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The Association Between Dry Eye Disease and Depression and Anxiety in a Large Population-Based Study

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Abstract

Purpose—To investigate the association between dry eye disease and each of depression and anxiety.

Design—Retrospective, case-control study

Setting: University of North Carolina outpatient clinics

Study Population: All patients over the age of 18 years old seen between July of 2008 and June of 2013 were included in the analysis.

Observation Procedure: Cases were defined according to ICD-9 diagnosis codes for dry eye disease, anxiety, and depression.

Outcome Measure: Separate odds ratios were calculated for dry eye disease and each of anxiety and depression. Similar odds ratios were also calculated between dry eye disease and rheumatoid arthritis, a systemic disease with a known association with dry eye, as a way of validating our approach.

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Results—A total of 460,611 patients were screened; 7,207 patients with dry eye were included, while 20,004 patients with anxiety and 30,100 patients with depression were included. The adjusted odds ratio for dry eye disease and anxiety was 2.8 (95% CI 2.6–3.0). For dry eye disease and depression, the odds ratio was 2.9 (95% CI 2.7–3.1).

Conclusions—We identified a statistically significant association between dry eye disease and each of depression and anxiety. Such an association has implications for ophthalmologists in the management and treatment of dry eye disease.

Introduction

Dry eye disease is a multifactorial chronic disease with variable prevalence. The International Dry Eye Workshop (DEWS) researchers have discussed extensively the inherent difficulty in defining its prevalence and demography.¹ Dry eye disease remains a largely symptomatic diagnosis, without a single defining diagnostic test.¹ Despite these difficulties, several population-based studies have reported the prevalence of dry eye, with quoted prevalence rates ranging from 5.5% to 33.7%. Other researchers argue that the true prevalence is considerably higher.^{2–12} Nevertheless, there is little question that dry eye remains a common and complex problem for health care providers. In addition, dry eye is associated with other ocular and systemic illnesses. Sjogren's syndrome, for example, is an autoimmune disease, which has as part of its diagnostic criteria the presence of dry eye. Rheumatoid Arthritis and dry eye are related to each other as well.^{13,14} Studies have found an association between dry eye and diabetes mellitus^{1,15} though other studies have not shown this link.¹⁶

More recently, several population-based studies have investigated a possible association between dry eye and depression. Wen et al (2012) observed an increased frequency of dry eye disease in 472 psychiatric patients being treated for a variety of psychiatric illnesses, including depression and anxiety.¹⁷ Likewise, Galor et al (2011) demonstrated an association between dry eye disease and post traumatic stress disorder as well as depression in a veterans population.¹⁸ Finally, a recent study from the Beijing Eye Study identified an association between dry eye disease and depression symptoms in an elderly population in Beijing.¹⁹ However, all current data available on this association has focused on a small population²⁰ or in an age-specific population such as the elderly.^{19,21}

The purpose of this study was to investigate the association between dry eye disease and both depression and anxiety in a large adult population in the United States. To our knowledge, this is the largest population in which these associations have been studied to date. In addition to depression, we analyzed the association between dry eye and another disease with an already known association, rheumatoid arthritis, to validate our analytical approach.

Methods

We performed a retrospective case-cohort study by performing a chart review using the Carolina Data Warehouse of all patients seen in the outpatient setting at the University of North Carolina between July of 2008 and June of 2013. The study design was prospectively

approved by the University of North Carolina Institutional Review Board. The Carolina Data Warehouse is a repository of clinical, research, and administrative data captured from the electronic health records of all patients who have entered into the University of North Carolina Health Care System since July 1, 2004. Our study population included any patient over the age of 18 years old at the time of data extraction with any data in the Carolina Data Warehouse. Cases were defined according to ICD-9 codes as follows: Dry Eye Disease (ICD-9 code 375.15), Anxiety (ICD-9 code 300, 300.00, 300.01, 300.02), Depression (311, 296.2x, 296.3x), or Rheumatoid Arthritis (ICD-9 code 714.0). Patients for whom age could not be determined were excluded.

Using the diagnostic codes outlined above, odds ratios were separately estimated between dry eye and each of the other diseases. We were primarily interested in the associations between the diagnosis of dry eye disease and each of depression and anxiety.

We used separate logistic regression models to estimate associational odds ratios, each adjusted for age group and gender, along with 95% confidence intervals. For purposes of de-identification, data were extracted from the Carolina Data Warehouse, and aggregated by gender and age group, with age groups pre-defined as 18 to 35 years, 36 to 50 years, 51 to 65 years, and older than 65 years. These age groups were defined prior to the data analysis. To explore the potential for differential associations across age groups, we fit additional models that included disease-by-age-group interactions. We report 95% confidence intervals for the associations within each of these age groups along with a test of the interaction term for comparing associations across age groups.

