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Therapeutic Strategies to Treat Dry Eye in an Aging Population

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Abstract

Dry eye (DE) is a prevalent ocular disease that primarily affects the elderly. Affecting up to 30% of adults aged 50 years and older, dry eye affects both visual function and quality of life. Symptoms of dry eye which include ocular pain (aching, burning), visual disturbances, and tearing can be addressed with therapeutic agents that target dysfunction of the meibomian glands, lacrimal glands, goblet cells, ocular surface and/or neural network. This review provides an overview of the efficacy, use, and limitations of current therapeutic interventions being used to treat DE.

1. Introduction

Dry eye (DE) is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability with potential damage to the ocular surface, accompanied by increased osmolarity of the tear film and inflammation of the ocular surface [1]. The most common symptoms of DE include pain (burning, dryness), visual disturbances (blurred vision, fluctuating vision) and tearing [2]. These symptoms are commonly encountered complaints in eye care offices and have been shown to decrease quality of life for patients [3, 4]. In the United States alone, it is estimated that 40 million people are affected by DE [5] and approximately two-thirds are women [6, 7]. As older age has been a consistent risk factor in DE studies [5], the prevalence of DE and its associated morbidity are expected to increase as the aged population grows [8]. Significant advances have been made in treating aging populations afflicted by DE since prior reviews [9].

2. Methods

A PubMed search was conducted including but not limited to the following terms: “dry eye”, “aging”, “lacrimal gland”, “meibomian glands”, “goblet cells” “inflammation”, “corneal nerves”, “conjunctivochalasis”, “eyelid laxity”, “therapeutics”, “artificial tears”, “Cyclosporine A (CsA)”, “eyelid hygiene”, “Orgahexa eye warmer”, “Blephasteam®”, “oral tetracyclines”, “manual expression”, “LipiFlow®”, “IPL laser”, “diquafosol tetrasodium”, “sodium hyaluronate”, “corticosteroids”, “loteprednol etabonate”, “tacrolimus”, “tofacitinib”, “omega-3 fatty acids”, “autologous serum”, “nerve growth factor”,

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"acupuncture", "PROSE lens" and "topical steroids." All searches were limited to the English language/translation. Articles were reviewed and those that discussed aging changes related to the lacrimal functional unit and/or therapeutic treatment strategies in DE were summarized.

3. Dry Eye and Aging

Why is dry eye more common in the aging population?—Dry eye is more common in the aging population likely because age has been found to affect all parts of the lacrimal functional unit, which includes the lacrimal gland, meibomian glands, goblet cells, ocular surface, and somatosensory nerves.

3.1 Aging and the lacrimal gland

The lacrimal gland is a compound tubuloacinar gland whose acini produce the aqueous component of tears. Several animal studies have demonstrated changes in structure and function of the lacrimal gland in older animals [10-14]. In a rat model, the lacrimal glands of older animals revealed acinar, stromal, and ductal changes on light microscopy (e.g. acini: degeneration, decreased density, nuclear changes, lipofuscin-like inclusions; stroma: increased collagen, ducts; dilation) [12]. Interestingly, these changes were more prominent in older female rats compared to males [12]. Older lacrimal glands were also found to synthesize less protein and secrete less fluid after stimulation with substance P, vasoactive intestinal peptide and 5-hydroxytryptamine [15]. Similar findings have been found in humans. On histopathology, older women had more frequent diffuse fibrosis and atrophy in the orbital lobe of their lacrimal gland than older men [16]. Older women also had decreased lacrimal gland thickness and area on MRI compared to their younger counterparts [17].

3.2 Aging and the meibomian glands

The meibomian glands are a special type of sebaceous gland found in the tarsal plates of the eyelids that produce meibum, an oily substance that prevents evaporation of tears. Healthy mice, ages 2-24 months, whose meibomian glands were examined showed reduced acinar tissue, altered PPARγ signaling, and decreased cell cycling with age [18]. Similarly, in humans without DE symptoms, *in vivo* laser scanning confocal microscopy (LSCM) demonstrated atrophic, nonobstructive aging changes in the meibomian glands (MGs) including decreased density and diameter and increased secretion reflectivity and acinar wall inhomogeneity [19]. Noncontact infrared meibography demonstrated decreased mean duct length and % acini area and increased gland dropout in older, asymptomatic individuals [20]. Meibum properties change with age with asymptomatic older individuals having less CH3and C=C groups and higher aldehyde-to-lipid hydroperoxide ratios than younger individuals, as detected with H nuclear magnetic resonance (NMR) spectra [21].

