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EFFECTS OF ANTIDEPRESSANT AGENTS ON CORNEA AND OCULAR SURFACE

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Abstract

Aim: Today, antidepressants, which are frequently prescribed by physicians for different purposes, have various effects on ocular tissues. The aim of this study is to evaluate the effects of different agents on the cornea and ocular surface.

Methods: For this purpose, 50 healthy controls and 336 patients were included in this study. The participants in this study were those who had never taken an antidepressant before and had been using only one antidepressant regularly for the last 1 year, had no known dry eye disease, had not undergone any ocular surgery, were not pregnant, non-smoker, glaucoma, contact lens use, thyroid ophthalmopathy and/or patients who do not have an additional disease that may cause dry eye such as facial paralysis, who do not use any topical and/or systemic drugs for other purposes, and healthy controls who do not have any disease are included. Demographic data, names of antidepressant agents, OSDI (ocular surface disease index) scores, tear break-up time, Schirmer test and SICCA ocular staining scores of all participants were recorded.

Results: Compared to the control group, all patient groups had higher OSDI scores and staining scores, and a lower Schirmer test result and a lower tear break-up time (all parameters, $p<0,001$). When specular microscope data were evaluated, cell density and hexagonality were found to be lower in all patient groups compared to the control group (all parameters, $p<0,001$). In the corneal topography data, there was a significant difference in all parameters in the patient groups when compared to the control group (all parameters, $p<0,001$).

Conclusions: In conclusion, all antidepressant agents, especially sertraline and escitalopram in the SSRI group, have adverse effects on the cornea and ocular surface. Among the current treatment options, agents in the SNRI group are more compatible with the ocular surface.

Keywords: *Antidepressant, cornea, drugs, ocular surface, toxicology*

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Introduction

Antidepressant agents are frequently used in psychiatry clinics. Agents in this group consist of monoamine oxidase inhibitors (e.g. selegiline, phenelzine), serotonin reuptake inhibitors (e.g. citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin-noradrenaline reuptake inhibitors (e.g. duloxetine, levomilnacipran, venlafaxine) and tricyclic antidepressant agents (e.g. amitriptyline, imipramine).[1]

This agents has side effects that affect many systems. These include primary sleep disorders such as restless legs syndrome and sleep apnea, sexual dysfunction, hepatotoxicity, weight gain, and cardiovascular side effects.[2-4]

Ocular side effects include decreased tear breakout time, angle-closure glaucoma, cataract and retinopathy.[5]

The aim of this study is to investigate the effects of various commonly used antidepressant agents on the cornea and ocular surface.

Materials and Methods

The participants in this study were those who had never taken an antidepressant before and had been using only one antidepressant regularly for the last 1 year, had no known dry eye disease, had not undergone any ocular surgery, were not pregnant, non-smoker, glaucoma, contact lens use, thyroid ophthalmopathy and/or patients who do not have an additional disease that may cause dry eye such as facial paralysis, who do not use any topical and/or systemic drugs for other purposes, and healthy controls who do not have any disease are included.

While creating the study population, patients using more than one anti-depressant, younger than 18 years of age, or using topical drops for any purpose were excluded.

Demographic data, names of antidepressant agents, OSDI (ocular surface disease index) scores, tear break-up time, Schirmer test and SICCA ocular staining scores of all participants were recorded.

In addition, CellChek XL (Konan Medical, California, USA) specular microscope and Scheimpflug imaging system (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany) were used as imaging methods.

Necessary permissions were obtained from the Clinical Research Ethics Committee of Mersin University before this study. Written informed consent was obtained from all patients in this study and the principles of the Declaration of Helsinki were adhered to throughout this study.

Mean and standard deviation values were used to define continuous variables. The conformity of continuous variables to the normal distribution was examined using the Shapiro-Wilk test. Student's t test was used to compare the relationship between two independent variables with normal distribution, and ANOVA was used to compare the means of more than two independent groups. The relationship between the two groups of variables that did not conform to the normal distribution was examined using the Mann Whitney U test, and the relationship between more than two groups was analyzed using the Kruskal-Wallis test.

The relationship between categorical variables was examined with the chi-square test. The statistical significance level was taken as $p < 0.05$. Analyzes were performed using SPSS 22.0 software for Windows (SPSS Inc., Chicago, IL).

