

DEPRESSION AND DRY EYE DISEASE: A NEED FOR AN INTERDISCIPLINARY APPROACH?

Thomas J. M. Weatherby¹, Venkat Ram Vasant Raman² & Mark Agius³

¹Churchill College, Cambridge, UK

²University College London, London, UK

³Centre for Mental Health Research in Association with The University of Cambridge, Cambridge, UK

SUMMARY

A recent meta-analysis including data from 22 studies including 2.9 million patients found that anxiety and depression are more prevalent in patients with dry eye disease (DED) than in controls. DED is a common disorder of the tear film which can cause ocular irritation, foreign body sensation and visual disturbance. However there is often a great discrepancy between signs and symptoms of DED, which the symptoms often being more associated with non-ocular disorders such as depression and PTSD than to tear film parameters. In this way it could be considered as more of a psychiatric than ophthalmic complaint. DED and depression feedback on one another in a synergistic manner. Severity of DED is associated with symptoms of anxiety and depression. Treatment of DED could help reduce depression symptoms, but also effective management of depression could help alleviate symptoms of DED. Complicating this however is the evidence that SSRIs can exacerbate DED. This makes the management of these comorbidities more difficult, however there are putative therapeutic targets which may be a source of future treatments for DED-associated depression.

In conclusion, it is clear that DED and depression are closely linked and influence one another in ways that drastically affect patients' lives. Collaboration between psychiatrists and ophthalmologists could be beneficial in the management of those with DED.

Key words: depression - dry eye disease - multidisciplinary care

* * * * *

Introduction

Dry eye disease (DED) is a common disorder of the tear film which can cause ocular irritation, foreign body sensation and visual disturbance. It has numerous causes including ageing, medications, Lasik refractive surgery and inflammatory conditions such as Sjögren's syndrome. A recent meta-analysis including data from 22 studies including 2.9 million patients found that anxiety and depression are more prevalent in patients with DED than in controls with an odds ratio of 2.92 (Wan et al. 2019). It has a significant effect on quality of life with patients with moderate to severe disease reporting an effect on their quality of life comparable to that of a disabling hip fracture (Buchholz et al. 2016). However there is often a great discrepancy between signs and symptoms of DED, which the symptoms more associated with non-ocular disorders such as depression and PTSD than to tear film parameters (Galor et al. 2015). In this way it could be considered as much a psychiatric as an ophthalmic complaint. In this narrative review, we will argue that patients with DED would benefit from shared management between psychiatrists and ophthalmologists to optimise both their ocular and mental health.

Dry eye disease and depression are linked

There is an established link between dry eye disease and psychiatric conditions such as depression. A study conducted in 2018 reported that severity of both DED and depression both rose and fell in tandem but it is worth noting that the link between DED and anxiety

did not reach statistical significance (Bitar et al. 2019). Importantly, Kaiser et al. found that subjective well-being did not correlate well with features of DED but with regards to depressive symptoms their findings were more in line with other studies (Kaiser et al. 2015). A retrospective case-control study conducted in North Carolina reviewed 7,000 patients between 2008 and 2013 with DED and reported the odds ratio for DED and depression to be 2.8. While this significant correlation suggests this link is not just present in a niche subset of the population, the authors acknowledge that confounding from the use of antidepressants may be influencing results (van der Vaart et al. 2015). The association is seen across multiple age groups with Asiedu et al. demonstrating that DED symptoms impacted depressive symptoms to a greater extent when compared to other psychosomatic symptoms in a young population (Asiedu et al. 2018).

Dry eye symptoms correlate more to psychiatric comorbidities than to ocular signs

In a study conducted by Gonzales et al, patients with dry-eye symptoms were 1.82 times more likely to have depressive symptoms. In addition, even non-specific ocular symptoms, such as burning, also coincided with much higher likelihood of expressing depressive symptoms (Gonzales et al. 2018). Symptoms of DED actually correlated more reliably with depression and post-traumatic stress disorder (PTSD) opposed to tear film criteria, such as ocular surface disease index (OSDI), Schirmer's test and corneal fluorescein staining

(Han et al. 2015). Thus the consequences of failing to treat DED are that depressive symptoms may worsen and the knock-on effect of this may lead to depression-associated sleep disorders (Ayaki et al. 2018).

Sleep disorders

Sleep disorders are common in DED, affecting around half of patients. These can be debilitating with sleep being impaired on a number of measures including long sleep latency, short duration and poor subjective quality (Ayaki et al. 2018). There are a number of possible mechanisms underlying disturbed sleep. Primary Sjögren's syndrome itself is associated with sleep disorders. Pain from nocturnal eye exposure could also be contributing. Depression is a significant contributing factor, and the poor sleep that can often be found in depression may be further exacerbated by the other factors in DED, and there could therefore be reciprocal effects thereby further worsening both the DED and depression. The authors of a recent review on this topic endorsed the involvement of liaison psychiatry as well as ocular interventions in the management of sleep problems in these patients (Ayaki et al. 2018).

