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CONTEMPORARY THERAPEUTIC APPROACHES TO DRY EYE SYNDROME: A SYSTEMATIC REVIEW OF CLINICAL EVIDENCE WITH IMPLICATIONS FOR OCULAR HEALTH AND QUALITY OF LIFE

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ABSTRACT

Background: Dry Eye Syndrome (DES), or Dry Eye Disease (DED), is a common, multifactorial condition affecting the tear film and ocular surface. It causes symptoms such as discomfort, visual disturbances, and inflammation. Treatments range from artificial tears and anti-inflammatory drops to newer approaches like light-based therapies, electrotherapy, and biological tear substitutes.
Objective: This systematic review evaluates current pharmacological and non-pharmacological treatments for DES, focusing on clinical effectiveness, safety, and evidence quality - particularly from randomized controlled trials.
Methods: A comprehensive search was performed in major databases for studies published between January 2010 and April 2025. Included studies were in English, involved human subjects with DES, and assessed specific treatments with measurable outcomes (e.g., tear production, symptom severity). Eligible studies included randomized controlled trials, observational studies, and systematic reviews with meta-analyses. Two reviewers independently screened and selected studies, data were extracted and analyzed descriptively due to heterogeneity.
Results: A wide range of therapies were identified. Artificial tears, especially preservative-free and hyaluronic acid-based, consistently improved symptoms and tear stability. Cyclosporine A showed moderate anti-inflammatory effects. Biological tear substitutes, like autologous serum and platelet-rich plasma, benefited severe cases. Non-pharmacological treatments such as intense pulsed light (IPL), low-level light therapy, electrotherapy, and acupuncture improved outcomes in meibomian gland dysfunction. Omega-3 and curcumin supplements had mixed but promising effects.
Conclusions: DES management should be personalized and multimodal. Although many treatments show benefits, variations in study designs limit comparability. More standardized, high-quality research is needed to guide evidence-based care.

KEYWORDS

Dry Eye Syndrome, Dry Eye Disease, Tear Film Instability, Artificial Tears, Cyclosporine A, Omega-3 Fatty Acids, Intense Pulsed Light, Electrotherapy, Acupuncture, Autologous Serum, Platelet-Rich Plasma, Hyaluronic Acid, Inflammation, Meibomian Gland Dysfunction, Curcumin, Non-Pharmacological Interventions, Biological Tear Substitutes, Topical Anti-Inflammatory Therapy, Tear Osmolarity, Systematic Review

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Introduction

Dry eye syndrome (DES), also known as dry eye disease (DED), is a common and often chronic condition having influence the ocular surface and tear film. This causes symptoms such as burning, stinging, grittiness, blurred vision, and general discomfort. These symptoms can have the influence on the functioning of the body during the day, including reading, driving, and screen use. Estimates of DES prevalence range widely - from 5% to 50% - depending on diagnostic criteria, population demographics, and environmental exposure [*Topical Corticosteroids, Liu et al. 2022*; *IPL Meta-Analysis, Qin et al. 2023*].

DES is a multifactorial disease characterized by instability of the tear film, hyperosmolarity, ocular surface inflammation, and, in some cases, neurosensory abnormalities [*Lutein Review, Chu & Huang 2024*]. Risk factors include older age, female sex, contact lens wear, prolonged use of digital screens, environmental conditions such as low humidity and wind, and systemic conditions like Sjögren's syndrome [*Topical Corticosteroids, Liu et al. 2022*; *Autologous Serum, Quan et al. 2023*]. The disease can be further categorized into aqueous-deficient and evaporative types, although many patients exhibit a combination of both forms [*IPL Meta-Analysis, Qin et al. 2023*].

Inflammation plays a central role in DES pathogenesis. Research has shown concentration increase of inflammatory cytokines and the presence of T-cell infiltration on the ocular surface in individuals with the condition. [*Topical Cyclosporine A, de Paiva et al. 2019*]

Consequently, therapeutic approaches are increasingly aimed at reducion inflammation and re-establishing the balance of the tear film. Diagnosing dry eye syndrome (DES) remains difficult because there is often a mismatch between the patient's reported symptoms and the clinical findings detected during evaluation. Common diagnostic tools include the Schirmer test, tear film break-up time (TBUT), corneal staining, and symptom questionnaires such as the Ocular Surface Disease Index (OSDI) [*Meta-Analysis HA, Yang et al. 2021*; *Lutein Review, Chu & Huang 2024*].

