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Review

PSYCHIATRIC DISORDERS AND DRY EYE DISEASE - A TRANSDISCIPLINARY APPROACH

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SUMMARY

Dry eye disease (DED) is a multifactorial disorder representing one of the most common ocular morbidities and a significant public health problem. It often results in eye discomfort, visual disturbances and potential damage to the corneal surface affecting quality of life (QOL).

In recent years, the relationship between DED and psychiatric disorders has been gaining attention. A number of epidemiological studies have reported a possible association between dry eye and psychiatric disorders showing that the subjective symptoms of dry eye can be affected not only by changes of the tear film and ocular surface but also psychological factors such as anxiety, depression, schizophrenia, post-traumatic stress disorder (PTSP) and subjective happiness. Apart from psychiatric disorders, psychiatric medications are also considered as risk factors for DED due to their influence on the tear film status. The incidence of ocular side effects increases rapidly with the use of polypharmacy, a very common form of treatment used in psychiatry.

There is often inconsistency between signs and symptoms of DED, where symptoms often are more related to non-ocular conditions including psychiatric disorders than to tear film parameters. Consequently, in many cases DED may be considered as a psychiatric as well as ophthalmological problem. Psychiatrists and ophthalmologists need to be aware of the potential influence of psychiatric disorders and medications on tear film stability. In treatment of psychiatric patients, an integrative and transdisciplinary approach will result in better functioning and higher QOL.

Key words: *dry eye disease - psychiatric disorders - psychiatric medications - transdisciplinary approach*

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INTRODUCTION

Dry eye disease (DED) is a multifactorial disorder that represents one of the most common ocular morbidities and a significant public health problem. It often results in eye discomfort; visual disturbances and potential damage to the corneal surface considerably affecting quality of life (QOL) (Moss et al. 2000, Behrens et al. 2006, Kaštelan et al. 2013a). The definition of DED has undergone multiple changes over the past two decades. The newest definition stems from a better understanding of the pathophysiology of the disease and is based on a consensus of numerous DED experts. At present DED is defined as a multifactorial disease characterized by a persistently unstable or deficient tear film that causes discomfort and visual impairment accompanied by variable degrees of ocular surface epitheliopathy, inflammation and neurosensory abnormalities (Tsubota et al. 2020).

The symptoms of DED include irritation, tears, itchiness, dryness; foreign body sensation, fatigue, blurred vision and fluctuating visual acuity (Smith et al. 2007). The signs are mainly associated with changes of the anterior segment of the eye. They are visible as tear deficiency, instability of the precorneal tear film, damage of the corneal or conjunctival epithelium and in severe cases serious damage and inflammation of the eye (Smith et al. 2007, Kaštelan et al. 2013a).

The prevalence of DED ranges from 5% to 34% with substantial variations between studies (Moss 2000, Smith et al. 2007, Kaštelan et al. 2013b, Hashemi et al. 2014, Pili et al. 2014, Bakkar et al. 2016, Stapelton et al. 2017, Liang et al. 2020). The causes of this variation are differences in disease definition, geographical location, race, sex, age and lifestyle of the study population (Kaštelan et al. 2013a). Other risk factors include computer use, vitamin or hormone intake or deficiencies, contact lens wear, radiation therapy, certain systemic and topical medications as well as some autoimmune and systemic diseases including psychiatric disorders. (Schein et al. 1997, Smith et al. 2007, Kaštelan et al. 2013b,c, Friedman 2010, Kawashima et al. 2020, Kuang et al. 2020, Kocer et al. 2015).

