

Ocular Surface Health in Connection with Anxiety and Depression: a Review

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Abstract: Psychosomatic ophthalmology emerged after World War II because patients attended clinics with symptoms that were not explained by physiological findings, subsequently it became clear that psychological distress could be associated with several ocular disorders, including dry eye syndrome. Dry eye disease is a common disorder with increasing prevalence due to environmental factors such as pollution, smoking, and sleep disorders. The burden of dry eye disease affects both patients and society, making it a very important target for investigation. Numerous studies showed that dry eye disease prevalence including the severity of the symptoms of dry eye is higher in patients suffering from depression and/or anxiety. Some studies suggest the implication of serotonin in tears being dysregulated by the disorders. The current review highlights the evidence of the association between anxiety, depression, and dry eye disease and summarizes the recent advances in research in this area, together with a brief explanation of the physiology of stress that could lead to psychological disorders.

Keywords: Ocular surface, dry eye, anxiety, stress, depression

Ocular Surface and Dry Eye

The ocular surface serves as a barrier protecting orbital structures from harmful substances, starting from ultraviolet light to any infectious organism, and has different roles, such as contributing to visual function. It is composed of several structures such as the sclera, conjunctiva, cornea, tear film, and eyelids.¹ The cornea is highly important for visual outcome because it focuses light rays on the retina with minimum scatter and comprises two-thirds of the refractive power of the eye.² It is avascular, and the most anterior layer of the cornea is the epithelial cell layer covered by a smooth and regular tear film, which provides lubrication and hydration to the cornea and entire ocular surface.³ Tear films are important components of the ocular surface because they also provide oxygen and are a source of immunoglobulins, lysozyme, and lactoferrin, all of which indicate the importance of the tear film in maintaining comfort, suppressing inflammation, preventing infections, healing injuries, and maintaining good visual quality.⁴ To ensure ocular comfort, tear film lubrication properties decrease shear forces from the lid margin during blinking.⁵ The tear film regulates the secretion of fluids containing the aforementioned protective factors. Therefore, reduced tear volume and/or altered composition would result in dry eye disease.

Dry eye disease is a worldwide issue, with a prevalence ranging between 5% and 50% of the population, and it is one of the most common reasons for visiting ocular health specialists. Dry eye is defined as

a multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film accompanied by ocular symptoms, in which an etiological role is played by instability and hyperosmolarity of the tear film, inflammation and damage to the ocular surface, and neurosensory abnormalities.⁶

Individuals with dry eye disease may have several discomfort symptoms, such as foreign body sensation, burning, blurry vision, photophobia, visual disturbances, grittiness, and itching. Such symptoms negatively affect the patients' quality of life.⁷

The risk factors for developing dry eye vary according to the environment and genetics. Low humidity, air-conditioned rooms, long hours of reading and exposure to screens, contact lens use, and smoking are among the factors that affect ocular surface health.⁸ Moreover, other factors such as advanced age, ethnicity, and sex can lead to dry eye. These factors are uncontrollable; however, autoimmune diseases and pharmacological factors are known risk factors for the development of dry eye.⁹ Autoimmune diseases include rheumatoid arthritis, Sjögren's syndrome, diabetes, rosacea, and seasonal allergies. Pharmacological factors, including the use of medications, such as beta-blockers, decongestants, diuretics, selective serotonin reuptake inhibitors, tricyclic antidepressant medications, oral contraceptives, and anxiolytics, are associated with dry eye.⁹

One of the underlying factors that could lead to ocular surface disease is psychological factors. It is well known that poor visual income is associated to psychological stress and decreased quality of life, as well as social isolation.^{10,11} However, studies have shown that both psychological stress and psychotropic medications can lead to the disease.¹²

Quality of Life and Dry Eye

Quality of life is one of the most important aspects affected by chronic diseases, in this sense, one cannot avoid mentioning recent studies investigating the effect of dry eye on life quality. A study conducted in the United States surveyed over 2000 participants with and without dry eye symptoms. Among patients reporting dry eye symptoms, over 68% were diagnosed with dry eye disease by a healthcare professional. Participants with dry eye had poorer vision-related quality of life, such as problems with self-care, pain, discomfort, and anxiety/depression, than those without dry eye. The aforementioned items scored five times worse in patients with dry eye than in the healthy subjects.¹³