Mechanism of link

DED and depression have been shown to have common risk factors including age and female sex, the latter suggesting there could be a hormonal component (Hallack 2005). The prevalence increases from 3.9% (aged 50–54) to 7.67% (aged above 80) and 5.7% (aged under 50) to 9.8% (aged over 75) in the US male and female population respectively (Han et al. 2017). However, the precise biological mechanism by which they are correlated is still equivocal as is the order in which they occur. Theories have been put forward suggesting that DED negatively impacts quality of life and this psychological burden complicates patients' emotional state thus contributing to depressive symptoms (Hallack 2005). However, biologically the link may relate to a central nervous system sensitisation in the hypothalamo-pituitary-adrenal axis as seen in conditions like PTSD and fibromyalgia; two other psychiatric conditions that share a link with dry eye disease (Bitar et al. 2019).

A population based cross-sectional study of risk factors for DED in British women found the strongest associations with chronic pain syndromes including irritable bowel syndrome, pelvic pain and fibromyalgia (Vehof et al. 2014). The authors postulated that this may represent a common aetiology involving somatisation or chronic pain predisposition. A multivariate twin study by the same investigators indicated there may be shared genetic factors underlying both DED and chronic pain syndromes (Mcintosh et al. 2016).

In addition to this there may also be more mechanistic links. Reduced tear break up time, a finding indicating dry eye, can be found in patients with fibromyalgia without any rheumatological disease such as Sjögren's syndrome (Türkyilmaz et al. 2013). DED

patients with incongruous features were found to have a decreased density of the corneal nerve further evidencing the theory that there may be a neurological dysfunction underlying this condition (Han et al. 2015).

Suicidal ideation

Both depression and chronic disease are both significant risk factors for suicidal ideation and suicide attempts, particularly chronic pain conditions (Ro et al. 2015, Ratcliffe et al. 2008). Dry eye symptoms are associated with an increased risk of suicidal ideation in Korean adults. The generalisability of this study is arguably limited by the high background suicide rate in the study population of South Korea. This effect remains after adjusting for confounders such as occupation, income, age and sex. The presence of sleep disorders, a common feature of DED, are a potential confounder. When sleep length is controlled for the effect remains, but long sleep latency, poor subjective quality and other features of sleep can also be perturbed in DED and weren't controlled for in this analysis (Um et al. 2018).

Age-related Macular Degeneration and psychological interventions

Given DED is associated with depression, some investigators have asked whether there are any other ocular disorders which also increase a patient's risk of depression. An analysis of the Korea National Health and Nutrition Examination Survey (KNHANES) found that depressive symptoms were more prevalent in patients with Age-related Macular Degeneration (AMD) (Ryu et al. 2017). However a later analysis of depression in the Beijing Eye Study found that dry eye was the only common ophthalmic complaint associated with an increased depression score and that AMD was not significantly linked (Jonas et al. 2018). However a comparatively low prevalence of depression (2%) in the study population calls into question the generalisability of these results. Despite the currently unclear literature surrounding depression in AMD, a systematic review last year found that psychological interventions combined with low vision rehabilitation reduced the rates of depression in those with AMD, but cautioned that more evidence is required to tailor these further to AMD patients (Senra et al. 2019).

Antidepressants

As well as DED and depression often coexisting, the treatment of one impacts on the management of the other. Antidepressants can cause and exacerbate dry eyes. This was particularly prominent with the anticholinergic effects of tricyclic antidepressants, but also occurs with SNRIs and SSRIs without known anticholinergic effects (Koçer et al. 2015).

The mechanisms underlying this link may involve NF-KB and potentially could lead to therapeutics specifically targeting depression associated dry eye

(Zhang et al. 2019). Due to the complexities surrounding the management of depression in patients with DED, and how common this comorbidity is, an integrated approach to treatment decisions has been proposed (Han et al. 2017).

Conclusion

DED and depression are intertwined conditions: perhaps linked in their aetiology, commonly comorbid, with mutually antagonistic effects, and complexly interacting management. Treatment of DED could help reduce depression symptoms, but effective management of depression could also help alleviate symptoms of DED (Kitazawa et al. 2018). However the use of antidepressant medication can exacerbate DED which in turn then could worsen the depression. The evidence for psychological interventions for prevention of depression in other ocular disorders is strong however, and so this may be a fruitful approach (Senra et al. 2019). Involvement of psychiatrists has been proposed before in managing associated sleep disorders and antidepressant use contributing to dry eye (Ayaki et al. 2018, Han et al. 2017). We would go further and propose that shared care of these patients between ophthalmologists and psychiatrists may produce the best management of both their ocular and mental health.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Thomas Weatherby - conceiving of project idea, literature review, drafting manuscript.

