

# Artificial Tears: A Systematic Review

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**Abstract:** Artificial tears are the mainstay of dry eye disease management, but also have a role in corneal abrasion and wound healing, pain and inflammation management, conjunctivitis, keratitis, contact lens rewetting and removal, and foreign body removal. A systematic review of randomized controlled trials (PROSPERO registration CRD42022369619) comparing the efficacy of artificial tears in patients with dry eye to inform prescribing choices using Web of Science, PubMed and Medline databases identified 64 relevant articles. There is good evidence that artificial tears improve symptoms of dry eye disease within a month of regular use, applied about four times a day, but signs generally take several months to improve. Not all patients with dry eye disease benefit from artificial tears, so if there is no benefit over a month, alternative management should be considered. Combination formulations are more effective than single active ingredient artificial tears. Artificial tears containing polyethylene glycol are more effective than those containing carboxymethylcellulose/carmellose sodium and hydroxypropyl methylcellulose. Those classified as having evaporative dry eye disease, benefit from artificial tears with liposomes, especially of higher concentration. The data available is limited by the definition of dry eye disease applied in published studies being variable, as well as the disease severity examined and compliance with artificial tears being rarely quantified.

**Keywords:** artificial tears, dry eye, comfort, contact lenses

Artificial tear drops are most commonly associated with the management of dry eye disease (DED). Artificial tears are typically included in first-line management options for dry eye, as they are easy to use, accessible in a wide range of formulations, and have a low risk-profile.<sup>1</sup> Most artificial tear preparations have been found to be effective in reducing the symptoms and signs of DED, however the Tear Film and Ocular Surface Society (TFOS) dry eye workshop in 2017 (DEWS II) concluded there had been relatively few high quality randomized controlled trials comparing different formulations with each other.<sup>1,2</sup> Furthermore, few clinical trials have compared the efficacy of different artificial tear products, and attempted to correlate this with patient characteristics, in order to aid management decisions for an individual.<sup>3,4</sup> The issue with this is that both practitioners and patients are faced with a bewildering array of different products with varying ingredients, and little or no clear way of knowing which is the most effective. Practitioners will often be asked “which is the best drop for dry eye”, but with no scientific evidence to base their answer on. In addition, other aspects that influence practitioner and patient choices are:

- formulation
  - percentage concentration<sup>5</sup>
  - molecular weight<sup>5</sup>
  - preservative used<sup>6</sup>
- storage bottle design.<sup>7–10</sup>

Patients may therefore face a trial-and-error approach to product selection, incurring mounting costs and frustration in the process. This will be felt even more keenly by patients who are highly price sensitive, since over-the-counter products are no longer easily available via National Health Service (NHS) subsidised prescriptions<sup>11</sup> in the UK. A recent study<sup>12</sup> on the reported experience of dry eye management across four continents identified that on average, DED still caused a

moderate impact on an individual's quality of life (median impact 3/10); less than half of the individuals in any country had undergone a consultation with an eye or health-care practitioner about their dry eye; about half had tried dry eye treatment, with artificial tears being the most common treatment, followed by warm compresses, and both therapies were rated as reasonably effective (median 5–7/10).

## Formulation

The majority of artificial tear products are aqueous-based and contain viscosity-enhancing agents, such as carbomer 940, carboxymethyl cellulose (CMC), dextran, hyaluronic acid, sodium hyaluronate (which has a smaller molecular size), hydroxypropyl guar (HP-guar), hydroxypropyl methylcellulose (HPMC hypromellose), polyvinyl alcohol, polyvinylpyrrolidone and polyethylene glycol, which aid lubrication and increase on-eye retention time.<sup>1</sup> Other ingredients may include osmotic agents, osmoprotectants, antioxidants, preservatives and inactives such as pH buffers, excipients and electrolytes.<sup>1</sup> Aqueous-based artificial tears target principally the muco-aqueous phase of the tear film, but have been shown to improve dry eye symptoms related to all subtypes of DED.<sup>2</sup>

In recent years, there has been an increase in the popularity and availability of lipid-based drops, which target the superficial tear lipid layer<sup>13,14</sup> as the emphasis on meibomian gland dysfunction and its role in evaporative dry eye continues to increase.<sup>1</sup> It has been demonstrated in randomised controlled trials that lipid-based drops are more effective at managing DED classified as evaporative.<sup>3,4</sup> These can take the form of nano-emulsion drops or liposomal sprays, which are applied to the closed eye and may be easier for those who struggle to instil drops, for example those with reduced manual dexterity or hand tremor. A completely water-free drop comprised of 100% lipid (perfluorohexyloctane) is available now, with the added benefit of being preservative-free.<sup>15</sup>

## Preservatives

Multidose eye drops, including artificial and medicated topical ocular drops, commonly contain preservatives to maintain sterility and prolong shelf life, however, these are also known to produce toxicity. Benzalkonium chloride, commonly found in multidose drops, can produce toxic, proinflammatory and detergent effects, which may actually lead to or exacerbate DED.<sup>16</sup> For this reason, there has been a move towards preservative-free and unit dose formulations, due to the risk of toxic and allergic reactions, especially when frequent instillation is required. Newer preparations may contain less damaging preservatives such as polyquaternium, or “vanishing” preservatives such as sodium perborate and purite, or feature specially designed bottles, which prevent the entry of microorganisms.<sup>17</sup> Preservative-free formulations are recommended for all types of dry eye, however this is even more important for severe dry eye or sensitive individuals, and more details can be found in the TFOS DEWS II iatrogenic report.<sup>6</sup>