Clinically, a diagnosis of DED requires objective findings from eye examination tests and subjective reports of dry eye symptoms. Many studies have found a discrepancy between subjective self-reported symptoms and objective findings in patients with DED,

which makes diagnosis and treatment of this disease challenging (Kawashima et al. 2020, Mizuno et al. 2010, Nichols et al. 2004a, Li et al. 2011, Wen et al. 2012, Hua et al. 2014, Hallak et al. 2015, Szakats et al. 2016, Kuang et al. 2020). Significant reasons for this inconsistency may be psychiatric disorders and mental status of the patient. A number of epidemiological studies have investigated the connection of mental status, psychiatric disorders and psychiatric medications with DED showing that in many cases non-ocular factors are more strongly associated with dry eye symptoms than tear film parameters (Kim et al. 2011, Galor et al. 2011, Wen et al. 2012, Labbe et al. 2013, Hallak et al. 2015, Szakats et al. 2016, Kitazawa et al. 2018, Liang et al. 2020).

In this review, the recent findings regarding the association between DED and psychiatric disorders and the influence of psychiatric medication on tear film quality was presented. Further the underlying pathophysiological mechanisms and treatment methods for dry eye symptoms combined with psychiatric disorders was discussed.

DRY EYE DISEASE AND PSYCHIATRIC DISORDERS

In recent years, the relationship between DED and psychiatric disorders has been gaining attention. Previous studies have reported a possible association between dry eye and psychiatric disorders showing that the subjective symptoms of dry eye can be affected not only by changes of the tear film and ocular surface but also psychological factors such as anxiety, depression, post-traumatic stress disorder (PTSP) and subjective happiness. (Ulusoy et al. 2019, Koçer et al. 2015, Chia et al.2003, Han et al. 2017, Kim et al. 2011, van der Vaart et al. 2015, Labbe et al. 2013, Na et al. 2015, Kitazawa et al. 2018, Lee et al. 2002, Liyue et al. 2016, Hallak et al. 2015, Yilmaz et al. 2015. Szakats et al. 2016, Li et al. 2011, Galor et al. 2015, Kawashima et al. 2020). The prevalence of DED symptoms in patients suffering from depression and anxiety was estimated between 21% to 52% (Ulusoy et al. 2019, Schiffman et al. 2000, Lu et al. 2008). Further, sleep and mood disorders were also found to be higher in patients with dry eye (Ayaki et al. 2016).

Investigations addressing the relationship between DED and psychiatric disorders have pointed out the role of psychological factors in the development of dry eye symptoms, particularly in elderly patients (Han et al. 2017, Galor et al. 2015, Kim et al. 2011). Several studies confirm the existence of an association between DED and depression with PTSD in US veterans (Galor et al. 2011, Galor et al. 2015, Fernandez et al. 2013). They established that dry eye symptoms were more strongly associated with depression and PTSD than tear film parameters (Galor et al. 2015) and that patients with depression and/or PTSD had more pronounced dry eye symptoms with similar tear film parameters in comparison to individuals without psychiatric comorbidities (Fernandez et al. 2013). Likewise, Yilmaz et al. (2015) in their case control study reported an association between family history of DED and the presence of stress and found that participants suffering from depression, stress and anxiety are more prone to DED.

In two Chinese studies, elderly patients with dry eye had higher depression and anxiety scores compared with the non-dry eye population. Among those patients, anxiety and depression scores significantly correlated to dry eye symptoms but not to dry eye objective signs namely the TBUT, corneal staining and Schirmer test (Kim et al. 2011, Labbe et al. 2013). In a study including Koreans over the age of 65, Kim et al. (2011) found that depression was related to dry eye symptoms in patients with normal or mildly reduced tear production suggesting that DED may be a somatization disorder in people with depression. Results from the Beijing Eye Study identified that depression scores were correlated with dry eye symptoms, but not dry eye clinical tests (TBUT, corneal staining, Schirmer test) (Labbe et al. 2013).

A nationwide population-based study conducted in Taiwan on 75.650 participants demonstrated that among patients having psychiatric disorders, DED is highly prevalent in certain subtypes such as depression, bipolar disorder and neurotic disorders, after adjusting for their other comorbidities (Liang et al. 2020). In a cross-sectional investigation Kitazava et al. (2018) found that patients with symptoms of depression and/or anxiety had higher Dry eye related quality of life scores (DEQ) meaning that they had more severe subjective symptoms than patients without depression or anxiety, whilst the objective symptoms of DED did not differ between groups.