Results

A total of 460,611 patients were included in the analysis; the clinic payer mix was estimated to be 50% Medicare, 25% private insurance, 15% Medicaid, and 10% uninsured. Of the 460,611 patients, there were 7,207 patients with dry eye, 20,004 patients with anxiety and 30,100 patients with depression. Seventy-six patient records were excluded because age could not be determined. Table 1 summarizes the aggregated data. Table 2 presents the prevalence of dry eye in patients with each of depression and anxiety, respectively.

The estimated odds ratio between dry eye disease and anxiety was 2.8, with a 95% confidence interval of (2.6, 3.0) (See Table 3). The estimated odds ratio between dry eye disease and depression was 2.9, with a 95% confidence interval of (2.7, 3.1). The estimated odds ratio between dry eye disease and rheumatoid arthritis was 3.2, with a 95% confidence interval of (2.8, 3.7). We found evidence that these associations differed across age groups (Table 4). Notably, there was a greater association with Dry Eye and Rheumatoid Arthritis in the youngest age group compared to the older age groups.

Discussion

The purpose of this study was to analyze the association between dry eye disease and each of depression and anxiety. As discussed previously, other studies of these associations had focused on a specific population, such as an elderly population in Beijing or a veterans affairs population.^{17,18} Our study, however, included over 7,000 patients with dry eye across

all age groups, which we argue represents a larger and more diverse population than previously studied.

We identified statistically significant associations between dry eye disease and each of depression and anxiety. Such an association is of importance to the eye care provider, who may serve as the entrance to medical care for patients. For example, in the case of diabetes mellitus, patients who have been previously undiagnosed with the disorder may present initially to the eye care provider due to a decrease in vision. Given our findings, we believe this may be the case for patients with depression and anxiety as well, who may present to seek medical care first with symptoms of dry eye. Perhaps there is a role for the eye care provider to initiate screening measures in dry eye patients for these comorbidities. To our knowledge, ours is the first study to discuss this as a possible role for the eye care provider.

Additionally, the association between dry eye and depression offers a potential therapeutic intervention target. The effects of adequate treatment of depression on successful therapy for other comorbid conditions has been demonstrated for other medical conditions such as chronic obstructive pulmonary disease²² and stroke.²³ Perhaps the treatment of dry eye disease, then, would also benefit from treatment of depression and/or anxiety.

Psychiatric diseases such as depression and anxiety have been linked to a number of chronic medical conditions, including arthritis, cancer, lung disease, heart disease, and diabetes, among others.^{24–27} Some have argued that such associations should have implications for treatment of both the psychiatric disease as well as the chronic medical illness in the primary care setting.²⁷ Given the nature of the association in our study, we offer that primary care providers should also view dry eye disease among the same group of chronic medical illnesses with implications for psychiatric disease. This recognition likewise should have screening and referral implications for primary care providers as well.

A major strength of this study is its size; to our knowledge, this is the largest population studied for such associations. The strength of our odds ratios reflects the size of the study and lends force to the associations demonstrated. A further strength lies in the inclusive nature of the study; unlike prior populations studied for an association between dry eye and depression, our population included all adult age groups and was not confined to a specific population, such as the veterans affairs population studied previously.¹⁸ As a result, the results of our study should be broadly generalizable.

Our study has limitations as well. Our population was entirely included from an academic medical center in North Carolina. However, we argue that our population is still more widely generalizable than other studies published on the same association. The clinic payer mix at our medical center reflects demographics which could be expected in a general ophthalmology clinic. In addition, we believe that the size and inclusivity of the population included in our study outweighs this limitation.

Another weakness of our study is its retrospective design, and as such causality cannot be determined by our analysis. Our primary research question was to assess the association of dry eye disease with depression or anxiety and the retrospective design was suited for this purpose. Furthermore, we argue that the therapeutic intervention advocated in our study

does not depend on causality. Treatment of depression has been shown to improve control of other chronic medical conditions^{22,23}. Therefore, from a clinical perspective, dry eye disease, anxiety, and/or depression require treatment. Adequate treatment requires that each disease be managed.