## Ideal Properties

It is important that artificial tear drops behave in a similar way to natural tears. One aspect of this is the physical property of rheology, which refers to the way fluids and soft solids flow. The viscosity of human tears is high between blinks, but reduces during each blink cycle in order to protect the ocular surface from damage due to fluid turbulence.<sup>1</sup> Hence, they do not display Newtonian behaviours and are referred to as having non-Newtonian properties. Hyaluronic acid has been the subject of a significant amount of research and has been shown to exhibit these non-Newtonian shear-thinning properties,<sup>18</sup> making it more like the tear film and hence suitable for use in artificial tears.<sup>19</sup> Hyaluronic acid, a common constituent of artificial tears, is a naturally occurring glycosaminoglycan, which is found in and around body cells and tissues, for example in synovial fluid, and vitreous and aqueous humour.<sup>20</sup> Its use in ophthalmology was pioneered by Andre Balazs in the late 1960s,<sup>21</sup> with Polack and McNiece<sup>22</sup> being the first to report its use in dry eye. Hyaluronic acid is water soluble and is capable of binding large quantities of water, compared to its own weight, but its physical properties vary depending upon its molecular weight.<sup>23</sup> There is evidence to suggest that high molecular weight hyaluronic acid (HMWHA) is clinically superior in the treatment of DED compared to its low molecular weight counterpart.<sup>24</sup> Furthermore, HMWHA has been found to be protective against corneal cell apoptosis due to benzalkonium chloride toxicity, ultraviolet light radiation and chemical burns,<sup>25–27</sup> as well as being anti-inflammatory and having a role in reducing pain sensation.<sup>24,28</sup>

## Artificial Tears for Dry Eye Disease

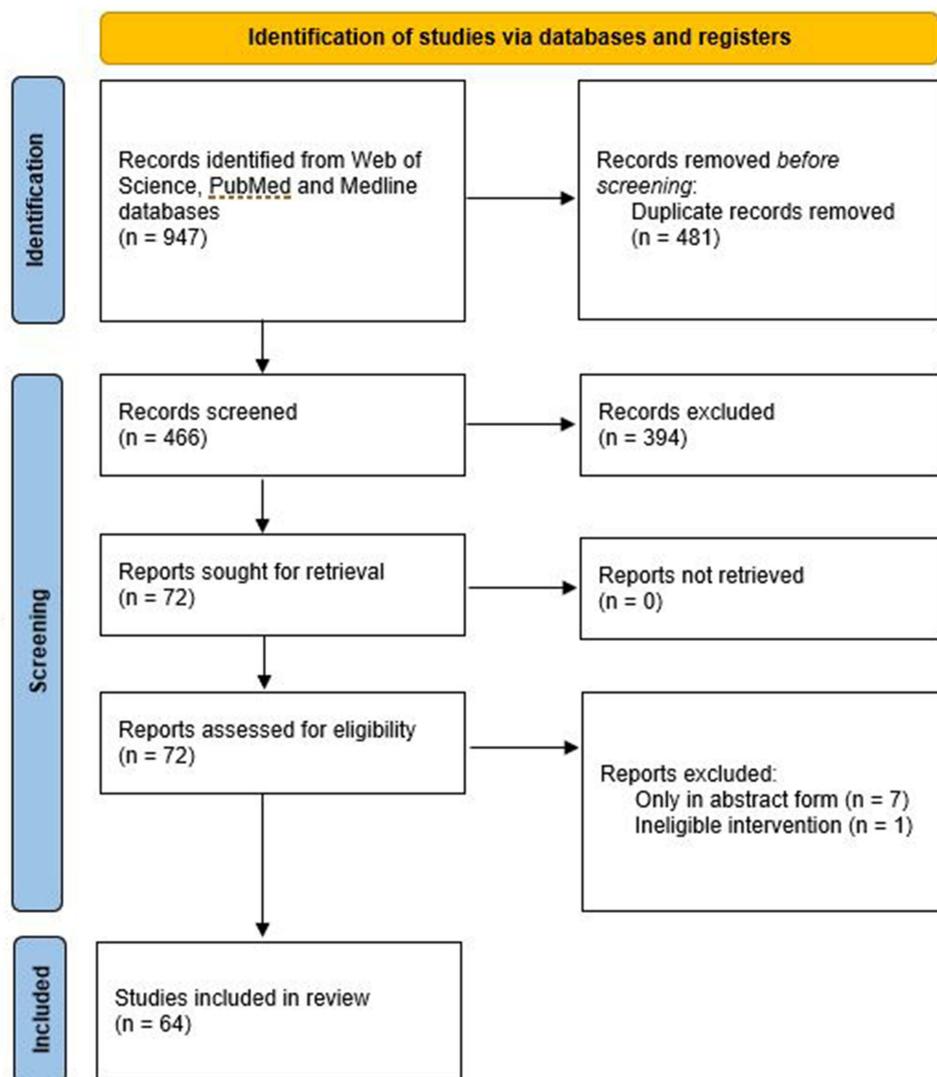
There have been several systematic reviews<sup>2,29–31</sup> conducted over the past decade, concluding that artificial tears are a safe and effective way of treating DED. A meta-analysis concluded that the effectiveness of sodium hyaluronate did not differ based on its preparation<sup>30</sup> and another<sup>32</sup> suggested that CMC appeared to be better than hyaluronic acid in treating DED, but the results were not statistically significant. Two recent reviews<sup>5,33</sup> both identified that while hyaluronic acid was effective in reducing the symptoms of DED, the ideal drop frequency and formulation (both concentration and molecular weight) for different ages and severities were yet to be investigated.

