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Authors' Affiliation:
[1]University Clinical Hospital, Poznań University of Medical Sciences, 49 Przybyszewskiego St, 60-355 Poznań, Poland
[2]Provincial Multispecialty Hospital in Leszno, 45 Jana Kiepury St, 64-100 Leszno, Poland
[3]HCP Medical Centre, 194 28 Czerwca 1956 r. St 61-485 Poznań, Poland

Orcid list:

Olga Wojtczak:	0009-0009-3726-437X
Kacper Zagaja:	0009-0003-9678-1162
Justyna Wróblewska:	0009-0003-5586-3938
Natalia Skrzypska:	0009-0006-0712-7495
Jakub Tarczykowski:	0009-0007-4010-5068
Szymon Stupnicki:	0009-0002-2263-5691
Maja Karmińska:	0009-0000-0916-4771
Wiktoria Głowacka-Kamińska:	0009-0002-5443-5256

*Corresponding author:
Olga Wojtczak,
University Clinical Hospital, Poznań University of Medical Sciences, 49 Przybyszewskiego St, 60-355 Poznań, Poland,
E-mail: olg.wojtczak@gmail.com

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DISCOVERY SCIENTIFIC SOCIETY

Dry Eye Disease - A Systematic Review of Diagnostic Methods and Current Therapies

Olga Wojtczak[1]*, Kacper Zagaja[1], Justyna Wróblewska[1], Natalia Skrzypska[1], Jakub Tarczykowski[1], Szymon Stupnicki[2], Maja Karmińska[2], Wiktoria Głowacka-Kamińska[3]

ABSTRACT

Dry Eye Disease is a condition that affects the surface of the eye and is characterized by an imbalance in the tear film. Those who suffer from the disease usually deal with symptoms such as irritation, changes in sight, and inflammation. This review inspects diagnostic and treatment techniques currently in use. It is based on recent clinical findings and technological developments. Tools such as dry eye questionnaires simplify symptom quantification, while Schirmer testing, tear break-up time, and surface staining remain the main objective measures. Present-day treatments range from favored artificial tears and topical anti-inflammatory medicaments (e.g., cyclosporine, lifitegrast) to novel secretagogues (e.g., varenicline nasal spray, diquafosol), lipid-enhancing agents (e.g., perfluorohexyloctane), and biologic therapies (e.g., autologous serum). Adjunct procedures like thermal pulsation, intense pulsed light, and punctal occlusion have often worked well in stubborn cases. Further, emerging modalities, such as neurostimulatory and nerve-targeted treatments, offer potential for managing neuropathic components of dry eye disease.

Keywords: dry eye disease, ocular surface, tear film instability, meibomian gland dysfunction

1. INTRODUCTION

A chronic disease that is classified as dry eye disease (DED) is a multi-faceted condition that results from changes in the stability of the ocular surface and the tear film. The tear film is a defence layer for the eye's surface and a functioning interface between the tear film and the atmosphere to maintain the refractive qualities of the eye. The tear film is composed of three structures: the mucinous layer, the aqueous layer, and the oily layer. Changes in the dynamics of the tear film caused by a lack of adequate aqueous secretion from the lacrimal glands and/or abnormal composition of the lipids produced by the meibomian glands will create the conditions for the development of DED (Britten-Jones et al., 2024).

According to the first edition of the TFOS Dry Eye Workshop (TFOS-DEWS) published in 2007, DED was defined as having two subtypes: evaporative DED

(EDE) and aqueous deficient DED (ADDE). Clinical practice, however, showed that these forms often coexist. As a result, the second TFOS Dry Eye Workshop (TFOS-DEWS II) expanded this classification to include three categories: ADDE, EDE, and a mixed type (Donthineni et al., 2023).

Reported prevalence ranges from 5% to 50%, with rates as high as 75% observed in adults aged 40 and older. On the other hand, only 2.7% of younger adults aged 18 to 45 experience DED. Despite variation across studies, the evidence consistently shows that symptomatic DED occurs more often in women and individuals of Asian descent. It affects approximately 344 million people worldwide (Rouen and White, 2018).

