



Dry eye syndrome: comprehensive etiologies and recent clinical trials

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Abstract Dry eye syndrome (DES) is multifactorial and likely to be a cause of concern more so than ever given the rapid pace of modernization, which is directly associated with many of the extrinsic causative factors. Additionally, recent studies have also postulated novel etiologies that may provide the basis for alternative treatment methods clinically. Such insights are especially important given that current approaches to tackle DES remains suboptimal. This review will primarily cover a comprehensive list of causes that lead to DES, summarize all the upcoming and ongoing clinical trials that focuses on treating this disease as well as discuss future potential treatments that can improve inclusivity.

Keywords Dry eye syndrome · Lacrimal functional unit · Ophthalmology

Introduction

DES is a relatively common clinical ophthalmic condition, characterized by a disorder of the precocular tear film and affecting approximately 1 out of 7 individuals aged 48 and above [1]. Besides DES, this condition can also be known as keratoconjunctivitis sicca (KCS), dry eye disease (DED), ocular surface disease (OSD) or dysfunctional tear syndrome (DTS) [2]. It is a dysfunction of the nasolacrimal unit (nasolacrimal glands, corneal surface and eyelids) which leads to defective or insufficient tear film formation [3].

The maintenance of a physiologically complete tear film is imperative for normal vision as it is, along with the cornea, responsible for focusing light onto the retina [4]. Additionally, it also functions to lubricate the eye, remove debris from the ocular surface as well as maintain nutrition and oxygenation of the ocular structures [5]. Patients who developed DES may experience ocular burning, blurred vision or even pain and often have a reduced quality of life as common daily tasks that require visual attention (e.g. reading, computer work, etc.) become significantly challenging. However, while treatments are available to minimize the negative impacts, they are often suboptimal and unable to specifically target the root cause(s) of this disease.

It is now known that DES can be caused by a non-exhaustive list of factors which include autoimmunity, hormonal imbalance, deleterious environmental

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settings and many more. Unbeknown to many, symptoms associated with dry eyes may even at times be indicative of undiagnosed systemic diseases which, if treated timely, may avoid life-threatening outcomes [5]. Over the years, given a more profound understanding of the various mechanisms involved in the development of this condition, a wide range of novel treatments are underway to provide more effective results and overcome limitations posed by conventional therapeutics utilized in the clinic currently. This review aims to summarize the causes of DES and its respective mechanism, explore ongoing clinical trials for DES treatment and lastly, discuss promising technologies that can potentially shape future treatment strategies.

Secretory components and tear film composition

The tear film is regulated by an integrated lachrymal functional unit (LFU) which consists of the lachrymal glands, cornea, conjunctiva, eyelids, meibomian glands, goblet cells as well as the sensory and motor nerves that connect them [6]. As measured by ultra-high resolution optical coherence tomography (OCT) and validated with interferometry techniques [7, 8], it was found that the tear film, when spread across the exposed conjunctiva and cornea, is approximately 2 to 5.5 μm thick [9]. Correspondingly, this extremely thin layer of film is constituted by an even thinner top layer of lipid (about 42 nm) [10] and a mucin-aqueous (mucoaqueous) layer with decreasing concentration of mucins from the cornea epithelium towards the lipid layer [11, 12].

The lipid layer is derived from meibum produced by the meibomian gland and secreted through the lid margins. Meanwhile, blinking helps to spread the lipid layer across the tear film through surface tension forces. This configuration functions to stabilize the film by preventing the aqueous component from evaporating too rapidly [13–15]. The aqueous fluid in the tear film, which contains water, electrolytes, small molecule metabolites, plethora of proteins (more than 1500 detected [16]) and peptides (more than 200 [17]) is mostly produced by the lacrimal glands. The aqueous portion in the mucoaqueous layer provides oxygen and nutrients to the underlying avascular corneal tissue and assist in flushing away epithelial debris, toxins and foreign bodies [18].

Secreted mucins are present in the aqueous component as well and are produced by the goblet cells present in the conjunctiva while transmembrane mucins (glycocalyx) that can extend up to 500 nm from the plasma membrane are formed on the apical surfaces of the corneal and conjunctival epithelia [19]. Mucins are large high molecular weight glycoproteins that contain one of more protein domains which are rich in serines and threonines extensively glycosylated via O-glycan attachments [20, 21]. They are essential for providing lubrication, hydration as well as protection against infection and injury [22, 23]. On the ocular surface, it was shown recently that they further maintain a disadhesive property to the apical epithelial cells such that, during blinking or sleeping, cell surfaces facing each other like the cornea and conjunctiva do not adhere to each other [24]. Together, these constituents maintain the tear film and any slight dysregulation such as decreased aqueous volume or abnormal production of mucins or lipids will lead to DES [25, 26].

