Special Issue

Sleep Disorders are a Prevalent and Serious Comorbidity in Dry Eye

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Purpose. Sleep is an essential life habit and closely associated with lifespan, diabetes, hypertension, and mental health. Sleep disorders are a prominent, but overlooked problem in patients with dry eye disease (DED), characterized by a poor sleep index, short sleep duration, long sleep latency, and poor subjective sleep. DED and sleep disorders are more prevalent in women than men. Moreover, sleep quality in DED is worse than in other eye diseases, including glaucoma, retinal diseases, cataract, and allergic and chronic conjunctivitis.

Methods. We reviewed the literature for studies investigating sleep and health, eyes and sleep, and DED and sleep, in terms of systemic and eye health, especially in women.

Results. Two studies reported that approximately half of patients with DED suffer from poor sleep. The severity of mood disorders, including anxiety and depression, is correlated strongly with sleep disorders in DED, and the symptoms and signs of DED, especially pain, also are correlated with sleep quality. Sleep disorders are documented in primary Sjögren's syndrome and an association with sleep apnea and depression is suggested. Primary Sjögren's syndrome includes arthritis and other rheumatic disease causing pain and fatigue; however, how sicca contributes to sleep disorders is not known.

Conclusions. Possible explanations for sleep disorders in DED may be depression, pain, and eye exposure at night. Reciprocal effects may be expected and consultation-liaison psychiatry is recommended for the management of sleep disorders in DED. Topical medication and lid heating also may be advantageous for sleep quality in DED.

Keywords: dry eye, sleep, depression

A sleep disorder is a serious health problem and eye diseases may be linked to sleep in many aspects.[1] There is an increased interest in the psychiatric profile of patients with dry eye disease (DED),[2,3] including depression and sleep disorders, since a neurologic and psychiatric pathophysiology may underlie DED. Since DED[4,5] and sleep disorders[6,7] are more prevalent in women than men, we reviewed sleep and health, eyes and sleep, and DED and sleep in terms of the systemic and eye health, especially of women.

Recent Progress in Japan and Around the World

Sleep disorders are a new aspect in the care of DED. This concept was first introduced in 2015, and to date, few reports have been published in this field. Epidemiologic studies, including cohort and case-control studies, have been published in the United States, Korea, and Japan. A detailed psychiatric and neurologic approach looking at the mental health of patients with DED may further contribute to sleep quality in DED.

Sleep is a Critical Habit for Life

Sleep is an essential event for life, and sleep disorders are closely associated with mortality,[8–10] motor accidents,[11] injuries, and mistakes.[12,13] Several diseases have a significant association with sleep disorders and sleep duration, including depression,[14,15] diabetes,[16] obesity,[17,18] hypertension,[19] and cardiovascular events.[20,21] Sleep disorders may be induced by systemic or brain disorders, medication, depression or other psychiatric disorders, aging, environmental problems, or inadequate lighting. Transmeridian air travel and social activity also may cause sleep and circadian rhythm disorders.[22]

The gold standard for evaluating sleep quality is an electroencephalogram (polysomnography). Other objective methods used in chronobiologic and sleep studies include actigraphy,[23,24] which uses a micromotion logger to record the sleep/wake cycle and is compatible with an electroencephalogram, and measurement of melatonin levels in the blood, saliva, and urine.[25] Subjective sleep quality can be measured with a sleep diary and questionnaire. The most popular and validated self-report questionnaire is the Pittsburg Sleep Quality Index (PSQI) and major parameters are sleep duration, sleep latency, sleep difficulty, subjective sleep, and sleep efficacy.[26]

Menopausal Women Suffer From Dry Eye and Sleep Disorders

DED develops predominantly in menopausal women and they are at risk for a variety of health problems, including sleep and

mood disorders,[27] and sleep apnea syndrome.[28] Circadian rhythm disorders complicated with sleep disorders increase the risk of breast cancer by as much as 1.5-fold.[29] Vasomotor symptoms, major symptom during menopause, may lead to a sleep disorder,[30] but sleep disorders in menopausal women are associated more closely with depression than vasomotor symptoms.[31] Sleep latency and anxiety are correlated with depression[32] and sleep medicine is effective.[33] Hormone replacement therapy (HRT) with estrogen is known to be effective for menopausal symptoms, including sleep.[34–36] One study[37] suggested that HRT may be effective for DED; however, this finding is controversial since other strictly controlled studies[38–40] have suggested that women who use HRT, particularly estrogen alone, are at increased risk of DED. Ophthalmologists caring for women who are taking or considering HRT should be aware of this potential adverse effect.