Dry eye syndrome treatment options are varied and can be customized according to the severity of the condition and its root cause. First-line therapies often involve artificial tears to supplement tear volume and stabilize the tear film. Hyaluronic acid-based artificial tears, in particular, have shown potential benefits due to their viscoelastic and water-retaining properties [*Meta-Analysis HA, Yang et al. 2021*]. Anyhow, The results of different studies vary, while certain analyses demonstrate statistically significant enhancements in tear film parameters, others find no distinct advantage compared to standard treatments. [*Meta-Analysis HA, Yang et al. 2021*].

Anti-inflammatory agents like topical cyclosporine A (CsA) and corticosteroids are also widely used. CsA works by modulating the immune response and increasing tear production, but its effectiveness has shown mixed results in clinical trials [*Topical Cyclosporine A, de Paiva et al. 2019*]. Topical corticosteroids may provide rapid inflammation relief; on the other hand, their long-term use is associated with safety concerns, such as increased intraocular pressure and a heightened risk of cataract formation. [*Topical Corticosteroids, Liu et al. 2022*].

Aside from conventional therapies, several newer treatments have appeard. Autologous serum eye drops, prepared from the patient’s own blood, are thought to deliver growth factors and nutrients similar to natural tears. Although encouraging, the available evidence is still limited and shows a degree of inconsistency. [*Autologous Serum, Quan et al. 2023*]. Lutein and other dietary antioxidants have been studied for their anti-inflammatory and antioxidant benefits, although evidence from randomized trials is still lacking. [*Lutein Review, Chu & Huang 2024*]. Light-based therapies like intense pulsed light (IPL) are gaining increasing attention, In Particular in individuals with meibomian gland dysfunction, as meta-analyses have shown benefits in reducing symptoms and enhancing tear film stability.[*IPL Meta-Analysis, Qin et al. 2023*].

Because there are many different treatment options and the results vary between studies, it's important to cautiously review the current research.. This review seeks to thoroughly assess both drug-based and non-drug treatments for dry eye syndrome, placing special emphasis on findings from randomized controlled trials. In doing so, our goal is to help clinicians select safe and effective treatments while also highlighting potential areas for future research.

Aim of the Study

The aim of this study is to systematically review current treatment options for Dry Eye Syndrome (DES), including both drug-based and non-drug therapies. By evaluating recent clinical evidence, especially from randomized controlled trials, this review seeks to identify effective and safe approaches for managing DES. The goal is to help guide clinical decisions and highlight areas where further research is needed.

Methods

Protocol and Registration

This systematic review was conducted to evaluate current treatment options for Dry Eye Syndrome (DES), focusing on both medication-based and non-medication-based therapies. The process followed accepted standards for systematic reviews, including thorough searching, screening, and analysis of the available scientific literature.

Search Strategy

A comprehensive search was carried out using several major medical and scientific databases. We included studies published between January 2010 and April 2025. The search focused on identifying relevant clinical research examining different types of interventions for DES. The results were screened for relevance, and duplicate entries were removed.

Inclusion and Exclusion Criteria

Studies were selected based on the following criteria:

- They were written in English,
- Included human participants diagnosed with dry eye syndrome,
- Investigated the effects of a specific treatment approach,
- Reported clinical outcomes such as symptom severity, tear production, or eye surface condition,
- Were designed as randomized controlled trials, observational studies, or systematic reviews with meta-analyses.

We excluded studies that:

- Involved animals or were conducted in laboratory settings,
- Lacked peer review,
- Did not report clear or measurable outcomes,
- Were opinion pieces, case reports, or editorial letters without sufficient clinical data.

Study Selection and Data Collection

Two reviewers independently screened the titles and abstracts of all identified studies. Full texts of potentially relevant articles were then reviewed to confirm eligibility. If there were any disagreements during the selection process, they were resolved by discussion or consultation with a third reviewer.