Etiology of DES

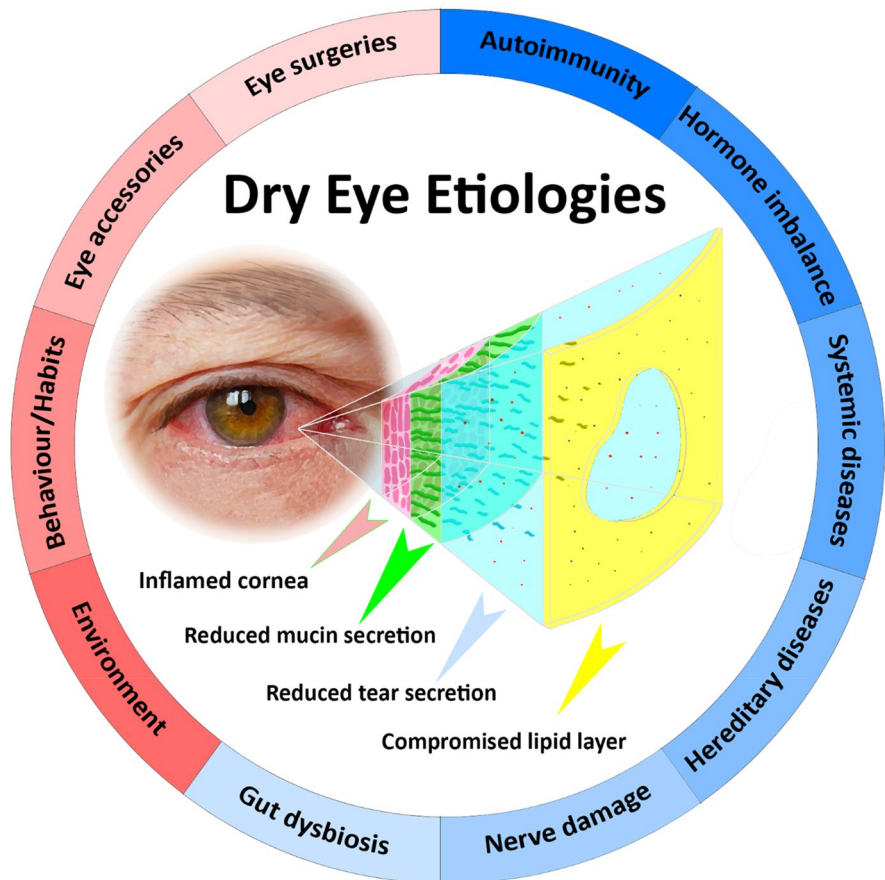
There are a multitude of factors that have been discovered to result in such dysregulations which, in general, can be classified as intrinsic and extrinsic. Intrinsic factors are defined as conditions present within the body and include autoimmunity [3, 27, 28], hormonal imbalance [29, 30], systemic diseases [31–34], hereditary diseases [35, 36], nerve damage [37, 38] and gut dysbiosis [39, 40]. On the other hand, extrinsic elements are derived from stimulus that occur outside the body and consist of environmental influences [41, 42], behaviour and/or habits [43–46], eye accessories [47] and eye surgeries [48, 49] (Fig. 1).

Intrinsic factors

Autoimmunity

Dry eyes caused by autoimmunity could be attributed to Sjögren's syndrome (SS), a chronic autoimmune disorder that primarily affects the salivary and lacrimal glands. Specifically, these exocrine glands are heavily infiltrated with lymphocytes (T cells and B cells) and macrophages which produces

Fig. 1 Schematic of dys-regulated tear film during DES and the various intrinsic (blue background) and extrinsic (red background) etiologies



pro-inflammatory signalling molecules such as IL-1, TNF- α and IFN- γ [28, 50–52]. CD4⁺ T cells are the primary immune effectors [53] and interact closely with antigen presenting-macrophages to provoke ocular disease development through inflammation-induced (IL-1 and IFN- γ) local tissue damage [51]. Additionally, they are also associated with peripheral neuropathy in the lacrimal glands, suggesting possible denervation and loss of function [54]. Besides CD4⁺ T cells, it was recently observed that highly cytotoxic activated CD8⁺ T cells are correlated with lacrimal gland epithelial cell death [50] and may account for the reduction in tear production. Given the varied possible causes of DES, the diagnosis of SS-induced dry eyes is relatively tedious and requires defined biomarkers for validation. Accordingly, it is known that the tear film of patients who developed SS contained elevated amounts of pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF- α . Their presence also corresponded to lower tear secretion levels [55–57].

Other biomarkers include MMP-9 [58, 59], HLA-DR [60, 61] and potentially MUC5AC [62].

Graves' ophthalmopathy, also known as thyroid eye disease, is another autoimmune condition that can lead to DES [63]. Patients afflicted with this disease produce excessive thyroid hormones which induce an inflammatory response in the orbital tissues [64]. Mechanistically, DES is caused by a combination of mechanical impairment of the lids [65] and autoantibodies targeting the thyroid-stimulating hormone receptors on the lacrimal gland [66]. Incomplete blinking due to lid impairment results in inadequate tear distribution over the ocular surface and excessive tear evaporation [65] while autoantibodies binding causes aberrant signal transduction in the lacrimal gland and subsequent tear hyposecretion [66].

While not commonly known, multiple sclerosis, where the central nervous system (CNS) becomes demyelinated, is also an autoimmune disease that is correlated to DES. Specifically, poor corneal sensory

impulse conduction due to demyelination can lead to insufficient tear production [67].