3.3 Aging and goblet cells

Goblet cells are glandular simple columnar epithelial cells, whose function is to secrete mucins. Goblet cells are interspersed in the bulbar conjunctivae in animals and humans. Several studies show decreased goblet cell density on the ocular surface of older animals,

including rats [12] and mice [13] (detected using histology), and humans (detected using *in vivo* confocal microscopy) [22].

3.4 Aging and inflammation

Inflammation is a well-recognized component of DE [23]. Older mice have been found to spontaneously develop a DE phenotype, with CD4+ T cell infiltration into the conjunctiva, expression of inflammatory cytokines (interferon-γ, IL-17, matrix metallopeptidase 9), and increased T and B cells in the lacrimal gland [13]. Interestingly, adoptive transfer of CD4(+) T cells isolated from these elderly mice transferred the disease into young immunodeficient recipients [13]. Rats similarly have been found to have increased mast and lymphocytic infiltration in their lacrimal glands with age [12]. Inflammation is a known sensitizer of peripheral nerves [24, 25] and increasing inflammation on the ocular surface with age alters the function of the corneal nociceptors and the function of the corneal somatosensory system.

3.5 Aging and the somatosensory system

Peripheral nerve changes are known to occur with age, with a decreased proportion of mechano- and/or heat-responsive C-nociceptors and a slower conduction velocity in response to repeated electrical stimulation seen in older as compared to younger rats [26]. In humans, both sensitization and desensitization of afferent C-fibers have been described with age, with a higher frequency of fibers with atypical discharge characteristics (13%) in older but not younger normal human subjects. Spontaneous activity, sensitization, loss of sensory function and a slower conduction velocity in response to high frequency stimulation (2 Hz) is seen in older individuals [27]. With regards to peripheral corneal nerves, confocal microscopy data has been mixed, with one study reporting significant declines in sub-basal nerve fiber density with age (0.9% per year) [28] and others reporting no alterations in number, density, or beadings of nerves with age [29, 30]. Central nerve changes also occur with age, with decreased connectivity and network integrity noted in healthy older adults [31]. The Cochet-Bonnet and Belmonte aesthesiometry devices have been used to assess the overall function of the corneal somatosensory and have found decreased corneal sensitivity with age in horses [32] and humans [33, 34].

3.6 Aging and compositional and functional changes

Compositional and function changes in the tear film have also been found with age. For example, infants have a much longer TBUT than adults, and a much lower spontaneous blink rate (less than one blink per minute in infants) which increases with age (up to 20 blinks per minute in adults) [35, 36]. Younger individuals also have lower lipid viscosity and higher lipid volume [37]. The increasing lipid viscosity seen with age may be attributed to decreasing meibum order and phase transition temperatures [38]. Additionally, decreased meibocyte differentiation and cell cycling have been seen with age [39], perhaps due to alterations in peroxisome proliferator–activated receptor γ (PPARγ), a lipid-activated nuclear hormone receptor that regulates lipid synthesis [39].

3.7 Aging and anatomic changes

Anatomic changes, such as conjunctivochalasis and eyelid laxity are associated with DE symptoms and abnormal tear parameters [40-41]. As with other involution changes, both of these entities are more common in older individuals [40, 42-43].

4. Therapeutic interventions

Given the myriad changes to the lacrimal functional unit that occur with age, clinicians must first assess which part of the lacrimal functional unit is most dysfunctional and align therapy with the location of dysfunction. The first line therapy of patients with DE begins with protection of the ocular surface with artificial tears. There are many available products that vary in viscosity, polymer material, and preservative. Additionally, some products include additional properties such as lipid replacement and hypo-osmolarity. A complete list of artificial tear properties and their preservatives can be found on the website http://www.dryeyezone.com/encyclopedia/lubricants.html. In general, patients should consider preservative free options if they use artificial tears more than four times a day. Gels and ointment are also available for night time use and for those with more severe aqueous tear deficiency (ATD) DE.