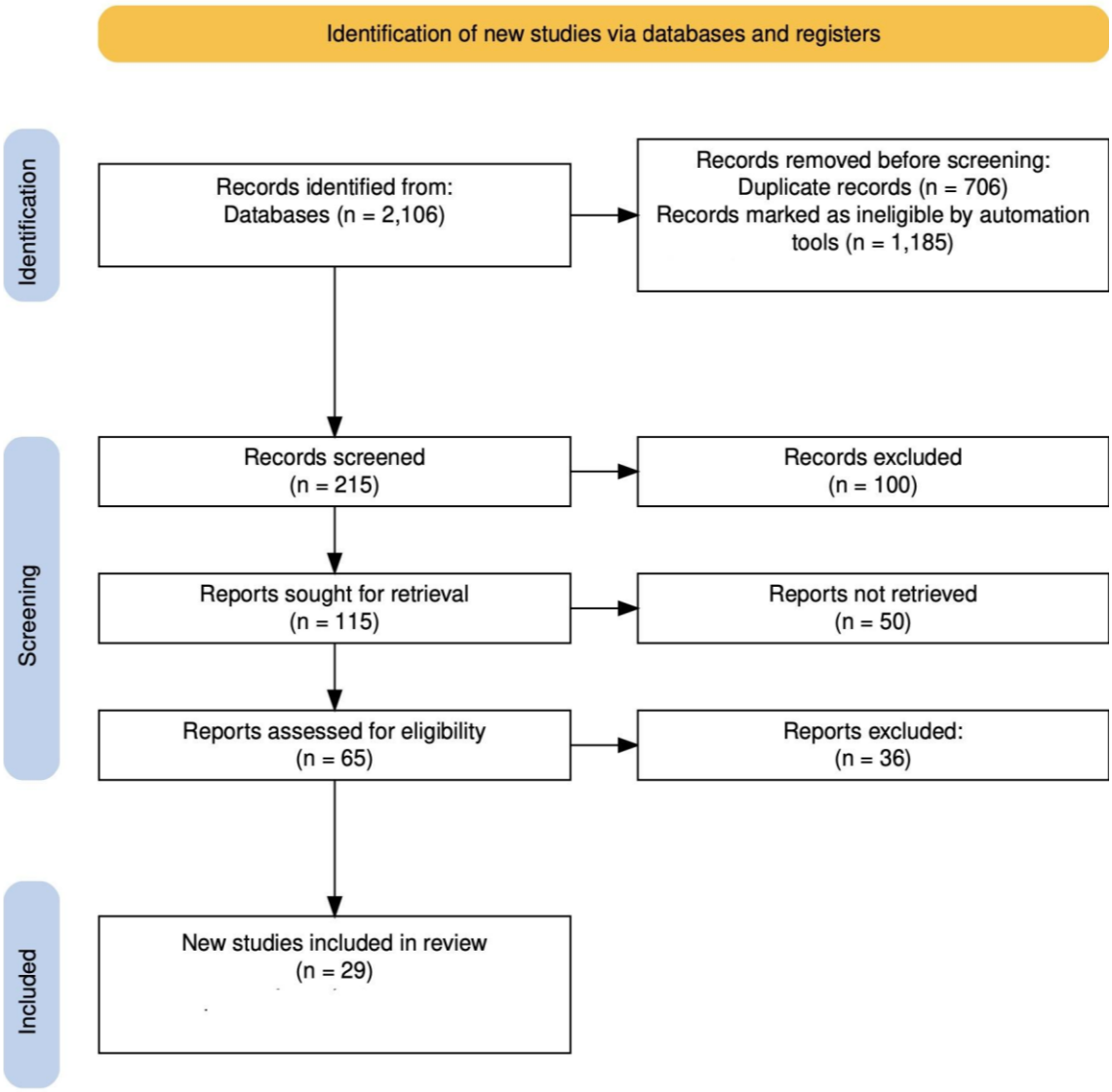

Figure 1. PRISMA flow diagram.