Close Association between DED and Sleep

The Pivotal Role of Eyes in Sleep

Sleep is regulated by the circadian clock located in the suprachiasmatic nucleus.[41] Eyes have a pivotal role in sleep, since intrinsically photosensitive retinal ganglion cells and melanopsin are major players for photoreception to reset the circadian clock.[42,43] The function of intrinsically photosensitive retinal ganglion cells is mostly a nonvisual response of photoreception of short wavelength light. Glaucoma[44] and cataracts[45] negatively affect retinal photoreception and intraocular transmittance of light, respectively, and have been investigated as a potential cause of sleep disorders in the elderly. Glaucoma may share similar sleep problems with DED, as discussed later.

Sleep Disorders are Prevalent and Severe in DED

A survey of 1000 visitors to general eye clinics in Japan[1] revealed that 18.0% had DED and PSQI results demonstrated that 42.1% of the patients with DED were poor sleepers (PSQI global score ≥ 6; Table). This was the highest percentage for all diagnostic groups, including glaucoma (34.9%), retinal disease (35.0%), and cataract (39.6%). The depression and anxiety index (Hospital Anxiety and Depression Scale [HADS])[46] also was poorest in the DED group (HADS score ≥ 10 in 43.5%), compared to other diagnostic groups, such as glaucoma (38.8%), retinal disease (43.2%), and cataract (36.9%). In addition, the DED group had the poorest subjective sleep, sleep duration, anxiety, and depression subscores, suggesting poor sleep quality in DED might be associated with mental status.

Kawashima et al.[47] reported the results of a survey of 383 office workers routinely involved in video display terminal tasks and the prevalence of DED was 65.0% in this cohort. The prevalence of sleep disorders was 45.0% and the mean PSQI was 5.4 ± 2.2 in this DED group, according to the same criteria as Ayaki et al.[1] (PSQI > 5.5), whereas the values for the non-DED group were 33.6% and 4.6 ± 2.3, respectively. The presence of DED, the Schirmer value, and DED symptom score were significantly correlated with PSQI. It is notable that the prevalence of sleep disorders and the PSQI in the DED group were similar in these two studies despite the mean age of the DED groups differing by 19 years (61.4 vs. 42.4 years), suggesting that video display terminal work may negatively affect sleep. Based on the results of these two studies, nearly half the patients with DED suffer from poor sleep and it may be associated with DED symptoms and mental status.

In a study of women aged 30–69 years, with and without DED,[48] the DED group exhibited a significantly poorer PSQI score than the non-DED group, especially in subjects 56 to 69 years old (4.92 ± 2.71, non-DED; 6.08 ± 2.92, DED), suggesting subjective sleep quality in the older group may be exacerbated by DED. On the other hand, the younger group (30–45 years) with DED showed a poorer mood index (HADS score, 13.18 ± 3.95) compared to the non-DED group (9.79 ± 5.82), suggesting that the younger group may be the most distressed of the three age groups of women. Across all age groups, the PSQI score was strongly correlated with the HADS score. These results demonstrated that DED has a considerable impact on sleep and mood in women.

Lee et al.[49] reported survey results of sleep duration in 15,878 Korean participants divided into five groups according to habitual sleep duration ($\leq$4, 5, 6–8, 9, and $\geq$10 hours), and demonstrated that the prevalence of DED was correlated with sleep duration, with an odds ratio (OR) for DED prevalence, after adjusting for age, sex, and sociodemographic factors (smoking habit, alcohol consumption, and level of exercise), of 1.30 for a short sleep ($\leq$4 hours), 1.2 for 5 hours, 0.89 for 9 hours, and 1.0 for $\geq$ 10 hours, compared to optimal sleep (6–8 hours). They discussed the significant association of sleep deprivation with DED risk, in relation to increased inflammation by tear hyperosmolarity, androgen levels, the parasympathetic nervous system, and blinking.