To date, there has been no review of studies which compared different artificial tears to identify whether certain formulations are more effective. Hence, with the objective to better understand the evidence for the effect of different artificial tears in managing dry eye, a search was made of the Web of Sciences databases (Clarivate Analytics, Philadelphia, USA) which includes the Science Citation Index Expanded covering over 9200 of the world's most impactful journals from 1900 to the present day along with PubMed (including MEDLINE) from its inception. The systematic review was prospectively registered on PROSPERO (CRD42022369619) and was conducted in the format prescribed by PRISMA (2020).<sup>34</sup> A search for “artificial tear\*” AND “randomi?ed” identified 481 unique results which were screened independently by two researchers (DB and DS) and verified by a third (JSW). Studies were eligible to be accepted if they were in full paper form (not abstracts or book chapters), compared two or more artificial tears against each other (not just with a placebo) and involved randomisation to avoid bias. This resulted in 64 papers being accepted (Figure 1) and the full text scrutinized for the key factors, which were tabulated in a spreadsheet and are summarised in Table 1. The study design, artificial tears compared, number and age profile of participants completing the trial, duration of use and dosing, tests conducted which showed a significant difference/did not differentiate between the products or change from baseline and general comments (dyes used for ocular surface staining, adverse events when reported and subanalyses) were extracted. Missing information is highlighted in the table and risk of bias analysis performed with the Cochrane Tool reported.<sup>35</sup> No data synthesis was attempted due to heterogeneity particularly in drop duration.

All studies are prospective (as expected) and involve parallel groups (unless stated otherwise) of dry eye patients (diagnosed using National Eye Institute, arbitrary or recently TFOS DEWS II criteria). However, less than half (20 out of 42) are registered with a clinical trials database and even those that are have high risk of bias characteristics,<sup>35</sup> hence the certainty of the result is generally low. The lack of a definitive severity classification has been identified as a factor in differentiating the effectiveness of the available artificial tears,<sup>31</sup> but previous attempts at a severity matrix table in TFOS DEWS I<sup>36</sup> led to patients being graded at different levels of severity by different tests and was abandoned in TFOS DEWS II,<sup>37</sup> severity to a dry eye patient is based on symptoms whereas it is more likely to be based on signs on the ocular surface to a cataract surgeon for example. While the intention of many of the analysed studies is to demonstrate non-inferiority compared to an established treatment, some are underpowered (see TFOS sample size recommendations)-<sup>37</sup> and/or both eyes included without accounting for the correlation between the two eyes<sup>38</sup> of an individual.<sup>39–43</sup> In most studies, fluorescein sodium is used for assessing corneal staining (although an appropriate blue light with a peak around 395nm [not cobalt blue whose peak is ~450nm] and yellow filter with a cut off around 500nm is often not stated).<sup>44</sup> Most studies use lissamine green for conjunctival staining (unless otherwise stated in Table 1) which is the recommended practice,<sup>37</sup> but few state the brand which can dramatically affect the staining observed.<sup>45</sup> Some studies<sup>46,47</sup> report differences even when they do not meet the standard criteria of  $p < 0.05$  and therefore any “difference” should be considered as noise in the data. While many trials comparing artificial tears are manufacturer initiated or sponsored, unless the research was conducted by the company or not conducted by a reputable research organisation, this should not lead to concerns regarding bias.

From the studies summarised to date (with the caveat that the effects might be affected by dry eye severity and full artificial tear formulation as well as the patient demographic) it would appear from direct comparisons between artificial tears that:

- Combination formulations are more effective than single active ingredient artificial tears.
  - The combination of CMC with hyaluronic acid is more effective than either in isolation.<sup>48,49</sup>



**Figure 1** PRISMA 2020 flow diagram of the systematic review search results.

**Notes:** PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.<sup>127</sup>

- Hyaluronic acid<sup>50</sup> and sodium hyaluronate<sup>51</sup> benefit from the addition of trehalose.
- CMC is enhanced by the addition of glycerine.<sup>52</sup>
- CoQ10 enhances the effectiveness of hyaluronic acid.<sup>53</sup>
- Newer versions of Systane (Complete and Balance) outperform earlier versions with less complexity (Ultra).<sup>54,55</sup>
- Some studies suggest sodium hyaluronate could be more effective than CMC<sup>40</sup> and carbomers,<sup>56</sup> while others find no difference,<sup>57,58</sup> the optimal percentage is not clear.<sup>59,60</sup>
- PEG containing artificial tears are more effective than those containing CMC<sup>61–65</sup> and HPMC.<sup>66,67</sup>
- Cationic formulations are more effective than sodium hyaluronate (for objective signs)<sup>68</sup> and polyvinyl alcohol.<sup>69</sup>
- Hyaluronic acid containing artificial tears might be better than those with HPMC,<sup>70</sup> but worse than those with CMC.<sup>39</sup>
- Carbomer containing artificial tears might be more effective than those based on PVA<sup>71</sup> or CMC<sup>72</sup> or cellulose/mineral oils,<sup>73</sup> but less<sup>56,74</sup> or as effective<sup>43</sup> as sodium hyaluronate.
- Most studies recommend 4x/day use, but reported/measured use is generally less than that advised.<sup>42</sup>

