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Topical pharmacologic treatments for dry eye disease: A systematic review

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ABSTRACT

Background: Topical pharmacologic treatments for dry eye disease (DED) address different aspects of tear film deficiency by decreasing ocular surface inflammation, stimulating mucin secretion, increasing tear production, or reducing excessive evaporation. This systematic review evaluated randomized controlled trials (RCTs) and prospective observational studies of topical ophthalmic medications for DED.
Methods: PubMed and Embase were searched from 1980 to February 2024. For studies meeting inclusion criteria, efficacy outcomes (signs and symptoms of DED) and adverse event data were extracted.
Results: A total of 107 publications covering topical prescription medications (anti-inflammatory agents cyclosporine and lifitegrast; mucin secretagogues diquafosol and rebamipide; tear evaporation inhibitor perfluorohexyloctane; tear production stimulator nasal spray varenicline), other commercially available products, and novel agents in development were identified. In RCTs, significant improvements relative to a control group were demonstrated more often for sign endpoints (e.g., corneal staining, Schirmer score) than for symptom endpoints (e.g., eye dryness, ocular discomfort). The evaluated treatments were well tolerated; instillation site reactions were the most commonly reported adverse events. Year-long safety extension studies demonstrated maintenance of efficacy, with no new safety signals identified. Studies differed in design, methodology, control group, and outcomes assessment, making it difficult to compare across products, and head-to-head studies were rare. Several new products are in late-stage development, which will likely lead to additional treatment options.
Conclusions: Current topical pharmacologic eye products improved signs, and sometimes symptoms, of DED and were well tolerated. Treatment selection should use a shared decision-making approach that takes DED etiology and patient preferences into account.

1. Introduction

Dry eye disease (DED) is a common disease of the ocular surface that is characterized by a loss of homeostasis of the tear film, leading to inflammation and damage to the corneal epithelial surface and conjunctiva [1]. Patients with DED typically report ocular irritation symptoms of dryness, grittiness, foreign body sensation, burning, stinging, light sensitivity, and ocular pain, as well as vision-related symptoms such as blurred and/or fluctuating vision [2]. These symptoms can significantly affect patients' visual function, physical and mental quality of life, work productivity, and daily activities [3,4].

The pathophysiology of DED is multifactorial and caused by dysfunction of one or more ocular structures that maintain a stable tear film [1,5]. The tear film is composed of an inner aqueous-mucin layer and an outer lipid layer [6–8]. The aqueous and mucin components are produced by lacrimal glands and conjunctival goblet cells, respectively,

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while the lipid layer is composed primarily of secretions from the meibomian glands, which are located along the upper and lower eyelids [7]. DED may be classified along a continuum as aqueous deficient (lacrimal tear production is reduced), evaporative (tear film evaporation is increased), or mixed [5]. Purely aqueous deficient DED is relatively rare because most patients have an evaporative component (of varying intensity) [9–11] due to altered profiles of secretory protein, lipid, and mucin [5,12]. Many patients with evaporative DED are observed to have meibomian gland dysfunction (MGD), which disrupts the tear film lipid layer, causing excessive evaporation [12]. Recent models describe DED as a double vicious circle of aqueous and evaporative features, with inflammation as a central driver [13]. Factors that contribute to the cycle of DED include imbalance between tear production and evaporation, abnormalities in tear film composition (e.g., lipid changes, lack of mucins), tear film instability, tear hyperosmolarity, inflammation, and ocular surface damage [13].

DED is diagnosed and assessed based on an evaluation of systemic conditions, patient-reported ocular symptoms, and ocular signs observed by clinicians on clinical examinations of the tear film (e.g., tear volume, tear film breakup time [TBUT]), ocular surface (e.g., corneal fluorescein staining, conjunctival lissamine green staining), and eyelid (e.g., meibomian glands and meibum) [14]. As a chronic and often progressive disease, DED often requires long-term treatment [1]. Topical ophthalmic medications have been developed to target one or more of the pathophysiologic mechanisms underlying DED, with the goal of reestablishing ocular surface homeostasis. These pharmacologic agents target distinct factors contributing to the cycle of DED, highlighting the complexity of DED treatment options. Potential modes of action include compensating for deterioration in tear film quality, decreasing ocular surface inflammation, increasing tear production, stimulating or mimicking mucin secretion, or reducing excessive tear evaporation [12]. As product availability for medical treatment of DED varies across countries and regions, including recent approvals and new product development, this systematic literature review evaluates the efficacy and safety of topical pharmacologic products from a global perspective. Along with randomized controlled trials (RCTs), this review also evaluates results from real-world studies, which typically include patients who are more representative of the patient population encountered in clinical practice.

2. Methods

2.1. Search strategy

PubMed and Embase were searched for the period from 1980 to February 2024 using search terms ((eye OR ocular) AND sicca) OR “dry eye”) [title/abstract] AND (random* OR prospective OR real-world) [title/abstract] and English [language].

2.2. Inclusion and exclusion criteria

Inclusion criteria were RCTs and prospective observational studies examining the effects of a topical pharmacological treatment on the signs and/or symptoms of DED. Studies of currently available and investigational products were included, as well as studies assessing combination treatments.

Exclusion criteria related to study design were preclinical (animal or in vitro) studies, retrospective studies, sample size of <25 patients per arm for randomized trials and <100 patients for prospective (uncontrolled) studies (as RCTs are considered more stringent than uncontrolled trials), controlled trials with a non-topical comparator, treatment duration <4 weeks, and study populations limited to a specific condition or procedure associated with DED (i.e., graft versus host syndrome, hematopoietic stem cell transplant, Sjögren’s syndrome, diabetes, and cataract or refractive surgery). Review articles were also excluded. Studies of the following topical treatments were outside the scope of this review and, therefore, excluded: artificial tears and ocular lubricants (e.g., hyaluronic acid, trehalose, carboxymethylcellulose, glycol), blood products (autologous serum, platelet-rich plasma), products intended for short-term use (steroids, antibiotics), and products no longer in development. Studies of systemic medications (e.g., oral pilocarpine) and office-based therapies (e.g., thermal pulsation, intense-pulsed light, punctal plugs) were excluded.

2.3. Selection of studies and data extraction

Study selection was performed with the assistance of Covidence software [15]. All citations identified by the searches were uploaded into Covidence, and duplicates were automatically removed. Article titles and abstracts were screened by two independent reviewers and verified by a third. Identified articles were retrieved and reviewed to confirm eligibility.

Data were extracted for outcome measures of the signs (i.e., ocular surface staining, TBUT, Schirmer test score) and patient-reported symptoms (i.e., Ocular Surface Disease Index [OSDI], ocular symptom scores (e.g., eye dryness, eye burning/stinging) based on visual analog scale, Symptom Assessment in Dry Eye questionnaire, Dry Eye-Related Quality of Life Score) of DED. Adverse event (AE) profiles and study discontinuations due to ocular AEs were used to evaluate safety and tolerability. In addition, AE severity (mild, moderate, severe) was extracted when available.

3. Results

3.1. Systematic search results

A total of 5816 publications were identified from PubMed and Embase, 2109 duplicates were eliminated, and 3707 articles were screened by titles/abstracts. Of the screened publications, 165 were retrieved for full-text review and assessed for eligibility, and 107 were selected for inclusion in the review (Fig. 1). The included publications reported efficacy and safety results of topical pharmacologic treatments from RCTs; follow-up analyses of RCTs, such as pooled analysis, subgroup analysis, post hoc analysis, and long-term extension; and prospective observational studies. Geographically, these studies were conducted across the globe, primarily in the United States, Asia, and Europe.

3.2. Efficacy and safety data for topical pharmacologic treatments

3.2.1. Cyclosporine: an immunomodulator/anti-inflammatory agent

Cyclosporine, an immunomodulator with anti-inflammatory properties, is frequently used for management of DED [16]. Cyclosporine inhibits phosphatase activity of calcineurin, leading to reduced interleukin-2 production, which, in turn, suppresses T cell proliferation and differentiation [17]. In patients with DED, cyclosporine targets the chronic inflammatory cycle in the ocular surface by inhibiting the activation of T cells and preventing apoptosis of conjunctival epithelial and goblet cells [18–20]. Goblet cells have a critical role in ocular surface health by producing immunoregulatory factors such as transforming growth factor beta (TGF-β) and by releasing mucins that improve wetting of the cornea and stability of the tears [21]. Several cyclosporine-based ophthalmic products (at concentrations of 0.05 %–0.1 %) are approved for the treatment of DED, with geographic variation in product availability (Table 1) [22–48].

