JSTMU Journal of Shifa Tameer-e-Millat University

https://j.stmu.edu.pk

Open Access

REVIEW ARTICLE

Antidepressants and ocular health: Addressing dry eye syndrome

Ayesha Mansoor[1], Shafaq Mansoor[2], Amjad Hayat Khan[3]*

[1, 2] Student Optometry, Department of Allied Health Sciences, Bashir Institute of Health Sciences Islamabad, Pakistan

[3] Assistant Professor, Department of Allied Health Sciences, Bashir Institute of Health Sciences Islamabad, Pakistan

Author`s Contribution

[1] Writing and formatting
[2] Writing and drawing figures
[3] Prof reading and mentoring

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

Correspondence

Amjid Hayat Khan
hkhan086@gmail.com

Article information

Submission date: 31-10-2023
Acceptance date: 15-04-2024
Publication date: 30-06-2024

Cite this article as *Mansoor A, Mansoor S, Khan A H. Antidepressants and ocular health: Addressing dry eye syndrome. JSTMU. 2024;7(1):86-94.*

A B S T R A C T

Dry eye syndrome (DES) is a common and multifactorial eye disease that can lead to visual disturbance if left untreated. DES arises from various factors such as reduced tear production and inflammation, affects the quality of vision, and can potentially lead to other eye diseases such as pterygium, pseudo pterygium, conjunctivitis, keratitis, corneal ulcers, and corneal dystrophy. Notably, there is an intriguing link between DES and depression, a commonly diagnosed psychiatric disorder characterized by decreased levels of neurotransmitters such as serotonin, dopamine, and norepinephrine. Antidepressants prescribed to treat depression work by increasing serotonin levels but paradoxically can lead to DES and other ocular side effects. In particular, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are known to contribute to DES development. This article unveils the factors that trigger DES and sheds light on the interconnected casual web. By explaining the intricacies of DES, this article aims to provide physicians and patients with a deeper understanding of the condition, enabling better management and treatment outcomes.

Keywords: *Antidepressants, Dry eyes syndrome, Kerato-conjunctivitis sicca, Serotonin, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)*

Introduction

Dry eye, also known as keratoconjunctivitis sicca (KCS) or dry eye syndrome (DES), is a clinically chronic condition often associated with the lacrimal glands. These glands produce tears in the eye that keep the eye moist and help prevent complications like DES. Two types of lacrimal glands have been identified in the human eye; the main lacrimal gland in the lacrimal pit of both eyes, located in the anterolateral part of the roof of the orbit below the eyebrow, and the additional lacrimal glands: Kraus's glands and wolf's glands. DES is a common complex eye disease considered multi-etiological eye disease. It is characterized by decreased tear secretion, inflammation, and damage to the eye's surface, eventually leading to blurred vision.[1-5]

The clinical diagnosis of DES is based on evaluating clinical features, signs, and symptoms, mainly through clinical testing. The patient complains of malaise, dryness, itching, photophobia, temporary blurred vision, foreign body sensation, and pain when blinking. These symptoms usually worsen in hot weather.[5,6] These symptoms may lead to DES which can persist for many years and adversely affect the patient's life.[4] The Basic clinical testing is important for the diagnosis of DES because it highlights the corneal and conjunctival features, specific to DES. The diagnostic testing is based on Henrik Sjogren's work, performed using Rose Bengal stain.[7-9] Other tests for DES include the Schirmer test, assessment of tear osmolarity, tear rupture time, and performing tear meniscus weighting.[10-17] The results of these tests in DES are a decrease in marginal tear strip, an increase in mucus production, and corneal filaments. It does not primarily cause loss of visual acuity but impairs

visual acuity due to the presence of corneal filaments and filiform mucus discharge.[18]

In the past, the development of novel sensitive treatment was refrained from due to the unknown etiology of DES. The inflammation was later found to be associated with DES, leading to the development of a sensitive treatment.[19] It was later concluded that DES is a multifactorial eye disease caused by changes in the lacrimal glands,[1-5] collagen diseases, and autoimmune diseases.[4, 6] DES can be classified as aqueous tear deficiency and evaporative tear dysfunction. The latter is due to environmental factors and Meibomian gland dysfunction. The meibomian gland secretes sebum that protects the eye from drying out. Malfunction of this gland decreases sebum secretion and eventually leads to DES. Tear deficiency is divided into four categories based on possible causes: pure DED, primary Sjogren's syndrome, secondary Sjogren's syndrome, and non-Sjogren's syndrome. Pure DED is due to dysfunction of the lacrimal gland. In addition, there may be congenital alacrima (no tear production at birth), denervation hyposecretion (lower tear production due to innervation defects such as in trigeminal ganglion surgery), and idiopathic hyposecretion (lower tear production due to an unknown cause). Primary Sjogren's syndrome results from Sjogren's syndrome, an autoimmune disease characterized by xerostomia (dry mouth) and DES. Sjogren's syndrome is associated with lymphatic inflammation and damage to the glands, particularly the lacrimal and salivary glands. Secondary Sjogren's syndrome is due to any other autoimmune disease such as rheumatoid arthritis or systemic lupus erythematous. Non-Sjögren's syndrome has other causes such as trauma, infection, and inflammation.[3-20] Regardless of the classification, DES is observed to be based on a T-cell-mediated autoimmune response and hyperosmolarity. This leads to a cascade of events in which large amounts of chemical mediators, e.g. B. serotonin, are released, which leads to cell damage. Damaged epithelial and goblet cells cause tear film instability, deficiency of normal mucus products, and chronic inflammation, leading to DES.[20-22] Treatment is important as DES is one of the most common ocular diseases and clinically presents as a chronic and progressive disease.[23] Occurrence varies and depends on (i) age: older people are affected more often than young people, (ii) race: common in Asians, and (iii) the disorders associated with medical conditions, particularly autoimmune disorders such as arthritis and systemic Lupus erythematous or Sjogren's syndrome or other eye diseases. Currently, DES in adolescents has been reported because of prolonged exposure to the digital screen and certain medications, such as antidepressants.[1]