2. REVIEW METHODS

The authors conducted a literature search in PubMed and Google Scholar for the English-language literature on DED published between 2016 and 2025, following the PRISMA selection process. The PubMed and Google Scholar search for records on DED was conducted from 2015 to 2025. Duplicate records were removed before reviewing titles and abstracts, with potentially relevant publications retrieved for full-text review. Eligible studies included randomized controlled trials, systematic reviews, and meta-analyses, providing information on the epidemiology, clinical diagnosis, pathophysiology, or treatment of DED. Excluded from the search were records of animals/in vitro research, conference abstracts, letters, studies that lacked sufficient methodology, were not relevant to DED, or contained incomplete data. The selection process is illustrated in Figure 1.

3. RESULTS & DISCUSSION

Diagnosis

Diagnosing DED should not rest on symptoms or clinical signs alone. There is a need for a structured approach. The diagnosis process includes using dry-eye questionnaires (such as the Ocular Surface Disease Index or DEQ-5) to evaluate risk factors and clinical symptoms, assessing ocular surface biology with a number of ocular surface homeostasis markers, and using tests to examine the velocity of the DED (Wolffsohn et al., 2017). At each level of this evaluation process, there are key steps that allow reliable classification of DED for appropriate treatment.

Risk factors

DED's causes are varied and diverse, influencing different elements of the lacrimal functional unit in multiple ways. The risk factors include residence, education level, obesity, dyslipidemia, alcohol and nicotine consumption, visual display terminal use, cataract surgery, contact lens, pterygium, glaucoma, maculopathy related to age, eye surgery, depression, PTSD, sleep apnea, allergies, high blood pressure, stroke, rosacea, gout, migraines, osteoporosis, tumors, meibomian gland dysfunction, and eczema. What's more, individuals with DED often suffer from systemic diseases. It links to numerous conditions, such as thyroid disorders, connective tissue diseases like systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, cardiovascular disease, chronic obstructive pulmonary disease, asthma, and various hormonal disturbances (Qian and Wei, 2022).

Dry eye questionnaires

The Ocular Surface Disease Index (OSDI-12) has 12 items across 3 domains: eye symptoms, vision-related activities, environmental triggers. It separates healthy individuals from those who have DED well. The OSDI score is calculated using a formula called "sum of all question scores times 100, divided by the number of questions answered, times 4". Thus, it results in a total score of 0-100 (Qin et al., 2024), where higher scores indicate more frequent symptoms and greater functional impact. The OSDI-12 asks respondents to report their experiences from the prior week. Dry Eye Questionnaire (DEQ-5) (Table 1) is a 5-item validated questionnaire. Patients report how often and how severe their eye discomfort, dryness, or watering has been in the last month, with this system allowing the grading of DED severity as mild (0 - 4), moderate (5 - 7), or severe (> 8) (Gross et al., 2022).

Homeostasis markers

Tear film homeostasis is disrupted when one or more clinical signs are present, including the following: 1) shortened non-invasive tear break-up time (NBUT < 10 s); 2) high tear osmolarity (≥ 308 mOsm/L); 3) significant difference in tear osmolarity from one eye to the other (> 8 mOsm/L); 4) clinically meaningful staining of ocular surfaces such as cornea, bulbar conjunctiva and eyelid margins (Wolffsohn et al., 2025).

The latest studies into the underlying inflammatory mechanisms of patients with DED suggest that there is an abnormal production of many different types of immune mediators - this leads to exaggerated immune responses due to excessive inflammatory activity that serves as the principal driver for the pathology of DED.

With this work, for the first time, specific inflammatory mediators were identified (including: pro-inflammatory cytokines, chemokines, growth factors, colony stimulating factors, certain enzymes, soluble adhesion molecules/soluble receptors, neurotrophic factors, mucins, heat shock proteins) which could serve as both biomarkers of the disease process, and as potential therapeutic targets to inhibit the progression of ocular surface injury (Kumar et al., 2023).