A 0.05 % cyclosporine anionic castor oil-in-water emulsion (Restasis; Allergan Inc, Irvine, CA, USA) was the first topical cyclosporine ophthalmic product approved by the US Food and Drug Administration (FDA) [20]. Two identical phase 3 studies conducted in the United States, which were combined for analysis, demonstrated improvements in Schirmer test score, corneal staining, blurred vision, and concomitant artificial tear use after 6 months of treatment compared with the vehicle

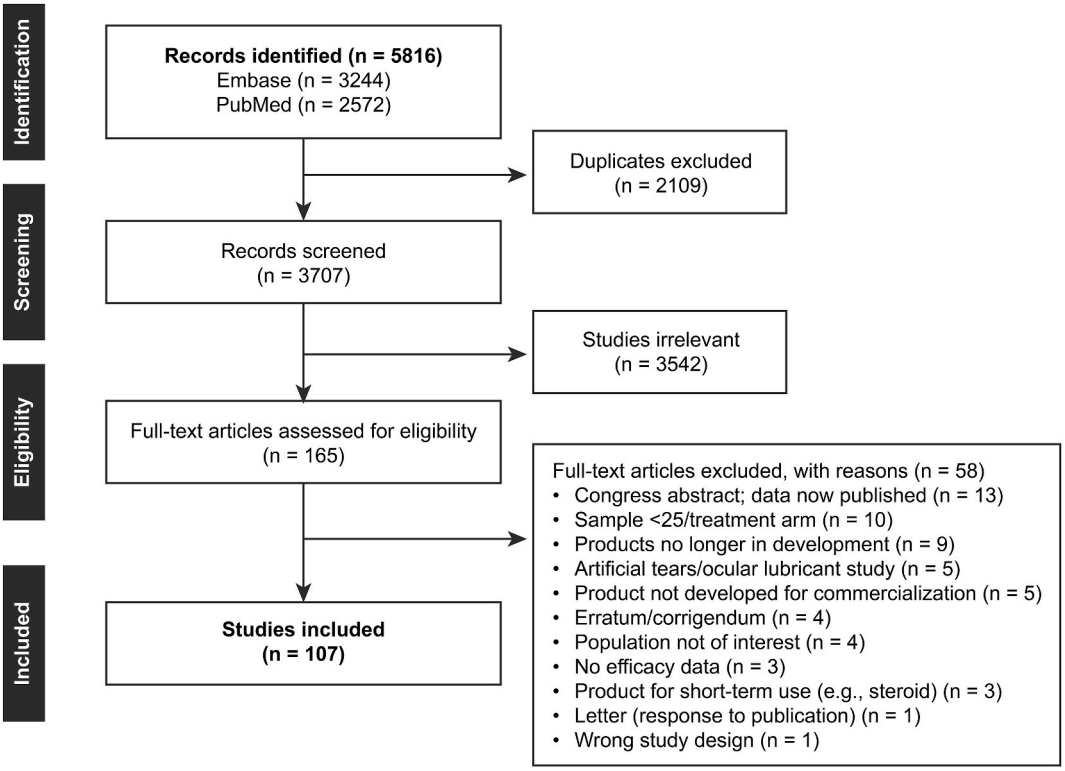

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

control [23]. No statistically significant between-group differences were observed for other DED symptoms (i.e., dryness, sandy/gritty feeling, burning/stinging, pain) [23]. Other studies conducted in the United States and Asia showed improvements in signs (e.g., corneal staining, Schirmer test) and symptoms (e.g., dryness, sandy/gritty feeling) of DED relative to baseline [25,29] or compared with vehicle control [28].

Because cyclosporine is a hydrophobic molecule with low aqueous solubility, various delivery systems have been developed to improve its ocular delivery and bioavailability [20]. Several of these products also use higher concentrations of cyclosporine, at 0.09 % or 0.1 %. A clear, aqueous nanomicellar solution of 0.09 % cyclosporine (Cequa; Sun Pharmaceutical, Cranbury, NJ, USA), approved in the United States and Europe, demonstrated significantly decreased corneal staining (beginning at day 28 [the first assessment timepoint]) and conjunctival staining (beginning at day 42 or 56) and significantly increased Schirmer test score (assessed at day 84) compared with vehicle in phase 3 trials [31,33], including post hoc analyses of Schirmer test scores in patient subgroups with greater baseline disease severity (baseline Schirmer test score <5 or <10 mm) [38,39]. However, reductions in the mean global symptom score were similar for cyclosporine 0.09 % and the vehicle control [38,39]. A 0.1 % cyclosporine cationic emulsion (Ikervis; Santen Pharmaceutical, Osaka, Japan), approved for DED in Europe, Asia, and Australia, demonstrated significant reductions in corneal staining and a biomarker of ocular surface inflammation (human leukocyte antigen−DR [HLA-DR] expression) in 6-month, randomized vehicle-controlled trials [40,41], with sustained improvements observed in longer-term, open-label studies [42,44]. A nonaqueous 0.1 % cyclosporine solution, which includes the semifluorinated alkane (SFA) perfluorobutylpentane as vehicle (CyclASol or Vevye; Novaliq, Heidelberg, Germany), was approved in the United States and recently also in Europe. In phase 3 trials, nonaqueous cyclosporine 0.1 % was superior to vehicle for reducing corneal staining [47,48]. The primary symptom endpoint (OSDI score [47] or eye dryness [48]) was not met in either study; however, one study found greater reductions in eye dryness (as a secondary endpoint) for nonaqueous 0.1 % cyclosporine versus vehicle [47].

Other novel cyclosporine formulations include a 0.05 % cyclosporine nanoemulsion (Zirun; Shenyang Xingqi Pharmaceutical, Shenyang, China) available in China [49,50], 0.05 % cyclosporine nanoemulsions (Clacier; Huons, Seongnam, South Korea; and TJ Cyporin N; Taejoon Pharmaceutical, Seoul, South Korea) available in South Korea [51,52], and a 0.05 % cyclosporine micellar nanoparticle emulsion (SGN-101; SGN Nanopharma, Tampa, FL, USA) available in India [53].

Most AEs reported for these cyclosporine formulations were of mild or moderate intensity [23,31,33,40,41,47,48]. In vehicle-controlled trials of 0.05 % cyclosporine emulsion, 0.09 % cyclosporine solution, and 0.1 % cyclosporine emulsion, the most common ocular AEs in cyclosporine-treated patients (15 %–30 %) were instillation site pain, ocular burning, or ocular irritation; 3 %–13 % of patients discontinued study participation because of AEs [23,31,33,40,41]. For the nonaqueous 0.1 % cyclosporine solution, the most common AEs were instillation-site reactions (3 %–10 %); the discontinuation rate due to AEs was 0.5 %–2 % [47,48].

3.2.2. *Non-cyclosporine anti-inflammatory agents*

Lifitegrast ophthalmic solution 5 % (Xiidra; Bausch + Lomb, Bridgewater, NJ, USA), approved in July 2016 in the United States, is a lymphocyte function-associated antigen 1 (LFA-1) antagonist (Table 2) [54–60]. Lifitegrast inhibits the interaction between cell surface protein LFA-1 integrin and its ligand intercellular adhesion molecule 1, which blocks recruitment and activation of T cells and inhibits secretion of inflammatory cytokines, thereby interrupting the inflammatory cascade involved in the pathogenesis of DED [61,62].

Across phase 3 studies (OPUS-1, OPUS-2, OPUS-3) conducted in the United States, lifitegrast demonstrated significant improvements compared with placebo in corneal staining and eye dryness, although results varied between studies, with OPUS-1 showing a significant reduction in the primary sign endpoint, OPUS-2 showing significant reduction in the primary symptom endpoint, and OPUS-3 confirming the findings of symptom improvement found in OPUS-2 [55–57]. The

Table 1
Summary of efficacy in clinical trials of cyclosporine products.