**Table I** Randomised Clinical Trials That Have Used Artificial Tears for the Treatment of Dry Eye Disease

| Paper                              | Design   | Comparators   | Participants Completing     | Age (Years)                    | Duration (Dosing)                             | Tests Showing Significant Difference  | Tests Not Differentiating Products   | Tests Showing Significant Difference   | Tests Showing no Change                            | General Comments   |
|------------------------------------|--|---|-----------------------------|--------------------------------|---|---|--|--|--|--|
|                                    |  |   |                             |                                |   |   |  |  |  |  |
| Amran et al 2014 <sup>69</sup>     | Randomized, open-label, multi-center study           | Cationic Emulsion - Cationorm<br>PVA-Povidone - Refresh   | N = 44<br>N = 35            | 61.3 ± 15.4<br>61.9 ± 12.5     | 4 weeks (4x/day)                              | Symptoms, TBUT, eyelid erythema, Conjunctival staining with Cationic                            | Schirmer's<br>Corneal staining   |  |  | Sub-analysis with MGD participants<br>CLINICAL TRIAL NOT REGISTERED  |
| Aragona et al 2020 <sup>48</sup>   | Randomized, double-masked, multi-center study        | CMC + HA - Optive Fusion UD<br>CMC - Refresh Optive Sensitive/Optive UD   | N = 180<br>N = 184          | 59.4 ± 13.8<br>57.5 ± 13.7     | 90 days (2x/day)                              | Lower ocular pain/discomfort<br>CMC-HA  | OSDI<br>TBUT<br>Ocular surface staining<br>Schirmer's II   | OSDI<br>Symptoms (VAS)<br>TBUT<br>Ocular surface staining                    | Schirmer's II                                      | 10% minor AE<br>CLINICAL TRIAL NOT REGISTERED  |
| Baeyens et al 2012 <sup>74</sup>   | Randomized, double-masked, multi-center study        | SH 0.18% - Vismed<br>Carbomer 0.3%<br>NaCL  | N = 100<br>N = 96<br>N = 96 | 59.3 ± 15.0<br>(across groups) | 84 days                                       | Symptoms & Corneal staining with SH vs saline   | Symptoms, corneal and conjunctival staining, Schirmer's, TBUT SH vs carbomer                                     | Symptoms<br>Corneal staining   | Conjunctival staining, Schirmer's, TBUT            | CLINICAL TRIAL NOT REGISTERED  |
| Barabino et al 2014 <sup>104</sup> | Randomized, double-masked, multi-center study        | CMC 0.5% / glycerin 0.9% - Optive<br>HA 0.2% / tamarind seed polysaccharide 0.2% - Xilolial                           | N = 25<br>N = 23            | 57.1 ± 17.4<br>52.2 ± 14.9     | 3 months (4x/day)                             | Symptoms with HA+TS   | TBUT<br>Ocular surface staining<br>Schirmer's  | OSDI<br>TBUT<br>Ocular surface staining                                      | Schirmer's   | CLINICAL TRIAL NOT REGISTERED  |
| Baudouin et al 2012 <sup>57</sup>  | Randomized, investigator-masked, multi-center study  | CMC 0.5% and Osmoprotectant - Optive<br>SH 0.18% - Vismed Multi   | N = 37<br>N = 29            | 58.1 ± 14.2<br>55.4 ± 13.4     | 3 months                                      | None  | Osmolarity, Schirmer's-I, OSDI, staining   | Osmolarity, Schirmer's-I, OSDI, staining                                     | None   | Clinical Trial NCT00987727<br>- only symptom primary and secondary outcomes and day 35 data missing<br>Cochrane Risk of Bias R? C?M-O?I-S-B? |
| Benelli et al 2010 <sup>62</sup>   | Randomized, investigator-masked, single-center study | CMC 0.5% - Cellufresh<br>PEG 400 2.5% - Blink Intensive<br>HP-guar 0.18%/PEG 400/PG - Systane                         | N = 20<br>N = 20<br>N = 20  | Not stated                     | 30 days (up to 4x/day)                        | Osmolarity with PEG400  | VA<br>Aberrometry Staining<br>TBUT<br>Schirmer's   | Aberrometry  | Osmolarity<br>VA<br>Staining<br>TBUT<br>Schirmer's | CLINICAL TRIAL NOT REGISTERED  |
| Brignole et al 2005 <sup>40</sup>  | Randomized, masked-observer, single-center study     | CMC 1% - Celluvisc<br>SH 0.18% - Vismed   | N = 11<br>N = 10            | 69 ± 2<br>57 ± 2               | 2 months (3x/day)                             | CD44, comfort (only at day 7), keratitis recovery with SH                                       | All other inflammatory markers, cornea and conjunctival staining, TBUT, corneal topography, tear meniscus height | Symptoms and ocular surface staining   | None   | Moderate dry eye and keratitis patients<br>CLINICAL TRIAL NOT REGISTERED   |
| Brodwall et al 1997 <sup>105</sup> | Randomized, investigator-masked, single-center study | Polyacrylic acid 0.2% - Visco Tears<br>PVA 1.4%   | N = 38<br>N = 41            | 60.2<br>61.8                   | 4 weeks (Drops/day a study variable; avg 3-5) | Symptoms (16/27 study days), hyperaemia, Rose Bengal staining, compliance with polyacrylic acid | TBUT<br>Schirmer's   | Symptoms & signs (unspecified)   | TBUT<br>Schirmer's                                 | CLINICAL TRIAL NOT REGISTERED  |
| Bron et al 1998 <sup>106</sup>     | Randomized, double masked, multi-center study        | Carbomer 940 0.2% - Lacrinorm/GelTears,<br>Laboratoire Chauvin<br>Carbomer 940 0.2% - Viscotears/Vidisic/<br>Lacrigel | N = 92<br>N = 87            | 58.6 ± 16.2<br>64.0 ± 14.0     | 4 weeks (4x/day)                              | None  | Symptoms<br>TBUT, Schirmer's, corneal and conjunctival staining  | Symptoms<br>TBUT,<br>Schirmer's,<br>fluorescein/<br>lissamine green staining | None   | AEs in n=21 Lacrinorm group and 17 Viscotears group<br>CLINICAL TRIAL NOT REGISTERED   |

(Continued)

Table I (Continued).