Hormonal imbalance

Hormones are known to influence both the lacrimal and meibomian glands [68]. Sex hormones, particularly androgens, appeared to account for many of the sex-related disease susceptibility of the lacrimal gland in a variety of species [69]. For instance, testosterone was able to upregulate and downregulate a substantial amount of lacrimal gland genes found to be highly and lowly expressed respectively in male vs. female mice [70, 71]. On the other hand, estrogen and progesterone only impacted a small percentage [71] of these differentially expressed genes between male and female mice [70]. Mechanistically, androgens have been demonstrated to regulate the lacrimal glands' fluid and protein secretion [72–74] through saturable, high-affinity and steroid-specific receptors binding in acinar and ductal epithelial cells [69, 75]. Accordingly, the lack of androgens was linked to lacrimal gland dysfunction and corresponding aqueous tear deficiency [30, 76], which helps to explain the higher DES prevalence among females [77, 78] since they are prone to reduced serum androgen levels during various stages of their life (lactation and menopause) [79, 80]. The meibomian glands, which are sebaceous in nature and contain acinar epithelial cells with androgen receptors, are also regulated by androgens [81, 82]. This form of regulation is dependent on 5 α -reductase, an enzyme crucial for the production of the potent androgen, 5 α -dihydrotestosterone (DHT). In the presence of DHT, these acinar cells display enhanced synthesis and secretion of lipids. Conversely, a reduction in DHT resulted in attenuated gland activity, size and lipid release [82, 83], which, in the context of DES, leads to the formation of an unstable tear film attributable to the increased rate of evaporation.

Systemic diseases

Diabetes mellitus (DM) is regarded as one of the leading systemic risk factors for DES due to the high prevalence (~18% to 54%) observed in Type 2 diabetic patients [84–86]. However, regardless of Type 1 or 2 diabetes, both conditions heighten the risk of developing LFU dysfunction such as corneal and

conjunctival epithelium damage due to increased levels of HbA1c in blood serum [87]. HbA1c are glycosylated haemoglobins and provide an estimate of the blood sugar levels of an individual over the last three months [88]. As the conjunctiva epithelium contains goblet cells, the damage sustained will also be associated with diminished mucin production. Additionally, hyperglycemia has been shown to activate aldose reductase, an enzyme that catalyzes the conversion of glucose to the cytotoxic sorbitol [89]. Correspondingly, elevated amounts of sorbitol within cells will lead to cellular apoptosis and ultimately lacrimal gland structure dysfunction followed by the reduction in tear secretion [31].

Xerophthalmia is a systemic disease that consists of a variety of eye disorders, including DES [90]. It is attributed to vitamin A deficiency and is the only vitamin deficiency disease in the world that causes major concern to the public health personnel [91, 92]. Vitamin A is crucial for maintaining the differentiation and proliferation of the conjunctiva and corneal epithelium [93] by inhibiting the upregulation of apoptotic signals [94]. The lack of vitamin A will therefore lead to loss of goblet cells and mucin production.

Hereditary diseases

Familial dysautonomia (FD), also known as Riley-Day syndrome, is a rare, hereditary autosomal recessive disorder that impairs the development of specific sensory and autonomic neurons during embryogenesis [35]. As a result of this maldevelopment, patients with FD are highly vulnerable to optic neuropathy during their childhood, which becomes worse as they age [36]. Without proper control of their LFU, they lack the ability to produce tears at a basal, reflex and emotional level [95].

Nerve damage

All the secretory functions in the LFU are regulated by autonomic nerves. The lacrimal gland is largely innervated by the Vasoactive Intestinal Peptide immunoreactive (VIP-IR) parasympathetic nerve fibers (secretory control) [96, 97] and, to a lesser extent, sympathetic nerve fibers (vasculature control) immunoreactive to Neuropeptide Y (NPY-IR), Tyrosine Hydroxylase (TH-IR) and Dopamine

β -Hydroxylase (DBH-IR) [98]. Upon stimulation, water and electrolytes, supplied by the blood, are transported into the duct system by the coordinated activation of ion channels and pumps [99–101]. Meanwhile, proteins produced and stored in the secretory granules of the lacrimal gland acinar cells will be released through stimulus-induced exocytosis [102] and carried along with the ionic fluid.

The meibomian gland and goblet cells in the conjunctiva is regulated by both parasympathetic VIP-IR and sympathetic DBH-IR and NPY-IR nerve fibers as well [97, 103, 104]. VIP-IR nerve fibers are located in close proximity to the acini and central duct of the meibomian gland where they influence the secretion of lipids, contributed by the meibocyte acinar cells, into the lumen of the duct system [97, 105]. On the other hand, VIP-IR nerve fibers are located at the epithelial-stroma junction in the conjunctiva, near the basal membrane of the goblet cells [104]. Upon receiving an appropriate stimulus, the secretory granules within the goblet cells fuse with each other and with the apical membrane to release the mucins, along with some amount of water and electrolytes, onto the ocular surface.

Correspondingly, the activity of these autonomic nerves are dependent on reflexes initiated by the activation of sensory neurons, which are present in high density, on the ocular surface [38]. At that location, they are very susceptible to direct injury caused by environmental factors and mechanical trauma [38]. Indirect forms of injury can also occur. For example, patients with aqueous tear deficiency from other causes may blink too frequently, which can generate enough stress to damage terminal nerve branches. Besides that, inflammation also plays a key role in altering the physiological state of the peripheral sensory neurons. Specifically, pro-inflammatory signalling molecules are able to either reduce the sensory neurons' threshold for activation (sensitization) or increase their ongoing nerve activity (excitation) [106]. Such changes are linked to the kinetics of the transduction ion channels and voltage-gated ion channels in the axonal membrane [107], affecting the generation and propagation of action potentials [108, 109]. Without consistent control over the activation of the autonomic nerve fibers, tear production will therefore be defective.