Ong et al.[50] assessed symptom progression in DED and determined ocular and nonocular risk factors associated with severe symptoms at 1 year in a longitudinal study of 120 veterans (mean age, 64 years). Nonocular risk factors included sleep disturbances (e.g., sleep apnea and insomnia), mental health status (e.g., posttraumatic stress disorder and depression), nonocular pain, and medications (e.g., anxiolytics and analgesics). Multivariable analysis revealed the most significant nonocular risk factors were sleep apnea (OR, 3.80), the Dry Eye Questionnaire 5 score (OR, 1.15), and the posttraumatic stress disorder score (OR, 1.04).

Galor et al.[51] investigated the association between DED and insomnia symptom severity in 187 patients (mean age, 63 years) and the DED group with high pain experienced more severe insomnia compared to the DED low pain group. They evaluated the pain of DED using numeric rating scales for pain, spontaneous burning pain, and sensitivity to wind and light. Black race, depression severity, and DED symptom severity were significantly associated with clinical insomnia. This investigation suggests that ocular pain may lead to sleep disorders in DED. Pain is known to be a serious issue for sleep quality[52] and it may explain why sleep disorders are seen in primary Sjögren's syndrome (pSS), as described later.

Sex Difference in Sleep Disorders in DED

Sleep disorders in women with DED aged 30 to 69 years are characterized by a poor PSQI global score (4.92 ± 2.71 for non-DED vs. 6.08 ± 2.92 for DED), poor subjective sleep score (1.10 ± 0.58 vs. 1.35 ± 0.77, respectively), longer sleep latency (16.0 ± 15.0 vs. 22.2 ± 22.8 minutes, respectively), and a late bedtime (23:30 ± 1:08 vs. 23:56 ± 1:07 hours, respectively).[48] The HADS score also is worse for women with (11.36 ± 6.27) than without (9.93 ± 5.40) DED. Using the same cohort as above, the PSQI and HADS scores were calculated for 114 men without and 38 with DED, aged 30 to 69 years (unpublished data). The men with DED showed significantly poorer results for the PSQI global score and subjective sleep score than men without DED. In addition, men with DED exhibited a poorer daytime dysfunction score and shorter sleep duration than men without DED. Using the PSQI global score, the severity of sleep disorders between men and

Table. Studies Evaluating Dry Eye and Sleep

Investigator	Design	Age*	*N* (DED/All)	Diagnostic Method for DED	Sleep Parameters	Other Parameters	Results
Ayaki[1]	Cross-sectional, observational study	61.4 (17.3)	247/730	Examinations and interview	PSQI	HADS	PSQI and HADS were worst in DED compared to other ocular diseases
Ayaki[48]	Cross-sectional, case-control study	53.2 (10.7)	106/213	Examinations and interview	PSQI	HADS	PSQI was worse in women with DED than without. Sleep was strongly correlated with mood.
Ayaki[53]	Cross-sectional, case-control study	61.1 (15.5)	301/503	Examinations and interview	PSQI	HADS	DED patients reported worse PSQI than patients with chronic and allergic conjunctivitis.
Kawashima[47]	Cross-sectional study	42.5 (8.4)	249/383	Examinations and interview	PSQI	Display working hours	45% of DED and 34% of non-DED patients reported poor sleep (PSQI > 5.5)
Galor[51]	Cross-sectional, case-control study	63 (11)	153/187	Examinations and series of questionnaires	7-item severity index	DEQS, OSDI, meibum quality, ocular pain rating scale, PHQ-9, PTSD	DED symptom severity was positively associated with sleep disorder severity
Ayaki[102]	Longitudinal, case-control study	62.6 (8.9) for new patients; 63.2 (16.2) for established	25 new DED patients; 46 established DED patients	Examinations and interview	PSQI	HADS	Patients with newly diagnosed DED exhibited a greater improvement in PSQI after DED treatment compared to those with established DED.
Lee[49]	Population-based survey	≥20	2835/15878	One question†	Sleep duration	Income, education, smoking, alcohol drinking, and exercise level as confounding factors	Prevalence of DED was lowest in the optimal sleep group (6–8 h/day)

DEQS, dry eye questionnaire; OSDI, ocular surface disease index; PHQ-9, patient health questionnaire-9; PTSD, posttraumatic stress disorder.