4.1 Lacrimal gland dysfunction

Cyclosporine (CsA) 0.05% emulsion is the only medication approved by the federal drug administration (FDA) for the treatment of DE. Cyclosporine's mechanism of action is through reduction of IL-2 levels and subsequent reduction of effector T cell function. Given this role, CsA likely targets inflammation on the ocular surface but also has been shown to improve aqueous production. An animal study examining the lacrimomimetic effect of CsA emulsion a few hours before and after administration found a significant increase in both tear production (lacrimal gland fluid flow rate and Schirmer's score) and blink rate compared to vehicle [44].

In vehicle controlled studies, the subjective symptom of ocular “dryness” is improved with CsA treatment over vehicle in many trials [45-52]. Likewise, a consistent improvement in the DE objective signs of corneal staining and Schirmer scores were seen [45-52]. CsA has been effective in more severe forms of aqueous tear deficiency (ATD) like Sjogren's syndrome [53]. Additionally, pre-treatment with CsA before DE onset in patients undergoing bone marrow transplant decreased DE severity [54].

4.2 Meibomian gland dysfunction

The most common cause of evaporative DE is meibomian gland dysfunction (MGD), a chronic condition that may involve functional abnormalities, blockage, atrophy, hypo or hypersecretion, and abnormal excreta from meibomian glands [1, 55]. The goal of any MGD regimen is to improve the stability of the tear film by improving lipid layer health [56]. Treatment of MGD typically begins with eyelid hygiene performed with warm water alone or combined with baby shampoo, applied with a wash cloth, cotton pad, or cotton tip applicator. Over the counter pads, such as OCuSoft, Eye Scrub, and Blephaclean, can also be used for this purpose. Fourteen controlled trials, with 508 participants, compared lid

hygiene alone (warm compresses, eyelid massage, lid scrubs, baby shampoo, sodium bicarbonate solution, saline and eyelid scrubbing/cleansing solutions) to lid hygiene plus medications, medications alone, placebo, or no treatment. Overall, the data support the use of lid hygiene for the treatment of MGD [57].

The use of devices to assist in lid hygiene implementation has also been studied. For example, in a prospective unmasked non-randomized study, 20 patients with MGD (defined as (1) occluded orifices and (2) either keratinization or mucocutaneous junction displacement) applied the Orgahexa eye warmer mask to the eyelids for 10 minutes, twice a day, for two weeks. There was an overall significant reduction in DE symptoms and signs, which included improved visual analog scores, staining, and lipid layer thickness [57]. The use of warming devices may be more effective than traditional warm-compresses because of improved standardization and patient compliance [58]. In one study, 50 patients with MGD (OSDI > 12, TBUT < 5, Foulks-Bron Scale 11-20) used warm-compress treatment for 3 weeks and Blephasteam®, an eye-lid warming device, for another 3 weeks. 18 patients did not respond to the warm compress treatment but saw significant improvement of signs and symptoms following treatment with Blephasteam® [58]. In other studies, Blephasteam®, used twice a day, for five days, was found to be safe and effective in reducing ocular discomfort and symptoms (n=175); ocular signs were not evaluated in these studies [59, 60].

In patients with more severe disease or those refractory to eyelid hygiene, oral or topical antibiotics are typically used. Options include oral doxycycline (20-100 mg daily to bid), minocycline (50-100 mg daily to bid) and azithromycin (250-500 mg daily to bid). These antibiotics are thought to have multiple effects on meibomian gland health, including targeting inflammation and reducing bacterial overgrowth [61, 62]. The administration of 50-100 mg of oral minocycline, twice a day for 8-12 weeks, taken either alone, or combined with artificial tears (0.1% sodium hyaluronate) and/or lid hygiene, showed benefit in improving clinical symptoms (burning, irritation, tearing, photophobia) and signs (eyelid margin/conjunctival redness, telangiectasia of lid margin, tear film stability) in four studies involving 106 patients with MGD (defined as (1) conjunctival erythema, (2) telangiectasias, (3) thickening, and (4) either irregularity of the eyelid margins or meibomian gland orifice inclusions) [63-66].