| Paper                                  | Design   | Comparators  | Participants Completing           | Age (Years)  | Duration (Dosing)             | Tests Showing Significant Difference   | Tests Not Differentiating Products                                     | Tests Showing Significant Difference   | Tests Showing no Change                               | General Comments  |
|--|--|--|-----------------------------------|--|-------------------------------|--|--|--|---|---|
|  |  |  |                                   |  |                               | Cross Comparator   |  | Compared to Baseline   |   |   |
| Calvao-Santos et al 2011 <sup>41</sup> | Randomized, open-label, single-center study                            | Tears Again [lipidic]<br>Opticol [aqueous]<br>Optive [mucin]<br>No treatment   | N = 7<br>N = 6<br>N = 7<br>N = 7  | 24 to 53 years   | 30 days (not stated)          | None   | OSDI<br>TBUT<br>Schirmer's   | Symptoms, Schirmer's for tears again   | TBUT  | Patients with digital eye strain. Compared drops primarily acting on one tear layer<br>CLINICAL TRIAL NOT REGISTERED  |
| Chiambaretta et al 2017 <sup>50</sup>  | Randomized, investigator-masked, multi-center study                    | HA-trehalose<br>HA   | N = 52<br>N = 49                  | 60.0 ± 12.2<br>58.5 ± 13.4   | 84 days (3–6x/day; average 4) | Symptoms with HA-trehalose   | Cornea & conjunctival staining   | OSDI [Schirmer's, TBUT, staining, hyperaemia, no statistics presented]         | None  | AEs: 3 with HA-trehalose vs 24 with HA<br>Clinical Trial NCT02023268 - only staining as primary outcome and day 35 data missing<br>Cochrane Risk of Bias R? C-M-O!!S-B?   |
| Christensen et al 2004 <sup>51</sup>   | Randomized, double-masked, multi-center study                          | PEG 400 0.4% / PG/HP-guar 0.3% - Systane CMC 0.5% - Refresh Tears  | N = 42<br>N = 45                  | 58.5<br>59.5   | 6 weeks (4x/day)              | Lissamine green staining, dryness, refreshed and FB symptoms with 0.5% PEG   | Fluorescein staining, use ratings, ocular signs or symptom frequency   | Corneal & conjunctival staining only with 0.4% PEG                             | Conjunctival staining with CMC                        | CLINICAL TRIAL NOT REGISTERED   |
| Cohen et al 2014 <sup>53</sup>         | Randomized, double-masked, multi-center study                          | CMC 1% - Refresh LiquiGel<br>PEG 400 0.4% / PG/HP-Guar 0.3% - Systane Gel  | N = 70<br>N = 67                  | 57.5 ± 16.6<br>56.5 ± 15.0   | 6 weeks (4x/day)              | Corneal staining with PEG  | Conjunctival staining, TBUT, symptoms                                  | Corneal staining   | Lissamine green staining, TBUT, symptoms              | CLINICAL TRIAL NOT REGISTERED   |
| Comez et al 2013 <sup>107</sup>        | Randomized, patient-masked, 2 group contralateral, single-center study | PG 0.3% and PEG 0.4% - Systane<br>SH 15% - Eystil<br>HPMC - Tears Naturale<br>CMC 0.5% - Refresh Tears   | N = 17<br>N = 13                  | 47.4 ± 14.5<br>46.3 ± 15.5   | 12 weeks (5x/day)             | None   | OSDI, Osmolarity, Schirmer's, TBUT                                     | OSDI, osmolarity, Schirmer's, TBUT   | None  | ~30% drop-out<br>CLINICAL TRIAL NOT REGISTERED  |
| Craig et al 2021 <sup>4</sup>          | Randomized, double-masked, multi-center study                          | Aminomethylpropanol, HP-guar - Systane Ultra<br>Dimyristoyl phosphatidylglycerol, HP-guar, mineral oil, polyoxl 40 stearate - Systane Complete | N = 49<br>N = 50                  | 43 ± 17<br>45 ± 16   | 6 months (4x/day +)           | Lipid thickness  | Symptoms, TMH, lipid, osmolarity, hyperaemia, expressibility, blinking | Symptoms (OSDI, DEQ-5, SANDE)<br>NIBUT, LWVE<br>Cornea & conjunctival staining | TMH, osmolarity, hyperaemia, expressibility, blinking | Symptoms improved @ 1+ month, LWVE @ 2+ months, lipid @ 3+ months staining @ 4+ months.<br>1 in 3 had no benefit in signs or symptoms. Those with lipid layer grade ≤ 3 benefit more from lipid-based drop<br>Clinical Trial ACTRN12619000390189 - additional questionnaire, acuity and lid data presented<br>Cochrane Risk of Bias R +C+M+O+I+S-B+ |
| Dausch et al 2006 <sup>76</sup>        | Randomized, investigator-masked, cross-over, multi-center study        | Liposomes - Tears Again<br>Carbomer triglycerides - Liposic  | N = 74 with deficient lipid layer | n=1 <25 years<br>n=9 25–45 years<br>n=16 46–60 years<br>n=49 >60 years | 6 weeks (3x/day)              | Symptoms, LIPCOF, TBUT, Schirmer's, lid margin inflammation with Tears Again |  | Symptoms, LIPCOF, TBUT, Schirmer's, lid margin inflammation                    | -   | Photo sequence of phospholipid liposomes sprayed on eyelid reaching ocular surface<br>CLINICAL TRIAL NOT REGISTERED   |