Gut dysbiosis

The human body is host to trillions of microbiota. Among the various regions, such as the oral cavity, respiratory tract, skin and gastrointestinal tract, that harbor these microorganisms [110], the colon is the organ which consists of the densest number of microbes [111]. This additional diversity of microbiome serves as a functional expansion of host genomes [112] and produces signaling molecules that facilitate host metabolism and regulation of host physiology [113]. Studies have revealed correlations between gut dysbiosis, defined as an imbalance of the gut microbiota diversity (disturbed or inversed *Firmicutes/Bacteroidetes* ratio), and DES. Specifically, this connection was hypothesized to occur through the gut dysbiosis-ocular surface-lacrimal gland axis which consists of five proposed immune-related mechanisms describing how ratio changes of gut commensal can lead to DES [114, 115]. For example, one of the mechanisms proposed involve the migration of gut dysbiosis-activated CD103⁺ or CXCR1⁺ dendritic cells or monocytes/macrophage to the ocular surface where they prime T cells to secrete pro-inflammatory cytokines in the ocular surface and lacrimal glands [114]. Consequently, the immune response mounted will lead to a decrease in goblet cells and acinar cells in the conjunctiva and lacrimal glands, respectively, resulting in reduced mucin and tear secretion.

Extrinsic factors

Environmental influences

The LFU is well-equipped to withstand tolerable amounts of impurities in the environment and prevent ocular surface damage through tear secretion. However, the protection provided by the tear film can be eroded if the pollution becomes too overwhelming, especially if it affects the function of the various secretory components in the LFU. Particulate matter smaller than 2.5 and 10 μm (PM_{2.5} and PM₁₀), which consists of inorganic dust, dirt, soot particles and organic allergens like pollen grains, mold and microbial colonies, are common pollutants associated with DES [116–121]. Excessive and prolonged exposure of these pollutants to the ocular surface were shown to trigger chronic inflammatory responses and induce

oxidative stress, both of which have cytotoxic effects on the secretory cells [41]. Similarly, gaseous pollutants such as NO₂, SO₂, O₃ and volatile organic compounds (VOCs) such as formaldehyde, toluene and acetone were all found to be positively correlated with DES through inflammatory and cytotoxic causes [122–125].

Even in the absence of impurities and reactive gases, constant exposure to extreme environmental conditions such as strong winds, low humidity, high temperature and high altitude can directly affect ocular health as well [125–127]. These scenarios reduce the tear film stability and cause faster tear evaporation [41], resulting in DES.

Behaviour and/or habits

Tobacco consumption is one of the main causes of morbidity and mortality globally and has been associated with a number of systemic disorders and conditions, including DES [43–45]. Besides conventional cigarettes, battery-powered electronic cigarettes (ECs), which deliver nicotine through a heated vapor [128], are also recently shown to increase the risk of developing dry eyes [129]. Accordingly, both types of cigarettes affect ocular functionality through the smoke and/or combustion by-products produced, leading to inflammation and subsequent decreased quantity and quality of tear secretion as well as ocular surface damage [129, 130].

Additionally, long-term usage of computer, tablet and cell phone can also result in DES [131]. It was observed that users blink less when using such display devices with a screen, which prevented the formation of a stable tear film and therefore leading to a faster rate of tear evaporation [46].

Eye accessories

Contact lenses provide an aesthetic means for ocular refractive error correction over glasses and an estimated 140 million people in the world use them [132]. This estimation has remained relatively consistent over the past decade despite numerous improvements in contact lens technology [133]. Correspondingly, a major reason for this observation arises from eye discomfort, mostly the sensation of dry eyes, after prolonged usage [134]. Specifically, the close proximity

of contact lens to the ocular surface poses a host of issues to the LFU and the tear film.

When fitted correctly, the contact lens cover the cornea completely and extends by ~2 mm onto the conjunctiva. In this configuration, every blink will cause it to move along the conjunctiva, which induces mechanical friction and goblet cells damage within the epithelium [135] over time [136, 137]. A reduction in goblet cell density will therefore lead to decreased mucin production and secretion, which affects tear film spreading. Besides that, contact lenses have also been associated with the loss of the meibomian gland and its orifice obstruction, resulting in impeded lipid synthesis and their transport to the tear film. Together, these dysregulations reduce the stability of the pre-lens tear film (PrLTF), the thin layer of fluid constrained between the cornea and the contact lens which is half the thickness of the normal pre-corneal tear film [138], and cause it to be susceptible to rapid evaporation, rupture and dry spot formation [139]. The lack of a consistent PrLTF is therefore a manifestation of DES.