It is important to remember that tetracyclines have side effects including photosensitization, vaginitis, gastrointestinal upset, hypersensitivity and are contraindicated in pregnant or lactating women and children younger than eight years old [57]. Given these side effects, topical antibiotics have been studied for MGD treatment. An *in vitro* study of azithromycin on human meibomian gland epithelial cells found that it stimulated accumulation of free and esterified cholesterol, phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositol [67]. In five studies (including 1 RCT) involving 169 individuals, administration of 1-2 drops of 1-1.5% topical azithromycin ophthalmic solution 1-2 times a day, for 3-30 days, provided significant improvement in DE symptoms and signs and restored lipid properties (improvement in spectroscopic measures of lipid composition) in patients with anterior or posterior chronic blepharitis [68-72]. By demonstrating a decrease in the OSDI score by over 20 points and increased tear break-up time and Schirmer scores, these studies suggest that topical azithromycin is more effective in treating the symptoms

and signs of MGD than lid hygiene alone. Two different RCTs (n=70) further demonstrated eradication of bacteria from the eyelid two weeks after treatment with topical antibiotics [73, 74].

Newer modalities in MGD treatment include procedures and devices that build on the concept of eyelid hygiene and/or manual expression, such as the LipiFlow® Thermal Pulsation System (Tear Science, Morrisville, NC) and intense pulsed light (IPL) laser. The LipiFlow® System uses heat and gentle pressure pulsations to unblock obstructed meibomian glands [75]. In a prospective, open-label study (with no control group) involving 21 patients with MGD (meibomian gland secretion score of ≤12 for 15 glands in the lower eyelid), a single LipiFlow treatment led to improved symptoms (based on OSDI scores) and signs (meibomian gland secretion scores, corneal fluorescein staining and TBUT) both one and nine months after treatment [75, 76]. Another emerging treatment for MGD is application of intense pulsed light (IPL) to the eyelid margins. In a prospective, double-masked, placebo-controlled, paired-eye study, the use of IPL with multiple sculpted pulses was evaluated in 28 patients with MGD. The IPL was applied to the eyelid margin of one eye, while the partner control eye received placebo treatment, at 1, 15 and 45 days after the baseline evaluation. The results from this study showed improved visual analog scale symptom scores from baseline in the IPL treated group and decreased SPEED scores, as well as a significant improvement in signs (non-invasive TBUT, lipid layer grade) [77]. A drawback to all these devices is that they typically include out-of-pocket costs and limited long-term data is available on outcomes.

4.3 Goblet cell dysfunction

It has been reported that patients with DE have lower goblet cell densities (2.11±0.78/mm) than control patients (8.84±4.66/mm) [78]. Diquafosol tetrasodium is a mucin analogue that exerts its effects through activation of the Gq protein-coupled P2Y2 receptor and stimulates nonglandular secretion of fluid and mucin from chloride channel activation [79]. While diquafosol tetrasodium is commercially available in Japan for the treatment of DE, it has not been approved for this use by the FDA in the US. One randomized, double-blinded, placebo-controlled study evaluated the efficacy of 1-2% diquafosol tetrasodium over a 24 week treatment period on 527 subjects with DE symptoms, Schirmer's ≤7 mm, and corneal staining ≥4 out of 15 [79]. A significant improvement in symptoms (by OSDI score) and signs (Schirmer's scores, rose bengal staining) in the diquafosol tetrasodium group was reported [80]. Two additional RCTs examined the effect of combining 0.1% sodium hyaluronate with 3% diquafosol tetrasodium in 214 patients over 1-3 months [80-81]. Significant improvements in subjective symptoms and objective signs (TBUT, Schirmer's score, staining scores) were reported with combination treatment over monotherapy [80-81], with one study additionally reporting significant improvement in goblet cell density and impression cytological findings [81].