|  |   |  |                             |  |  |  |  |  |   |   |
|--|---|--|-----------------------------|--|--|--|--|--|---|---|
| Davitt et al 2010 <sup>64</sup>        | Randomized, double-masked, single-center study                                | PEG 400/PG/HP-guar CMC 0.5% - Optive   | N = 52<br>N = 53            | 33 x 18–64 years, 19 x ≥65 years<br>41 x 18–64 years, 12 x ≥65 years | 6 weeks (4x/day)   | Cornea & conjunctival staining with PEG 400/PG/HP-guar group | Symptoms, TBUT   | Symptoms   | TBUT  | CLINICAL TRIAL NOT REGISTERED   |
| Diaz-Llopis et al 2019 <sup>108</sup>  | Randomized, investigator-masked, multi-center study                           | Seawater spray - Quinton CMC 0.5% -Viscofresh  | N = 60<br>N = 60            | 68.1 ± 6.3<br>66.8 ± 8.4   | 12 weeks (5x/day)  | OSDI, IL-1 β and IL-6 with seawater spray                    | Cornea & conjunctival staining, Schirmer I, osmolarity, TBUT, TMH  | OSDI, Cornea & conjunctival staining                     | Schirmer I, osmolarity, TBUT, TMH                         | CLINICAL TRIAL NOT REGISTERED   |
| Downie et al 2020 <sup>109</sup>       | Randomized, double-masked, multi-center study                                 | CMC, glycerin, flaxseed oil and castor oil and osmoprotectants (levocarnitine, Erythritol & trehalose) (OM3) Refresh Optive Advanced | N = 120<br>N = 122          | 54.3 ± 17.3<br>52.8 ± 16.7   | 90 days (2x/day +)   | Combined corneal / conjunctival staining with OM3            | OSDI<br>TBUT   | OSDI<br>TBUT<br>Combined corneal / conjunctival staining | None  | AEs (OM3 0% vs ROA 4.1%)<br>Clinical Trial NCT02553772<br>Cochrane Risk of Bias R +C+M+O+I+S+B?   |
| Dumbleton et al 2009 <sup>110</sup>    | Randomized, double-masked, single-center study                                | PEG 400 0.25% - Blink gel tears<br>CMC 1% - Refresh Liquigel   | N = 56<br>N = 54            | 46.3 ± 19.3<br>47.2 ± 19.1   | 30 days (3x/day)   | Symptoms with PEG  | Phenol red test, TMH, NIBUT, hyperaemia, corneal and conjunctival staining   |  | Hyperaemia, corneal and conjunctival staining             | No notable AE's<br>CLINICAL TRIAL NOT REGISTERED  |
| Essa et al 2018 <sup>3</sup>           | Randomized, investigator-masked, crossover, single-center study               | SH 0.4% - Clinitas Soothe<br>SH 0.15% - Hyabak Phospholipid liposomes -Tears Again<br>CMC - TheraTears                               | N = 50 (for all treatments) | 60.8 ± 14.2  | 4 weeks (drops/day a study variable; average 2–3)          | None   | OSDI<br>NIBUT<br>FBUT<br>TMH<br>Phenol Red LIPCOF<br>Ocular surface staining<br>Lipid layer grading Osmolarity (baseline visit only) | OSDI<br>LIPCOF<br>Conjunctival staining                  | NIBUT<br>FBUT<br>TMH<br>Phenol Red<br>Lipid layer grading | Artificial tears performed similarly. However, osmolarity balanced preferred in those with low baseline tear volume and liposomal spray for those with lipid layer deficiency.<br>Clinical Trial NCT02420834<br>Cochrane Risk of Bias R? C?M-O?!+S+B? |
| Fogt et al 2019 <sup>111</sup>         | Randomized, observer-masked, crossover, non-dispensing, single-center study   | Omega 3 - Refresh Optive MEGA-3<br>Refresh Optive  | N = 19<br>with thin lipid   | 46.5 ± 8.7   | 60 minutes (Single application)                            | Lipid layer thickness (overall), Symptoms with MEGA-3        | None   | Lipid layer thickness<br>Symptoms                        | Symptoms<br>Schirmer's                                    | Clinical Trial NCT03380624<br>- 15 min data missing<br>Cochrane Risk of Bias R? C?M-O?!+S-B?  |
| Fondi et al 2018 <sup>112</sup>        | Randomized, patient-masked, crossover single-center study                     | SH and trehalose - Thealoz Duo<br>HA, trehalose and carbomer - Thealoz Duo Gel   | N = 40 (for both treatment) | 43.7 ± 12.3  | 1 week (actual 3.2 ± 2.6x/day HT & 1.9 ± 2.2x/day HTC-gel) | None   | Corneal / conjunctival staining<br>TBUT<br>Sleep quality   | Corneal / conjunctival staining<br>TBUT<br>Sleep quality | None  | Clinical Trial NCT02980913<br>Cochrane Risk of Bias R? C?M-O?!+S+B?   |
| Garcia-Lazaro et al 2011 <sup>67</sup> | Randomized, investigator masked, cross-over, single-center study              | PEG 400 2.5% - Blink Intensive Tears<br>HPMC 0.3% - Artific Tears  | N = 20                      | 57.5 ± 8.4   | 1 month (3x/day)   | Tear meniscus volume with PEG                                | None   | Tear meniscus volume                                     | None  | CLINICAL TRIAL NOT REGISTERED   |
| Gensheimer et al 2012 <sup>113</sup>   | Randomized, double-masked, contralateral, non-dispensing, single-center study | Glycerin 1% with PLL-g-PEG - Eyeon<br>PG 0.3% and PEG 0.4% - Systane   | N = 16                      | 44.5   | 120 mins (single application)                              | NIBUT, TBUT with glycerine                                   | None   | NIBUT with glycerine                                     | TBUT  | CLINICAL TRIAL NOT REGISTERED   |

(Continued)

Table I (Continued).