There are several studies demonstrating a link between depression and DES as many depressed patients have been diagnosed with depression.[24-31] Most importantly, antidepressants are the main cause of DES in depressed patients.[32-33] DES is a complex eye disease that consists of many symptoms and leads to chronic eye diseases that can affect our vision. Therefore, in the current review, we would like to highlight the association between antidepressants and DES, as it is common in patients with depression.

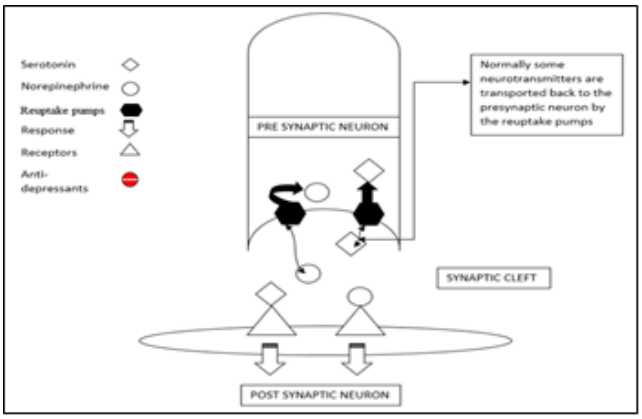

Figure 1: Normal reuptake mechanism keeps in check the neurotransmitter concentration in the synaptic cleft

Association Between DES and Depression

Depression as a Psychiatric Disorder

Depression is an idiopathic cognitive disorder caused by a longstanding condition, substance abuse, or a combination of social, economic, and genetic factors.[34,35] It is one of the most common mental disorders, if left untreated it can lead to suicide in the worst case.[36] The exact etiology of depression and its pathophysiological basis need to be elucidated, hence it can be considered simply as a multi-etiological disorder.[34-38] Studies of the

brain have found that the hippocampus, which is a crucial part of the brain responsible for both memory and learning, is primarily affected by stress and depressive states. Therefore, it is a crucial target for antidepressants.[39-41] The biochemical origin of depression is due to the depletion of the monoamine neurotransmitters serotonin, norepinephrine, and dopamine in the brain.[36-42] This is consistent with the primitive monoamine hypothesis based on the mechanism of action of first-generation antidepressants.[43,44] According to the monoamine hypothesis, low monoamine concentration is the most important biochemical factor leading to depression.[36] The monoamine hypothesis was later discarded and replaced by the monoaminergic receptor theory, which held that depression was due to a defect in the postsynaptic monoamine receptors that made them unresponsive to monoamine neurotransmitters. In the 1980s, the monoaminergic receptor hypothesis was developed, which suggested that depression is due to decreased sensitivity of the postsynaptic receptors, which are supposed to bind to the monoamines produced by the presynaptic neuron.[45,46]

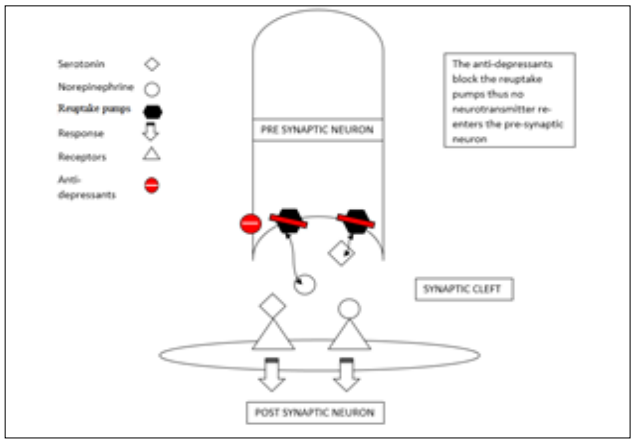

Figure 2: Blockage of reuptake mechanism in presence of antidepressants leads to increase of neurotransmitter concentration in the synaptic cleft

An Overview of Antidepressants

Antidepressants, as the name suggests, are used for the treatment as well as the management of depression.[47] The most prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressant agents (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants. Among these antidepressants, TCAs and MAOIs are prescribed less frequently, and SSRIs and SNRIs are most prescribed to treat depression.[48]