Results

This study included 50 healthy controls, 92 patients taking escitalopram, 54 patients taking sertraline, 51 patients taking fluoxetine, 63 patients taking duloxetine and 76 patients taking venlafaxine. The mean age of all participants shows a statistically significant difference ($p=0,017$). The mean age of the patients in the escitalopram group was higher than the control group ($p < 0,001$) and the mean age of the patients in the fluoxetine group was lower ($p < 0,001$).

Table 1. Demographic data of the participants

	Control	Escitalopram	Sertraline	Fluoxetine	Duloxetine	Venlafaxine	p
n	50	92	54	51	63	76	
Age (years)	41,9 ±6,8	48,1 ±5,7	45,9 ±5,1	38,6 ±4,6	43,5 ±6,4	40,7 ±6,2	0,017
Male	23 (46%)	35 (38%)	20 (37%)	18 (35,3%)	22 (34,9%)	36 (47,4%)	0,542
Female	27 (54%)	57 (62%)	34 (63%)	33 (64,7%)	41 (65,1%)	40 (52,6%)	

The gender distribution between healthy controls and patient groups was similar (p=0,542). (Table 1)

Compared to the control group, all patient groups had higher OSDI scores and staining scores, and a lower Schirmer test result and a lower tear break-up time (all parameters, p<0,001). When the patient subgroups were compared with each other, the most different results (except Schirmer) were seen in the sertraline group. The group with the lowest Schirmer test result is the patients in the escitalopram group. (Table 2)

When specular microscope data were evaluated, cell density and hexagonality were found to be lower in all patient groups compared to the control group (all parameters, p<0,001). In patient subgroups, the most different results (lowest cell density, highest coefficient of variation, and lowest hexagonality) were recorded in sertraline and escitalopram groups. (Table 3)

In the corneal topography data, there was a significant difference in all parameters in the patient groups when compared to the control group (all parameters, p<0,001). In the subgroup analysis, the highest corneal thickness was measured in the venlafaxine group. The highest total and central corneal density values were recorded in the sertraline group. (Table 4)

Table 2. Ocular surface data of the participants

	Control	Escitalopram	Sertraline	Fluoxetine	Duloxetine	Venlafaxine	p
n	50	92	54	51	63	76	
OSDI	6,2 ±0,9	38,1 ±5,0	43,2 ±7,9	32,3 ±9,7	39,8 ±8,8	41,1 ±6,4	< 0,001
Schirmer (mm)	26,8 ±2,9	18,6 ±2,7	23,6 ±3,6	21,4 ±1,8	21,3 ±1,7	20,8 ±2,1	< 0,001
SICCA	1,08 ±0,32	1,96± 0,71	2,54 ±0,88	1,93 ±0,66	1,85 ±0,57	1,98 ±0,63	< 0,001
TBUT (sec)	19,58 ±3,47	9,58 ±2,38	7,63 ±1,49	10,55 ±2,29	8,41 ±1,16	9,39 ±1,79	< 0,001

Table 3. Comparison of specular microscopy results of the participants

	Control	Escitalopram	Sertraline	Fluoxetine	Duloxetine	Venlafaxine	p
n	50	92	54	51	63	76	
Cell density (CD) (/mm^3)	2854,3 ±176,7	2378,3 ± 192,9	2575,6 ± 164,8	2790,8 ± 189,6	2843,2 ± 197,2	2850,1 ± 152,8	< 0,001
Coefficient of variation (CV) (%)	25,1 ± 4,8	27,9 ±3,6	26,8 ±3,7	23,8 ±4,4	23,04 ±3,1	23,7 ±4,3	< 0,001
Hexagonality (HEX) (%)	46,02 ± 3,1	33,9 ±3,7	32,7 ±4,6	45,6 ±5,9	43,1 ±3,5	42,5 ±7,1	< 0,001

Table 4. Comparison of corneal topography results of the participants

	Control	Escitalopram	Sertraline	Fluoxetine	Duloxetine	Venlafaxine	p
n	50	92	54	51	63	76	
CCT (µm)	528,1± 91,3	541,9± 85,1	553,2± 73,7	532,5± 72,8	537,4 ±93,6	548,2± 88,9	< 0,001
Corneal density (Total) (GSU)	19,1 ± 3,7	21,6 ± 3,8	22,3± 4,2	19,5 ± 4,3	19,1 ± 3,2	19,7 ± 4,2	< 0,001
Corneal density (0-2 mm) (GSU)	12,7± 1,8	13,4 ± 1,9	13,5± 1,8	12,8 ± 1,5	12,7 ± 1,6	12,9 ± 1,9	< 0,001

Discussion

Antidepressant agents have effects on different systems and organs. In this present study, we investigated its effects on the ocular surface and cornea.