4.4 Inflammation

Inflammation plays a vital role in the development of aqueous deficient DE [82-83]. Topical corticosteroids bind and activate the cytosolic glucocorticoid receptor and promote anti-inflammatory gene expression in leukocytes and lymphocyte apoptosis [84-85]. New

biomarkers, such dendritic cell density, assessed via confocal microscopy, have been shown to correlate with treatment-related inflammation changes and may help predict response to topical corticosteroids [86]. Although the long-term use of corticosteroids has complications, a brief course has proven effective in DE [84, 87]. In a randomized, double-masked, placebo-controlled CT and a retrospective noncomparative case series (n=85), patients with a DE diagnosis treated with 0.5-1% topical loteprednol etabonate or methylprednisolone three or four times daily for four weeks showed greater improvement in symptoms of eye redness and objective variables, which include corneal staining, bulbar and tarsal conjunctival hyperemia scores [87, 88].

Tacrolimus, a calcineurin inhibitor which inhibits the production of IL-2, has also been evaluated in DE, after its successful use in vernal keratoconjunctivitis and graft-versus-host disease (GVHD) [89]. While it's mechanism of action is similar to CsA, it has a significantly greater potency *in vitro*, with effects at 100 times lower concentrations [90]. While systemic tacrolimus has been used in DE associated with GVHD, there are adverse side effects that need to be taken into account when treating with long-term systemic therapy [91]. Topical tacrolimus, 0.03% and 0.1% drops or ointment, may be a promising treatment for DE in patients with Sjogren's syndrome or GVHD, although in its current formulation and similar to CsA, side effects of ocular pain (burning, stinging) limit its use [92-94].

The JAK-2 inhibitor, tofacitinib, is an immunomodulator that has been evaluated in DE. While oral tofacitinib is approved in the US for rheumatoid arthritis, topical tofacitinib has been evaluated in phase II clinical trials (CTs) but is not commercially available for as a treatment for DE. In a Phase I/II prospective, randomized, vehicle-and comparator-controlled trials, topical tofacitinib 0.0003-0.005% was used in 327 patients with DE (by (1) DE symptoms, (2) Schirmer's ≥1 mm and ≤ 7 mm, and (3) corneal staining ≥4), once or twice a day for eight weeks [95]. There was an improvement in both symptoms (OSDI) and signs (Schirmer's test, corneal staining) of DE. In this trial, the primary end point was the proportion of patients who achieved 10 mm or more of Schirmer wetting (without anesthesia) at the end of eight weeks. Although greater response rates were observed for tofacitinib 0.001% twice daily (27.3%), 0.005% twice daily (25.5%), and 0.005% once daily (26.1%) compared to vehicles (20.0%), the differences were not statistically significant [95]. The doses of tofacitinib were well tolerated in patients and had a reasonable safety profile [95].

Omega-3 essential fatty acids have been shown to reduce inflammation [9]. Diets rich in omega-3 fatty acids, such as tuna fish, or omega-3 supplements, such as fish oil or flak seed oil, have been reported to lower the risk of chronic DE and improve symptoms and signs. One RCT of 61 patients with symptomatic MGD found improved mean OSDI, TBUT, lid margin inflammation, meibomian gland expression, and Schirmer's test at 3 months in 30 patients using oral supplement containing omega-3 versus 31 control patients [96]. In addition, sub-clinical markers of inflammation (HLA-DR expression on the ocular surface), as measured by fluorescence intensity quantification, was significantly reduced in the fatty acids group (p=0.041), after a 3-month supplementation with omega-3 and omega-6 fatty acids, vitamins, and zinc [97].

4.5 Corneal somatosensory pathway dysfunction

There is a growing understanding that many patients diagnosed with DE describe features of neuropathic pain, including spontaneous pain, dysesthesias (unpleasant, abnormal sensation), hyperalgesia (exaggerated pain response to suprathreshold noxious stimuli), and allodynia (pain response to normally non-noxious stimuli) [98]. Neuropathic pain (i.e. pain caused by a lesion or disease of the somatosensory nervous system) results from damage and/or hypersensitization of peripheral or central corneal and conjunctival somatosensory nerves (peripheral and central sensitization). Autologous serum (AS) is a therapy of interest in treating corneal somatosensory pathway dysfunction in DE given its biochemical properties, including the presence of various neuromediators (including nerve growth factor) that may affect corneal nerve function [99].