Eye surgeries

Surgical procedures for ocular refractive errors such as laser-assisted in situ keratomileusis (LASIK), photorefractive keratectomy (PRK) and small incision lenticule extraction (SMILE) are recognized risk factors for developing dry eye [48, 49, 140]. This is attributable to a limitation posed by these surgical procedures where the sensory nerves present on the ocular surface will inevitably get damaged [48, 49, 140]. Without reliable sensory detection, the corneal sensation become impaired, which decreases basal and reflex tearing as well as rate of blinking [141–143]. Moreover, sensory denervation will also disrupt tear production by the lacrimal gland, leading to reduced tear secretion [144]. In addition to nerve damage, these refractive surgeries are also known to inflict damage to the conjunctival goblet cells [145–147]. Consequently, a reduction in goblet cell density signifies reduced mucin production and therefore, reduced tear film stability. Inflammatory responses induced as a result of postoperative wound-healing process is the last contributing factor to DES.

Altogether, these factors constitute the major known causes of DES. For clarity, they are compiled and summarized in Table 1.

Table 1 Summary of all the intrinsic and extrinsic etiologies and how they lead to dry eyes

Etiology		How it leads to DES	References
Autoimmunity	Sjögren's syndrome	- Lymphocytes and macrophages infiltrate lacrimal glands - ↑ inflammatory cytokines, ↑ cell death, ↓ tear secretion	[28, 50–52]
	Graves' ophthalmopathy	- Excessive thyroid hormones - ↑ inflammation in orbital tissue - Lid impaired mechanically, ↓ rate of blinking, ↑ tear evaporation - Autoantibodies target lacrimal gland, ↓ tear secretion	[64–66]
	Multiple sclerosis	- Poor corneal sensory impulse conduction - ↓ tear secretion	[67]
Hormonal imbalance	Androgens	- Androgens bind to steroid-specific receptors in epithelial cells - ↓ androgens, lacrimal and meibomian gland dysfunction, ↓ tear secretion, ↓ lipid secretion, ↑ tear evaporation	[30, 69, 72–76, 82, 83]
Systemic diseases	Diabetes mellitus	- ↑ HbA1c in blood serum - Corneal and conjunctival epithelium damage, lacrimal gland dysfunction - ↑ goblet cell death, ↓ mucin secretion, ↓ tear secretion	[31, 87, 89]
	Xerophthalmia	- Vitamin A deficiency - ↓ goblet cells, ↓ mucin secretion	[91–94]
Hereditary diseases	Familial dysautonomia	- Impaired sensory and autonomic neurons - Lack LFU control, no tears produced	[35, 95]
Nerve damage	VIP-IR nerve fibers	- VIP-IR nerve fibers regulate lacrimal and meibomian gland and goblet cells - Damage to the nerve itself or to its corresponding sensory neurons leads to ↓ tear secretion, ↓ lipid secretion, ↓ mucin secretion	[38, 96, 97, 103, 104]
Gut dysbiosis	Firmicutes/Bacteroidetes ratio	- Altered ratio lead to dendritic cells' and macrophages' migration to ocular surface - T cells primed by their presence, secrete pro-inflammatory cytokines - ↓ acinar and goblet cells, ↓ tear and mucin secretion	[114, 115]
Environment	PM _{2.5} and PM ₁₀	- Prolonged exposure to ocular surface causes inflammation and damage - ↓ secretory cells	[41]
	Gaseous pollutants	- Prolonged exposure to ocular surface causes inflammation and damage - ↓ secretory cells	[122–125]
	Extreme weather conditions	- Strong winds, low humidity, high temperature and high altitude - ↓ tear film stability, ↑ tear evaporation	[41, 125–127]
Behavior and/or habits	Conventional and battery-powered electronic cigarettes	- Smoke and/or combustion by-products produced - Ocular surface inflammation and damage - ↓ quality and quantity of tear	[129, 130]
	Display devices	- ↓ rate of blinking, ↓ tear film stability, ↑ tear evaporation	[46]

Table 1 (continued)

Etiology		How it leads to DES	References
Eye accessories	Contact lenses	- Mechanical friction, ↓ goblet cells, ↓ mucin secretion - Meibomian gland damaged, ↓ lipid secretion - ↓ tear film stability, ↑ tear evaporation	[135–139]
Eye surgeries	LASIK, PRK, SMILE	- Damaged sensory nerves and goblet cells - ↓ rate of blinking, ↓ mucin production, ↓ tear secretion, ↓ tear film stability, ↑ tear evaporation	[48, 49, 140–147]

Upcoming clinical trials for DES treatment

Method of search

A primary search was conducted using ClinicalTrials (<http://clinicaltrials.gov>) and the key words used were dry eye, keratoconjunctivitis sicca, dryness, ocular, ophthalmic and optic. The search filters ‘Not yet recruiting’, ‘Recruiting’, ‘Enrolling by invitation’ and ‘Active, not recruiting’ were then applied to sieve out all the upcoming clinical trials related to these keywords. From there, the studies were reviewed and included only if they are associated with DES treatment.

Search results

All the pending and current clinical trials that focused on DES treatment were compiled and tabulated in Table 2. Applying the ‘Not yet recruiting’ filter yielded a total of 47 studies, of which 14 were relevant for this review. For the ‘Recruiting’ filter, there were a total of 146 studies and 34 of them were relevant. Meanwhile, the ‘Enrolling by invitation’ filter provided a total of 10 studies and 5 of them were found to be relevant. Lastly, the ‘Active, not recruiting’ filter returned a total of 23 studies and 7 of them were screened to be relevant.