DED identification tests

Tests to identify DED generally involve identifying that the condition exists, rather than an evaluation of the cause of the condition. Tests typically used to evaluate these aspects include the stability and osmolarity of the tear film, the amount of tears produced, and the staining of the ocular surface. TBUT of less than 10 seconds and osmolarity of tears that are greater than 307 mOsm/L would indicate that the function of the tear film is abnormal. Evaluation of the stain of the ocular surface and the Schirmer test (less than 10-15 mm) assist with confirming the diagnosis (Papas, 2023; Brott et al., 2025).

Grading of the disease severity

There is a substantial need in the medical world for an objective grading system for DED. Despite proposing and trying many various tests, in clinical settings tests, such as the Schirmer test and OSDI questionnaire, are primarily used. The Schirmer test gives results in millimeters that correspond to levels of severity of dry eyes associated with various ranges of measurement (0-5 mm = severe dryness; 5-10 mm = moderate; 10-15 mm = possibly dry; >15 mm = normal). The OSDI score is divided into four categories: normal (0-12), mild (13-22), moderate (23-32), and severe (33-100) (Brott et al., 2025; Hashmani et al., 2020).

Treatment

Artificial Tear Substitutes

The initial treatment for DED is usually done with using over-the-counter artificial tears (AT) and lubricating eye drops. While AT can refill the deficient tear film to brighten the symptoms, their ability to restore tear film stability is limited when there is advanced or reduced tear quality present. Consequently, the modern AT formulations include a variety of properties for viscosity levels, osmoprotection, and lipids added to produce a product that resembles the natural tear. Systematic reviews report that AT performed regularly improve both signs and symptoms of DED (Semp et al., 2023). The use of either standard formula (1.0% carboxymethylcellulose) or enhanced formula (1.0% carboxymethylcellulose with 0.9% glycerin) had improved OSDI score in both groups progressively from baseline to Day 30 (Lievens et al., 2019). These data show evidence of AT being effective in relieving symptoms and support the role of AT as first-line therapy for DED. Although AT provide symptomatic relief to the patient, they do not address the cause (inflammation or gland dysfunction). Therefore, AT are often used in combination with other therapies.

Topical Anti-Inflammatory Medications

Emulsions of topical cyclosporine A (CsA) 0.05% and lifitegrast 5% are some of the most commonly used medications to improve corneal staining and lower the inflammatory markers associated with DED. These treatments are then frequently prescribed for prolonged use and can require weeks to demonstrate maximum therapeutic benefit. Recent studies have been performed to find a way to shorten the time to therapeutic onset and improve tolerability with immunomodulators. In a Phase 3 clinical trial, a novel waterless form of cyclosporine - CyclASol (0.1%) - resulted in a statistically significant decrease (i.e., superior treatment effect) in the total amount of corneal fluorescein staining observed at 1 month versus the vehicle group. The results indicated that 72% of patients receiving CyclASol achieved a clinically relevant ≥3-grade improvement in their corneal staining compared to only 56% of patients receiving the vehicle. These results provide evidence that the therapeutic onset of CyclASol is faster than that of CsA emulsions; however, there was no difference between the treatment and vehicle groups for dryness symptoms at that time point (Akpek et al., 2023).

Topical lifitegrast (an LFA-1 integrin antagonist) also demonstrated a similar decrease in symptom scores and inferior corneal fluorescein staining compared to the vehicle control at 12 weeks in separate Phase 3 clinical trials, providing an additional immunomodulatory therapeutic option for patients (Holland et al., 2017). The only other medication that has been approved to treat dry eye exacerbations in the short term is loteprednol etabonate ophthalmic suspension 0.25% (Eysuvis). In clinical trials, a 2-week course of loteprednol 0.25% produced rapid relief in both signs and symptoms of DED compared to placebo. The steroid incorporates mucus-penetrating nanoparticle technology as a means of improving ocular delivery to the surface of the eye. In doing so, it provides a significantly greater likelihood of penetrative benefit into the cornea - approximately 3.6 times greater than older steroid formulations (Gupta and Venkateswaran, 2021). Use is limited to no more than 14 days. Clinicians ought to be aware of the potential adverse effects of corticosteroid use, such as elevated intraocular pressure and the associated risk of cataract development (Cutolo et al., 2019).