Study, Population, and Design	Treatment(s)	Signs	Symptoms
0.05 % cyclosporine anionic castor oil-in-water emulsion (Restasis; Allergan, USA)			
Stevenson D et al., 2000 [22] • Adults ≥21 y with DED (n = 162) • Ph 2, MC, DM, R, VC (USA)	Cyclosporine 0.05 % (n = 31), 0.1 % (n = 32), 0.2 % (n = 34), 0.4 % (n = 32) vs VC (n = 33) BID for 12 wks	Moderate-to-severe DED subset (n = 90): • Improvements vs baseline in conjunctival rose bengal staining and superficial punctate keratitis at week 4 • 0.1 % – most consistent improvement in objective and subjective endpoints • 0.05 % – most consistent improvement in patient symptoms • No clear dose-response relationship	Moderate-to-severe DED subset (n = 90): • Improvements vs baseline in dryness (week 4) and OSDI scores (week 12), and vs baseline (week 4) and VC (week 12) in sandy or gritty feeling
Sall K et al., 2000 [23] • Adults with moderate to severe DED (n = 877) • Ph 3, MC, DM, R, VC (USA)	Cyclosporine 0.05 % (n = 293) and 0.1 % (n = 292) vs VC (n = 292) BID for 6 months	• Improvement vs VC in change from baseline in corneal staining (P ≤ 0.044 for both doses at month 4 and P = 0.008 for 0.05 % dose at month 6) and STS (P = 0.009 for 0.05 % at month 3 and P ≤ 0.05 both doses at month 6)	• Improvement vs VC in change from baseline in blurred vision and concomitant artificial tear use (P ≤ 0.014 for 0.05 % at month 6)
Stonecipher K et al., 2005 [24] • Pts with DED (n = 5884) • MC, pt survey (USA)	Cyclosporine 0.05 % before vs 30-day and 60-day after treatment	• Not evaluated	• Improvements vs baseline in symptom severity and activity impairments at 30 and 60 days after treatment (P < 0.001) • Onset of relief within 1 wk in 32 % and within 3 wks in 73 % of pts • Decreased use of artificial tears in ≥60 % of pts at 30 and 60 days after treatment
Perry HD et al., 2008 [25] • Adults ≥21 y with DED nonresponsive to artificial tears (n = 158) • MC, prospective (USA)	Cyclosporine 0.05 % BID in pts with mild (n = 62), moderate (n = 69), and severe (n = 27) DED for 3–16 months	• Improvement vs baseline in TBUT, CFS, conjunctival lissamine green staining, and STS in mild, moderate, and severe subgroups (P < 0.05, except STS in mild subgroup); follow-up duration 3–16 months	• Improvement vs baseline in OSDI scores (assessed after 3 months) overall and in mild, moderate, and severe subgroups (P < 0.015)
Willen CM et al., 2008 [26] • Contact lens wearers with DED (n = 44) • SC, DM, PBO-C (USA)	Cyclosporine 0.05 % (n = 22) vs PBO (artificial tears; n = 22) BID for 3 months	• No difference vs PBO in corneal staining, TBUT, and STS at 3 months	• No difference vs PBO in OSDI and NEI-RQL-42 at 3 months
Su MY et al., 2011 [27] • Adults ≥21 y with DED in remission after cyclosporine 0.05 % BID for >1 year (n = 100) • SC, R, M, prospective (USA)	Continue cyclosporine 0.05 % BID (n = 50) vs decrease dosage to QD (n = 50) for 6 months	• Improvement with QD vs baseline in TBUT (P = 0.0003) and conjunctival lissamine green staining score (P = 0.024) and no change with QD vs baseline in CFS and STS at 6 months • No difference with QD vs BID in TBUT, conjunctival lissamine green, CFS, and STS at 6 months	• No change with QD vs baseline in OSDI at 6 months • Improvement with QD vs BID in OSDI at 6 months (P < 0.05)
Chen M et al., 2010 [28] • Adults 18–65 y with moderate to severe DED (n = 233) • MC, DM, R, VC (China)	Cyclosporine 0.05 % (n = 116) vs VC (n = 117) BID for 8 wks	• Improvement vs VC in change from baseline in corneal staining (P ≤ 0.05 at wks 4 and 8) and STS (P = 0.035 at wk 8)	• Improvement vs VC in change from baseline in total symptom score (P < 0.01 at wks 2, 4, 8), ocular dryness (P = 0.04 at wk 8), and foreign body sensation (P ≤ 0.02 at wks 4 and 8)
Byun Y et al., 2011 [29] • Adults >18 y with moderate to severe DED nonresponsive to conventional treatment (n = 392) • M, OL, prospective (Korea)	Cyclosporine 0.05 % BID + artificial tears for 3 months	• Improvement vs baseline in conjunctival staining and STS at 3 months (P < 0.01)	• Improvement vs baseline in ocular symptom scores of stinging/burning, itching, sandiness/grittiness, blurred vision, light sensitivity, pain or soreness and use of artificial tears at 3 months (P < 0.0001)
Shah S et al., 2017 [30] • Pts with DED (n = 90) • SC, R, active control (Nepal)	Cyclosporine 0.05 % BID (n = 45) vs CMC 0.5 % QID (n = 45) for 6 wks	• No between-treatment difference in improvement of TBUT and STS at wk 6 • Improvement in CFS at wk 6 with cyclosporine (P < 0.001)	• No between-treatment difference in improvement of eye symptoms at wk 6
0.09 % cyclosporine clear, aqueous nanomicellar solution (Cequa; Sun Pharmaceutical, USA)			
Tauber J et al., 2018 [31] • Adults ≥18 y with DED for ≥6 months (n = 455) • Ph 2b/3, MC, DM, R, VC (USA) Schechter 2022 [32]: Day 14 analysis	Cyclosporine 0.09 % (n = 152) or 0.05 % (n = 151) vs VC (n = 152) BID for 12 wks	• Improvement with both doses vs VC in change from baseline in conjunctival staining, tCFS, and STS at wk 12 (P ≤ 0.024) • [Post hoc] Improvement with 0.09 % vs VC in percentage of pts with ≥10 mm improvement in STS at wk 12 (P = 0.007) • Numerical improvement with 0.09 % vs VC in change from baseline in conjunctival staining, tCFS, and TBUT at 14 days	• No between-treatment difference in improvements in SANDE total global symptom score from baseline to wk 12 Numerical improvement with 0.09 % vs VC in change from baseline in SANDE total global symptom score at 14 days
Goldberg DF et al., 2019 [33] • Adults ≥18 y with DED for ≥6 months (n = 744) • Ph 3, MC, DM, R, VC (USA) • Sheppard 2021 [34] worst-eye efficacy analysis	Cyclosporine 0.09 % (n = 371) vs VC (n = 373) BID for 12 wks	• Improvement vs VC in percentage of pts with ≥10 mm improvement in STS at wk 12 (P < 0.001) • Improvement vs VC in change from baseline in total conjunctival lissamine green staining at wks 8 and 12 and tCFS at wks 4, 8, and 12 (P < 0.01) • Improvement vs VC in % of eyes with clear central corneas at wks 4, 8, and 12 (P ≤ 0.04) • In the worse eye: improvement vs VC in change from baseline in total conjunctival lissamine green staining at wks 8 and 12 and % of pts with clear central corneas at wks 4 and 12 (P < 0.02)	• No between-treatment difference in improvements in SANDE total global symptom score from baseline to wk 12

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Table 1 (*continued*)

Study, Population, and Design	Treatment(s)	Signs	Symptoms
Rajpoot M et al., 2022 [35] • Adults >18 y with DED (n = 450) • MC, DM, R (India)	Cyclosporine 0.05 % emulsion (n = 225) vs cyclosporine 0.09 % nanomicellar aqueous solution (n = 225) BID for 3 months	• Improvement with cyclosporine 0.09 % vs 0.05 % in change from baseline in tear film osmolarity (P < 0.001), conjunctival lissamine green staining score (P = 0.002), CFS (P = 0.011), and STS (P = 0.001) at 3 months, but not TBUT	• No between-treatment difference in improvement in dry eye symptoms at 3 months
Smyth-Medina R et al., 2019 [36] Malhotra R et al., 2019 [37] • Pts pooled from ph 2b/3 and ph 3 studies	Cyclosporine 0.09 % (n = 523) vs VC (n = 525) BID for 12 wks	• Improvement vs VC in % of eyes with ≥10 mm improvement in STS, % of eyes with >50 % increase in STS, and % change from baseline in STS at wk 12 (P < 0.0001) • Improvement vs VC in change from baseline in total conjunctival staining at wks 4, 8, and 12 (P ≤ 0.03) – Improvement vs VC in change from baseline in the inferior and superior zones at wks 4, 8, and 12 and in the lateral zone at wks 8 and 12 • Improvement vs VC in change from baseline in tCFS at wks 4, 8, and 12 (P ≤ 0.001) - Improvement vs VC in corneal clearing in the central, inferior, lateral, and medial zones at wks 4, 8, and 12 (except for the lateral zone at wk 4)	• No between-treatment difference in improvements in SANDE total global symptom score and symptoms of dryness and irritation from baseline to wk 12
Sheppard J et al., 2020 [38] • Pts with baseline STS <10 mm from pooled ph 2b/3 and ph 3	Cyclosporine 0.09 % (n = 311) vs VC (n = 310) BID for 12 wks	• In subgroup with baseline STS <10 mm: improvement vs VC in % of eyes with ≥10 mm improvement in STS and change from baseline in STS at wk 12 (P ≤ 0.0001)	• In subgroup with baseline STS <10 mm: no between-treatment difference in improvements in SANDE total global symptom score from baseline to wk 12
Toyos M et al., 2022 [39] • Pts with baseline STS <5 mm from pooled ph 2b/3 and ph 3	Cyclosporine 0.09 % (n = 133) vs VC (n = 113) BID for 12 wks	• In subgroup with baseline STS <5 mm: improvement vs VC in % of worse eyes with ≥10 mm improvement in STS and change from baseline in STS in the worse eye at wk 12 (P ≤ 0.04)	• Not evaluated in this analysis
0.1 % cyclosporine cationic emulsion (Ikervis; Santen, Japan)			
Leonardi A et al., 2016 [40] • Adults ≥18 y with severe keratitis and severe DED (n = 245) • SANSIKA: Ph3, MC, DM, R, VC (Europe)	Cyclosporine 0.1 % (n = 154) vs VC (n = 91) QD for 6 months	• Improvement vs VC in change from baseline in CFS (P = 0.037) and conjunctival surface inflammation (HLA-DR expression; P = 0.021) at 6 months	• No between-treatment difference in improvement in OSDI at 6 months
Baudouin C et al., 2017 [41] • Adults with persistent moderate to severe DED (n = 492) • SICCANOVE: Ph 3, MC, DM, R, VC (Europe)	Cyclosporine 0.1 % (n = 242) vs VC (n = 250) QD for 6 months	• Improvement vs VC in change from baseline in CFS at 1 month (P = 0.002), 3 months (P = 0.030), and 6 months (P = 0.009)	• Improvement vs VC in % of pts with ≥25 % improvement in ocular discomfort at 6 months (P = 0.048), but no between-treatment difference in the change in global score of ocular discomfort
Baudouin C et al., 2017 [42] • Pts treated in 6-month OL extension (n = 207) • SANSIKA (part 2)	Two groups: continued cyclosporine 0.1 % (n = 128) or switched from VC to cyclosporine 0.1 % (n = 79) for additional 6 months	• Continuous improvements in CFS and % of pts with corneal clearing in both groups between 6 and 12 months • Conjunctival surface inflammation (HLA-DR expression): reduction maintained in continuation group and expression reduced in switch group between 6 and 12 months	• Continuous improvements in OSDI and global symptom scores in both groups between 6 and 12 months
Labetoulle M et al., 2018 [43] • Pts with CFS ≤2 after ≥6 months of treatment (n = 63) • Post-SANSIKA: 24-month OL extension	Discontinued cyclosporine 0.1 % after achieving CFS ≤2 (n = 62)	• Relapse rate 38.7 % during the 2-year follow-up post-SANSIKA (34.9 % in continuation group [≥12 months of cyclosporine 0.1 %] and 47.4 % in VC switch group [≥6 months of cyclosporine 0.1 %]) • Per year, pts spent median time of 8.5 wks at CFS score 1, 14.7 wks at CFS 2, 2.0 wks at CFS 3, and 0 wks at CFS 4 or 5	• Not evaluated
Geerling G et al., 2022 [44] • Adults >18 y with severe keratitis and DED insufficiently controlled by artificial tears (n = 472) • PERSPECTIVE: MC, prospective, Obs (Europe)	Cyclosporine 0.1 % QD for 12 months	• Improvement vs baseline in CFS score, severity of eyelid and conjunctival erythema, and TBUT at wk 4 and through 12 months (P < 0.001)	• Improvement vs baseline in severity of ocular symptoms (foreign body sensation, burning/stinging, itching, eye pain, blurred vision, and photophobia) at wk 4 and through 12 months (P < 0.001)
Leonardi A et al., 2019 [45] • All DED pts (n = 734), severe DED (n = 319), SS (n = 269), and SS with severe DED (n = 130) pooled from 2 ph3 studies	Cyclosporine 0.1 % (n = 395) vs VC (n = 339) QD for 6 months	• Improvements vs VC in % of CFS–OSDI responders (improvement in both CFS by ≥ 2 grades from baseline and OSDI score by ≥ 30 %) in the overall population (*P* = 0.015), and in the severe DED (P = 0.038) and SS with severe DED (P = 0.030) subgroups at 6 months • Improvements vs VC in reducing median HLA-DR expression at 6 months (P = 0.002)	
0.1 % cyclosporine SFA-based nonaqueous solution (Vevye; Novaliq, Germany)			
Wirta DL et al., 2019 [46] • Adults >18 y with moderate to severe DED not responding to artificial tears (n = 207) • Ph2, MC, DM, R, VC (USA)	Nonaqueous cyclosporine 0.05 % (n = 51) and 0.1 % (n = 51) vs VC (n = 52) and OL cyclosporine 0.05 % (Restasis; n = 53) BID for 16 wks	• Improvement with nonaqueous cyclosporine 0.05 % or 0.1 % vs OL Restasis in change from baseline in tCFS and cCFS at wk 4 (P ≤ 0.05) • Improvement with nonaqueous cyclosporine 0.1 % vs OL Restasis in change from baseline in tCFS at wk 12 (P ≤ 0.05) and vs vehicle in change from baseline in cCFS at wk 4 (P ≤ 0.05)	• Numerical improvement with nonaqueous cyclosporine 0.1 % vs VC and no difference vs OL Restasis in change from baseline in total OSDI at wks 12 and 16