For each of these filter categories, the studies-of-interest were further grouped according to various treatment types such as biologic, drug, device, drug delivery system, dietary supplement, physical activity, combinatorial as well as unknown. Here, biologics are distinct from drugs and defined as large complex biological molecules or a combination of molecules that can be derived from carbohydrates, lipids, proteins, nucleic acids, whole cells and even tissues. On the other hand, drugs are designated as

molecules that are synthesized chemically and have well-characterized molecular structures. Based on the classification, around 50% of the recent clinical trials will be utilizing biologics and drugs for DES treatment. These therapeutics vary greatly and will mostly be concocted into a solution for delivery as eye drops. Among them, cyclosporine will be one of the most commonly tested anti-inflammatory drug. Even though cyclosporine was already approved for use in clinics to treat DES [207, 208], many of these studies are attempting to further improve its potency by testing different concentrations (NCT04835623), duration (NCT04144413) and delivery method such as sustained release (NCT04541888) and nanoencapsulation (NCT04172961). On the other hand, hyaluronic acid and its salt derivative, sodium hyaluronate, will be the most popular biologics utilized in these studies to constitute artificial tears with lubricating [156, 209] and antibacterial properties [210, 211]. As they were also FDA approved, improvements included the addition of other dietary supplements (NCT04485533) and lubricants (NCT03697876).

Besides biologics and drugs, medical devices are also quite commonly employed, especially for DES caused by Meibomian Gland Dysfunction (MGD). These commercial devices such as Tear-Care System (NCT04309799, NCT04795752) and MiBo Thermoflo (NCT03767530) usually have components that are attached to the users’ eyelids for providing heat and/or pressure which enhances meibum lipid flow [162, 212]. For other causes of DES, one study will be investigating the efficacy of quantum molecular resonance (QMR) on patients with DES (NCT04320563). QMR is a recent innovative technology that involves the application of low-power high-frequency oscillating electrical currents (4 to 64 MHz), a range which resonates with biological tissues, in order to elicit cellular

Table 2 A summary of upcoming and ongoing clinical trials for DES treatment as of Feb 2022. Most of the treatments will be delivered in the form of eye drops

Identifier	Status	Treatment/Intervention	Treatment type	Route of administration	Phase	Related literatures
NCT05169931	Not yet recruiting	Amniotic membrane extract	Biologic	Ophthalmic (Eye drops)	1	[148, 149]
NCT04938908	Not yet recruiting	Probiotic from bacterial lysate	Biologic	Ophthalmic (Eye drops)	2	[150]
NCT04608084	Not yet recruiting	Autologous platelet rich plasma	Biologic	Ophthalmic (Eye drops)	4	[151, 152]
NCT04510428	Not yet recruiting	Ocular Surface Immune Globulin (OSIG)	Biologic	Ophthalmic (Eye drops)	2	N.A
NCT04819269	Not yet recruiting	Tivanisiran (siRNA against TRPV1)	Biologic	Ophthalmic (Eye drops)	3	[153, 154]
NCT04704531	Not yet recruiting	Lagricel Ofteno (Sodium hyaluronate 0.4%)	Biologic	Ophthalmic (Eye drops)	2	[155, 156]
NCT03953703	Not yet recruiting	Levocarnitine	Drug	Oral	2	[157]
NCT04668118	Not yet recruiting	Diquafosol	Drug	Ophthalmic (Eye drops)	4	[158, 159]
NCT04835623	Not yet recruiting	Cyclosporine 0.09% ophthalmic solution	Drug	Ophthalmic (Eye drops)	4	[160]
NCT04965974	Not yet recruiting	Digital blue light blocking filter	Device	N.A	N.A	N.A
NCT04877483	Not yet recruiting	Acupuncture	Device	N.A	N.A	[161]
NCT04309799	Not yet recruiting	Tear Restore Mask (warms the eyelids)	Device	N.A	N.A	[162]
NCT04541888	Not yet recruiting	CsA eye gel (cyclosporine-based gel)	Drug delivery system	Ophthalmic (Eye drops)	3	[163]
NCT04679883	Not yet recruiting	5% GLH8NDE	N.A	Ophthalmic (Eye drops)	2	N.A
NCT05136170	Recruiting	Oxervate (cenegermin a.k.a. rhNGF 20mcg/mL)	Biologic	Ophthalmic (Eye drops)	3	[164]
NCT05109702	Recruiting	Tanfanercept (0.25% HL036 ophthalmic solution)	Biologic	Ophthalmic (Eye drops)	3	[165]
NCT04899518	Recruiting	ALY688 ophthalmic solution	Biologic	Ophthalmic (Eye drops)	2 and 3	[166]
NCT04633213	Recruiting	HBM9036 (TNF- α inhibitor)	Biologic	Ophthalmic (Eye drops)	3	[167, 168]
NCT04615455	Recruiting	Allogeneic adipose-derived mesenchymal stem cells (injection into lacrimal gland)	Biologic	Transplant	2	[169]
NCT04877210	Recruiting	Insulin (in diabetics)	Biologic	Ophthalmic (Eye drops)	1	[170]

Table 2 (continued)