Additionally, our study was limited to those who presented for care, which demonstrates a possible area of confounding. However, the primary aim of our study was simply to investigate a possible association between dry eye and depression and anxiety. Furthermore, data were extracted only in the aggregate, which precluded both controlling for individual-level characteristics other than gender and age as well as simultaneously modeling all disease-dry eye associations. As argued above, we feel that the strength of the association proven by our study outweighs this limitation.

An additional weakness of the study is possible confounding by the medications used to treat depression. Antidepressant use has been identified as a risk factor for dry eye.^{5,28,29} However, this association has been primarily linked to anticholinergic effects of such medications as tricyclic antidepressants. Expert consensus within the University of North Carolina Psychiatry Department is that the use of tricyclic antidepressants has decreased markedly in recent years. In contrast, selective serotonin reuptake inhibitors, the newest and now most often used class of antidepressant medications, are thought to have less anticholinergic activity, which suggests that their contribution to dry eye may be less.³⁰

Similarly, we did not gather data regarding the level of treatment each patient had received for either dry eye or depression or anxiety. Our study was designed to assess a large and diverse population in order to definitively support the proven association. As such, it was not feasible to further distinguish where on the therapeutic spectrum each case occurred. However, as we describe previously, we argue that the size and generalizability of our population allows for the demonstration of a strong association, and that this outweighs this weakness.

Our study identified statistically significant associations between dry eye and the psychiatric diseases of depression and anxiety in a large population study. The nature of these associations, including causality as well as a possible link to antidepressant medications, warrant further study. Further study of these associations may also focus on the treatment of depression and anxiety and possible therapeutic effects on the management of dry eye, given similar results in the treatment of other medical diseases associated with these psychiatric conditions. The associations described in this study are applicable to clinical practice, with respect to eye care, primary care, and psychiatric care for patients with dry eye disease.

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takes responsibility for the integrity of the data and the accuracy of the data analysis, and contributed to every aspect of the manuscript.

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Table 1

The Association between Dry Eye Disease and Depression and Anxiety: aggregated data from the Carolina Data Warehouse. Case defined using ICD 9 diagnosis codes for each disease entity, and further divided by age.

Gender	Age Group	Total	With Dry Eye	With Anxiety	With Depression	With Rheumatoid Arthritis
Female	18 to 35	96,847	493	3,779	5,373	243
	36 to 50	71,791	847	3,942	5,893	662
	51 to 65	64,966	1,646	3,861	6,103	1,096
	> 65	53,799	1,958	2,560	4,123	933
Male	18 to 35	43,832	204	2,007	2,331	65
	36 to 50	41,859	439	1,847	2,564	155
	51 to 65	47,762	670	1,838	3,128	358
	> 65	39,755	950	993	1,887	326

Table 2

Estimated prevalence of dry eye in patients with or without each of depression and anxiety.

	With Dry Eye	Without Dry Eye	Total
With Anxiety	823 (4.0%)	20,004 (96.0%)	20,827
Without Anxiety	6,384 (1.5%)	433,400 (98.5%)	439,784
With Depression	1,302 (4.2%)	30,100 (95.8%)	31,402
Without Depression	5,905 (1.4%)	423,304 (98.6%)	429,209
Total	7,207	453,404	460,611

Table 3

Estimated odds ratios between dry eye disease and each of depression, anxiety and rheumatoid arthritis

Disease	Adjusted Odds Ratio [*]	95% Confidence Interval
Anxiety	2.8	(2.6, 3.0)
Depression	2.9	(2.7, 3.1)
Rheumatoid Arthritis	3.2	(2.8, 3.7)

* Adjusted for patient gender and age group

Table 4

Estimated odds ratios between dry eye disease and each of depression, anxiety and rheumatoid arthritis, by age group.

Disease Age group	Adjusted Odds Ratio *	95% Confidence Interval	P-Value [†]
Anxiety			0.001
18 to 35	2.4	(1.8, 3.1)	
36 to 50	2.0	(1.7, 2.4)	
51 to 65	3.0	(2.6, 3.4)	
> 65	3.1	(2.7, 3.5)	
Depression			0.004
18 to 35	2.1	(1.7, 2.7)	
36 to 50	2.5	(2.2, 2.9)	
51 to 65	3.1	(2.8, 3.5)	
> 65	3.1	(2.8, 3.4)	
Rheumatoid Arthritis			0.003
18 to 35	6.8	(3.6, 12.8)	
36 to 50	3.7	(2.6, 5.2)	
51 to 65	3.8	(3.1, 4.6)	
> 65	2.5	(2.0, 3.1)	

* Adjusted for patient gender.

[†] P-value from test of interaction between disease and age group.