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Table 1 (*continued*)

Study, Population, and Design	Treatment(s)	Signs	Symptoms
Sheppard JD et al., 2021 [47] • Adults ≥18 y with DED not responding to artificial tears (n = 328) • ESSENCE: Ph 2b/3, MC, DM, R, VC (USA)	Nonaqueous cyclosporine 0.1 % (n = 162) vs VC (n = 166) BID for 12 wks	• Improvement vs VC in change from baseline in tCFS at wks 2, 4, 8, and 12 (P ≤ 0.04) – Similar pattern of improvement for cCFS • Improvement vs VC in change from baseline in conjunctival lissamine green staining over time, starting at wk 4 (P = 0.0003)	• Improvement vs VC in change from baseline in EDS and frequency of dryness at wk 4 (P = 0.03) • No between-treatment difference in improvement in total OSDI at wk 4
Akpek EK et al., 2023 [48] • Pts with DED (n = 834) • ESSENCE-2: Ph 3, MC, DM, R, VC (USA)	Nonaqueous cyclosporine 0.1 % (n = 423) vs VC (n = 411) BID for 4 wks	• Improvement vs VC in change from baseline in tCFS (P = 0.03), % of tCFS responders (≥3 grade reductions; P < 0.001), conjunctival lissamine green staining (P = 0.001), cCFS (P = 0.04), % of cCFS responders (≥1 grade reductions; P = 0.04) at wk 4	• No between-treatment difference in improvement in EDS and blurred vision at wk 4

BID, twice daily; cCFS, central corneal fluorescein staining; CFS, corneal fluorescein staining; CMC, carboxymethyl cellulose; DED, dry eye disease; DM, double-masked; EDS, eye dryness score; HLA-DR, human leukocyte antigen-antigen D related; M, masked; MC, multi-center; NEI-RQL-42, National Eye Institute Refractive Error Quality of Life Instrument; Obs, observational; OL, open-label; OSDI, Ocular Surface Disease Index; PBO, placebo; PBO-C, placebo-controlled; Ph, phase; pts, patients; QD, once daily; QID, four times daily; R, randomized; SANDE, Symptom Assessment in Dry Eye; SC, single center; SFA, semifluorinated alkanes; SS, Sjögren's syndrome; STS, Schirmer test score; TBUT, tear film break up time; tCFS, total corneal fluorescein staining; VC, vehicle control; wk, week; y, year.

severity of patient-reported eye dryness was relatively low at baseline in the study that failed to meet the primary symptom endpoint (OPUS-1) [55]. A post hoc analysis of clinical trial data from OPUS-2 and OPUS-3 revealed that a significantly greater proportion of patients experienced clinically meaningful improvements in corneal staining and eye dryness with lifitegrast compared with placebo [60]. Throughout a year-long RCT, the adjunctive use of artificial tears was less common in the lifitegrast group compared with the placebo group [58].

Across clinical trials of lifitegrast, in which treatment duration ranged from 12 weeks to 1 year, most AEs were mild or moderate (1.0 % of patients had a severe ocular AE), and no serious ocular AEs were reported [63]. The most common ocular AE with lifitegrast was instillation site irritation (15.2 %), and the most common nonocular AE was dysgeusia (14.5 %) [63]. After instillation, drop comfort scores with lifitegrast quickly improved and approached placebo levels within 3 min [64]. Discontinuations due to AEs occurred in 7 % of patients receiving lifitegrast [63].

SKQ-1 (Visomitin, Mitotech LLC, Moscow, Russia) is a mitochondrial-targeted antioxidant approved for use as an eye drop in Russia, with positive findings from an RCT conducted in Russia and Ukraine [65]. RCTs conducted in the United States failed to meet their primary endpoints [66,67].

3.2.3. *Mucin secretion stimulators*

Mucins, primarily produced by corneal and conjunctival epithelia, form a gel that preserves corneal surface wettability and maintains a healthy tear film [8]. Alteration of mucin in the tear film has been implicated in the pathogenesis of DED [68,69]. Diquafosol ophthalmic solution 3 % (Diquas; Santen Pharmaceutical, Osaka, Japan), approved in Japan, China, South Korea, and other Asian countries (Table 3) [70–80], is a $P2Y_2$ receptor agonist that acts on conjunctival tissues to promote the secretion of aqueous tears and mucins [81,82].

In a phase 2 study conducted in Japan, diquafosol 3 % significantly improved corneal and conjunctival staining and dry eye sensation symptoms versus placebo [70]. In phase 3 studies (one in Japan, one in China/Singapore), ocular surface staining was significantly reduced from baseline and diquafosol 3 % was superior to 0.1 % hyaluronate control for improvement in rose bengal (but not fluorescein) staining [71,75]. Large phase 4 and real-world observational studies in China, South Korea, and Japan confirmed the clinical utility of diquafosol 3 %, either as monotherapy or in combination with cyclosporine or other topical ocular drops [73,74,77–80].

No serious AEs were reported in diquafosol clinical trials [70,71,75]. In real-world studies, AEs were reported in 6 % and 11 % of patients, respectively, during short-term and longer-term treatment [73,77,80]. The most common ocular AEs across clinical trials and real-world studies of diquafosol were eye irritation (2 %–12 %) and eye discharge (3 %–5 %) [70,71,75,77]. Rates of study discontinuation due to AEs were low in RCTs (1 %–4 %) [70,71,75].

Rebamipide 2 % (Mucosta; Otsuka Pharmaceutical, Tokyo, Japan), approved in Japan (Table 3) [83–88], is a quinolinone derivative that increases mucin production [89,90]. A phase 3 study in Japan demonstrated greater efficacy of rebamipide compared with 0.1 % sodium hyaluronate in improving corneal and conjunctival staining and symptoms of foreign body sensation and ocular pain [84]. A randomized placebo-controlled study found significant improvements in corneal staining, TBUT, and eye dryness for rebamipide versus placebo [83]. Findings from single-center studies in India and a small study in Japan suggest that rebamipide may be more effective than sodium hyaluronate 0.1 % [87] or cyclosporine 0.1 % [86], and similar to diquafosol 3 % [85] for improving the signs and symptoms of DED. No serious treatment-related AEs were reported with rebamipide; the most common AE was dysgeusia (10 %–16 %) [83,84].

3.2.4. *Tear evaporation inhibitor*

Perfluorohexyloctane (PFHO) ophthalmic solution (Miebo; Bausch + Lomb, Bridgewater, NJ, USA) is a nonaqueous, steroid-free, preservative-free, FDA-approved treatment for DED (Table 4) [91–96]. A physiologically inert SFA with amphiphilic properties [97], PFHO forms a monolayer at the air-liquid interface of the tear film to inhibit evaporation and facilitate ocular surface healing [98]. PFHO (NovaTears; Novaliq, Heidelberg, Germany) was first approved in Europe as a CE product; however, studies did not meet the selection criteria for inclusion in this review.

In phase 2 and phase 3 trials of PFHO conducted in the United States, all enrolled patients had clinical signs of MGD [91,93,94], the most common cause of evaporative DED [13]. In these studies, PFHO consistently improved signs (e.g., corneal staining) and symptoms (e.g., eye dryness, burning/stinging) of DED compared with saline solution control, with significant between-group differences seen as early as week 2 [91,93,94]. Sustained improvements in DED signs and symptoms were observed in a 52-week open-label extension study [95]. A randomized, saline-controlled study conducted in China confirmed and extended the findings from the US studies [96]. Across controlled trials of PFHO, most ocular AEs were mild or moderate and no serious ocular AEs were reported; 0–3 % of patients discontinued treatment because of AEs [91,93,94,96]. The open-label extension study confirmed that PFHO maintained a low rate of ocular AEs for 1 year; there were no serious ocular AEs, and 2 % of patients discontinued treatment because of ocular AEs [95]. The most common ocular AE across PFHO studies was blurred

Table 2
Summary of efficacy in clinical trials of lifitegrast.