The existence of a poor correlation between dry eye symptoms and dry eye signs may be the cause of dilemmas in clinical trials related to issues pertaining to DED (Szakats et al. 2016, Sullivan et al 2014, Nichols et al. 2004a, Nichols et al. 2004b). A report including 53 patients with DED and 41 controls demonstrated that depressive symptom scores using the Beck Depression Inventory (BDI) showed a significant association with dry eye symptoms estimated by the Ocular Surface Disease Index (OSDI) questionnaire (Hallak et al. 2015). These findings suggest that depression and anxiety may affect the development of dry eye symptoms and may be one of the causes for inconsistencies between subjective symptoms and objective signs of DED. This conclusion is additionally supported by the study conducted by Szakats et al. (2016) which showed that the scores of psychological questionnaires, including the Shortened Health Anxiety Inventory (SHAI), Shortened BDI and Beck Anxiety Inventory (BAI) were significantly cor-

related with the OSDI. An interesting finding was that among patients having typical dry eye symptoms, 14.2% had no objective evidence of DED whilst 82.1% of the asymptomatic patients showed objective signs of dry eye.

Research including newly diagnosed patients is particularly valuable since the prevalence of dry eye in patients with no previous psychiatric medication use can explain the impact of depression itself or other psychiatric disorders on the occurrence of DED. Tiskaoglu et al. (2017) showed a clear association between depression as an illness and objective parameters of DED. In their research, Schirmer test values were significantly lower, TBUT intervals shorter and Oxford scores higher in patients with depression implying that DED may be directly related to or be caused by depression.

In a case-control study Li et al. (2011) reported that depression and anxiety scores within the DED group were significantly higher than in the controls. At the same time, the prevalence of patients with DED experiencing anxiety and depression was significantly higher than in the control group. Further, they found that anxiety scores were correlated with the OSDI and educational level in the DED group. However, they failed to find a significant association of depression scores with objective symptoms namely the Schirmer test, TBUT and corneal fluorescein staining.

Some psychological and mental health issues such as sleep disorders, anxiety, depression and mood disturbances have also shown to be triggering factors for DED indicating a mutually reversible relationship between DED and mental health status. (Kim et al 2011, Dibajnia et al. 2012, Ayaki et al. 2016, Hallak et al. 2015, Han et al. 2017, Galor et al. 2018, Kuang et al. 2020). A study investigating the association between subjective happiness and signs and symptoms of DED among 672 Japanese office workers showed that participants with a higher level of subjective happiness were less aware of dry eye symptoms. As a result, they may tend not to focus on their symptoms of dry eye and thus are less likely to report them even in the presence of objective signs of the disease. Participants with lower Subjective Happiness Scale scores reported more severe symptoms despite normal objective ophthalmological findings since they were more likely to be conscious of and concerned about the symptoms of DED that they were experiencing (Kawashima et al. 2016). Additionally, several investigators have reported an association between sleep disturbances and DED (Kawashima et al. 2020, Galor et al. 2018, Ayaki et al. 2016). Insomnia is common in the elderly and sedatives including benzodiazepines are frequently prescribed to alleviate this problem. The mechanism involved in the connection between insomnia and DED may be due to insomnia itself or may be the result of the prescribed medications (Kawashima et al. 2020). It has also been shown that patients with DED who do not adhere to advice regarding treatment often experience anxiety and depression (Han et al. 2017, Nepp 2016).

