tear meniscus height[45] and continuity evaluation, phenol red thread test[46] (Zone-Quick, Showa Yakuhin Kako Co., Tokyo, Japan & Menicon Spain), fluorescein tear BUT,[47] and corneal and conjunctival fluorescein staining (observed with a no. 12 yellow Wratten filter),[48] and corneal and conjunctival lissamine green staining[49] (observed with a no. 25 red Hoya filter). Staining was evaluated at five regions of the cornea (central, superior, inferior, nasal, and temporal) and four regions of the conjunctiva (superior, inferior, nasal, and temporal).[50] Each region was graded with a 0 to 4 scale and a total staining score was obtained by adding each individual grade. Blinking completion was also recorded. A sole, skilled optometrist performed all the tests to prevent any between-examiner variability that could arise from multiple examiners. The examiner was masked to the responses of the questionnaires.

Data Analysis

Statistical analysis of the data was performed with the SPSS software 17.0 for Windows. All data were examined for normality using the Kolmogorov-Smirnov test, which revealed several instances of non-normal distribution. As such, non-parametric statistical analyses were used. No statistical difference could be found between right and left eyes. Therefore, data from right eyes was arbitrarily chosen for statistical purposes. The Wilcoxon signed rank test for repeated measures was used to evaluate the differences between Q1 and Q2 VVAS scores for each particular symptom. Spearman rho correlations were used to determine the relationship between total Q1 and Q2 VVAS scores, which were obtained by the summation of all individual symptom scores, and clinical dry eye tests, as well as between the different tests under examination. A new variable, defined as symptom recollection, was generated by the summation of all individual symptoms differences between Q1 and Q2, as expressed in absolute value. Subsequently, the relationship between symptom recollection and age, as well as between symptom recollection and interval in days between Q1 and Q2 was explored with the Spearman rho correlation analysis. The contributions of gender and global symptoms severity on symptom recollection were evaluated with an independent samples Wilcoxon rank sum test. A p value of 0.05 or less was considered to denote statistical significance throughout the study.

RESULTS

Subject Demographics

Of the original 32 subjects, 26 subjects completed the study. Of the remaining six subjects, three failed to return for the follow-up visit and another three did not comply with the previously instructed maximum 10 days interval between Q1 and Q2. The age of the participants ranged between 19 and 61, with a mean ± SD of 37.73 ± 12.39 years. Sixteen of the subjects were female (age: 40.12 ± 13.69 years) and 10 were male (age: 33.90 ± 9.35 years).

Seventy-three percent of the sample were contact lens wearers, with a higher percentage of daily (94.74%) than extended (5.26%) wearing modalities. Rigid gas-permeable lenses were fitted to 21.05% of the contact lens wearers. Conventional hydrogel and silicone-hydrogel contact lenses were evenly distributed among the rest of wearers.

Q1 and Q2 Scores

Scores for Q1 and Q2 are summarized in Table 1 in terms of mean ± SD. Considerable between-symptom variability was observed. Indeed, some symptoms were graded with a higher score in Q2 than in Q1, while subjects followed a reversed behavior when grading other symptoms. Comparison within each particular pair of symptoms revealed that, of the seven evaluated symptoms, only on two occasions were statistically significant differences found between Q1 and Q2 scores, namely for the symptoms of irritation

TABLE 1.
Q1 and Q2 scores

	Irritation[a]	Dryness	Scratchiness[a]	Grittiness	Soreness	Changeable vision	Light sensitivity
Q1	53.46 ± 30.40	61.38 ± 22.87	47.15 ± 36.17	37.65 ± 32.49	45.08 ± 31.49	24.69 ± 29.47	31.00 ± 37.71
Q2	47.69 ± 34.92	59.46 ± 28.20	39.85 ± 36.62	41.58 ± 34.32	38.08 ± 30.44	30.15 ± 31.45	27.31 ± 34.38

Each symptom was graded on a 100 mm in length VVAS. Results are displayed as mean ± SD.
[a]The value denotes a statistically significant difference between Q1 and Q2 ($p < 0.05$).