Antidepressants have been divided into three groups: first-generation antidepressants (FGAs), second-generation antidepressants (SGAs), and third-generation antidepressants (TGAs). First-generation antidepressants include TCAs and MAOIs, which were used in the 1960s. Although MAOIs have been extremely influential drugs, however, lack of selectivity and significant adverse effects limited their prescriptions.[49,50] As an alternative, TCAs were introduced which have been used to treat various mental illnesses. However, due to their antagonistic effect on the muscarinic, adrenergic, and histaminergic receptors they have various systematic side effects.[51]

The second-generation antidepressants are jointly known as SGA and include drugs that were primarily developed between the 1980s and 1990s. SGAs include SSRIs, SNRIs, noradrenergic and specific serotonergic antidepressants (NaSSAs), 5-HT2A antagonists-reuptake inhibitors (SARIs), and noradrenaline reuptake inhibitors (NARIs). Due to their minimal systematic side effects, SSRIs are clinical substitutes for TCAs.[52,53] These drugs are used as first-line treatment for depression in both children and adults due to their improved drug safety profile and efficacy.[54] They are prescribed to one in six adults [55,56] and are the most commonly prescribed antidepressants SNRIs, NaSSAs, and NARIs are used as the primary drugs of choice to treat depression. The third-generation antidepressants are called TGAs, and their mechanism of action is based on the non-monoaminergic mechanism.

Mechanism of Action of Antidepressants

Drugs used to treat mental illness significantly affect the nervous system and the release of neurotransmitters.[56] At the synapses of the brain, antidepressants target neurotransmitter pumps and the presynaptic receptors. They regulate the concentration of neurotransmitters at these synapses, altering the signal transduction and downstream secondary signaling pathways, which subsequently leads to long-term

transcriptional changes in enzymes and receptors.[57] Several hypotheses have been proposed about the mechanism of action of antidepressants: (i) monoamine hypothesis-biogenic amine hypothesis, (ii) monoaminergic receptor hypothesis, (iii) signaling adaptation hypothesis, and (iv) neuroplasticity hypothesis. According to the monoamine hypothesis, antidepressants currently on the market act on the principle of inhibition of the reuptake mechanism and affect the concentration of neurotransmitters at the synapses or in the presynaptic neurons.[58] Depression is due to low levels of monoamine neurotransmitters, among which serotonin is one of the most important neurotransmitters targeted by antidepressants.[36] Antidepressants increase serotonin concentration by blocking the reuptake pumps or serotonergic receptors (SERT) in presynaptic neurons.[56] Figure 1 and 2, thereby increasing serotonin levels in the CNS,[56] making it available to postsynaptic receptors for signaling.

The monoamine hypothesis cannot explain the delayed therapeutic effect of antidepressants. The increase in monoamine concentration should have been achieved within a few hours but took longer, so this hypothesis was rejected.[43] The monoaminergic receptor hypothesis has been developed, and according to this hypothesis, antidepressants affect the sensitivity of presynaptic receptors rather than the reuptake mechanism.[45] However, the delayed therapeutic effect could not be understood and this mechanism could not explain the mode of action of all antidepressants, although the mechanism of action of SSRIs and TCAs was consistent with this hypothesis.[32]

The post-synaptic signaling mechanism is based on the signaling adaptation hypothesis which was developed to understand the delayed therapeutic effects of antidepressants. This hypothesis assumes that antidepressants induce adaptive changes in the post-receptor signaling cascades and that these changes occur slowly, leading to the observed delayed therapeutic response.[52] As neuroscience advanced in the 2000s, a more advanced hypothesis emerged the neuroplasticity hypothesis. According to this hypothesis, antidepressants affect neuroplasticity, cellular flexibility, and synaptic plasticity.[39] The neuroplasticity hypothesis explains the multiple mechanisms of the anti-depressant effects.

Regardless of the mechanism of action, antidepressants affect monoamine neurotransmitters. Serotonin is not the only neurotransmitter affected. Other neurotransmitters affected are acetylcholine, dopamine, and norepinephrine/noradrenaline.[37] SSRIs such as direct effect on the serotonergic and cholinergic systems and therefore indirectly affect the dopaminergic and noradrenergic systems.[51] For example, SSRIs such as fluoxetine have an antagonistic effect on one of the serotonergic receptors, thereby indirectly increasing norepinephrine and dopaminergic transmission.[51] Similarly, through its direct anticholinergic effect, paroxetine blocks norepinephrine reuptake and sertraline blocks dopamine reuptake.[56] These drugs have 300- to 3000-fold higher selectivity for the serotonin transporter compared to the norepinephrine transporter, and thus block serotonin reuptake, resulting in an increase in serotonin concentration in the synaptic cleft without blocking activity at the alpha-adrenergic receptors.[60,68] Therefore, they have minimal systemic side effects. SNRIs and TCAs are not SERT specific and can directly block norepinephrine reuptake pumps by a similar mechanism,[49] thus TCAs have more severe ocular side effects compared to SSRIs. TCAs are associated with xerostomia, urinary retention, and constipation which are part of Sjogren's syndrome and thus can lead to DES due to Sjogren's syndrome.[30]