Associations between the signs and symptoms in DED are rarely reported (Ichinohe et al. 2016, Nichols et al. 2004a, Schiffman et al. 2000) and one of the possible explanations may be that subjective symptoms are influenced by psychiatric or psychogenic factors. Some investigators found a significant relationship between a patient's symptoms and their psychogenic status, such as depression, anxiety or feelings of subjective happiness (Ichinohe et al. 2016, van der Vaart et al. 2015, Na et al. 2015, Labbe et al. 2013, Hallak et al 2015, Kawashima et al. 2020, Fernandez et al. 2013, Kim et al. 2015). In addition, sensitivity to pain has been reported to play a significant role in the severity of DED (Vehof et al. 2013, Galor et al. 2015). It was also observed that a significant correlation between neuroticism and DED symptoms exists suggesting that the patients personality which is the basis of numerous psychological elements, has some impact on subjective symptoms (Ichinohe et al. 2016). This finding may be an explanation for discrepancies between symptoms and signs of DED.

On the other hand, there are only a few studies in which depression has been found to be associated with both symptoms and signs of dry eye. Wen et al. (2012) reported an increased frequency of DED and abnormal tear film parameters (TBUT, Schirmer's test and corneal staining) in 472 psychiatric patients being treated for depression and anxiety. DED was more prevalent among older patients with a longer history of psychiatric disease and was associated with antidepressant use particularly selective serotonin reuptake inhibitors (SSRI). Wan et al. (2016) conducted a meta-analysis and systematic review regarding DED and mental disorders. They analysed 22 studies consisting of 2.980.026 participants in total (485.709 DED patients and 2.494.317 non-DED subjects) reporting the prevalence, incidence, severity of depression and/or anxiety in DED patients. The studies relied on a number of self-administered psychiatric questionnaires in order to confirm the presence and severity of depression and anxiety. Their results confirmed the association of depression and anxiety with DED, irrespective of the underlying aetiologies of dry eye and ethnicity.

It was established that chronic discomfort and pain from dry eye symptoms might have a negative impact on cognitive processes, sleep, mood and mental health (Fine 2011). Disturbances in visual perception and performance may induce and aggravate symptoms of depression and anxiety (Miljanovic et al. 2007, Fine 2011, Kawashima et al. 2020). Somatization is common in depression and it could influence the perception of ocular discomfort (Wan et al. 2016). Previous studies reported that depression is more closely correlated with

dry eye symptoms than to dry eye signs, supporting the hypothesis that somatisation contributes to dry eye symptoms in patients with depression (Galor et al. 2015, Kim et al. 2011, Li et al. 2011, Labbe et al. 2013, Fernandez et al. 2013).

In addition, it has been reported that high pain sensitivity and low pain tolerance were associated with symptoms of DED (Vehof et al. 2013) and that they were more closely aligned to non-ocular pain than to tear film parameters (Galor et al. 2015). In a large population-based study, including 6.655 women over the age of 19, it was found that the participants with DED showed increased risk for severe psychological stress, anxiety and depression (Na et al. 2015). Although anti-depressant medications are known risk factors for inducing DED (Kobashi et al 2018, Wen et al. 2012), it has been shown that depression itself is also involved in its occurrence and development (Kobashi et al. 2018, Galor et al. 2012).

DRY EYE AND PSYCHIATRIC MEDICATIONS

Apart from the disease process itself, antidepressant, antianxiety and antipsychotic medication use are considered as risk factors for DED due to the potential side effects on the tear film status (Moss et al. 2000, Wong et al. 2011, Wen et al. 2012). This association is primarily connected to the anticholinergic effects of tricyclic antidepressants (TCAs) which cause dry eye symptoms and affect tear film status due to decreased tear secretion. (Wong et al. 2011, Fraunfelder et al. 2012). The newer and now most often used class of antidepressant medications including SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs) are considered to have less anticholinergic activity and as such less likely to cause dry eye (Wong et al. 2011).