($Z = -2.23$; $p = 0.029$) and scratchiness ($Z = -2.19$; $p = 0.025$).

Spearman rho correlation analysis between age of subjects and symptom recollection and between number of days between Q1 and Q2 and symptom recollection failed to disclose any instance of statistical significance. An independent samples Wilcoxon analysis of the contribution of gender to symptom recollection exposed that females had a slightly better, and statistically significant different ($Z = -1.98$; $p = 0.048$), recollection of their symptoms than males.

To further examine the mechanisms of symptom recollection, subjects were subdivided into two groups based on their ability to correctly recall their symptoms to within a 25% margin of error. Independent samples comparison between these two subgroups revealed that subjects whose initial symptoms were more severe had a tendency to recall those symptoms better than subjects whose symptoms were milder (Fig. 1). This difference was found to be statistically significant ($p = 0.007$).

Clinical Dry Eye Tests

Table 2 explores the relationship between the diverse clinical dry eye tests under evaluation, as well as age, displayed as Spearman rho correlation coefficients. Significant and strong positive correlations were encountered between tear meniscus height and phenol red thread test ($r = 0.61$; $p = 0.001$) and between fluorescein and lissamine green staining ($r = 0.78$; $p < 0.001$), with a weaker but still significant correlation between tear meniscus height and BUT ($r = 0.49$; $p = 0.011$) and between phenol red thread test and fluorescein staining ($r = -0.46$; $p = 0.017$). A negative significant correlation between age and BUT was observed ($r = -0.40$; $p = 0.044$). No additional associations between age and any other clinical signs could be determined.

No significant association could be discerned between tear meniscus height and tear meniscus continuity. All clinical tests were found to be independent of blinking completion with the exception of fluorescein staining, with incomplete blinking displaying higher global fluorescein staining scores than complete blinking ($Z = -1.97$; $p = 0.049$). Incidentally, when only inferior staining was considered, both fluorescein and lissamine green staining were more frequent in subjects with incomplete than with complete blinking.

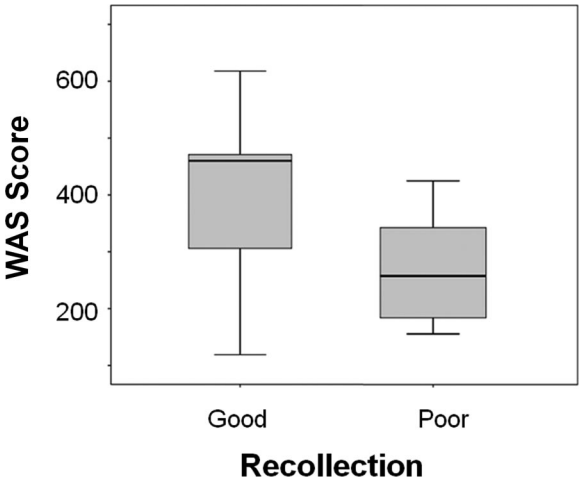

FIGURE 1.

Box plot representation of recollection vs. symptoms severity (total Q1 VVAS score). Subjects were subdivided in two groups (good recollection and poor recollection) according to their ability to recall their symptoms, in Q2, to within a 25% margin of error of Q1.

Association between Symptoms and Signs

With the sole exception of the Q2 scoring of scratchiness, no additional statistically significant associations between symptoms and signs could be determined neither when total Q1 and Q2 VVAS scores were investigated nor when each symptom was individually assessed. Scratchiness score was found to be positively correlated with fluorescein staining ($r = 0.47$; $p = 0.015$) and negatively correlated with tear meniscus height ($r = -0.44$; $p = 0.023$), phenol red thread test ($r = -0.39$; $p = 0.046$), and BUT ($r = -0.41$; $p = 0.037$). Interestingly, this correlation was only encountered in Q2, whereas Q1 scoring of scratchiness displayed no association with any clinical sign.