| Paper                                       | Design  | Comparators  | Participants Completing         | Age (Years)   | Duration (Dosing)                                    | Tests Showing Significant Difference                               | Tests Not Differentiating Products  | Tests Showing Significant Difference                             | Tests Showing no Change   | General Comments   |
|---|---|--|---------------------------------|---|--|--|---|--|---|--|
|   |   |  |                                 |   |  | Cross Comparator   |   | Compared to Baseline   |   |  |
| Gokul et al 2018 <sup>54</sup>              | Randomized, double-masked, contralateral, non-dispensing, single-center study | Systane Balance<br>Systane Ultra   | N = 30                          | 27 ± 9  | 30 mins (following 2.5 mins in adverse conditions)   | Lipid thickness with liposomal Systane Balance                     | NIBUT   | Lipid thickness, NIBUT   | Glare acuity, temperature variation, TMH                        | CLINICAL TRIAL NOT REGISTERED  |
| Greene et al 1992 <sup>66</sup>             | Randomized, double-masked, single-center study                                | CMC 1.0% - Celluvisc Lubricant<br>HPMC 0.3% - Tears Naturale 2                     | N=28?<br>N=28?<br>severe        | ??  | 2 months (8x/day)                                    | Symptoms, corneal erosions and impression cytology grades with CMC | Schirmer's Corneal & conjunctival staining<br>Lid & conjunctival swelling | Corneal staining, Symptoms, impression cytology grade (CMC only) | Schirmer's  | CLINICAL TRIAL NOT REGISTERED  |
| Iester et al 2000 <sup>70</sup>             | Randomized, open-label?, multi-center, study                                  | HPMC 0.3%<br>HA 0.4%   | N = 55<br>N = 58                | 56.4 ± 12.8<br>52.2 ± 10.6  | 2–3 months (6x/day)                                  | Symptoms, Tear ferning Osmolarity, impression cytology With HA     | TBUT Staining<br>Schirmer's I   | TBUT, staining, Schirmer's I, symptoms<br>Impression cytology    | -   | Ferning, osmolarity and impression cytology only measured in ~33% of sample each<br>CLINICAL TRIAL NOT REGISTERED  |
| Jacobi et al 2012 <sup>114</sup>            | Randomized, open-label? Single-center study                                   | HP-Guar - Systane UD<br>Tamarindus indica seed polysaccharide 1% - VISINE INTENSIV | N=14<br>N=14                    | 44 ± 8 overall  | 3 months (5x/day)                                    | TBUT with HP-Guar  | OSDI<br>Schirmer's II<br>LIPCOF<br>Corneal & conjunctival (rose Bengal)   | TBUT<br>LIPCOF<br>OSDI with HP-Guar                              | Schirmer's II<br>LIPCOF<br>Corneal & conjunctival (rose Bengal) | CLINICAL TRIAL NOT REGISTERED  |
| Jenkins et al 2020 <sup>115</sup>           | Randomized, double-masked, multi-center study                                 | Systane Balance<br>Refresh Optive advanced   | N = 117<br>N = 114              | 56.7 ± 14.7<br>55.6 ± 16.4  | 35 days (4x/day)                                     | TBUT with Systane  | Symptoms  | Symptoms<br>TBUT   | None  | 2 lipid based drops<br>Clinical Trial NCT02776670 - exploratory lid wiper epitheliopathy and questionnaire additionally reported<br>Cochrane Risk of Bias R +C+M!O!-S+B? |
| Johnson et al 2006 <sup>60</sup>            | Randomized, double-masked, contralateral, single-center study                 | SH 0.1%<br>SH 0.3%<br>NaCL 0.9%  | N = 13 (for all treatments)     | Range 21–34   | 6 hours (single application)                         | NIBUT (0.3% SH performed better than 0.1% SH)                      | Symptoms  | Symptoms<br>NIBUT  | None  | CLINICAL TRIAL NOT REGISTERED  |
| Johnson et al 2008 <sup>56</sup>            | Randomized, double-masked study, single-center study                          | Carbomer 934 0.3% - Lacryvisc<br>SH 0.18% - Vismed                                 | N = 33<br>N = 32                | Median 36<br>Median 39<br>Range 21–64                                       | 1 month (drops/day a study variable; median 2.1–2.3) | Corneal & conjunctival staining with SH                            | Symptoms<br>NIBUT<br>TBUT   | Symptoms<br>Corneal & conjunctival staining                      | NIBUT<br>TBUT   | CLINICAL TRIAL NOT REGISTERED  |
| Khaireddin and Schmidt, 2010 <sup>116</sup> | Randomized, multi-center study  | HA - Vismed light<br>Phospholipid - Tears Again                                    | N = 103<br>N=113<br>Evaporative | n=9 <25 years,<br>n=26 25–45 years,<br>n=42 46–60 years,<br>n=139 >60 years | 3 months<br>3x/day +                                 | LIPCOF, lid inflammation<br>NIBUT with Tears Again                 | Schirmer's  | LIPCOF, lid Inflammation<br>NIBUT                                | Schirmer's  | CLINICAL TRIAL NOT REGISTERED  |
| Khanal et al 2007 <sup>117</sup>            | Randomized, investigator-masked, single-center study                          | Castor oil 0.1.25%<br>HPMC 0.32% - Artelac Single Dose Unit                        | N = 27<br>N = 26                | Unclear from text   | 1 month (3x/day)                                     | Tear evaporation with HPMC   | Schirmer's, osmolarity  | Tear evaporation;<br>Lipid layer with castor oil                 | Schirmer's, osmolality  | CLINICAL TRIAL NOT REGISTERED  |