Venkat Ram Vasant Raman - literature review, drafting manuscript.

Mark Agius - reviewing manuscript, editorial input.

References

1. Asiedu K, Dzasimatu SK, Kyei S: *Impact of Dry Eye on Psychosomatic Symptoms and Quality of Life in a Healthy Youthful Clinical Sample*. *Eye Contact Lens* 2018; 44(Suppl 2):S404–9
2. Ayaki M, Tsubota K, Kawashima M, Kishimoto T, Mimura M, Negishi K: *Sleep Disorders are a Prevalent and Serious Comorbidity in Dry Eye*. *Invest Ophthalmol Vis Sci* 2018; 59:143–50
3. Bitar MS, Olson DJ, Li M, Davis RM: *The Correlation Between Dry Eyes, Anxiety and Depression: The Sicca, Anxiety and Depression Study*. *Cornea* 2019; 38:684–9
4. Buchholz P, Steeds CS, Stern LS, et al.: *Utility assessment to measure the impact of dry eye disease*. *Ocul Surf* 2006; 4:155–161
5. Gonzales JA, Chou A, Rose-Nussbaumer JR, Bunya VY, Criswell LA, Shiboski CH, et al.: *How Are Ocular Signs and Symptoms of Dry Eye Associated With Depression in Women With and Without Sjögren Syndrome?* *American Journal of Ophthalmology* 2018; 191:42–8
6. Hallak J: *Dry Eye Disease and Depression: Epidemiological and Biological Links*. University of Illinois, 2015
7. Han SB, Yang HK, Hyon JY, Wee WR: *Association of dry eye disease with psychiatric or neurological disorders in elderly patients*. *Clin Interv Aging* 2017; 12:785–92
8. Jonas JB, Wei WB, Xu L, Rietschel M, Streit F, Wang YX: *Self-rated depression and eye diseases: The Beijing Eye Study*. *PLoS ONE* 2018; 13:e0202132
9. Kaiser T, Janssen B, Schrader S, Geerling G: *Depressive symptoms, resilience, and personality traits in dry eye disease*. *Graefes Arch Clin Exp Ophthalmol* 2019; 257:591–9
10. Kitazawa M, Sakamoto C, Yoshimura M, Kawashima M, Inoue S, Mimura M et al.: *The Relationship of Dry Eye Disease with Depression and Anxiety: A Naturalistic Observational Study*. *Translational Vision Science & Technology* 2018; 7:35
11. Koçer E, Koçer A, Özütçü M, Dursun AE, Krpınar İ: *Dry Eye Related to Commonly Used New Antidepressants*. *J Clin Psychopharmacol* 2015; 35:411-3
12. Mcintosh AM, Hall LS, Zeng Y, et al.: *Genetic and Environmental Risk for Chronic Pain and the Contribution of Risk Variants for Major Depressive Disorder: A Family-Based Mixed-Model Analysis*. *PLoS Med* 2016; 13:e1002090
13. Ratcliffe GE, Enns MW, Belik SL, Sareen J: *Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective*. *Clin J Pain* 2008; 24:204-10
14. Ro J, Park J, Lee J, Jung H: *Factors that affect suicidal attempt risk among korean elderly adults: a path analysis*. *J Prev Med Public Health* 2015; 48:28-37
15. Ryu SJ, Lee WJ, Tarver LB, et al.: *Depressive Symptoms and Quality of Life in Age-related Macular Degeneration Based on Korea National Health and Nutrition Examination Survey (KNHANES)*. *Korean J Ophthalmol* 2017; 31:412-423
16. Senra H, Macedo AF, Nunes N, Balaskas K, Aslam T, Costa E: *Psychological and Psychosocial Interventions for Depression and Anxiety in Patients With Age-Related Macular Degeneration: A Systematic Review*. *Am J Geriatr Psychiatry* 2019
17. Türkyilmaz K, Türkyilmaz AK, Kurt EE, Kurt A, Öner V: *Dry eye in patients with fibromyalgia and its relevance to functional and emotional status*. *Cornea* 2013; 32:862-6
18. Wan KH, Chen LJ, Young AL: *Depression and anxiety in dry eye disease: a systematic review and meta-analysis*. *Eye (Lond)* 2016; 30:1558-1567
19. Zhang X, Yin Y, Yue L, Gong L: *Selective Serotonin Reuptake Inhibitors Aggravate Depression-Associated Dry Eye Via Activating the NF-κB Pathway*. *Invest Ophthalmol Vis Sci* 2019; 60:407-419

Correspondence:

Thomas Weatherby, MD
Churchill College
Cambridge, UK
E-mail: tw418@cam.ac.uk