Key data were extracted from each included study. This included information about the authors, year of publication, study design, number of participants, type of treatment used, duration of treatment, outcome measures, and main results. The studies were then grouped based on the type of therapy they examined.

Quality Assessment

The quality of the included randomized studies was assessed using a standard risk of bias tool. Observational studies were evaluated with a validated scale commonly used for non-randomized research. Only studies with acceptable levels of methodological quality were included in the final analysis.

Data Synthesis

Due to differences in the types of interventions, study designs, and outcome measures, the data were analyzed using a descriptive approach. Studies were organized into categories based on the kind of treatment being tested, and their results were compared and summarized. Special attention was given to findings from well-designed randomized controlled trials to ensure reliability.

This structured approach allowed for a clear overview of current treatments for dry eye syndrome and helped identify promising therapies as well as areas where more research is needed.

Literature Review Results

Dry Eye Disease (DED) is a multifactorial condition that affects millions of people worldwide, leading to discomfort, visual disturbances, and reduced quality of life. In recent years, a wide range of therapeutic strategies have been explored, from dietary supplements and artificial tears to advanced technologies like light-based therapies and electrotherapy. This section summarizes and combines results from multiple clinical studies evaluating both pharmacological and non-pharmacological interventions for DED.

Omega-3 fatty acids have been extensively investigated for their anti-inflammatory effects and potential benefits in treating DED. In a study conducted in India, Bhargava et al. assessed the effectiveness of omega-3 supplements in visual display terminal (VDT) users who are susceptible to dry eye due to prolonged screen exposure. Participants were randomly assigned to receive omega-3 capsules or olive oil (placebo) for six months. The omega-3 group demonstrated significant improvements in symptoms, tear production, tear stability, and goblet cell density, in particular in those with initially low omega-3 blood levels [Bhargava et al., 2023]. In contrast, the U.S.-based DREAM trial, which involved 535 individuals with moderate to severe DED, found no statistically significant differences between omega-3 supplementation and placebo after one year. In the omega-3 group, it was observed a slight improvement in tear osmolarity, but it was not clinically significant. [Oydanich et al., 2020]. These divergent results imply that omega-3 may be more effective in populations with lower initial dietary intake of omega-3 fatty acids, possibly explaining regional variations in outcomes.

Artificial tears continue to be a fundamental component in the treatment of dry eye disease and numerous studies have examined enhancements to their formulations. Wang et al. explored the combined use of 0.3%

sodium hyaluronate (SH) with esculin and digitalis glycosides (EAD), compared to SH or EAD alone. Combined therapy showed improved results in tear break-up time (TBUT), Schirmer's scores, and corneal staining, with a total effectiveness rate of 88.5% [Wang et al., 2025]. Another trial by Belalcázar-Rey et al. evaluated preservative-free SH/chondroitin sulfate (SH/CS-PF) eye drops in a large multicenter study. All treatments showed effectiveness in relieving DED symptoms and improving ocular surface health. However, preservative-free solutions were associated with slightly fewer side effects, supporting their preferred use in long-term treatment. [Belalcázar-Rey et al., 2021].

Another study by Downie et al. involves the use of OM3 tears containing linseed oil and trehalose. Compared to a formulation lacking these components, OM3 significantly reduced corneal and conjunctival staining, particularly in patients with evaporative DED. It was also better tolerated [Downie et al., 2020]. Complementing this, Ali et al. showed that lowering tear osmolarity through regular use of artificial tears improved both objective and subjective parameters, This confirms that osmolarity is a key biomarker in the treatment of ZED. [Ali et al., 2022].

Several trials investigated cyclosporine, an immunomodulatory drug, in various formulations. A study by Wirta et al. evaluated a novel water-free cyclosporine 0.1% formulation used twice a day for a year. Patients showed enhanced tear production and reduced staining of the ocular surface. They also reported high levels of satisfaction, suggesting the formulation is well-suited for long-term use. [Wirta et al., 2025]. 0.05% cyclosporine (CsN) nanoemulsion was compared with 0.15% hyaluronic acid (HA) in mild to moderate DED. CsN was more effective than HA in enhancing TBUT and reducing corneal staining over a 12-week period, though some patients reported mild discomfort. [Moon et al., 2024].