Study, Population, and Design	Treatment(s)	Signs	Symptoms
Lifitegrast ophthalmic solution 5 % (Xiidra, Bausch + Lomb, Bridgewater, NJ, USA)			
Semba CP et al. (2012) [54] • Adults ≥18 y with DED (n = 230) • Ph 2, MC, DM, R, PBO-C (USA)	Lifitegrast 0.1 % (n = 57), 1 % (n = 57), 5 % (n = 58) vs PBO (n = 58) BID for 12 wks	• Improvements vs PBO in change from baseline in iCFS at wk 12 (P < 0.05 for 1 % and 5 % doses vs PBO) • Improvements vs PBO in change from baseline in STS at wk 2 (P < 0.05 for 5 % dose vs PBO)	• Improvements vs PBO in change from baseline in visual-related OSDI subscale score at wk 2 and wk 12 (P < 0.05 for 1 % and 5 % doses vs PBO)
Sheppard JD et al. (2014) [55] • Adults ≥18 y with DED (n = 588) • OPUS-1: Ph 3, MC, DM, R, PBO-C (USA)	Lifitegrast 5 % (n = 293) vs PBO (n = 295) BID for 12 wks	• Improvements vs PBO in change from baseline in CFS (inferior, P = 0.0007; superior, P = 0.0392; total, P = 0.0148) and conjunctival lissamine green staining (nasal, P = 0.0039; total, P = 0.0086) at wk 12 – Improvements in nasal (P = 0.0018) and total lissamine green scores (P = 0.0149) observed at wk 2	• No between-treatment difference in change from baseline in visual-related OSDI subscale score at wk 12 • Improvements vs PBO in mean ocular discomfort score (P = 0.0273) and EDS (P = 0.0291) at wk 12
Tauber J et al. (2015) [56] • Adults ≥18 y with DED (EDS ≥40, recent artificial tear use) (n = 718) • OPUS-2: Ph 3, MC, DM, R, PBO-C (USA)	Lifitegrast 5 % (n = 358) vs PBO (n = 360) BID for 12 wks	• No between-treatment difference in change from baseline in inferior and total corneal and nasal conjunctival lissamine green staining at wk 12	• Improvements vs PBO in change from baseline in EDS at wk 12 (P < 0.0001) • Improvements vs PBO in change from baseline in ocular discomfort score (nominal P = 0.0005) and eye discomfort score (nominal P < 0.0001) at wk 12
Holland EJ et al. (2017) [57] • Adults ≥18 y with DED (EDS ≥40, recent artificial tear use) (n = 711) • OPUS-3: Ph 3, MC, DM, R, PBO-C (USA)	Lifitegrast 5 % (n = 355) vs PBO (n = 356) BID for 12 wks	• Not evaluated	• Improvements vs PBO in change from baseline in EDS at wk 2 (P < 0.0001), wk 6 (P < 0.0001), and wk 12 (P = 0.0007) • Improvements vs PBO in change from baseline at wk 6: – Eye discomfort (nominal P = 0.0048) – Foreign body sensation (nominal P = 0.0418) – Itching (nominal P = 0.0318)
Donnenfeld ED et al. (2016) [58] • Adults ≥18 y with DED • SONATA: Ph 3, MC, DM, R, PBO-C (USA)	Lifitegrast 5 % (n = 220) vs PBO (n = 111) BID for 1 year	• Not evaluated	• Percentage of pts not using artificial tears higher for lifitegrast vs PBO while on therapy
Holland EJ et al. (2016) [59] • Post-hoc analyses: OPUS-1 subgrouped by baseline EDS <40 or ≥ 40) • OPUS-2 EDS early timepoint assessment	Lifitegrast 5 % vs PBO BID for 12 wks	• OPUS-1 subgroup with mild-to-moderate symptomatology (baseline EDS <40): improvements vs PBO in change from baseline in iCFS at wk 12 (P < 0.0001) • Improvement more pronounced than in the overall population	• OPUS-1 subgroup with moderate-to-severe symptomatology (baseline EDS ≥40, recent artificial tear use): improvements vs PBO in change from baseline in EDS at wk 12 (P = 0.0178) • OPUS-2 recruited pts with moderate-to-severe symptomatology: improvements vs PBO in change from baseline in EDS at wk 2 (P = 0.0003)
Holland EJ et al. (2021) [60] • Pts subgrouped by baseline iCFS (≤1.5, >1.5) and baseline EDS (<60, ≥60) • Pooled analysis of OPUS-2 and OPUS-3	Lifitegrast 5 % (n = 713) vs PBO (n = 716) BID for 12 wks	• Increase vs PBO in percentage of pts with ≥ 1-point improvement in iCFS at wk 12 (P = 0.02) • Increase vs PBO in percentage of pts with ≥ 3-point improvement in tCFS at wk 12 (P = 0.01) • Subgroup with baseline iCFS >1.5 and EDS ≥60 had the greatest improvement vs PBO in sign (≥3-point improvement in tCFS) and each symptom above and the following composite signs and symptoms at wk 12: – ≥ 30 % improvement in EDS and ≥ 1-point improvement in iCFS (P < 0.001 vs PBO) – ≥ 30 % improvement in EDS and ≥ 3-point improvement in tCFS (P < 0.001 vs PBO) – ≥ 30 % improvement in global symptom score and ≥ 1-point improvement in iCFS (P < 0.001 vs PBO) – ≥ 30 % improvement in global symptom score and ≥ 3-point improvement in tCFS (P = 0.001 vs PBO)	• Increase vs PBO in percentage of pts with ≥30 % improvement in EDS at wk 12 (P < 0.001) • Increase vs PBO in percentage of pts with ≥30 % improvement in global symptom score at wk 12 (P < 0.001)

BID, twice daily; CFS, corneal fluorescein staining; DED, dry eye disease; DM, double-masked; EDS, eye dryness score; iCFS, inferior corneal fluorescein staining; MC, multi-center; OSDI, Ocular Surface Disease Index; PBO, placebo; PBO-C, placebo-controlled; Ph, phase; pts, patients; R, randomized; STS, Schirmer test score; tCFS, total corneal fluorescein staining; wk, week; y, year.

Table 3
Summary of efficacy in clinical trials of diquafosol and rebamipide.

Study, Population, and Design	Treatment(s)	Signs	Symptoms
Diquafosol ophthalmic solution 3 % (Diquas, Santen Pharmaceutical, Osaka, Japan)			
Matsumoto Y et al. (2012) [70] • Adults ≥20 y with DED (n = 286) • Ph 2, MC, DM, R, PBO-C (Japan)	Diquafosol 1 % (n = 96) vs 3 % (n = 96) vs PBO (n = 94) 6 times a day for 6 wks	• Improvement in CFS score with both doses vs PBO at wk 4 ($P < 0.05$) and only with diquafosol 3 % vs PBO at wk 6 ($P = 0.005$) • Improvement with both doses vs PBO in rose bengal corneal and conjunctival staining scores at wks 4 and 6 ($P \leq 0.007$)	• Improvement in dry eye sensation symptom score with both doses vs PBO at wk 4 ($P < 0.05$) and only with diquafosol 1 % vs PBO at wk 6 ($P = 0.004$)
Takamura E et al. (2012) [71] • Adults ≥20 y with DED (n = 287) •Ph 3, MC, DM, R, active control (Japan)	Diquafosol 3 % 6 times a day (n = 144) vs sodium hyaluronate 0.1 % (n = 143) for 4 wks	• Non-inferiority of diquafosol vs sodium hyaluronate in improving CFS score from baseline to wk 4 • Superiority of diquafosol vs sodium hyaluronate in improving rose bengal corneal and conjunctival staining score from baseline to wk 4 ($P = 0.010$)	• Improvement with diquafosol vs sodium hyaluronate in symptom score of heaviness at wk 4 ($P = 0.033$)
Kamiya K et al. (2012) [72] • Adults ≥20 y with DED (sodium hyaluronate monotherapy insufficient) (n = 32) • MC, R, prospective study (Japan)	Diquafosol 3 % 6 times a day + sodium hyaluronate 0.1 % in one eye for 4 wks	• Improvements vs baseline at wk 4 in: –CFS and rose bengal corneal and conjunctival staining scores ($P = 0.02$) –TBUT ($P = 0.049$)	• Improvements vs baseline at wk 4 in subjective symptoms of dry eye sensation ($P = 0.004$), pain ($P = 0.02$), and foreign body sensation ($P = 0.02$)
Yamaguchi M et al. (2014) [73] • Pts with DED (no prior diquafosol) (n = 3196) • MC, OL, prospective, Obs (real-world) (Japan)	Diquafosol 3 % for 2 months 6 times a day (70 %) 4 times a day (22 %)	• Improvements vs baseline at 1 and 2 months ($P < 0.001$) in corneal and conjunctival fluorescein staining score and TBUT –Improvements observed regardless of the degree of severity according to the corneal and conjunctival fluorescein staining score or therapeutic pattern (±previous and concomitant medications)	• Improvements vs baseline at 1 and 2 months ($P < 0.001$) in subjective symptom total score –Improvements observed regardless of the degree of severity or therapeutic pattern
Yamaguchi M et al. (2015) [74] •Pts who met the Japanese criteria for DED diagnosis and received diquafosol as monotherapy (n = 965)		•Diquafosol monotherapy: Improvements vs baseline at 1 and 2 months ($P < 0.01$) in corneal and conjunctival fluorescein staining score and TBUT regardless of: –Contact lens use –Meibomian gland dysfunction –Conjunctivochalasis	•Diquafosol monotherapy: Improvements vs baseline at 1 and 2 months ($P < 0.01$) in subjective symptom total score regardless of: –Contact lens use –Meibomian gland dysfunction –Conjunctivochalasis
Gong L et al. (2015) [75] • Adults 21 to < 70 y with DED (n = 489) • MC, R, active control (China and Singapore)	Diquafosol 3 % 6 times a day (n = 241) vs sodium hyaluronate 0.1 % (n = 248) for 4 wks	• Non-inferiority of diquafosol vs sodium hyaluronate in improving CFS score from baseline to wk 4 • Superiority of diquafosol vs sodium hyaluronate in improving rose bengal staining scores from baseline to wk 4 ($P = 0.019$)	• Improvements vs baseline in subjective symptoms were found in both groups
Yang JM et al. (2015) [76] • Adults ≥18 y with moderate-severe DED (n = 60) • SC, NR, prospective study (South Korea)	Diquafosol 3 % 6 times a day (n = 29) vs cyclosporine 0.05 % BID (n = 31) for 3 months	• Improvements with diquafosol vs cyclosporine in tear clearance rate ($P = 0.002$) and corneal staining score ($P < 0.001$) at 1 month; no differences at 3 months • Improvements with diquafosol vs cyclosporine in TBUT at 1 and 3 months ($P < 0.001$) • Improvement with cyclosporine vs diquafosol in conjunctival staining score at 3 months ($P < 0.001$)	• Improvements with diquafosol vs cyclosporine in OSDI score ($P = 0.014$) at 1 month; no difference at 3 months
Ohashi Y et al. (2020) [77] • Pts with DED (no prior diquafosol) (n = 580) • MC, OL, Obs (real-world) (Japan)	Diquafosol 3 % for 12 months 6 times a day (70 %) 4 times a day (25 %)	• Improvement vs baseline at 3, 6, 9, and 12 months ($P < 0.001$) in: –Fluorescein staining scores (cornea, temporal conjunctiva, and nasal conjunctiva) –TBUT	• Improvements vs baseline in the DEQS overall summary score, ocular symptoms score, and impact on daily life score at 3, 6, 9, and 12 months ($P < 0.001$)
Eom Y et al. (2021) [78] • Adults ≥19 y with DED (n = 357) • MC, Obs (real-world) (South Korea)	Diquafosol 3 % 6 times a day for 8 wks Groups: Monotherapy (n = 196) Add: added to existing eye drop regimen (n = 150) Switch: replaced part of the existing medication (n = 11)	• TBUT increased from baseline to wk 4 and wk 8 in Monotherapy and Add groups ($P < 0.001$) –TBUT increased from baseline to wk 8 in Switch group ($P = 0.001$) • tCFS and conjunctival staining scores decreased from baseline to wk 4 and wk 8 in Monotherapy and Add groups ($P < 0.001$) –tCFS decreased from baseline to wk 8 in Switch group ($P < 0.05$)	• Improvement vs baseline in OSDI scores at wk 4 and wk 8 in Add and Monotherapy groups ($P < 0.001$), but not in the Switch group
Eom Y et al. (2022) [79] • Adults 19 to < 80 y with DED (n = 279) • MC, NR, Obs (general health care setting) (South Korea)	Diquafosol 3 % 6 times a day (n = 99) vs cyclosporine 0.1 % (n = 93) vs diquafosol + cyclosporine (n = 87) for 12 wks	• Both monotherapies and combination therapy improved TBUT, tCFS, and conjunctival staining scores from baseline to wk 12 (all $P < 0.0001$) • Change from baseline in TBUT was higher with combination therapy vs cyclosporine monotherapy ($P = 0.0011$)	• All 3 treatments improved from baseline to wk 4 and wk 12 (all $P < 0.0001$) in: – SANDE symptom frequency, severity, and combination evaluation scores – DEQS domain scores (impact on daily life, bothersome ocular symptoms, and questionnaire summary)