Identifier	Status	Treatment/Intervention	Treatment type	Route of administration	Phase	Related literatures
NCT04683796	Recruiting	Autologous platelet rich plasma vs. autologous serum	Biologic	Ophthalmic (Eye drops)	3	[171–173]
NCT04217785	Recruiting	Umbilical cord serum	Biologic	Ophthalmic (Eye drops)	1 and 2	[174, 175]
NCT03953118	Recruiting	Azithromycin (antibiotic)	Drug	Oral	4	[176]
NCT04357795	Recruiting	Cequa™ (Cyclosporine 0.09%) ophthalmic solution	Drug	Ophthalmic (Eye drops)	4	[177]
NCT05213156	Recruiting	Oxatrex (0.3% ofloxacin)	Drug	Ophthalmic (Eye drops)	4	[178]
NCT04030962	Recruiting	AGN-242428 (ROR γ inhibitor) + AGN-231868 (chemokine antagonist)	Drug	Ophthalmic (Eye drops)	1 and 2	[179]
NCT05056155	Recruiting	Systane Complete (0.6% propylene glycol)	Drug	Ophthalmic (Eye drops)	N.A	N.A
NCT04735393	Recruiting	Reproxalap (covalent inhibitor of RASP)	Drug	Ophthalmic (Eye drops)	3	[180, 181]
NCT04734210	Recruiting	SURF-200 (beta-methasone sodium phosphate)	Drug	Ophthalmic (Eye drops)	2	N.A
NCT04172961	Recruiting	Nanomicellular cyclosporine formulation	Drug	Ophthalmic (Eye drops)	4	[160]
NCT04144413	Recruiting	Ikervis (1 mg/ml cyclosporine formulation)	Drug	Ophthalmic (Eye drops)	3	[160]
NCT04553432	Recruiting	Omnigen (processed amniotic membrane)	Device	N.A	4	[182]
NCT05203796	Recruiting	Transcutaneous pulsed electrical stimulation (NuEyne 02)	Device	N.A	N.A	[183]
NCT04795752	Recruiting	TearCare system (thermal treatment)	Device	N.A	N.A	[184]
NCT04120584	Recruiting	Forma eye applicator (radio frequency treatment)	Device	N.A	N.A	N.A
NCT04320563	Recruiting	Rexon-eye (4 to 64 MHz, quantum molecular resonance)	Device	N.A	N.A	[185]

Table 2 (continued)

Identifier	Status	Treatment/Intervention	Treatment type	Route of administration	Phase	Related literatures
NCT03767530	Recruiting	MiBo Thermoflo (thermal therapy)	Device	N.A	N.A	[186]
NCT04730336	Recruiting	Tixel (peri-orbital fractional thermo-mechanical treatment)	Device	N.A	N.A	N.A
NCT04763018	Recruiting	iTEAR100 (neuro-stimulate external nasal nerve)	Device	N.A	N.A	[187]
NCT04096898	Recruiting	Senofilcon A contact lens	Device	N.A	N.A	[188, 189]
NCT04498468	Recruiting	DEXTENZA (Dexamethasone-loaded intracanalicular insert)	Drug delivery system	Implant	4	N.A
NCT05119920	Recruiting	Pilocarpine ophthalmic topical cream	Drug delivery system	Eyelid	2	N.A
NCT04527887	Recruiting	Dexamethasone-loaded intracanalicular insert	Drug delivery system	Implant	4	[190]
NCT04645446	Recruiting	Pro-ocular gel (loaded with 1% progesterone)	Drug delivery system	Transdermal	2	[191]
NCT05027087	Recruiting	Blueberry gummy	Dietary supplement	Oral	3	[192]
NCT04785261	Recruiting	Artelac eye drops + Vidisic gel + traditional chinese medicine formula	Drug + Biologic	Ophthalmic (Eye drops) + Oral	2	[193]
NCT04413279	Recruiting	Dexamethasone-loaded intracanalicular insert + Lipi-Flow thermal pulsation	Drug delivery system + Device	Implant	4	[190, 194]
NCT03652051	Recruiting	AZR-MD-001 (topical ointment)	N.A	Ophthalmic (Eye drops)	2	N.A
NCT03302273	Enrolling by invitation	Corneal epithelial stem cells	Biologic	Transplant	N.A	[195, 196]
NCT04056221	Enrolling by invitation	Acupuncture	Device	N.A	N.A	[161]
NCT04884217	Enrolling by invitation	Pro-ocular gel (loaded with 1% progesterone)	Drug delivery system	Transdermal	2	[191]
NCT04421300	Enrolling by invitation	Smiling exercise	Physical activity	N.A	N.A	[197]
NCT04658927	Enrolling by invitation	iLUX (applies heat and compression to eyelids) + Dexamethasone-loaded intracanalicular insert	Device + Drug delivery system	Implant	4	[190, 198]

Table 2 (continued)