Antidepressant medications such as TCAs, SSRIs or SNRIs exhibit antagonistic effects on the muscarinic receptors causing adverse effects such as DED, dry mouth and constipation. (Wong et al. 2011). Dry mouth was observed less frequently in SSRI than in TCA users since SSRIs have weaker anticholinergic effects (Wilson & Mottram 2004). Most antipsychotics for schizophrenia and some medications for Parkinson's disease, such as dopamine and levodopa show a certain level of anticholinergic effects (Wong et al. 2011). Patients using SSRIs demonstrated lower Schirmer scores independent of the duration of antidepressant use as compared with those using SNRIs however both had an increased risk potential for DED (Kocer et al. 2015). A further explanation for the connection may be that SSRIs can alter the tear serotonin level, which in turn influences the corneal nerve sensitivity (Acan & Kurtgoz 2017). The fact that serotonin is found in human tears and its receptors are present in conjunctival tissue support the notion that depression may precipitate DED (Marti & Brennan 1994, Acan & Kurtgoz 2017). The use of psychiatric medications may have additional effect on the ocular surface and tear secretion via the muscarinic and adrenergic receptors present in human conjunctival epithelium (Enríquez de Salamanca et al. 2005).

A study comparing dry eye in bipolar patients using mood stabilizers with patients without treatment suggested that lithium carbonate and sodium valproate prescribed for bipolar disorder were also associated with decreased TBUT, thus contributing to dry eye (Dibajnia et al. 2012).

The impact of psychiatric medications on the eye can be identified with a complete and thorough ophthalmological examination. The incidence of ocular side effects increases rapidly with the use of polypharmacy, which is very common in treating psychiatric patients. There are no established guidelines for psychiatric medication use regarding DED and psychiatrists and ophthalmologists need to be aware of the potential medication-induced adverse effect of psychiatric drugs on tear film stability. Thus, in order to prevent these side effects clinicians should attempt to use the lowest dose possible to achieve the desired therapeutic effect.

MECHANISMS OF THE ASSOCIATION BETWEEN DRY EYE AND PSYCHIATRIC DISORDERS

Several mechanisms may play a role in the association between DED and mental disorders (Kim et al. 2011, Galor et al. 2012, Liang et al. 2020, Tiskaoglu et al. 2017). Female sex, menopause and an increased omega-6: omega-3 ratio are common risk factors for both diseases indicating a shared pathogenesis (Kim et al. 2011, Miljanović et al. 2007, Tiskaoglu et al. 2019). Both depression and DED are multifactorial diseases largely related to inflammatory processes (Tiskaoglu et al. 2017). Previous reports showed a dysregulation of neuropeptides and an increased production of inflammatory cytokines in patients with depression (Kobashi et al. 2018, Werner & Coveñas 2010, Maes et al. 1997), which are also mechanisms involved in DED (Galor et al. 2012). An increase in the production of inflammatory cytokines interleukin-1 (IL-1), IL-2, IL-6, IL-8 and TNF-a is seen in both diseases (Li et al. 2011). These cytokines and neuropeptides may simultaneously lead to ocular surface inflammation and exacerbation of negative emotional status.

Depression and pain use the same biological pathways through neurotransmitters such as adrenaline and serotonin (Işik-Ulusoy & Ulusoy 2021). Likewise a recent study reported the role of serotonin in the secretion of tears from the lacrimal gland, showing that tear serotonin concentration is positively correlated with symptoms and signs of DED (Chhadva et al. 2015). It

has been hypothesized that neurotransmitters released near the Meibomian gland affect its secretions to the ocular surface (Tiskaoglu et al. 2017). This further suggests that disturbances of the serotonin receptors located in the conjunctiva can influence the Meibomian glands function leading to tear film deficiency in patients with depression (Tiskaoglu et al. 2017, Işik-Ulusoy & Ulusoy 2021).