DISCUSSION

The principal objective of this study, which was designed to offer additional information to the ongoing debate centered on the discrepancy between clinical signs and symptoms in dry eye, was to investigate the ability of patients to recall their dry eye symptoms. The contribution of age, gender, and recall period on symptom recollection, as well as the relationship between the diverse clinical signs and between symptoms and signs was explored.

TABLE 2.

Spearman rho correlation coefficient of the relationship between tear meniscus height, phenol red thread test, fluorescein tear BUT, corneal and conjunctival fluorescein staining, corneal and conjunctival lissamine green staining, and age

	Meniscus height	Phenol red thread	BUT	Fluorescein staining	Lissamine staining	Age
Meniscus height	—	0.61[a]	0.49[b]	−0.21	−0.19	−0.08
Phenol red thread	—	—	0.385	−0.46[b]	−0.281	−0.252
BUT	—	—	—	−0.15	−0.18	−0.40[b]
Fluorescein staining	—	—	—	—	0.78[a]	0.05
Lissamine staining	—	—	—	—	—	0.03

[a]The value denotes a statistically significant correlation with $p < 0.001$.

[b]The value denotes a statistically significant correlation with $p < 0.05$.

Q1 and Q2 Scores

The symptoms under investigation were irritation, dryness, scratchiness, grittiness, soreness, changeable vision, and light sensitivity. These symptoms have been frequently associated with mild to moderate cases of tear deficiency in both contact lens wearers and non-wearers.[40,41] Analysis of the results revealed that, although most of these symptoms might be believed to describe similar experiences or to reflect differences in word choice rather than actual physical differences in sensation, subjects with tear deficiency seem capable to separate irritation from soreness, or grittiness from scratchiness, and to grade them accordingly. Indeed, symptoms recall was revealed to follow a heterogeneous behavior, with different symptoms being graded at different intensities. Furthermore, with the exception of irritation and scratchiness, no statistically significant difference could be discerned within the same type of symptom between Q1 and Q2, that is, although different symptoms scored very differently, the same symptom showed a certain degree of self-consistency from Q1 to Q2 or, in other words, symptom recollection was fair. These results are in agreement with published literature.[18,51]

Previous researchers have suggested that different symptoms may be an actual manifestation of different domains of the disease and that patients with evaporative dry eye may not experience the same frequency and/or intensity of their symptoms than patients with aqueous deficiency.[11] It could therefore be speculated that an exhaustive questionnaire, notwithstanding its time-consuming nature, is essential to gain a good understanding of the symptomatology of each individual patient.

The fact that no significant influence of age and recall period on symptom recollection could be discerned may perhaps be attributed to the limited sample size and age distribution of this study and to the self-imposed restriction of 10 days as maximum recall period, which aimed at mirroring that of some of the most commonly used questionnaires. However, the relevance of these results demands further investigation as one of the main handicaps preventing a direct comparison between the different standardized dry eye questionnaires is, precisely, their disparity in recall periods.

It was assumed that ocular discomfort recollection was governed by similar mechanisms as pain recollection. Pain intensity processing has been found to be distributed across an array of functionally distinct regions within the human brain and to be influenced by such aspects as memory of past painful events and pain intensity at the moment of recall.[39,52] Similarly, some patients have a higher tolerance to pain or, in this case, ocular irritation, when compared with others. Pain recollection has also been observed to be gender dependent. Although differences in pain report for women at different stages in the menstrual cycle have been reported,[53] in general, women have been found to be relatively more accurate in their recall of pain than men.[35] In agreement with pain research, this study showed that, by evaluating the contribution of genre to symptom recollection, females were able to recall their symptoms better than males. In addition, both mechanical and cold receptors on human corneas have been found to show adaptation to repeated suprathreshold stimuli, with a reduction in perceived intensity after multiple exposures to the same physical stimulus intensity.[54,55] It may be speculated whether this type of short-term adaptation contributes to long-term symptom variability.