The eye is the second most frequently affected organ by drug poisoning after the liver.[31,32] The eye is susceptible to drugs because of its anatomical or embryological structure. Although relatively small in mass, the eye is blessed with a large and rich blood supply, allowing any chemical in the blood to reach any part of it.[42] Another reason for its medical vulnerability is the eye's visual system, which is made up of multiple tissues lineages. The innermost layer of the eye, the retina which is responsible for vision, is an embryological derivative of the brain ectoderm.[37] Another factor that makes the eye vulnerable to medical side effects is the high rate of metabolism in the eye particularly in the retina and optic disc.[55] The side effects of medicine on the eye can vary in severity. It can range from complete absence to

devastating consequences, and from transient and reversible to completely irreversible.[56]

Antidepressants can cross the blood-brain barrier and enter the central nervous system (CNS), where they enhance their therapeutic effect. They also affect the peripheral nervous system and smooth muscle fibers.[33] Because the eye is an embryonic derivative of the CNS, any psychiatric drug can harm it. All antidepressants have various side effects on the eye.[41] These include DES, decreased accommodation (accommodation is the ability of our lens to change shape depending on our distance from the observed object), blurred vision (mainly with paroxetine), mydriasis (dilated pupils), cycloplegia (ciliary muscle paralysis), ocular dystonia (rarely), optic neuropathy (rare), maculopathy (with sertraline), retinopathy, lid enlargement, and angle-closure glaucoma are most common.[34] Antidepressants that play an important role in triggering DES include TCAs [33,] and SSRIs.[34-38] **Error! Reference source not found.** lists all drugs that belong to these anti-depressant classes.

SSRIs are known to cause and exacerbate depression due to their impairment of watery and mucous secretion.[29] SSRIs have a direct effect on the serotonergic and cholinergic systems and therefore indirectly affect the dopaminergic and noradrenergic systems.[31] These drugs compete with acetylcholine, a parasympathetic neurotransmitter, for the postsynaptic muscarinic receptors. Since the nervous innervation for tear flow is only parasympathetic and thus competes with acetylcholine, SSRIs interfere with its signaling. This leads to tear film instability caused by decreased signaling to tear secretion.[20] Another possible reason for the occurrence of DES could be the increased serotonin level in the eye.[56] Serotonin in the tear film influences corneal nociceptor sensitization, high serotonin levels decrease corneal sensitivity and tear flow.[25] Elevated levels of serotonin contribute as an ocular surface inflammatory agent and therefore lead to apoptosis in the corneal epithelium, which is a clear clinical sign of DES.[5, 13] To assess the significant changes in ocular structure, tear films of patients consuming SSRIs were examined. Approximately 75% of patients taking SSRIs had tear breakup times of less than 10 seconds and more discoloration of superficial corneal epithelial dots. However, no significant difference was observed in the Schirmer 1 test. These results showed that serotonin largely affected the ocular surface by reducing corneal sensitivity but had no effect on tear production. Elevated levels of serotonin can decrease tear film sensitivity, tear reflexes, and corneal nerve sensitivity, causing DES.[29]

The TCAs have an anticholinergic effect, a serotonergic effect, and an antihistaminic effect, all of which together contribute to DES.[31] TCAs most commonly cause mydriasis and cycloplegia along with blurred vision and/or presbyopia. TCAs antagonism to the noradrenaline\norepinephrine uptake and its effects on alpha-adrenergic receptors stimulate DES and other ocular side-effects. SSRIs have a significantly higher propensity for dry eye syndrome than TCAs.[36]

Preventing Antidepressants-Induced DES

Precaution is the key to avoiding DES, especially when it occurs due to medication. Antidepressants are the only therapeutic indication for the treatment or management of not only depression but other mental health conditions such as anxiety and stress. Patients who are about to start taking SSRIs or other antidepressants should be well-informed about all the details of the drug. Likewise, the psychiatrist should always point out the possible side effects of the drugs and instruct the patient to be aware of any noticeable changes in normal bodily function.[34] A routine ophthalmologic examination to clarify possible ocular side effects is also required. If psychiatrists, optometrists, and patients are aware of all potential side effects of the drugs used and take early precautions, most serious and potentially irreversible eye damage can be prevented.[31-33]

Healthy communication with the patient is the duty of a healthcare professional and is essential to the treatment of the patient.[23] Studies suggest that the behavior of patients and psychiatrists toward each other leads to an increase in the unhealthy use of antidepressants. When taking medication over a long period, psychiatric patients often fail to reveal and explain their visual symptoms in detail.[22-26] This can either be due to patient discomfort towards the psychiatrist or substance abuse or overuse on the part of the patient.[84] But the delayed recognition of

DES makes it chronic and the prognosis is usually delayed, mostly leading to other chronic eye diseases.[18-21]

The ocular side effects mostly vanish by stoppage of the medicines in use but in clinical practice, artificial tears are usually prescribed.[25] Newer antidepressants like SSRIs and SNRIs should be preferred and in the case of TCAs desipramine and nortriptyline should be preferred as they have less anticholinergic side effects.[27] SSRIs are known to cause DES and since SSRIs are the most effective drugs against depression and are used as a drug of choice for the treatment of depression, therefore, their use cannot be discontinued. So, to overcome the anticholinergic side effects of either TCAs or SSRIs it is recommended to use pilocarpine 1% solution 1 drop almost four times daily, cholinergic agents such as bethanechol chloride which is used 10–30mg/day and contact lenses.[26]

But if the complications still exist it is recommended to use other classes of antidepressants like SNRIs which can also inflict DES but to a lesser extent as compared to SSRIs. NaSSAs, SARIs, NARIs, MAO inhibitors, TGAs, and other atypical antidepressants can also be brought into application in case of chronic DES.