Escitalopram is a selective serotonin reuptake inhibitor (SSRI). It is generally used by clinicians in cases of geriatric depression.[6] Fluoxetine is used to a greater extent in cases of depression at a young age.[7] The mean age of the study groups differs statistically. The reason for this can be shown as the preference of different agents for patients in different age groups by clinicians. In addition, depression affects women at a higher rate. Although the majority of patients in all subgroups in our study were female, the distribution between groups did not differ. This finding is consistent with the literature.[8]

Many previous studies have reported that antidepressant agents affect the ocular surface. In a study that included 330 eyes of 165 patients using antidepressants, observed that the tear break-up time was shortened, the Schirmer test result was decreased, and the frequency of dry eye was higher in the patient group compared to the control group. In the sub-groups, reported that patients taking

SSRI had worse findings than patients taking SNRI.[9]

In another study, all dry eye tests and tear meniscus parameters were found to be significantly lower in the antidepressants group (Schirmer test, 11,4 ± 6,7 mm vs 22,5 ± 5 mm; TBUT, 5,3 ± 2,9 seconds vs 13,4 ± 1,7 seconds; tear meniscus height, 290,3 ± 133,6 µm vs 459,8 ± 180,3 µm, respectively). In addition, the OSDI score in the antidepressants group was significantly higher than in the control group (31,1 ± 21,2 ve 17,4 ± 11,8, respectively).[10]

In our study, patients were divided according to antidepressants subgroups. In all patient subgroups, OSDI and corneal staining scores were higher and Schirmer and tear break-up times were lower than healthy controls. In addition, the patients in whom these changes were most evident were those in the sertraline group. All these data have proven that antidepressant agents affect the ocular surface and cause dry eye symptoms. It can be said that especially SSRI agents affect the ocular surface more than SNRI agents.

Healthy control and patient groups were evaluated by specular microscopy. According to these data, the lowest endothelial cell density and hexagonality and the highest coefficient of variation were measured from patients receiving escitalopram. The reason for this data is that this group is the group with the highest average age. Patients in the sertraline group had lower endothelial cell density and hexagonality compared to healthy controls. The coefficient of variation was higher. This finding may have arisen due to the cytotoxicity of sertraline. Sertraline has a cytotoxic effect in many tissues with different mechanisms.[11,12]

In a study on this topic, sertraline was shown to cause cytotoxicity in corneal epithelial cell culture via Ca-independent pathways.[13] In another study, sertraline and paroxetine were shown to cause astrocyte dysfunction.[14]

In the corneal topography findings, the corneal densitometry values of the patients receiving sertraline and escitalopram were found to be higher than the healthy controls. No statistical difference was found between the patients in the other group and the control group. The relatively older age of the patients in the escitalopram group may be the reason for these findings. In the sertraline group, the number of corneal endothelial cells was found to be lower, and it is thought that the increase in corneal densitometry is due to this reason.

In a tertiary referral center study, no change was found in corneal density at 3-month follow-up in 11 patients receiving escitalopram and 10 patients receiving sertraline. Compared to our data, the relatively small number of patients included in this study and the short follow-up period of 3 months reduced the reliability of this study. Longer-term and larger population studies are needed to observe this effect.[15]

Limitations of this study; the findings of patients taking antidepressants before and after treatment were not compared, due to the retrospective nature of this study, the need for research in larger populations, and longer follow-up to observe the effect.

The strengths of this study are quantitative evaluation with corneal topography and specular microscopy in addition to ocular surface examination, it includes different agent subgroups, and the examination of more than one agent with similar mechanism of action.

Conclusion

In conclusion, all antidepressant agents, especially sertraline and escitalopram in the SSRI group, have adverse effects on the cornea and ocular surface. Among the current treatment options, agents in the SNRI group are more compatible with the ocular surface.

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Declarations
Ethics committee approval was obtained from Mersin University Ethics committee.

Consent for publication
All authors agree to the publication. Informed consent was obtained from all subjects for publishing their data in the manuscript.

Competing interests
All authors declare that they have no competing interests.

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