In 2020, a similar study was conducted in the UK, in where 2000 participants were recruited to answer several questionnaires. Approximately 50% of the participants had dry eye disease, and among them, they were classified according to severity using the Eye Dryness Score/Visual Analog Scale. The results showed that socioemotional functioning and activity limitations decreased globally with an increase in disease severity. Moreover, a greater impact on work has been observed in patients with severe dry eye patients. In general, vision-related quality of life is associated with dry eye.¹⁴

Another small-scale study examined the effects of dry eye on work productivity and non-work-related performance. This study did not depend only on subjectively answered questionnaires but required a visit to the ophthalmologist clinic where patients had a full diagnostic examination, such as Schirmer's test with local anesthesia, tear break-up time, corneal fluorescein staining, and conjunctival lissamine green staining. All tests were performed using an Ocular Surface Disease Index (OSDI) questionnaire. To determine the effect of dry eye on work productivity, participants completed a patient-administered Work Productivity and Activity Impairment (WPAI) questionnaire, which was adapted for dry eye.¹⁵ Of the 102 participants, 3.9% reported taking time off work in the past week due to dry eye symptoms. From the overall population in the study, a mean of 0.8 hours was lost from work for reasons linked to dry eye. Importantly, the study calculated an average productivity impairment of 28.8% in all patients due to dry eye. The OSDI results showed a significant correlation between presenteeism and productivity impairment ($r = 0.5$, $p < 0.0001$); ($r = 0.5$, $p < 0.0001$, respectively).

Stress Response Physiology

Stress refers to any physical or psychological stimulus disturbing homeostasis. Several observations and studies conducted at the beginning of the last century by physiologist Walter Bradford Cannon led to the birth of the "fight-or-flight" response.^{16,17} The contribution of both the homeostasis concept and "fight-or-flight" response resulted in the foundation of stress research.

Processing stressful situations involves complex mechanisms that affect the body and the brain. When a person perceives either a real or a potential threat, certain molecules that interact with their receptors in the periphery of the brain are released, leading to a stress response that results in the restoration of homeostasis.^{18,19} These stressors could be physical, such as hemorrhage, or psychological, such as predator-related cues. Each type of stressor is processed by distinct neural circuits in the brain, although they may overlap on some occasions. The identification of a stressor results in the release of its final mediating molecule. The sympathetic-adreno-medullary (SAM) axis secretes noradrenaline and norepinephrine, while the hypothalamus-pituitary-adrenal (HPA) axis secretes glucocorticoids.²⁰ Once these axes are activated by a stressor, a rapid response is generated to ensure homeostatic restoration. Stress response promotes energy production, metabolic changes, digestive and reproductive system suppression, and immune system activation.²¹ Stress

response is a complex process that depends on the timing and duration of the stressor. For instance, physical stressors usually require an immediate systemic reaction; hence, they activate the sympathetic adrenomedullary system to provide a quick physiological adaptation leading to short-lasting effects such as alertness and vigilance. The second phase involves the hypothalamic-pituitary-adrenal axis, resulting in an amplified and long-lasting response that is associated with environmental and life experiences.^{22,23}

One of the known stressors is related to visual problems, and several studies have shown that patients with visual impairments are more susceptible to anxiety, poor quality of life, and other psychological illnesses.²⁴ The following section explains the association between DES, anxiety, and depression.