Discussion

DES is an ocular syndrome that can lead to other ocular disorders if left unchecked.[1,3] This condition is increasing in developed countries though it is considered multifactorial, and its proper etiology is still not understood.[4] DES is linked with xerostomia, mainly in Sjogren syndrome, which is an inflammatory disorder marked by decreased glandular secretions.[20-22] This association is owing to etiological reasons.[2] DES is managed by tear gel or artificial tears but to treat DES the etiological cause should be eradicated.[19] DES is also an adverse effect associated with the application of antidepressants.[34-38] Depression is one of the most common mental disorders. In scientific language, it is a deficiency of monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine in certain areas of the brain.[42] Depression is treated or combated with antidepressants.[47] The primary mode of action of these drugs, as suggested by the monoamine theory, is to increase the levels of neurotransmitters such as serotonin and norepinephrine.[28]

Researchers in recent years have found that depression is usually followed by DES and that most depressed patients are likely to be diagnosed with DES as an associated eye disease.[29] There are reports of the association between psychiatric disorders and DES.[24-30,31] In research DES in patients with depression has been diagnosed as a subjective symptom rather than an objective symptom.[6] It has been hypothesized that DES symptoms are more severe in patients with more severe depressive symptoms since somatic disorders tend to worsen when depression occurs.[13]

Therefore, it was hypothesized that the prognosis of DES in depression patients would be slow. However, research has not observed a significant difference between the prognosis of DES in healthy patients and that in patients with depression.[16] Hence, it could not be understood why depression was associated with DES. Studies showed that the level of serotonin in the tear film was elevated, eventually leading to DES. This showed that antidepressants were a cause of DES in patients with depression,[14] since serotonin level increased is the main function of these drugs to treat depression.[18]

Many studies suggest that DES is related to antidepressant use,[19] however, the link between DES and antidepressants could not be confirmed because only two of the studied population used antidepressants, and even after their removal the test results were not changed since the test was performed on a small number of patients it can be assumed that the results might have been different in a larger number of patients.[3-9] It is not necessary that DES be followed by depression but that depression can lead to DES its biological and pathological components.[6]

DES patients experience lifelong discomfort in their eyes, giving them a constant sense of grief and discomfort, leading to depression.[36] Depression is a common finding in eye patients as it can have a major impact on the patient's life.[37] However, more research is needed to understand the association between depression and antidepressants in DES.

Table 1: List of medicines used for the treatment of depression, leading to dry eyes syndrome

Drug Class	Drug name	Ocular side-effect	Therapeutic indication	Action mechanism	References
TCAs	Clomipramine (Anafranil, Placil), Doxepin (Deptran, Sinequan), Nortriptyline (Allegron, NortriTABS), Imipramine (Tofranil, Tolerade) Dosulepin/dothiepin (Dothep), Amitriptyline (Endep, Entrip), Chlorpromazine	Decreased lacrimation and dry eye, mydriasis, cataracts, blurred vision, corneal edema, corneal epithelial keratopathy, abnormal pigmentation of the eyelids/ conjunctiva or cornea or peripheral retina, and acute angle closure glaucoma due to pupil block.	Neuropathic pain, post-traumatic stress disorder, obsessive-compulsive disorder (OCD), phobias, panic disorders, and generalized anxiety.	Inhibit reuptake of both serotonin (5HT) and nor-adrenaline/nor-epinephrine into pre-synaptic nerve terminals by acting on serotonergic receptors (SERT) and alpha-adrenergic receptors.	(34-38, 42, 52, 53, 56)
SSRIs	Escitalopram (Lexapro), Fluoxetine (Fluotex, Lovan, Prozac, Prozet, Zactin), Fluvoxamine (Facerin, Luvox, Movox, Voxam), Sertraline (Eleva, Sertra, Sertracor, Setrona, Xydep, Zoloft), Paroxetine (Aropax, Extine, Paxtine, Roxet, Roxtine), Citalopram (Celapram, Celica, Cipramil, Talam)	Dry eye, mydriasis, intraocular pressure elevation, acute angle closure crisis Rare: ocular dystonia, oculogyric crisis, diplopia, optic neuropathy, maculopathy (sertraline), eyelash loss (escitalopram)	Generalized anxiety disorder, bipolar depression, OCD, panic disorders, post-traumatic stress disorder, and social phobia	Inhibit reuptake specifically of 5HT by binding to SERT	(34-38, 42, 52, 53, 56)

Conclusion

Systemic side effects can also occur during therapy in people suffering from depression. Disorders such as DES, in particular, are common in people with depression and are often associated with the use of antidepressants. To mitigate these issues, raising patient awareness and maintaining a strong patient-physician relationship are vital to not only combat depression without relying solely on antidepressants but also to prevent potential side effects such as DES. Physicians must carefully evaluate patients prescribed antidepressants and educate them about potential visual effects to allow for timely detection and treatment. Emphasizing a proactive approach, avoiding depression altogether, and adopting a healthy lifestyle are important steps in protecting against associated pathologies. By recognizing the complex relationship between mental health and eye health, one can empower patients to take responsibility for their well-

being and embark on a journey of individual healing and resilience. Together, we can envision a future where comprehensive care and patient-centered strategies lead to better, healthier, and more fulfilling lives for those struggling with depression and its complexities.