(*continued on next page*)

Table 3 (*continued*)

Study, Population, and Design	Treatment(s)	Signs	Symptoms
Wang W et al. (2023) [80] • Adults ≥18 y with DED (n = 3000) • Ph 4, MC, OL (real-world) (China)	Diquafosol 3 % 6 times a day for 1 month	• At wk 2 and wk 4: – Decrease in tCFS vs baseline (P < 0.05) in overall population and all age and sex subgroups – Increase in TBUT vs baseline (P < 0.05) in overall population and all age and sex subgroups – Increase in STS results vs baseline (P < 0.05) in all age and sex subgroups	• Not evaluated
Rebamipide 2 % (Mucosta, Otsuka Pharmaceutical, Tokyo, Japan)			
Kinoshita S. et al. (2012) [83] • Adults ≥20 y with DED for >20 months (n = 308) • Ph 2, MC, DM, R, PBO-C (Japan)	Rebamipide 1 % (n = 103) and 2 % (n = 102) vs PBO (n = 103) QID for 4 wks	• Improvement vs PBO in change from baseline to LOCF in CFS and conjunctival lissamine green staining scores (P < 0.001 for both doses vs PBO) and TBUT (*P* < 0.05 for both doses vs PBO)	• Improvement vs PBO in change from baseline to LOCF in symptom scores of foreign body sensation, dryness, photophobia, eye pain, and blurred vision (P ≤ 0.025 for both doses vs PBO [except 1 % vs PBO for photophobia])
Kinoshita S et al. (2013) [84] • Adults ≥20 y with DED for >20 months (n = 188) • Ph 3, MC, M, R, active control (Japan)	Rebamipide 2 % QID (n = 93) vs sodium hyaluronate 0.1 % (n = 95) for 4 wks	• Non-inferiority and improvement (P = 0.006) vs sodium hyaluronate in change from baseline to LOCF in CFS score • Superiority vs sodium hyaluronate in change from baseline to LOCF in conjunctival lissamine green staining (P < 0.001)	• Improvement vs sodium hyaluronate in symptoms of foreign body sensation (P = 0.004) and eye pain (P = 0.014) at LOCF
Shimazaki J et al. (2017) [85] • Adults 20–60 y with DED (n = 67) • MC, OL, R, prospective (Japan)	Rebamipide 2 % QID (n = 33) vs diquafosol 3 % 6 times a day (n = 34) for 8 wks	• No significant difference between treatments in improvements in TBUT from baseline to wks 2 and 4	• No significant difference between treatments in improvements in DEQS scores from baseline to wks 2, 4, and 8
Patil A et al. (2019) [86] • Adults ≥50 y with DED for ≥2 months (n = 80) • SC, R, active control, prospective (India)	Rebamipide 2 % QID (n = 40) vs cyclosporine 0.1 % (n = 40) for 6 months	• Improvements vs cyclosporine in STS and TBUT at 3, 4, 5, and 6 months (*P* ≤ 0.04 for all)	• Improvements vs cyclosporine in OSDI score at 3, 4, 5, and 6 months (P ≤ 0.03 for all)
Sharma AK et al. (2021) [87] • Pts with DED (n = 130) • SC, R, active control, prospective (India)	Rebamipide 2 % QID (n = 65) vs sodium hyaluronate 0.1 % 6 times a day (n = 65) for 6 wks	• Improvements vs sodium hyaluronate in STS (P = 0.019), TBUT (P = 0.007), and conjunctival lissamine green staining (P = 0.007) at wk 6	• Improvements vs sodium hyaluronate in symptom score at wk 4 (P = 0.033) and wk 6 (P = 0.001)
Jain K et al. (2023) [88] • Pts (any age) with DED (n = 80) • SC, R, case control, prospective (India)	Rebamipide 2 % QID (n = 40) vs control (carboxymethylcellulose 0.5 %; n = 40) for 12 wks	• Improvement vs control in TBUT change from baseline to wk 12 in subgroups with moderate and severe baseline TBUT score (P = 0.0001 for both subgroups) • Improvement vs control in CFS and rose bengal staining score change from baseline to wk 12 in subgroups with mild, moderate, and severe staining scores at baseline (P ≤ 0.04 for all subgroups)	• Improvement vs control in OSDI score change from baseline to wk 12 in subgroup with severe baseline OSDI score (P = 0.04)

BID, twice daily; CFS, corneal fluorescein staining; DED, dry eye disease; DEQS, Dry Eye-related Quality of Life Score; DM, double-masked; LOCF, last observation carried forward; M, masked; MC, multi-center; NR, nonrandomized; Obs, observational; OL, open-label; OSDI, Ocular Surface Disease Index; PBO, placebo; PBO-C, placebo-controlled; Ph, phase; pts, patients; QID, four times daily; R, randomized; SANDE, Symptom Assessment in Dry Eye; SC, single center; STS, Schirmer test score; TBUT, tear film break up time; tCFS, total corneal fluorescein staining; wk, week; y, year.

vision (1 %–4 %) [91,93–96]. According to the Chinese study, patient satisfaction was higher for PFHO compared to the saline control [96]. Patient satisfaction was also high in the open-label extension study conducted in the United States, and concomitant use of artificial tears was low (<5 % of patients) [95].

3.2.5. *Tear production stimulator*

Varenicline solution nasal spray (Tyrvaya 0.03 mg; Oyster Point Pharma, Princeton, NJ, USA), approved by the FDA for the treatment of DED (Table 5) [99–105], is a nicotinic acetylcholine receptor agonist that is believed to stimulate tear production by activating the trigeminal parasympathetic pathway that innervates the lacrimal functional unit [106].

In phase 2 and phase 3 clinical trials, varenicline nasal spray showed significantly greater improvements in Schirmer test scores compared to the vehicle control after 4 and 12 weeks of treatment [99–101]. At most assessments, eye dryness was also significantly reduced with varenicline 0.03 mg compared to the vehicle control [100,101]. Improvements in tear production and eye dryness were observed across patient subgroups defined by disease severity (baseline Schirmer score of ≤5 vs > 5 mm; eye dryness score <40 vs ≥ 40 or < 60 vs ≥ 60) [103,105]; age, sex, race, ethnicity, and artificial tear use [102]; or menopausal status [104].

A pooled analysis of RCTs evaluated the safety of varenicline nasal spray [107]. The most common AEs were nonocular and included sneezing (82 %–84 %, depending on dose), coughing (16 %–20 %), throat irritation (13 %–16 %), and instillation site (nose) irritation (8 %–13 %) [107]. Ocular AEs occurred at a low incidence, with reduced visual acuity (4 %) and conjunctival hyperemia (3 %) reported as the most common [107]. Among patients using varenicline 0.03 mg, 2 % discontinued treatment because of AEs [107].