Association Between Dry Eye Disease, Anxiety, and Depression

Several pieces of evidence have highlighted the relationship between psychiatric and ocular surface health. Prior knowledge was obtained through retrospective studies using patient information from eye-care clinics and/or psychiatric facilities.²⁵ Cooperation among public health, psychology, and eye care specialists sheds light on the significant correlation between ocular surface health and mental health status. It is still unclear whether this is the cause or consequence; however, several studies have highlighted an association between these factors.²⁶

An example of a large retrospective study included 2,454,458 patients who were admitted to the Veterans Affairs Eye clinic between 2006–2011, cases of dry eye included in the study were patients diagnosed by the International Classification of Disease Codes. Statistics show that 24% of patients with depression had dry eye disease, compared to 18% of non-depressed patients with dry eye disease. It is worth mentioning that the study relied on ICD9 code 375.15 for dry eye considering tear insufficiency and not the symptoms of dry eye. Nonetheless, such differences in prevalence could also be affected by other factors, such as psychotropic medication, especially because veterans are commonly diagnosed and treated for depression, anxiety, and/or post-traumatic stress disorder. Several studies have demonstrated the effects of psychotropic drugs on ocular surfaces. In fact, the use of psychotropic medication was shown to increase the risk of developing dry eye by 2-fold.²⁷ A possible explanation for psychotropic medications causing a higher risk of developing dry eye is the presence of serotonin in both the conjunctiva and the human tears, which could be coupled with dysregulation of neuropeptides in depression sufferers.²⁸ A recent study done in Shanghai in 2019 targeted patients treated with serotonin reuptake inhibitors, a widely prescribed class of medication for depression and anxiety, revealed that this class of treatment increased tear serotonin levels and numerous inflammatory cytokines genes were elevated in the treated group compared to placebo. These genes were encoded to TNF α , IL1 β , and IL10 and the proapoptotic gene *AIF*, *BAD*, and *BAX* levels were increased in the treated group, indicating a high rate of ocular surface cell apoptosis.²⁹ Being medicated for psychiatric illnesses is a sound reason for patients with depression to be referred to an eye-care specialist for revision.²⁷

Another large-population retrospective study conducted in the outpatient setting of the University of North Carolina confirmed the association between dry eye disease, depression, and anxiety. Charts of patients seen between 2008 and 2013 were included in the study, resulting in a total of 460,611 cases, after excluding those with missing data. Similar to the previously mentioned study, we used the same international classification of disease codes for dry eye disease (ICD9 code 375.15), anxiety, and depression. The results showed an estimated odds ratio between dry eye and anxiety of 2.8, with a 95% confidence interval of (2.6, 3.0), and an estimated odds ratio between dry eye disease and depression of 2.9, with a 95% confidence interval of (2.7, 3.1). This study confirmed a statistically significant association between dry eye, depression, and anxiety. It also presented a major strength because it included a more generalized adult population compared to veterans only in a previous study.³⁰

In addition, evidence shows an association between dry eye and depression; however, there was also a difference between patients with dry eye symptoms and those who were diagnosed but were asymptomatic. A study conducted in 2013 in Beijing included 1456 participants who underwent a full ophthalmic evaluation for dry eye diagnosis, such as the Schirmer test, tear film breakup time (TBUT), and meibomian gland dysfunction evaluation, together with answering questions regarding the symptoms of dry eye. Participants also completed a Chinese depression scale adapted from the Zung Self-Rated Depression Scale. In the mentioned study, results showed that depression cases were higher in participants diagnosed with dry eye disease (13.7 \pm 0.4% vs 8.6 \pm 0.3%, OR: 1.68; 95% CI 1.10 to 2.55; $p=0.021$). Moreover, the mean depression score was significantly higher in the patients who reported dry eye symptoms than in

those who did not. Furthermore, patients with depression experienced more dry eye symptoms than those without, opposite to clinical signs of dry eye such as the tear break up time, Schirmer test, and the corneal staining, which showed no association with depression in this study.³¹ Unlike more recent research in 2022, which included 535 subjects in a multicentre study in the United States, the study showed that both signs and severity of dry eye symptoms were associated with depression. Moreover, tears inflammatory marker such as interleukin 1 β , IL-6, IL-8, IL-17A, IL-10, interferon γ (INF- γ), and tumor necrosis factor (TNF- α) were measured to elucidates the pathophysiology of such correlation, results did not show differences among depression status.³² Nevertheless, it is noteworthy that the lack of association found could be because all the study subjects were suffering from depression and the aim was to see the association with the depressive status and not to compare it with healthy group.