* Mean (standard deviation) of DED group.

† "Until now, have you ever had symptoms of dry eye syndrome before: for example, a sense of irritation or dryness of the eye?"

women with DED is similar; however, the HADS score for men is not different between the DED and non-DED groups, suggesting depression and anxiety may have a stronger impact on the sleep of women with DED than on men with DED.

More Severe Sleep Disorders Occur With DED than Other Irritating Eye Diseases

According to a survey of patients with DED, chronic conjunctivitis, and allergic conjunctivitis, those with DED showed the poorest PSQI and HADS scores[53] (6.4 ± 3.3 and 11.1 ± 6.6 for severe DED, 5.5 ± 3.1 and 9.8 ± 5.7 for mild DED, 5.5 ± 3.2 and 9.5 ± 5.6 for chronic conjunctivitis, and 5.0 ± 2.8 and 8.9 ± 6.0 for allergic conjunctivitis, respectively). Sleep duration and sleep efficacy also were poorest in the severe DED group. The investigators speculated that patients with DED may be distressed by sensory discomfort, optical disturbance, or by psychologic distress from the disease itself. These factors affect patients and may lead to depression and sleep disorders. Patients with DED suffer from irritation and dryness and these symptoms may continue for life and can worsen at any time, which is the nature of the difference of DED from chronic conjunctivitis and allergic conjunctivitis.

Eyes are Disturbed at Night With DED

The results of closed-eye studies and elevated tear matrix metaprotease-9 in DED suggest that patients with DED may have more inflammatory processes than controls during sleep.[54,55] Patients with DED have a high prevalence of obstructive sleep apnea,[56–59] and its therapy, continuous positive airway pressure, may worsen DED.[60] Air conditioning and sleep position[61,62] also may worsen DED. Asplund[63] reported that nocturia is more prevalent in people with ocular and oral dryness than in those without, according to the survey results of 6103 elderly participants. Sleep deprivation reduces tear secretion and impairs the tear film.[64] Patients with DED have uncomfortable eyes in the morning and they are unhappy, as indicated by a web survey (Kokune-Takahashi A, et al. *IOVS* 2017;58:ARVO Asia Poster 159).

In 1994, Kurihashi[65] described a unique therapy for DED and sleep disorders of wearing a moisture aid consisting of a wet gauze eye mask during sleep; this has become an established treatment for chronic blepharitis.[66–68]

DED has a Considerable Psychiatric Profile

Several reports and reviews describe a close association between DED and depression, anxiety, stress, posttraumatic stress disorder, and sleep disorders. On the other hand, sleep deprivation and medications for psychiatric disorders may partly suppress tear secretion because lacrimal secretion is under neural regulation.[69,70] The association of DED with neurologic problems, such as neuropathic pain, chronic pain syndrome, peripheral neuropathy, and central nervous system manifestations, also has been documented by several investigators.[2]

Patients with DED are Depressive

Depression as a comorbidity of DED has been described extensively, including in three systematic reviews and meta-analyses.[2,3,71–86] This is an important point, since depression is closely associated with sleep disorders.[72,73] Zheng et al.[3] reviewed the literature and reported that the highest prevalence of depression among ophthalmic patients was in those with DED (29%), followed by glaucoma (25%), age-related macular degeneration (24%), and cataract (23%), evaluated with the Beck Depression Inventory, Center for Epidemiologic Studies Depression Scale, and HADS. Wan et al.[71] conducted a systematic review and meta-analysis of 22 studies that reported the prevalence, incidence, and/or severity grading of depression and/or anxiety in patients with DED. They reported that DED was associated with an increased prevalence of depression (OR, 2.92) and anxiety (OR, 2.80). Subgroup analyses revealed that the prevalence and severity of depression are greatest in pSS (described below). Certain antidepressants are anticholinergic and may worsen DED by suppressing lacrimal secretion.[87–90] Labbe et al.[76] discussed the relationship between DED and depression. The symptoms of DED may induce depression and, in turn, depression and its medication might induce DED; additionally, they have common risk factors, such as female sex and age. Dysregulation of neuropeptides and an increased production of inflammatory cytokines also are present in both diseases.