Tear Secretagogues and Neurostimulatory Treatments

Therapies that stimulate the patient's own tear production have developed over the years. Oral secretagogues, such as pilocarpine and cevimeline (systemic cholinergic agonists), are approved for severe DED connected to Sjögren's syndrome - they increase tear and saliva secretion. Systemic side effects (sweating, flushing) can limit persistent use, though. Topical secretagogues are useful as well.

Probably the most talked-about new secretagogue is the varenicline solution nasal spray. Varenicline works as a nicotinic acetylcholine receptor agonist. When applied through the nose, it triggers the trigeminal parasympathetic pathway. In the ONSET-2 trial, twice-daily varenicline nasal spray (0.03 or 0.06 mg) led to ≥10 mm increases in Schirmer score at 4 weeks in ~47–49% of treated patients, versus 28% with placebo ($P<0.0001$). At 4 weeks, the average tear production was significantly greater in the varenicline group than in the vehicle group.

Symptom-related outcomes were not as clearly different between the varenicline and placebo groups. Improvements in dryness scores due to treatment were present; however, not all comparisons to placebo were significantly different (Wirta et al., 2022). This neurostimulatory approach is the first drug to activate tear reflexes via the nose-eye neural circuit. Overall, secretagogue therapies - both systemic and local - offer an approved strategy (pilocarpine, cevimeline, varenicline spray) to boost natural tears, especially in ADDE. They are notably useful in Sjögren's or other cases with tear hyposecretion, and continuing research (e.g., other neuromodulation devices) is expanding this category.

Other Pharmacologic Innovations

Nowadays, there are more ways to manage DED. Perfluorohexyloctane is one example that stands out among new medications. This semifluorinated alkane spreads over the tear film to reduce evaporation. It targets meibomian gland dysfunction-related dry eye by stabilizing the lipid layer. A Phase 3 trial showed that perfluorohexyloctane significantly improved patients' corneal fluorescein staining and symptom scores compared to placebo. In summary, there were no statistically significant differences found between either of the assessment tools used in this study; this supports the fact that the improvements seen with treatment as compared to placebo occur only through improving the lipid layer of the tear film rather than by having a direct effect on the output of those glands (Tian et al., 2023). While many newer products have already been developed and launched, additional products remain under development and are expected to be launched soon. These newer therapies tend to work alongside standard methods, often by targeting specific components of the tear film or the inflammatory processes involved in DED.

Botulinum Toxin

In patients exhibiting light sensitivity, treatment approaches used in other photophobia-associated conditions, such as migraine, may be relevant. Botulinum toxin, known for its effectiveness in treating light sensitivity associated with migraines, has also been looked at for relieving ocular pain. In a retrospective study involving 27 patients who showed signs of neuropathic eye pain, injections based on a modified migraine treatment protocol led to pain improvement in about 74% of the group (20 out of 27) after one month. Relieving DED symptoms with a migraine treatment option is most likely possible because the underlying causes are somehow connected (Locatelli et al., 2025).

Non-Pharmacologic Interventions

Warm Compresses and Eyelid Warming Therapies

Applying warmth to the eyelids has been a widely used method for quite some time to improve the secretion from the meibomian glands, especially in cases of EDE. It is a non-medication option that many find helpful. Warm compresses, generally maintained at 40-45 °C, are applied to soften thickened meibum in the gland ducts, thereby promoting its subsequent release. People often recommend this method for dry eye that is connected to meibomian gland dysfunction, mostly because of its simplicity. In 2024 a randomized trial looked at whether a self-heating eyelid mask worked better than the traditional warm towel in patients with meibomian gland dysfunction-related dry eye. After 4 weeks, the mask group showed significantly greater improvement in symptom scores (including OSDI) and corneal fluorescein staining than the hot towel group.