3.2.6. *Other products*

Other products available globally for the treatment of DED include violet oil [108], *Houttuynia* (traditional Chinese medicine) eye drops [109], topical vitamin D drops [110], homeopathic eye drops [111], chloroquine 0.03 % [112,113], manuka honey [114,115], pranoprofen 0.1 % + sodium hyaluronate 0.1 % [116], and diclofenac 0.1 % + cyclosporine 0.05 % [117]. Improvements in one or more measures of the signs (ocular surface staining, TBUT, Schirmer test score) and symptoms of DED were shown with these products versus either placebo control or an active control such as artificial tears; however, the results were primarily based on small, single-center studies.

Table 4
Summary of efficacy in clinical trials of perfluorohexyloctane.

Study, Population, and Design	Treatment(s)	Signs	Symptoms
Perfluorohexyloctane (PFHO) ophthalmic solution (Miebo; Bausch + Lomb, Bridgewater, NJ, USA)			
Tauber J et al. (2021) [91] • Adults ≥18 y with DED (n = 336) • SEECASE: Ph 2, MC, DM, R, Sal-C (USA)	PFHO QID (n = 114) and BID (n = 111) vs saline BID or QID (n = 111) for 8 wks	• Improvement vs saline in change from baseline in tCFS score at wk 8 (P < 0.001 for QID and P = 0.009 for BID vs saline) • Improvement in tCFS started at wk 2 (P ≤ 0.05 for both doses vs saline)	• Improvement vs saline in change from baseline in EDS at wk 8 (P < 0.001 for QID and P = 0.002 for BID vs saline) • Improvement in EDS started at wk 2 (P < 0.05 for both doses vs saline)
Sall KN et al. (2020) [92] • Post hoc analysis	Post hoc: Subgroups: Baseline MGD score ≥7 (n = 125); STS ≥10 (n = 128)	• Post hoc: Improvements more pronounced in subgroups with: – Baseline MGD score ≥7 (P ≤ 0.01 vs saline) – STS ≥10 (P ≤ 0.01 vs saline)	• Post hoc: Improvements more pronounced in subgroups with: – Baseline MGD score ≥7 (P ≤ 0.01 vs saline) – STS ≥10 (P ≤ 0.001 vs saline)
Tauber J et al. (2023) [93] • Adults ≥18 y with DED for ≥6 months and MGD (n = 597) • GOBI: Ph 3, MC, DM, R, Sal-C (USA)	PFHO (n = 303) vs saline (n = 294) QID for 8 wks	• Improvement vs saline in change from baseline in tCFS score at wk 2 (*P* = 0.001) and wk 8 (P < 0.001) and in cCFS score at wk 8 (P < 0.001 vs saline)	• Improvement vs saline in change from baseline in EDS at wk 2 (P < 0.01) and wk 8 (P < 0.001) and in eye burning/stinging score at wk 8 (P = 0.006 vs saline)
Sheppard JD et al. (2023) [94] • Adults ≥18 y with DED for ≥6 months and MGD (n = 620) • MOJAVE: Ph 3, MC, DM, R, Sal-C (USA)	PFHO (n = 311) vs saline (n = 309) QID for 8 wks	• Improvement vs saline in change from baseline in tCFS score at wk 2 (P = 0.001) and wk 8 (P < 0.001) and in cCFS score at wk 8 (P < 0.001 vs saline)	• Improvement vs saline in change from baseline in EDS and in eye burning/stinging score at wk 2 and wk 8 (P < 0.001 vs saline for all)
Protzko EE et al. (2024) [95] • Pts who completed GOBI (n = 208) • KALAHARI: Ph 3, MC, OL, single-arm extension (USA)	PFHO QID for 52 wks	• Patients continuing PFHO from GOBI maintained improvements in tCFS through wk 52 • Patients who were treated with saline and switched to PFHO showed improvement in tCFS by week 4 that was maintained through wk 52	• Patients continuing PFHO from GOBI maintained improvements in EDS through wk 52 • Patients who were treated with saline and switched to PFHO showed improvements in EDS by week 4 that were maintained through wk 52 • Improvements in ocular symptom scores and OSDI scores were similar between the PFHO continuation group and the saline switch group by wk 4 and were maintained through wk 52
Tian L et al. (2023) [96] • Adults ≥18 y with DED for ≥6 months and MGD (n = 312) • Ph 3 MC, DM, R, Sal-C (China)	PFHO (n = 156) vs saline (n = 156) QID for 8 wks	• Improvement vs saline in change from baseline in tCFS score at wk 4 (P = 0.03) and wk 8 (P < 0.001) • Improvement vs saline in change from baseline in CFS score in central region at wk 2 (P = 0.04), in temporal region at wk 4 (P = 0.05), and in inferior, nasal, and temporal regions at wk 8 (P ≤ 0.03) • Improvement vs saline in response rate of tCFS score (≥3 reductions from baseline) at wk 8 (P = 0.001)	• Improvement vs saline in change from baseline in EDS at wk 2 (P = 0.04), wk 4 (P = 0.006), and wk 8 (P < 0.001) • Improvement vs saline in response rate of EDS (≥30 % reduction from baseline) at wk 8 (P = 0.003) • Improvement vs saline in change from baseline in OSDI score at wk 8 (P = 0.003) • Improvement vs saline in burning/stinging sensation (P < 0.01), symptoms of pain (P = 0.01), awareness of DED symptoms (P < 0.01), and frequency of dryness (P < 0.01) at wk 8

BID, twice daily; cCFS, central corneal fluorescein staining; CFS, corneal fluorescein staining; DED, dry eye disease; DM, double-masked; EDS, eye dryness score; MC, multi-center; MGD, meibomian gland dysfunction; OL, open-label; OSDI, Ocular Surface Disease Index; PFHO, perfluorohexyloctane; Ph, phase; pt, patient; QID, four times daily; R, randomized; Sal-C, saline-controlled; STS, Schirmer test score; tCFS, total corneal fluorescein staining; wk, week; y, year.

3.2.7. Agents in development

A number of novel agents for the treatment of DED are in development (Supplemental Table 1), including several currently in phase 3 trials. Most of these agents have anti-inflammatory properties, while others feature novel mechanisms to stimulate tear or mucin production or to repair and regenerate ocular epithelia.

4. Discussion

This comprehensive systematic literature review evaluated the results of RCTs and real-world studies of topical pharmacologic treatments for DED published up to February 2024. Treatments with regulatory approval in the United States, Asia, or Europe were included, as were other commercially available products and those currently in development.

The diagnosis of DED and the evaluation of treatment efficacy involve both clinical signs and patient-reported symptoms [2]. However, the correlation between signs and symptoms is often weak and inconsistent [2]. Across RCTs, significant improvements relative to a control group have been demonstrated more often for sign endpoints (e.g., corneal staining, Schirmer score) than for symptom endpoints (e.g., eye dryness, ocular discomfort). Notably, PFHO is the only treatment that has consistently demonstrated statistical significance on both the primary sign endpoint and the primary symptom endpoint [91,93,94]. Lifitegrast demonstrated superiority relative to placebo for a primary sign and primary symptom endpoint in separate phase 3 studies [55,56], with significant symptom improvement also confirmed in a third trial [57]. Cyclosporine products consistently showed superiority over the control group for improving signs of DED, whereas reduction in DED symptoms varied across studies (Table 1). Reasons for the greater difficulty in demonstrating improvement in symptom endpoints than sign endpoints may include low initial symptom levels, symptoms due to concurrent allergies that have not been adequately treated, damage to sensory nerves making symptoms an unreliable indicator of efficacy, inability of participants to differentiate adverse effects of treatment (e.g., redness, discharge) from dry eye symptoms, and onset of improvement in signs of inflammation (e.g., corneal or conjunctival) before symptom improvement occurs. Further, the symptom assessment tools (e.g., visual analog scale of symptom scores) may lack sensitivity and can be influenced by patient perception.

The timing of the first postbaseline assessment varied across studies. Onset of efficacy was observed as early as 2 weeks for PFHO [93,94], lifitegrast [55,57], and varenicline [101], while it varied (from 2 weeks to 1 month or more) for cyclosporine-based products [23,31,33,40,41,

Table 5
Summary of efficacy in clinical trials of varenicline.