Five studies (including 3 RCTs) compared the effectiveness of 20-50% diluted AS to conventional therapies and normal saline for 80 patients with DE in treatment periods that ranged from 2 weeks to 3 months. All studies reported statistically significant improvement in symptoms and signs (TBUT, staining, impression cytology) in patients receiving AS over conventional therapies [100-104]. Widespread use of AS is currently limited, however, by the lack of a commercially available methodology to obtain therapy.

Nerve Growth Factor (NGF), a protein found in serum, helps regulate the growth and survival of neurons [105]. Higher levels of NGF have been reported in patients with DE when compared to healthy patients [106]. One prospective, randomized, placebo-controlled, double-masked phase 2 CT evaluating treatment with an agent that mimics that effect of NGF (MIM-D3, a TrkA receptor agonist) twice per day over 28 days in 150 patients with DE (defined as worsening corneal staining and ocular discomfort in the Controlled Adverse Environment) found statistically significant improvements in symptoms and signs of DE with therapy [106].

Acupuncture, another therapy that likely affects nerve function [107], has been investigated as a treatment for DE [108]. Interestingly, acupuncture has been reported to affect the signs of DE more than its symptoms. In 3 open label RCTs (n=137) comparing the effects of acupuncture and artificial tears on DE (inclusion criteria not available) [108], the acupuncture group noted significant improvements in signs (TBUT, Schirmer's test, fluorescein staining) over the artificial tear group [108]. In 3 different RCTs (n=182) comparing the use of acupuncture with artificial tears to the use of artificial tears alone [109-111], one RCT reported significant improvement in TBUT, Schirmer's test, and frequency of artificial tear usage [109]. One study reported significant improvement in Schirmer's test and frequency of artificial tears usage, while the other found no significant improvement in symptoms or signs [108]. Another randomized placebo-controlled study compared the use of true versus sham acupuncture for 42 patients with DE (TBUT <10 sec and Schirmer's <10mm) [112] and found improvement in symptoms and signs in both groups, with no advantage of true acupuncture over sham acupuncture.

The PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem) lens, a fitted lens that bathes the entire cornea in artificial tears, is thought to help DE symptoms in those with peripheral sensitization by covering and protecting corneal free nerve endings. This therapy

markedly improves symptoms and quality of life in patients with severe DE caused by graft versus host disease, although clinical signs were not evaluated [113].

4.6 Anatomical changes

Exposure and irritation of the ocular surface due to eyelid laxity is something clinicians must be aware of, due to its high frequency in the older population [40]. Palliative treatments such as lid shields, lid taping, nocturnal lubrication, topical steroids, lid scrubbing, and punctal plugs have been used [114], but their discomfort and impracticality, especially the risks and dangers associated with topical steroid use, have shifted treatment more toward surgical interventions that tighten the eyelid such as full thickness wedge excision, lateral tarsal strip, lateral/medial canthal plication, and medial canthal strip [115]. Conjunctivochalasis, characterized by redundant conjunctival folds, is another anatomic abnormality that interferes with tear film integrity and can lead to DE symptoms [116]. Artificial tears and or topical anti-inflammatory agents are usually prescribed initially for symptomatic treatment [117]. Resection or thermal cautery of excess conjunctiva is considered when medical approaches fail.

5. Conclusion

To summarize, the changes that occur in the lacrimal gland, meibomian glands, ocular surface, somatosensory system, and anatomy with aging likely underlie the known association between aging and DE. It is important to consider both the benefits and risks of each dry eye therapy and tailor the treatment approach appropriately. While topical corticosteroids can improve symptoms and signs of DE, they have potential side effects, especially when used chronically. These include intraocular pressure elevation and cataract formation and as such, these agents should be used judiciously and by those who can monitor for these side effects. Additionally, one must consider its multiple etiologies and co-morbidities, along with patient socio-economic issues and compliance. Clinicians must be aware of the heterogeneous nature of the disease and choose therapies in a step-ladder approach that align with location of dysfunction.

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Key points

- Dry eye in the aging population is associated with changes to the lacrimal gland, meibomian glands, ocular surface, somatosensory system and anatomy of the eye.
- In order to individualize dry eye therapy, physicians must be aware of the heterogeneous nature of the disease and align treatment to address the location of dysfunction.