By 12 weeks, patients using the heating mask had excellent outcomes in almost all measures (symptoms, TBUT, staining, meibum quality) except Schirmer values, compared to those using a moist towel. Maintaining a consistent therapeutic heat level, achieved more effectively with the disposable mask than with the cooling towel, results in better clinical results. Both methods were safe; however, some patients in each group reported minor discomfort. The demand for sustained, daily use of warm compresses is regularly emphasized - benefits tend to plateau after some weeks of ongoing use and can regress in case of therapy discontinuation (Wang et al., 2024).

Procedural Interventions

Intense Pulsed Light Therapy

Intense pulsed light (IPL) has emerged as an important adjunct treatment for refractory meibomian gland dysfunction and rosacea-associated dry eye. IPL, which was first used in dermatology to treat conditions like rosacea and telangiectasias, includes applying broad-spectrum light - roughly between 500 and 1200 nm - to the skin around the eyes. Treatment typically needs several sessions - usually three or four - which take place some weeks apart. Lately, a few randomized controlled trials have turned up promising results.

For example, a 2022 multicenter study compared a newer IPL device with a traditional model. This study included 132 patients experiencing DED symptoms associated with meibomian gland dysfunction. After two treatment sessions - one week apart, both groups improved OSDI scores, TBUT, tear volume, and meibomian gland assessments by Day 14. The new-generation IPL showed non-inferiority to the standard device in overall success rate. It also produced larger average gains in TBUT, tear meniscus height, and meibum quality, which is encouraging clinically. There was no report of significant adverse effects (Jiang et al., 2022). All things considered, IPL has become a useful option for treating EDE.

Punctal Occlusion (Tear Drainage Occlusive Devices)

When aqueous tear deficiency is significant, conserving the tears on the ocular surface can provide relief. Punctal plugs are occluders placed in the lacrimal puncta or canaliculi. They are still in use for moderate to severe DED, especially when lubricants and anti-inflammatory drugs are not enough to control symptoms. Plugs are available in dissolvable collagen or hydrogel materials, as well as more durable silicone designs. Numerous studies have shown that punctal occlusion increases tear film volume and can improve dry eye signs. A meta-analysis of clinical trials found that punctal plugs significantly improve Schirmer test scores and TBUT in patients with dry eye, and also result in enhanced symptom scores compared to no plugging (Chen et al., 2025). Nowadays, there is an ongoing investigation for methods to reduce complications like plug loss. One of the methods involves an injectable, in-situ forming "liquid plug" using a thermosensitive hydrogel. A 2021 study randomized dry eye patients to receive an intracanalicular injection of hydroxybutyl chitosan (HBC) hydrogel in one eye, with a traditional VisiPlug placed in the contralateral eye for comparison. These two methods turned out as effective: after 4 weeks, both eyes showed clear improvements in OSDI, tear meniscus height, and a trend toward less corneal staining. There were no differences between HBC and standard plugs in these outcomes at 1 and 4 weeks. Interestingly, at 12 weeks the original plug showed slightly better tear meniscus and phenol red thread test results than HBC - which had partly degraded. Safety was comparable, with low rates of minor irritation and no serious events (Lin et al., 2021). This pilot trial suggests that "personalized" plug solutions (which conform to the patient's punctal size) can be as safe and initially as effective as preformed plugs; however, the longevity of occlusion remains an issue. While the findings are promising, they require additional confirmation in larger, well-powered studies.

Overall, punctal occlusion is an established, adjunctive treatment (with broad regulatory approval) that can significantly benefit ADDE.