Sleep Disorders are a Common Comorbidity of pSS

Patients with pSS are affected by fatigue, daytime sleepiness, and insomnia. Several reports describe the pSS-related psychiatric status as sleep disorders, depression, and anxiety.[91–101] Sleep disorders in pSS are characterized as a long sleep latency and severe sleep difficulty due to pain. Ocular complications, such as the presence of sicca, have been surveyed in a few studies, however, no study has referred to ocular findings.

Hackett et al.[91] completed a systematic review of nine studies of sleep disturbances in pSS and concluded that a range of sleep disturbances are commonly reported in pSS patients; that is, prevalent night awakenings and increased obstructive sleep apnea in pSS compared to controls. In these studies, sleep disturbance was determined using sleep diaries, the Epworth Sleepiness Scale, the 15-item Dutch questionnaire on sleep quality, and polysomnography, and showed a longer sleep latency, short sleep duration, and low sleep efficacy in pSS. Sicca symptoms, nocturnal pain, and nocturia have been indicated as factors associated with sleep disorders in pSS. Recommended management strategies include cognitive behavioral therapy for insomnia, nocturnal humidification, and artificial saliva sprays.

Priori et al.[92] assessed the sleep quality, quality of life and mood disorders in patients with pSS using the PSQI, Short Form Health Survey 36, Functional Assessment of Chronic Illness Therapy fatigue scale, and HADS. The mean PSQI global score had higher pathologic values (8.6 ± 4.6) than in controls (5.6 ± 2.2). Additionally, the HADS subscales correlated with the PSQI subscales, while no correlation with the Functional Assessment of Chronic Illness Therapy fatigue scale or disease indexes emerged.

Theander et al.[93] studied the prevalence of fatigue and daytime sleepiness in pSS and concluded that fatigue is the main problem for patients with pSS, while sleepiness is a minor problem. Patients had significantly more frequent episodes of anxiety and nocturia and woke up more often during the night than controls. They described 13% of patients with pSS reported sicca symptoms disturbing sleep.

Kok et al.[100] reported a positive association between chronic sleep disorders and pSS (hazard ratio, 2.0) in a population-based longitudinal study. Valtysdottir et al.[101] compared the Gothenburg quality of life instrument between pSS and rheumatoid arthritis and the patients with pSS had a significantly higher scoring rate for anxiety and also depression, compared to those with rheumatoid arthritis. Shen et al.[98] reported that the adjusted hazard ratio of depressive, anxiety,

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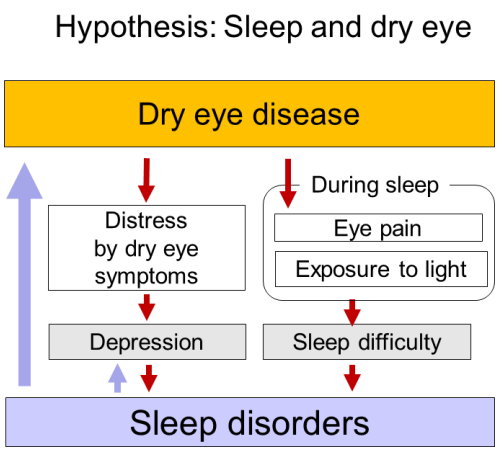

Figure. Hypothesis for sleep disorders in patients with DED. Patients with DED may be distressed by sensory discomfort or optical disturbance, or have psychologic distress from the disease itself. During sleep, patients may feel pain and brightness during incomplete eye closure, producing inflammatory processes leading to sleep difficulty; this causes a vicious spiral of DED, depression, and sleep disorders.

and sleep disorders in patients with pSS was significantly higher at 1.829, 1.856, and 1.967, respectively, than those of controls during follow-up from 2000 to 2008.