A pooled analysis of two Phase III trials examined the use of cyclosporine 0.1% in patients with dry eye disease, both with and without cataracts. The study found that 59% of participants experienced significant improvement in central corneal staining within 15 days, with effectiveness also observed in pseudophakic patients and a favorable safety profile overall [Akpek et al., 2024]. Using a different methodology, a separate study analyzed insurance claims to compare Restasis (cyclosporine 0.05%) with other topical treatments. Results indicated that Restasis users required fewer visits to an ophthalmologist and incurred lower costs, highlighting the potential economic benefits in addition to clinical effectiveness. [Nelson et al., 2022].

Biological tear substitutes have emerged as a promising option for patients with treatment-resistant dry eye disease. A comparison between 100% autologous platelet-rich plasma (APRP) and autologous serum (AS) showed that both therapies led to significant improvements in OSDI scores and ocular surface condition. Their effectiveness was similar, but APRP had the advantage of being easier to prepare. [Jongkhajornpong et al., 2024].

The effectiveness of Quantum Molecular Resonance (QMR) electrotherapy with the Rexon-Eye device was evaluated in patients with mixed-type dry eye disease. This approach was tested for its potential therapeutic benefits. After four weekly treatment sessions, significant improvements in OSDI, TBUT, meibomian gland function, and inflammatory markers such as reduced MMP-9 levels were observed. The procedure was reported to be safe and well-tolerated [Trivli et al., 2023].

Photobiomodulation therapies are gaining recognition as effective options for managing MGD-related dry eye disease. A combination of intense pulsed light (IPL) and low-level light therapy (LLLT) applied over three sessions led to significant improvements in TBUT, OSDI scores, and meibum quality, without any serious side effects [D'Souza et al., 2023]. In a separate randomized controlled trial, standalone LED-LLLT resulted in better fluorescein corneal staining and Schirmer's test scores, with no reported adverse events, confirming both its safety and therapeutic potential [Park et al., 2022].

Complementary treatment methods such as acupuncture are gaining increasing attention in clinical settings. One study comparing traditional acupuncture at the BL1 (Jingming) point with artificial tears showed that the acupuncture group had significantly increased tear production and symptom relief, although the results for TBUT and corneal staining were similar in both groups. [Zhang et al., 2022]. Another investigation focused on laser acupuncture (LA), which involves non-invasive light stimulation. The LA group showed significant improvement in OSDI and TBUT scores compared with sham treatment. This indicates that both traditional acupuncture and laser acupuncture can be effective adjunctive therapies for moderate to severe dry eye syndrome [Hu et al., 2021].

Natural compounds with anti-inflammatory properties, such as curcumin, may be a potential treatment for dry eye syndrome. In one study, oral bio-enhanced curcumin combined with carboxymethyl cellulose (CMC) eye drops led to significant improvements in OSDI scores and TBUT, with minimal side effects reported [Kapil et al., 2025]. Another trial using a curcumin-soy phospholipid complex alongside sodium

hyaluronate drops showed enhanced symptom relief and reduced ocular redness, further supporting curcumin's therapeutic potential [Borselli et al., 2022].

Topical bevacizumab 0.05%, a VEGF inhibitor, was evaluated in patients with severe dry eye disease. The study results showed significant improvements in TBUT and OSDI scores without any adverse events. These findings indicate that anti-angiogenic therapy may be beneficial in cases of DED characterized by increased inflammation. [Kasetsuwan et al., 2020].

Tears Again® and Ectoin® Eye Spray - two preservative-free eye sprays were found to significantly improve TBUT, reduce ocular redness, and alleviate symptoms within just 10 days of use. Ectoin® showed comparable effectiveness to the liposomal spray, highlighting its potential as a beneficial treatment for mild to moderate dry eye disease [Nosch et al., 2021].

Discussion

This systematic review examined a broad range of current therapeutic strategies for Dry Eye Syndrome (DES), emphasizing the complexity and multifactorial nature of the condition. DES is influenced by tear film instability, ocular surface inflammation, neurosensory abnormalities, and environmental or systemic risk factors. As a result, effective treatment requires a personalized and often multimodal approach.