Another approach was used to study dry eye disease in psychiatric patients at Shanghai Mental Health Center in 2012. The researchers hypothesized that dry eye is very common in patients with depression or anxiety; hence, this study was conducted mainly to assess the prevalence of dry eye disease in patients with depression and/or anxiety disorders. The study included 472 participants, all of whom had anxiety disorders with or without depression. The results showed that 60% of psychiatric patients had dry eye disease, and 81% had experienced dry eye symptoms.³³ These percentages are much higher than the prevalence of dry eye in a randomly selected population from the same region in China, where the prevalence of dry eye was approximately 30%.³⁴

Recent prospective studies have confirmed a relationship between dry eye disease, anxiety, and depression. In this sense, a study published in 2019 at the University of North Carolina Kittner Eye Center included 45 subjects suffering from dry eye disease with a mean age of 65.5 ± 13.3 , of which, 37.8% had been clinically diagnosed with depression and anxiety and 33% were on antidepressants. The study was based on the initial diagnosis of dry eye disease in the eye care clinic, where patients were given a plan of treatment for dry eye, together with a questionnaire for the subjective evaluation of dry eye symptoms and both the Personal Health Questionnaire Depression Scale and the Generalized Anxiety Disorder Scale. All tests were performed at baseline, and the follow-up period was set at 3–6 months to repeat the same tests. At baseline, worse dry eye symptoms were correlated with worse anxiety and depression scales. At the time of follow-up, the results showed a significant improvement in both dry eye disease symptoms and anxiety levels but no statistically significant improvement in the depression scale. These results suggest that ocular surface care and treatment can improve anxiety levels in patients.³⁵

The number of studies associating dry eye with anxiety and depression has increased dramatically in the past few years, particularly with the COVID-19 era and its burden on society. The pandemic has obliged societies to make drastic changes in lifestyle owing to lockdowns, working from home, online classes, and a significant decrease in outdoor activities. One cannot ignore the fact that it affected several aspects of our lives, and studies are increasingly published in this regard. Increased use of visual display terminals during the pandemic has been associated with fewer blink intervals and excessive tear evaporation, leading to dry eye disease. However, social isolation due to home confinement resulted in higher anxiety and depression rates than pre-COVID.^{36–38} A study conducted in China recruited 428 participants from March to April 2021 and confirmed a strong association between dry eye symptoms and both anxiety and depression. The percentage of dry eye patients with comorbid anxiety and depression was 24.30%. Other factors such as sleep quality and educational level have also been shown to affect depression and anxiety symptoms.³⁹ Another study in China recruited 321 patients with dry eye symptoms measured using OSDI questionnaire at the Tianjin Medical University Eye Hospital clinic and found that 26.79%, 26.48%, and 16.82% suffered from anxiety, depression, or both, respectively.⁴⁰

Studies confirming this association are increasing, and more studies are needed to elucidate the pathophysiology that leads to both psychological disorders and dry eye as well as possible biomarkers. Several theories to explain the pathophysiology of this association were suggested, a potential mechanism involves sleep disorders present in patients with anxiety and depression. This disorder involves a decrease in blood pressure and a reduction in renin-angiotensin-aldosterone system hormones that cause a state of relative dehydration and subsequently affect tear production.⁴⁰ However, more studies are needed to elucidate the mechanism behind observed findings.

Summary

Psychosomatic ophthalmology emerged after World War II because patients attended clinics with symptoms that were not explained by physiological findings.⁴¹ Subsequently, it became obvious that stress factors had a negative effect on biological

processes such as homeostasis of the tear film. Evidence in the current review showed the association between dry eye disease, depression, and anxiety. Also, some studies reported inflammatory markers such as cytokines were elevated in tears of patients with depression. Although several theories explain the pathophysiology behind the association, more studies are still needed to determine the pathways responsible for the relationship between all disorders. Further research to understand whether it is a cause or a consequence, together with the study of possible molecules leading to dry eye in patients with psychological disorders is needed as the prevalence of psychological stress is increasing.

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Disclosure

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