After subjects were allocated into two groups based on their ability to correctly recall their symptoms to within a 25% margin of error, symptom recollection was found to increase with the severity of the symptoms. This behavior has also been reported in a previous pain study, which observed that evaluation of stimuli near threshold was more difficult than evaluation of clearly suprathreshold stimuli.[52] It could be postulated that if this study had included more severe forms of dry eye disease, the significance of this pattern would have been more pronounced.

Clinical Dry Eye Tests

The relationship between clinical tests, or the absence of it, shows interesting results, mostly mirroring published research. It may be relevant to mention that the strong correlation between tear meniscus height and the phenol red thread test, which should not be unexpected given that both tests measure tear volume and/or production, was not confirmed by previous authors.[21,56] Fluorescein and lissamine green staining also displayed a strong correlation.

Tear meniscus height and continuity were found to be independent of each other. This is an interesting finding that suggests that both tests are not interchangeable, that is, they measure different aspects of the tear film and should always be performed together to properly evaluate tear function.

Severe forms of dry eye disease are usually associated with corneal and conjunctival epitheliopathies, which result in higher grades of fluorescein and lissamine green staining than those encountered in this study. The observed relationship between inferior staining and incomplete blinking may indicate that milder types of exposure epitheliopathies occur at an early stage in tear film deficiencies. A much larger sample size should be required, however, to confirm this reasoning.

The relationship between age and the various clinical tests is in agreement with the repeatedly reported increase in dry eye incidence in the elderly population. The fact that only age and BUT displayed a statistically significant correlation, could be attributed to the limited age distribution of the present sample.

Association between Symptoms and Signs

The usual lack of association between symptoms and clinical signs was encountered, mirroring earlier investigations. The results from the dry eye tests which were conducted at the optometric practice moments after the patients were instructed to complete the recollection questionnaires showed no correlation with either Q1 or Q2 scores. Therefore, the original conjecture that aimed at explaining the lack of association between signs and symptoms with the inability of patients to properly recall their symptoms when questioned about it before ocular examination could not be ascertained. Had this assumption proved true, some type of correlation between Q1 scores and clinical signs would have arisen from the results, which was not the case.

Previous authors have observed anecdotal evidence of associations between a particular clinical sign and an individual symptom or combination of symptoms. The severity of dryness was found to correlate with both BUT and Schirmer 1 values.[9] The same study revealed a direct correlation between dryness and corneal fluores-

cein staining and between the combined score of dryness and irritation and the Schirmer 1 test values. The present research found a similar incidental association between the Q2 score for scratchiness and the values of several dry eye tests. Interestingly, this association was absent when Q1 scores were examined. However, the real significance of this discovery remains obscure and demands further investigation.

Finally, a number of limitations of the study should be considered when interpreting these findings, the most important of which is sample size. Indeed, a more ambitious study should be designed to validate the present results with a more powerful parametric statistical analysis. Besides, some kind of mechanism for monitoring patient compliance with the given instructions should be implemented. With the actual study design, questions arise concerning whether patients were honest about completing the home questionnaire when they felt their symptoms and whether they did return to the optometric practice within 10 days, as required by the study (this was a reason for exclusion). The actual effect of present symptoms recall, which has been proved to influence pain quantification, is uncertain. The use of a third questionnaire would have allowed subjects to grade their symptoms and to investigate how symptoms severity contributed to symptom recollection. It is unclear, though, whether subjects would have been able to correctly manage their responses to these questionnaires. The sample under evaluation comprised both contact lens wearers and non-wearers, but this was not considered a limitation. Indeed, although contact lens wear has been associated with an increase in symptomatology in patients with tear deficiency, this effect could have gained relevance if absolute VVAS scores had been investigated instead of relative differences between Q1 and Q2.

We believe that ocular dry eye symptomatology has not been sufficiently explored in terms of pain research, although it may be assumed that ocular irritation is a painful stimulus. The field of pain research is wide-ranging, with extensive published literature. Dry eye investigators may benefit from perusing existing knowledge on pain and by finding novel ways to interpret their data to better understand such a complex condition as dry eye.

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