Identifier	Status	Treatment/Intervention	Treatment type	Route of administration	Phase	Related literatures
NCT03697876	Active, not recruiting	PRO-165 (contains chondroitin sulphate, sodium hyaluronate)	Biologic	Ophthalmic (Eye drops)	1	[156, 199]
NCT03937882	Active, not recruiting	RGN-259 (contains T β 4)	Biologic	Ophthalmic (Eye drops)	3	[200, 201]
NCT03878628	Active, not recruiting	Allogeneic adipose tissue-derived mesenchymal stem cells (injection into lacrimal gland)	Biologic	Transplant	1	[169]
NCT04485533	Active, not recruiting	VisuXL gel (contains Coenzyme Q10, Vitamin E, sodium carboxymethylcellulose) + HYLO (contains sodium hyaluronate)	Biologic	Ophthalmic (Eye drops)	N.A	[156, 202, 203]
NCT04425551	Active, not recruiting	Micropulse laser	Device	N.A	N.A	[204]
NCT04608942	Active, not recruiting	Jett Plasma Medical Lift (remove hyperkeratinized layer to unblock gland ducts)	Device	N.A	N.A	[205]
NCT04181593	Active, not recruiting	OmegaD softgels (Omega-3)	Dietary supplement	Oral	3	[206]

responses [213]. This procedure will be performed using Raxon-Eye, a noninvasive, QMR-based patented instrument. Patients will wear the device like an eye mask and electrodes will stimulate their periorbital region during the therapy for enhanced tear secretion.

The rest of the treatment types form the minority within the list of clinical trials. These included drug delivery systems that will provide sustained release through dexamethasone-loaded implants (NCT04527887, NCT04413279, NCT04658927) and hydrogels (NCT04541888, NCT04645446, NCT04884217), dietary supplements consisting of vitamins and lipids (NCT04181593) as well as physical activities for boosting well-being (NCT04421300).

Future prospects for DES treatment

As discussed, DES could be caused by a large variety of factors. However, current treatments mainly addressed the symptoms by hydrating or lubricating the ocular surface without tackling the root problems [148]. Besides creating unhealthy dependence in patients, such approaches will also lead to significant financial burden due to recurring treatment costs. Therefore, it is encouraging to witness the trajectory of upcoming DES treatment strategies where cellular and tissue regeneration in the LFU are the key focus. Specifically, studies that employ blood components such as platelet rich plasma or serum hold great promise in the clinics not only for treating DES but for other diseases as well [214]. However, like many other treatment

options, allogeneic stem cell and body fluid therapy come with their own limitations that cannot be easily circumvented. Most notably, they involve invasive procedures and may deter patients from opting for this method. Additionally, the effectiveness of these components in inducing favorable outcomes is highly dependent on the patients' suitability as well.

Therefore, for treatments to be inclusive, they should be varied and multipronged. In our opinion, one promising alternative is gene therapy, which enables the alteration of genetic sequences within tissues and cells with recombinant nucleic acids [215]. Commonly used nucleic acids such as DNA, mRNA, siRNA, miRNA and anti-sense oligonucleotides can be strategically delivered into a defective target cell or tissue in order to either restore the gene(s) responsible for disease suppression or inhibit the gene(s) related to disease development [216]. Besides its versatility, these nucleic acids can also be administered noninvasively for DES treatment. Accordingly, the efficacy of this technology will be investigated in one of the upcoming clinical trials listed in Table 2 which utilizes Tivanisiran (NCT04819269), a novel 19 nucleotide siRNA for suppressing the expression of the transient receptor potential cation channel subfamily V member 1 (TRPV1) [153]. TRPV1 is a pain receptor found in some components of the LFU [217] and the responses it mediates in the sensory neurons was found to be associated with the development of inflammation and neuropathic pain [218]. The delivery of this siRNA-based eye drop will potentially result in the reduction in TRPV1's expression in the ocular tissues and therefore, alleviate inflammation and improve tear secretion [219]. Of note, naked nucleic acids are very inefficiently uptaken by cells as they possess similar negative charges as the cell membrane, which leads to electrostatic repulsion [220, 221]. Delivery vehicles are required to transport nucleic acids across the cell membrane and herein determines the success of gene therapy. Recently, a breakthrough in vaccination strategy has shed valuable insights about the optimal form of nucleic acid carriers. Specifically, the Pfizer vaccine for Covid-19 utilizes a specially formulated liposome for delivering mRNAs into cells with great efficiency [222]. With the approval of this revolutionary delivery platform, gene therapy is thus in a favorable position to take off.

Another prospective DES treatment option is fecal microbiota transplantation (FMT), which is the transfer of fecal materials from a healthy donor into the intestinal tract of an ill or diseased recipient. By doing so, the recipient's gut microbial composition can be adjusted to resemble the healthy donor's, thereby conferring health benefits [223]. Since DES was found to be associated with gut dysbiosis, FMT is a potentially relevant and practical technique for treatment. However, there were not many clinical trials investigating the efficacy of FMT on DES patients as it was only quite recently that a correlation between DES and gut dysbiosis was uncovered. The first and only study was completed on June 2020, which explored the effects of FMT on patients with SS (NCT03926286). Alternatively, we may also expect ocular microbiota transplantation in future as studies have identified microbiome differences between closed dry eye patients and healthy closed eye patients [224–226].

Conclusion

DES is a relatively common ophthalmic disease that can manifest in various degrees of severity and can be caused by many factors. While not life threatening, patients may often have to continuously endure discomfort or even pain, which puts a damper in their quality of life. Given the multitude of conditions which DES can originate from, a variety of treatment options is critical to ensure inclusivity and effectiveness. Encouragingly, current clinical trials are trending towards this notion and investigating promising research-backed treatments like stem cell therapy, blood component therapy and gene therapy. If successful, these strategies may define treatments for other diseases in future as well.

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Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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