Previous studies showed that patients with depression have a lower pain threshold often complaining of more intense dry eye symptoms compared to patients without depression. "Neuropathic pain" caused by neural dysfunction plays a role in unexplained chronic pain in DES and depression (McMonnies 2017). Chronic discomfort, visual impairment, frequent doctor visits, medical expenses and the need for frequent instillations of artificial tears (Han et al. 2017, Kitazava et al. 2018) can additionally affect social interactions leading to increased psychological stress, depression and anxiety (Kim et al. 2011, Liyue et al. 2016, Li et al. 2011).

Somatization, frequently related to depression, may be a predisposition for the development of dry eye symptoms and may influence the perception of ocular discomfort (Kim et al. 2011, Fine 2011). Patients with depression and anxiety may suffer from central sensitization, which affects pain perception and pain related behaviour (Galor et al. 2015). They can interpret ocular sensations differently than their healthy counterparts and their mood may influence perception of dry eye symptoms (Kawashima et al. 2016). Previous studies reported that depression is more closely correlated with dry eye symptoms, than to dry eye signs; supporting the hypothesis that somatization at least in part contributes to overall dry eye symptoms in depressive patients (Galor et al. 2015, Kim et al. 2011).

Biological as well as psychological components can contribute to the development of depression and anxiety in DED patients. Dry eye symptoms may result in constant feelings of discomfort or distress, which in turn cause or aggravate mood disorders (Ayaki et al. 2016).

MANAGEMENT OF DRY EYE RELATED TO PSYCHIATRIC DISORDERS

Treatment of DED is based on alleviating the typical signs and symptoms of dry eye associated with ocular surface inflammation, discomfort, visual disturbances and tear film instability. DED is a common disorder of the tear film, which causes ocular irritation, foreign body sensation and visual disturbances. However, there is often inconsistency between signs and symptoms of DED, where these symptoms are more often related to non-ocular disorders including depression and PTSD than to tear film parameters. This may be further complicated by the fact that psychiatric medications can additionally intensify symptoms making the management of these comorbidities more difficult (Weatherby et al. 2019) As such, in many cases DED may be considered as a psychiatric as well as ophthalmological problem. It has been shown that DED and depression are related in a synergistic manner. Effective treatment may help minimise symptoms of depression and alternatively, effective management of depression could help alleviate symptoms of DED.

Although symptoms are characteristic for DED, research has shown that less than 60% of subjects with objective signs of DED are symptomatic. Therefore, using only symptoms for establishing the diagnosis is likely to exclude a significant number of patients with DED, particularly those with early and mild forms of the disease. Further, discordance between dry eye signs and symptoms as well as an unsatisfactory response to conventional topical treatment may be a reason for considering the influence of psychological or neurological factors (McMonnies 2017). In those patients, treatment of accompanying psychiatric problems can be valuable in relieving dry eye symptoms. Considering the reciprocal influence between DED and psychiatric disorders, comprehensive management of both conditions would be beneficial (Ayaki et al. 2016).

CONCLUSION

DED is a multifactorial disease and is often associated with various psychological conditions and the use of psychiatric medications. The relationship between DED and numerous psychiatric disorders indicates shared pathophysiological mechanisms and mutual effect. The severity of subjective symptoms of dry eye is influenced by mental status and the identification and management of psychological disorders may improve the patients' subjective ocular symptoms and ultimately their QOL.

It is important to recognize psychiatric symptoms in DED patients particularly those with therapy-resistant dry eye syndrome and adopt timely and appropriate treatment strategies. A transdisciplinary approach and combined effort of psychiatrists and ophthalmologists could be beneficial in the management of patients with inconsistent dry eye symptoms and signs irresponsive to conventional DED treatment.

Contribution of individual authors:

Snježana Kaštelan: idea, concept and design of article, literature searches, writing manuscript, approval of final version.

Ivana Bakija, Marija Bogadi, Ivana Orešković, Boris Kasun, Marta Gotovac & Antonela Gverović Antunica: comments on the concept of article, literature searches, writing some parts of manuscript, approval of the final version.

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