Ophthalmic Measures Followed by a Consultation-Liaison Psychiatry Service are Recommended for Sleep Disorders in DED

Ophthalmologists occasionally may encounter poor sleepers complaining of DED symptoms if the patient is a shift worker, nursing mother, or taking psychiatric medication. In addition to referring the patient to a psychiatrist, gynecologist, or other specialist for further management, they could treat DED with ophthalmic measures and the ocular improvement may lead to an advantageous effect on mood and sleep. One study evaluated the effect of topical medication on the sleep of patients with DED and suggested that a consultation-liaison psychiatry service (i.e., collaboration with psychiatrists and other medical specialists may be helpful for patients with DED and potential psychiatric problems).[102] The study evaluated sleep quality in 71 patients with DED using a questionnaire-based survey before and after topical treatment for DED. The effectiveness of sleep and ophthalmic services in assisting with sleep problems in patients with eye disease was assessed using the PSQI and HADS. Significant improvement in the PSQI was found ($P < 0.05$) and strongly correlated with improvement in the HADS score for new patients ($P < 0.05$), but not for patients with established DED. A sleep service in this eye clinic has been opened and provides sleep hygiene, blue-light shield eyewear and wearable and desktop blue-light emitting lamps according to the patients' sleep problems. The service also prescribes melatonin agonist and sedative herbs. Another DED therapy reported to be effective for sleep and the autonomous nervous system is lid-heating during sleep.[65,66,103,104] Sleep disorders and DED are common health problems in menopausal women and HRT has been proven effective for menopausal sleep disorders, however, it is controversial for DED.[34–40] Moreover, relieving the pain of DED may produce a reciprocal influence, since pain, sleep, and depression interact with each other.[105,106]

Possible Explanation for Sleep Disorders in DED

A direct connection between DED and sleep has not been determined; however, an apparent association between sleep and depression,[72,73] and between depression and DED has been well described in several reports. The current hypothesis for sleep disorders in DED is shown in the Figure. Firstly, depression may be considered as a possible causality in sleep disorders in DED. Several studies have demonstrated an association between the severity of sleep disorders, depression, and DED. Depression may induce DED and sleep disorders, and in turn, ocular diseases could induce depression, as reported in DED and glaucoma. The emotional burden due to the nature of the disease, and the medication burden could typically cause sleep disorders[44,107] in ocular patients with depression.[107–111] Furthermore, DED often develops in glaucoma patients, since glaucoma medication is toxic to the ocular surface.[112] Secondly, it is highly likely that pain[113–115] in patients with DED may be associated with sleep disorders. Sleep disorders with pain have been suggested in pSS and other rheumatic diseases.[116] Pain is known to affect sleep quality in many diseases and a low threshold of pain is linked to sleep disorders.[106,117] Thirdly, eye exposure may be frequent in patients with DED and this also could lead to sleep difficulty. DED, depression, and sleep disorders may be involved in a vicious spiral.

Future Directions

The prevalence of DED and sleep disorders is increasing in modern society and these diseases have common exacerbating factors, including stress, a blue-light-rich environment, and 24-hour shift work. Research into sleep disorders in ocular patients has been historically performed by ophthalmologists and epidemiologists; however, involvement of psychiatrists and gynecologists should be further encouraged for a more comprehensive management. Objective methods, such as actigraphy, melatonin measurement, and polysomnography, would precisely confirm sleep quality in patients with DED. As DED is a multifactorial disease, multiple approaches also may be effective for sleep disorders in DED. Similarly, a psychiatric and neuronal approach may be simultaneously advantageous to both conditions.

Conclusions

Sleep disorders are a serious health problem and ophthalmologists should be aware of the fact that DED in patients may be complicated by sleep and mood disorders. Although ophthalmologists may not be familiar with somnology, they should first listen to the patient (Sir William Osler, 1849–1919) to relieve them from distress. Then, they can use eye drops, other ophthalmic interventions, sleep hygiene, and psychiatric consultation to further alleviate their symptoms.

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