Peripheral Trigeminal Transcutaneous Electrical Nerve Stimulation (TENS)

Finally, emerging neuromodulation devices seek to address cases of dry eye pain with neuropathic features. Transcutaneous electrical nerve stimulation delivered to the supraorbital or infraorbital regions of the face in the form of external trigeminal nerve stimulation has been studied as a treatment for ocular pain (Cai and Zhang, 2020). In one study, periocular TENS was found to produce significant reductions in death-related ocular pain compared with artificial tears alone. Nevertheless, the underlying mechanisms for this improvement in phantom craniofacial pain (both subjective and objective) vary between TENS devices and study designs. These results support the assertion that TENS devices are likely to be effective in reducing ocular pain and may also alter tear production parameters. In order for clinicians to clearly document their efficacy, define appropriate patient selection criteria, and determine long-term outcomes, further research (including randomized controlled trials) is needed.

Biologic Blood-Derived Therapies

Autologous serum tears (ASTs) and plasma rich in growth factors (PRGF) remain promising biologic therapies for various subtypes of DED, even with a corneal nerve component (Soni and Jeng, 2016). These blood-based agents replace some of the substances present in natural tears, such as cytokines and growth factors. They also carry other bioactive molecules that control inflammation and might help nerve recovery. High costs create additional difficulties for long-term implementation.

Although there is growing evidence of their effectiveness, results vary widely across studies. Clinical guidelines do not define their role with confidence. Nevertheless, several studies point to a therapeutic benefit (Quan et al., 2023). Twenty-seven randomized controlled trials including transcription studies about the use of AST versus AT in treatment for DED were published through October 2024. A meta-analysis of these trials revealed that compared to patients treated with AT, patients treated with AST were considerably improved in: Schirmer's test, TBUT, fluorescein staining of the cornea; and in OSDI symptoms ($p<0.001$) (He, 2024).

These results may appear encouraging, but small sample sizes, open-label designs, and heterogeneity in protocols limit many of the studies. Case series and non-experimental reports restrict current data, with strong evidence remaining lacking. Table 1 presents a summary of the information contained in the review.

Table 1. Summary of DED - Definition, Diagnosis, and Treatment Approaches.

Definition & Epidemiology	Multifactorial disease characterized by tear film instability and ocular surface inflammation. Prevalence ranges from 5-50%, more common in women and older adults.
Classification	Three types: Aqueous-Deficient (ADDE), Evaporative (EDE), and Mixed.
Risk Factors	Age, female sex, screen use, contact lenses, ocular surgery, systemic diseases (e.g., Sjögren's, RA, thyroid disorders), meibomian gland dysfunction.
Diagnosis	Symptom questionnaires (OSDI, DEQ-5), tear break-up time (TBUT) (<10 s), osmolarity (≥308 mOsm/L), Schirmer test (<10-15 mm), ocular surface staining, disease severity grading.
First-Line Treatment	Artificial tears and lubricants for symptomatic relief.
Advanced Therapies	Cyclosporine, lifitegrast, corticosteroids, secretagogues (varenicline), lipid-based drops, IPL, punctal plugs, biologic tears.

4. CONCLUSION

DED is a multifactorial condition that requires a comprehensive strategy for both diagnosis and treatment. Recent advances in understanding inflammation and neural involvement underlying the condition have allowed the development of novel treatment options. Clinicians are no longer just treating symptoms. Frankly, they now focus more on finding what actually causes the problem. Using reliable diagnostic tools with customized combination therapies often gives better outcomes and longer-lasting health for the eye surface. More high-quality research and agreed diagnostic and treatment protocols are still needed to improve DED care.

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Authors' Contributions

Olga Wojtczak and Kacper Zagaja designed the study. Olga Wojtczak, Kacper Zagaja, Justyna Wróblewska and Natalia Skrzypska conducted the literature search and data extraction. Szymon Stupnicki and Jakub Tarczykowski were responsible for drafting the initial manuscript. Wiktoria Głowacka-Kamińska contributed to the critical revision of the manuscript. Maja Karmińska supervised the project and provided final editorial oversight. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

Informed consent

Not applicable.

Ethical approval

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on reasonable request to the corresponding author.

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