Artificial tears are the most commonly used first-line therapy, especially in mild to moderate cases. Hyaluronic acid (HA)-based artificial tears, particularly preservative-free formulations, were shown to improve tear break-up time (TBUT), Schirmer's scores, and reduce corneal staining. Studies like those by Wang et al. and Belalcázar-Rey et al. suggest that enhanced or preservative-free formulations offer greater safety and efficacy, especially with long-term use.

The effectiveness of omega-3 fatty acid supplementation in DES treatment remains inconsistent. Bhargava et al. found significant improvements in symptoms, tear stability, and goblet cell density in visual display terminal users, whereas the large U.S.-based DREAM trial did not report clinically meaningful benefits. This contrast may be explained by regional dietary differences, indicating that omega-3 efficacy may depend on baseline nutritional intake.

Topical anti-inflammatory agents, particularly cyclosporine A (CsA), continue to be essential in treating moderate to severe cases. Newer formulations such as water-free emulsions and nanoemulsions demonstrated improved tear production and reduced ocular staining, along with good tolerability. However, some patients still experience discomfort, and onset of therapeutic action can be delayed. Corticosteroids offer faster symptom relief but are generally recommended for short-term use due to risks like increased intraocular pressure and cataract formation.

Biological tear substitutes such as autologous serum (AS) and autologous platelet-rich plasma (APRP) have shown promise in patients with more severe or refractory DES. Both therapies resulted in improved OSDI scores and ocular surface healing, with APRP having the added benefit of easier preparation. These blood-derived treatments offer nutrients and growth factors similar to natural tears and are particularly valuable for patients with systemic autoimmune conditions.

Device-based and light-based therapies are emerging as effective non-pharmacological treatments. Intense pulsed light (IPL), low-level light therapy (LLLT), and Quantum Molecular Resonance (QMR) electrotherapy showed improvements in tear film stability, meibomian gland function, and patient-reported symptoms. These treatments are especially beneficial in evaporative DES and meibomian gland dysfunction (MGD), offering non-invasive, repeatable therapeutic options.

Complementary methods such as traditional acupuncture and laser acupuncture (LA) have also shown effectiveness in increasing tear production and reducing symptoms. Their safety and minimal side effects make them suitable as adjunctive therapies. Similarly, oral curcumin supplements combined with standard drops demonstrated anti-inflammatory effects and symptom relief in multiple studies.

Other novel approaches include topical VEGF inhibitors like bevacizumab and preservative-free eye sprays (e.g., Ectoin®), which were effective in improving TBUT, ocular redness, and symptom severity.

Overall, the reviewed literature confirms that while many therapies provide benefits, treatment outcomes vary depending on disease severity, underlying etiology, and patient characteristics. Variability in study design, sample size, and outcome measures complicates direct comparisons. Furthermore, the frequent mismatch between clinical signs and patient-reported symptoms continues to challenge accurate diagnosis and treatment evaluation. Incorporating both subjective tools like the OSDI and objective biomarkers such as tear osmolarity and MMP-9 levels may help guide more effective and individualized treatment decisions.

Conclusions

Dry Eye Syndrome (DES) is a complex and common condition that requires individualized treatment. While artificial tears remain the first-line therapy, newer preservative-free and hyaluronic acid-based formulations offer better safety and comfort. Anti-inflammatory treatments like cyclosporine A and short-term corticosteroids are helpful in more severe cases, though responses vary.

Biological tear substitutes, such as autologous serum and platelet-rich plasma, show promise for patients with treatment-resistant DES. Newer non-drug therapies - like intense pulsed light, electrotherapy, and acupuncture - also offer benefits, especially in meibomian gland dysfunction. Natural supplements such as curcumin and omega-3 fatty acids may be useful as adjunctive options. Because of differing study results and varied patient responses, treatment should be personalized. More high-quality research is needed to guide clinical decisions and improve outcomes for people living with DES.

Authors' Contributions Statement

All authors have read and agreed with the published version of the manuscript.

All authors have reviewed and agreed to the publication of the final version of the manuscript.

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