References

1. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. Tfos dews ii epidemiology report. Ocular surface. 2017; 15(3):334-65. DOI: https://doi.org/10.1016/j.jtos.2017.05.003
2. Craig JP, Nelson JD, Azar DT, Belmonte C, Bron AJ, Chauhan SK, et al. TFOS DEWS II report executive summary. Ocular surface. 2017; 15(4):802-12. DOI: https://doi.org/10.1016/j.jtos.2017.08.003
3. Jerkins GW, Pattar GR, Kannarr SR. A review of topical cyclosporine a formulation—a disease-modifying agent for keratoconjunctivitis Sicca. Clin Ophthalmol (Auckland, NZ). 2020; 14:481. DOI: https://doi.org/10.2147/OPTH.S228070.
4. Tsubota K, Yokoi N, Shimazaki J, Watanabe H, Dogru M, Yamada M, et al. New perspectives on dry eye definition and diagnosis: a consensus report by the Asia Dry Eye Society. Ocular surface. 2017; 15(1):65-76. DOI: https://doi.org/10.1016/j.jtos.2016.09.003
5. 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. Transl vis sci technol. 2018; 7(6):35. DOI: https://doi.org/10.1167/tvst.7.6.35
6. Gonzales JA, Shiboski SC, Bunya VY, Akpek EK, Rose-Nussbaumer J, Seitzman GD, et al. Ocular clinical signs and diagnostic tests most compatible with keratoconjunctivitis sicca: a latent class approach. Cornea. 2020; 39(8):1013. DOI: https://doi.org/10.1097/ICO.0000000000002311.
7. Benelli U, Nardi M, Posarelli C, Albert TG. Tear osmolarity measurement using the TearLab™ Osmolarity System in the assessment of dry eye treatment effectiveness. Cont Lens Anterior Eye. 2010; 33(2):61-7. DOI: https://doi.org/10.1016/j.clae.2010.01.003
8. Bunya VY, Fernandez KB, Ying G-S, Massaro-Giordano M, Macchi I, Sulewski ME, et al. A Survey of Ophthalmologists Regarding Practice Patterns for Dry Eye and Sjogren's Syndrome. Eye Cont Len. 2018; 44(Suppl 2):S196. DOI: https://doi.org/10.1097/ICL.0000000000000448.
9. Bunya VY, Fuerst NM, Pistilli M, McCabe BE, Salvo R, Macchi I, et al. Variability of tear osmolarity in patients with dry eye. JAMA Ophthalmol. 2015; 133(6):662-7. DOI: https://doi.org/10.1001/jamaophthalmol.2015.0429.
10. Bunya VY, Langelier N, Chen S, Pistilli M, Vivino FB, Massaro-Giordano G. Tear osmolarity in Sjogren's syndrome. Cornea. 2013; 32(7):922. DOI: https://doi.org/10.1097/ICO.0b013e31827e2a5e.
11. Pepose JS, Sullivan BD, Foulks GN, Lemp MA. The value of tear osmolarity as a metric in evaluating the response to dry eye therapy in the clinic and clinical trials. Am J Ophthalmol. 2014;57(1):4-6. e1. DOI: https://doi.org/10.1016/j.ajo.2013.10.020.
12. Rabbets W. Why is your eye dry? S A Pharmacist Assistant. 2023; 23(2):22-4.
13. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. Tfos dews ii pathophysiology report. Ocular Surface. 2017; 15(3):438-510. DOI: https://doi.org/10.1016/j.jtos.2017.05.011
14. Abidi A, Shukla P, Ahmad A. Lifitegrast: a novel drug for the treatment of dry eye disease. J Pharmacol Pharmacother. 2016; 7(4):194-8. DOI: https://doi.org/10.4103/0976-500X.195920.
15. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo C-K, et al. TFOS DEWS II definition and classification report. Ocular Surface. 2017; 15(3):276-83. DOI: https://doi.org/10.1016/j.jtos.2017.05.008
16. Liyue H, Chiang PP-C, Sung SC, Tong L. Dry eye-related visual blurring and irritative symptoms and their association with depression and anxiety in eye clinic patients. Curr Eye Res. 2016; 41(5):590-9. DOI: https://doi.org/10.3109/02713683.2015.1056804
17. Hallak JA, Tibrewal S, Jain S. Depressive symptoms in dry eye disease patients: a case-control study using the Beck Depression Inventory. Cornea. 2015; 34(12):1545. DOI: https://doi.org/10.1097/ICO.0000000000000641.
18. Na K-S, Han K, Park Y-G, Na C, Joo C-K. Depression, stress, quality of life, and dry eye disease in Korean women: a population-based study. Cornea. 2015; 34(7):733-8. DOI: https://doi.org/10.1097/ICO.0000000000000464.
19. Yilmaz U, Gokler ME, Unsal A. Dry eye disease and depression-anxiety-stress: A hospital-based case-control study in Turkey. Pakistan journal of medical sciences. 2015; 31(3):626. DOI: https://doi.org/10.12669/pjms.313.7091.
20. Wen W, Wu Y, Chen Y, Gong L, Li M, Chen X, et al. Dry eye disease in patients with depressive and anxiety disorders in Shanghai. Cornea. 2012; 31(6):686-92. DOI: https://doi.org/10.1097/ICO.0b013e3182261590.
21. Park C, Rosenblat JD, Brietzke E, Pan Z, Lee Y, Cao B, et al. Stress, epigenetics, and depression: a systematic review. Neurosci Biobehav Rev. 2019; 102:139-52. DOI: https://doi.org/10.1016/j.neubiorev.2019.04.010.
22. Yang L, Zhao Y, Wang Y, Liu L, Zhang X, Li B, et al. The effects of psychological stress on depression. Curr Neuropharmacol. 2015; 13(4):494-504. DOI: https://doi.org/10.2174/1570159x1304150831150507.
23. Narayanan V. Ocular Adverse effects of antidepressants–need for an ophthalmic screening and follow-up protocol. Ophthalmol Res. 2019; 10(3):1-6. DOI: https://doi.org/10.9734/or/2019/v10i330107
24. Huider F, Milaneschi Y, Van der Zee MD, De Geus EJ, Helmer Q, Penninx BW, et al. Major depressive disorder and lifestyle: correlated genetic effects in extended twin pedigrees. Genes. 2021; 12(10):1509. DOI: https://doi.org/10.3390/genes12101509.
25. Maguire MJ, Marson AG, Nevitt SJ. Antidepressants for people with epilepsy and depression. Cochrane Database of Systematic Reviews. 2021(4). DOI: https://doi.org/10.1002/14651858.CD010682.pub3.
26. De Oliveira CL, Bolzan JA, Surget A, Belzung C. Do antidepressants promote neurogenesis in adult hippocampus? A systematic review and meta-analysis on naive rodents. Pharmacol. Ther. 2020; 210:107515. DOI: https://doi.org/10.1016/j.pharmthera.2020.107515.
27. Kohl C, Wang X-D, Grosse J, Fournier C, Harbich D, Westerholz S, et al. Hippocampal neuroligin-2 links early-life stress with impaired social recognition and increased aggression in adult mice. Psychoneuroendocrinology. 2015; 55:128-43. DOI: https://doi.org/10.1016/j.psyneuen.2015.02.016.

28. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiat. 2010; 9(3):155. DOI: https://doi.org/10.1002/j.2051-5545.2010.tb00298.x.
29. Racagni G, Popoli M. Cellular and molecular mechanisms in the long-term action of antidepressants. Dialogues in clinical neuroscience. 2022. DOI: https://doi.org/10.31887/DCNS.2008.10.4/gracagni.
30. Brett J, Karanges EA, Daniels B, Buckley NA, Schneider C, Nassir A, et al. Psychotropic medication use in Australia, 2007 to 2015: changes in annual incidence, prevalence and treatment exposure. Aust N Z J Psychiatry. 2017; 51(10):990-9. DOI: https://doi.org/10.1177/0004867417721018.
31. Malhi GS. The right services, at the right time, for the right people. The Lancet Psychiatry. 2019; 6(10):800-2. DOI: https://doi.org/10.1016/S2215-0366(19)30187-7.
32. Mondal AC, Fatima M. Direct and indirect evidence of BDNF and NGF as key modulators in depression: role of antidepressants treatment. Int J Neurosci. 2019; 129(3):283-96. DOI: https://doi.org/10.1080/00207454.2018.1527328.
33. Rief W, Nestoriuc Y, von Lilienfeld-Toal A, Dogan I, Schreiber F, Hofmann SG, et al. Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials. Drug Saf. 2009; 32(11):1041-56. DOI: https://doi.org/10.2165/11316580-000000000-00000.
34. Richa S, Yazbek J-C. Ocular adverse effects of common psychotropic agents. CNS Drug. 2010; 24(6):501-26. DOI: https://doi.org/10.2165/11533180-000000000-00000.
35. Ménard C, Hodes GE, Russo SJ. Pathogenesis of depression: Insights from human and rodent studies. Neuroscience. 2016; 321:138-62. DOI: https://doi.org/10.1016/j.neuroscience.2015.05.053.
36. Caviedes A, Lafourcade C, Soto C, Wyneken U. BDNF/NF-κB signaling in the neurobiology of depression. Curr Pharm Des. 2017; 23(21):3154-63. DOI: https://doi.org/10.2174/1381612823666170111141915.
37. Pitsillou E, Bresnehan SM, Kagarakis EA, Wijoyo SJ, Liang J, Hung A, et al. The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. Mol Biol Rep. 2020; 47(1):753-70. DOI: https://doi.org/10.1007/s11033-019-05129-3.
38. Lochmann D, Richardson T. Selective serotonin reuptake inhibitors. Antidepressants: Springer; 2018. p. 135-44.
39. Sabella D. Antidepressant medications. Am J Nurs. 2018; 118(9):52-9. DOI: https://doi.org/10.1097/01.NAJ.0000544978.56301.f6.
40. Jakubovski E, Johnson JA, Nasir M, Müller-Vahl K, Bloch MH. Systematic review and meta-analysis: Dose-response curve of SSRIs and SNRIs in anxiety disorders. Depression Anxiety. 2019; 36(3):198-212. DOI: https://doi.org/10.1002/da.22854.
41. Ghaffariyeh A, Chamacham T. Tricyclic Antidepressants: Potential Therapeutic Alternatives for Treatment of Dry Eye Symptoms After LASIK. J Refract Surg. 2008; 24(8):770-2. DOI: https://doi.org/10.3928/1081597X-20081001-01
42. Sönmez İ, Aykan Ü. Psychotropic drugs and ocular side effects. Turk J Ophthalmol. 2013; 43:270-7.
43. Mullins N, Lewis CM. Genetics of depression: progress at last. Curr Psychiatry Rep. 2017; 19(8):1-7. DOI: https://doi.org/10.1007/s11920-017-0803-9