Study, Population, and Design	Treatment(s)	Signs	Symptoms
Varenicline solution nasal spray (Tyrvaya 0.03 mg, Oyster Point Pharma, Princeton, NJ, USA)			
Quiroz-Mercado H et al. (2022) [99] • Adults ≥22 y with DED (n = 123) • MYSTIC: Ph 2, SC, R, DM, VC (Mexico)	Varenicline 0.03 mg (n = 41) and 0.06 mg (n = 41) vs VC (n = 41) BID for 12 wks	• Improvement vs VC in change from baseline in STS at wk 12 (P = 0.01 for 0.03 mg and P = 0.007 for 0.06 mg vs VC) • Improvement vs VC in percentage of pts with ≥1 0-mm improvement from baseline in STS at wk 12 (NS for 0.03 mg and *P* = 0.024 for 0.06 mg vs VC)	• Not evaluated
Wirta D et al. (2022) [100] • Adults ≥22 y with DED (n = 182) • ONSET-1: Ph 2b, MC, DM, R, VC (USA)	Varenicline 0.006 mg (n = 47), 0.03 mg (n = 48), and 0.06 mg (n = 44) BID vs VC (n = 43) for 4 wks	• Improvement vs VC in change from baseline in STS at wk 4 (P < 0.001 for 0.03 mg and 0.06 mg vs VC)	• Improvement vs VC in change from baseline in EDS at wk 4 (P = 0.02 for 0.03 mg vs VC) • Improvement vs VC in change from baseline in EDS in controlled adverse environment chamber at wk 3 (P = 0.006 for 0.03 mg and P = 0.001 for 0.06 mg vs VC)
Wirta D et al. (2022) [101] • Adults ≥22 y with DED (n = 758) • ONSET-2: Ph 3, MC, DM, R, VC (USA)	Varenicline 0.03 mg (n = 260) and 0.06 mg (n = 246) BID vs VC (n = 252) for 4 wks	• Improvement vs VC in percentage of pts with ≥10-mm improvement from baseline in STS at wk 4 (P < 0.0001 for both doses vs VC)	• Improvement vs VC in change from baseline in EDS at wk 4 (P = 0.04 for 0.03 mg and P = 0.001 for 0.06 mg vs VC)
Epitropoulos AT et al. (2022) [102] • Pts subgrouped by baseline age, sex, race, ethnicity, and artificial tear use (n = 602) • Pooled analysis of ONSET-1 and ONSET-2	Varenicline 0.03 mg BID (n = 308) vs VC (n = 294) for 4 wks	• No treatment–subgroup interactions in percentage of pts with ≥10-mm improvement from baseline in STS at wk 4 or change from baseline in STS at wk 4	• No treatment–subgroup interactions in change from baseline in EDS at wk 4
Katz J et al. (2022) [103] • Pts pooled and subgrouped by baseline EDS severity (mild and moderate-severe) (n = 891) • Pooled analysis of ONSET-1 and ONSET-2	Varenicline 0.03 mg (n = 308) and 0.06 mg (n = 289) vs VC (n = 294) for 4 wks Subgroups: Baseline EDS <40 and ≥40 mm	• Improvement vs VC in change from baseline in STS at wk 4 in study eyes (P < 0.001 for 0.03 mg and 0.06 mg doses vs VC) and fellow eyes (P < 0.001 for 0.03 mg and 0.06 mg doses vs VC) • Improvement vs VC in percentage of pts with ≥10-mm improvement from baseline in STS at wk 4 in study eyes (P < 0.0001 for 0.03 mg and 0.06 mg doses vs VC) and fellow eyes (P < 0.0001 for 0.03 mg and 0.06 mg doses vs VC) • Improvement vs VC in study and fellow eyes of the same 2 measures in pts with baseline EDS <40 and ≥40 mm	• Not evaluated
Nijm LM et al. (2023) [104] • Women subgrouped by PM and non-PM status (n = 449) • Pooled analysis of ONSET-1 and ONSET-2	Varenicline 0.03 mg vs VC in PM pts (n = 120 vs n = 122) and non-PM pts (n = 102 vs n = 105) for 4 wks	• No treatment–subgroup interaction in change from baseline in STS at wk 4 and percentage of pts with a ≥10-mm improvement in STS from baseline to wk 4	• No treatment–subgroup interaction in change from baseline in EDS at wk 4
Sheppard JD et al. (2023) [105] • Pts subgrouped by baseline STS or EDS severity (mild-moderate and severe) (n = 602) • Pooled analysis of ONSET-1 and ONSET-2	Varenicline 0.03 mg (n = 308) vs VC (n = 294) BID for 4 wks Subgroups: Baseline STS of ≤5 and >5 mm; EDS <60 and ≥ 60	• No treatment–subgroup interactions in change from baseline in STS at wk 4 and percentage of pts with a ≥10-mm improvement in STS from baseline to wk 4	• No treatment–subgroup interactions in change from baseline in EDS at wk 4

BID, twice daily; DED, dry eye disease; DM, double-masked; EDS, eye dryness score; MC, multi-center; NS, not significant; Ph, phase; PM, postmenopausal; pts, patients; R, randomized; SC, single center; STS, Schirmer test score; VC, vehicle control; wk, week; y, year.

Table 6
Challenges in comparing approved products for DED: heterogeneity in study design.

Study Parameter	Heterogeneity
Study design	• Multicenter vs single center • Single arm vs multiple arm • Randomized vs nonrandomized • Double masked vs open label
Trial duration	• 4 weeks to 16 months
Patient population	• Differences in race, ethnicity, and nationality • Contact lens wearers with DED • Moderate to severe vs severe DED • Patients with DED and MGD • Patients with DED nonresponsive to artificial tears/conventional therapies
Control group	• Uncontrolled • Vehicle control • Saline control • Active control
Outcomes assessed: signs	• Corneal staining • Conjunctival staining • TBUT • STS
Outcomes assessed: symptoms	• Ocular symptom scores (e.g., eye dryness, eye burning/stinging) based on VAS • OSDI • SANDE • DEQS

DED, dry eye disease; DEQS, Dry Eye-related Quality of Life Score; MGD, meibomian gland dysfunction; OSDI, Ocular Surface Disease Index; SANDE, Symptom Assessment in Dry Eye; STS, Schirmer test score; TBUT, tear film break up time; VAS, visual analog scale.

47,48]. Longer-term studies showed that the benefits achieved during the initial months of treatment were generally sustained for 1 year or longer. The management of DED typically requires long-term treatment to prevent recurrence of symptoms [16].

Due to variations in design, methodology, populations, and outcomes assessment, comparing approved products is challenging, and head-to-head studies are scarce (Table 6). Future studies should use standardized efficacy measures and a head-to-head design to compare treatment efficacy of products. Topical pharmacologic products also are rarely compared with artificial tears in clinical trials. Although results varied in individual studies comparing cyclosporine-based products with over-the-counter lubricants, a systematic review and meta-analysis found that cyclosporine was more effective than artificial tears in increasing TBUT, reducing corneal staining, and alleviating DED symptoms [118].

All approved treatments were generally well tolerated. Serious ocular AEs rarely occurred. The most common AEs were related to transient effects after instillation, such as burning/stinging, ocular irritation, and blurred vision. The new, water-free formulation of cyclosporine appears to offer improved tolerability compared to previous formulations, as evidenced by lower rates of ocular AEs and fewer treatment discontinuations due to AEs in clinical trials [47,48]. No new safety concerns were identified in longer-term studies of any approved products, including a postmarketing safety analysis of lifitegrast over 7 years of global use [119].

The availability of topical pharmacologic treatments for DED varies by region. Cyclosporine products are available worldwide, but formulations vary with differing concentrations of cyclosporine and various delivery methods. Varenicline is currently available only in the United States as of this writing, whereas diquafosol and rebamipide are commonly used in Asia but not available in the United States or Europe. PFHO was approved as a medical device in Europe, where it is available over the counter, and as a drug in the United States, where its use requires a prescription. In clinical practice, treatment choice may depend on tolerability, cost, and convenience, which may be determined, in part, by local factors, as was seen in a discrete choice experiment investigating patients' medication preferences in the management of DED [120].

Besides product availability, the etiology of DED may influence the initial choice of pharmacologic treatment. For instance, varenicline nasal spray, which is designed to increase tear production, may be selected for patients with primarily aqueous-deficient DED, while PFHO, which inhibits tear film evaporation, may be preferred for those with evaporative DED. Notably, all patients enrolled in PFHO clinical trials had DED and clinical signs of MGD. Factors considered indicative of patients who may benefit from a product with anti-inflammatory properties include the presence of corneal or conjunctival staining, which indicates that the inflammatory cycle has been triggered, and results of point-of-care tests evaluating the presence or absence of matrix metalloproteinase-9 (MMP9), a marker of inflammation.

The management of DED typically follows a stepwise approach that begins with the use of warm compresses, eyelid hygiene (e.g., lid wipes or scrubs), and over-the-counter lubricants, progressing to other treatments if adequate relief is not obtained [12]. Topical pharmacologic therapies are often used in addition to eyelid hygiene and over-the-counter lubricants. In addition to the topical pharmacologic products reviewed herein, other treatment options include office-based therapies such as thermal pulsation (e.g., LipiFlow; Johnson & Johnson), intense-pulsed light, and manual expression of meibomian glands, which are used primarily in patients with evidence of MGD, and a home-based device that stimulates tear production (iTEAR100; Olympic Ophthalmics). Systematic reviews of thermal pulsation [121] and intense pulsed light therapy [122] are covered in other publications.

A strength of this systematic review is the inclusion of a broad range of high-quality studies, including RCTs, post hoc pooled or subgroup analyses, longer-term extension studies, and prospective real-world observational studies. We reviewed topical pharmacologic treatments available worldwide to provide a comprehensive overview of current topical medications for DED. Real-world studies typically include patients who would have been excluded from clinical trials and are more representative of the patient population encountered in clinical practice. Additionally, real-world studies augment the safety findings from RCTs by evaluating AEs and other safety measures in larger patient populations. Study limitations include the exclusion of specific dry eye populations, such as patients with Sjögren's syndrome or graft versus host disease and those who have undergone cataract or refractive surgery, which were beyond the scope of this review.

5. Conclusions

This systematic review summarizes the efficacy and safety results from RCTs and prospective observational studies of topical ophthalmic medications for DED conducted over more than 20 years. Despite variations across studies, improvements in clinical signs of DED were widely observed, whereas symptom reduction was less consistent. Although AE profiles differed between treatments, all were generally well tolerated. For patients who obtain inadequate relief from initial therapies, subsequent treatment selection should use a shared decision-making approach that takes DED etiology and patient preferences into account.

CRediT authorship contribution statement

Louis Tong: Writing – review & editing, Conceptualization. **Zuguo Liu:** Writing – review & editing, Conceptualization. **Afsun Şahin:** Writing – review & editing, Conceptualization. **Koray Gümüş:** Writing – review & editing, Conceptualization. **Elisabeth M. Messmer:** Writing – review & editing, Conceptualization. **José M. Benítez-del-Castillo:** Writing – review & editing, Conceptualization. **Marc Labetoulle:** Writing – review & editing, Conceptualization. **Clara C. Chan:** Writing – review & editing, Conceptualization. **Laura M. Periman:** Writing – review & editing, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2025.07.010.

Data availability

The results of the systematic literature review are presented in the tables that accompany this article.

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