44. Wu T, Jia X, Shi H, Niu J, Yin X, Xie J, et al. Prevalence of mental health problems during the COVID-19 pandemic: A systematic review and meta-analysis. J Affect Disord. 2021; 281:91-8. DOI: https://doi.org/10.1016/j.jad.2020.11.117.
45. Acan D, Kurtgoz P. Influence of selective serotonin reuptake inhibitors on ocular surface. Clin Exp Optom. 2017; 100(1):83-6. DOI: https://doi.org/10.1111/cxo.12415. Epub 2016 Jul 31.
46. Zhang L, Yu F, Hu Q, Qiao Y, Xuan R, Ji G, et al. Effects of SSRI Antidepressants on Attentional Bias toward Emotional Scenes in First-Episode Depressive Patients: Evidence from an Eye-Tracking Study. Psychiatry Invest. 2020; 17(9):871-9. DOI: https://doi.org/10.30773/pi.2019.0345.
47. Isik-Ulusoy S, Ulusoy MO. Influence of different antidepressants on ocular surface in patients with major depressive disorder. J Clin Psychopharmacol. 2021; 41(1):49-52. DOI: https://doi.org/10.1097/JCP.0000000000001325.
48. Koçer E, Koçer A, Özsütçü M, Dursun AE, Kirpinar I. Dry eye related to commonly used new antidepressants. J Clin Psychopharmacol. 2015; 35(4):411-3. DOI: https://doi.org/10.1097/JCP.0000000000000356.
49. Arenas Rojas ÁV, Torrado Val E, Garrido Fernández M. Intervención familiar en diagnóstico reciente e inicio de tratamiento del cáncer infantil. Apuntes de Psicologia. 2016; 34(2-3):211-220.
50. Pierre JM. Abuse of psychiatric medications: not just stimulants and benzodiazepines. Curr Psychiatr. 2019; 18(1):11.
51. Ciobanu AM, Dionisie V, Neagu C, Bolog OM, Riga S, Popa-Velea O. Psychopharmacological treatment, intraocular pressure and the risk of glaucoma: a review of literature. J Clin Med. 2021; 10(13):2947. DOI: https://doi.org/10.3390/jcm10132947
52. Scapagnini G, Davinelli S, Drago F, De Lorenzo A, Oriani G. Antioxidants as antidepressants. CNS Drug. 2012; 26(6):477-90. DOI: https://doi.org/10.2165/11633190-000000000-00000.
53. Van Der Vaart R, Weaver MA, Lefebvre C, Davis RM. The association between dry eye disease and depression and anxiety in a large population-based study. Am J Ophthalmol. 2015; 159(3):470-4. DOI: https://doi.org/10.1016/j.ajo.2014.11.028.
54. Szakáts I, Sebestyén M, Németh J, Birkás E, Purebl G. The role of health anxiety and depressive symptoms in dry eye disease. Curr Eye Res. 2016; 41(8):1044-9. DOI: https://doi.org/10.3109/02713683.2015.1088955
55. Li M, Gong L, Chapin WJ, Zhu M. Assessment of vision-related quality of life in dry eye patients. Invest Ophthalmol Vis Sci. 2012; 53(9):5722-7. DOI: https://doi.org/10.1167/iovs.11-9094
56. Kang H-J, Kim S-Y, Bae K-Y, Kim S-W, Shin I-S, Yoon J-S, et al. Comorbidity of depression with physical disorders: research and clinical implications. Chonnam Med J. 2015; 51(1):8-18. DOI: https://doi.org/10.4068/cmj.2015.51.1.8
57. Alderson SL, Foy R, Glidewell L, McLintock K, House A. How patients understand depression associated with chronic physical disease–a systematic review. BMC Fam Pract. 2012; 13(1):1-19. DOI: https://doi.org/10.1186/1471-2296-13-41
58. Chhadva P, Lee T, Sarantopoulos CD, Hackam AS, McClellan AL, Felix ER, et al. Human tear serotonin levels correlate with symptoms and signs of dry eye. Ophthalmol. 2015; 122(8):1675.