|  |   |  |                             |                            |  |  |   |   |  |  |
|--|---|--|-----------------------------|----------------------------|--|--|---|---|--|--|
| Labetoulle et al 2018 <sup>118</sup>   | Randomized, double-masked, multi-center study                           | HP-Guar - HA dual-polymer – Systane Hydration SH 0.15% - Hyabak                                  | N = 50<br>N = 49            | 61.7 ± 12.3<br>56.7 ± 14.3 | 6 weeks (4x/day)   | None   | Symptoms, TBUT, ocular surface staining   | Ocular surface staining   | Symptoms, TBUT                             | Fluorescein dye only<br>Clinical Trial<br>NCT02470429<br>- exploratory end points additionally reported in n=30<br>Cochrane Risk of Bias R +C+M?O?I+S+B? |
| Lahia et al 2020 <sup>119</sup>        | Randomized, double-masked, single-center study                          | Sacha inchi microemulsion (SIME) HA 0.2%   | N = 26<br>N = 26            | 53.3 ± 12.6 overall        | 1 month (3x/day)   | Ocular protection index with SIME                                  | Symptoms, Corneal & conjunctival staining, TBUT                                     | Symptoms, osmolarity in hyperosmolar subgroup. Corneal and conjunctival (nasal) staining, TBUT & lid redness only with SIME | Osmolarity, Conjunctival temporal staining | Fluorescein dye only<br>Clinical Trial<br>NCT03569202<br>Cochrane Risk of Bias R +C+M+O+I+S+B+   |
| Lee et al 2011 <sup>58</sup>           | Randomized, observer-masked, single-center study                        | CMC 0.5% - Refresh Plus SH 0.1% - Hynex  | N = 33<br>N = 32            | 39 ± 14.6<br>37 ± 13.4     | 2 months (6x/day)  | None   | Corneal & conjunctival staining<br>TBUT Symptoms                                    | Cornea & conjunctival staining<br>TBUT Symptoms   | None                                       | Fluorescein staining only<br>CLINICAL TRIAL NOT REGISTERED   |
| Lievens et al 2019 <sup>52</sup>       | Randomized, double-masked, multi-center study                           | CMC 1.0% and glycerin 0.9%<br>CMC 1.0%   | N = 94<br>N = 94            | ≥ 18 years of age          | 1 month (2x/day +)   | Symptoms<br>Corneal staining<br>TBUT<br>With CMC-GLY at day 7 only | Symptoms<br>Corneal staining<br>TBUT<br>at all other time points                    | Symptoms, corneal staining, and TBUT  | None                                       | Clinical Trial<br>NCT02280473<br>Cochrane Risk of Bias R +C+M+O+I+S+B+   |
| Marner et al 1996 <sup>71</sup>        | Randomized, open-label, crossover, multi-center study                   | Carbomer gel - Lubrithal PVA 1.4% - Lacril/ Liquifilm  | N=54 (for all treatment)    | 64.3, range 38–89          | 2 weeks (drops/day a study variable (carbomer 3.9 vs PVA 4.6x) | Symptoms, TBUT. Instillation frequency with carbomer               | Schirmer's I<br>Ocular surface staining, Corneal sensitivity                        | Schirmer's I, TBUT, ocular surface staining, symptoms   | None                                       | Rose Bengal only used<br>AEs 33% with carbomer, 8% with PVA<br>CLINICAL TRIAL NOT REGISTERED   |
| Mihaltz et al 2018 <sup>43</sup>       | Randomized, investigator-masked, single-center study                    | Carbomer, triglycerides - Artelac Lipids UD<br>SH - Artelac Splash Edo UD                        | N=10<br>N=13                | 55.5 ± 11.3<br>53.8 ± 17.9 | 3 months (4x/day +)  | None   | Schirmer's, TBUT, Ocular surface staining<br>Symptoms<br>MG dropout<br>aberrations  | Schirmer's, TBUT, Ocular surface staining   | None                                       | Lipid drops better for those with >50% MG dropout improving Schirmer's & aberrations<br>CLINICAL TRIAL NOT REGISTERED                                    |
| Muntz et al 2020 <sup>55</sup>         | Randomized, double-masked, contralateral crossover, single-center study | Lipid, PG, HP-guar and mineral oil - Systane Complete<br>PEG 400, PG and HP-guar - Systane Ultra | N = 28 (for all treatments) | 29 ± 9                     | Single application – adverse environment                       | Symptoms, lipid layer quality, NIBUT with Systane complete         | TMH<br>Hyperaemia   | Symptoms, Lipid layer quality only with Systane Complete  | TMH<br>Hyperaemia                          | Clinical Trial<br>ACTRN12619000361101<br>Cochrane Risk of Bias R +C+M+O+I+S+B?   |
| Nelson and Farris, 1998 <sup>120</sup> | Randomized, double-masked, multi-center study                           | PVA 1.4% - Liquifilm SH 0.1%   | N = 16<br>N = 20            | 52.3 ± 16.4<br>64.8 ± 10.8 | 8 weeks<br>8x/day +  | -  | Symptoms, Osmolality, TBUT, rose bengal staining, Schirmer's I, impression cytology | Symptoms, Osmolality, TBUT, rose bengal staining, Schirmer's I  | Impression cytology                        | CLINICAL TRIAL NOT REGISTERED  |

(Continued)

Table I (Continued).

| Paper                                   | Design   | Comparators  | Participants Completing                | Age (Years)  | Duration (Dosing)                              | Tests Showing Significant Difference  | Tests Not Differentiating Products   | Tests Showing Significant Difference  | Tests Showing no Change                           | General Comments   |
|---|--|--|--|--|--|---|--|---|---|--|
|   |  |  |  |  |  | Cross Comparator  |  | Compared to Baseline  |   |  |
| Ousler et al 2007 <sup>65</sup>         | Randomized, double-masked crossover, single-center study | PEG & HP-Guar - Systane<br>CMC - Refresh Tears<br>CMC - Refresh Endura                           | N = 50                                 | 62.7   | Single application                             | TBUT, Ocular protection index with Systane  | Blink rate   | No comparison presented   |   | No difference between CMC products<br>CLINICAL TRIAL NOT REGISTERED  |
| Park et al 2017 <sup>59</sup>           | Randomized, investigator-masked, multi-center study      | SH 0.1%<br>SH 0.15%<br>SH 0.3%<br>Cyclosporine 0.05%   | N = 43<br>N = 41<br>N = 47<br>N = 45   | 44.1 ± 13.9<br>46.2 ± 14.0<br>44.8 ± 16.2<br>45.2 ± 15.4 | 12 weeks (5–6x/day)                            | Schirmer's (0.15% SH group)   | Corneal & conjunctival staining<br>TBUT  | Corneal & conjunctival staining<br>TBUT   | Schirmer's  | AEs 13% 0.1% SH, 20% 0.15% SH, 13% 0.3% SH, 31% 0.05% CS group.<br>Clinical Trial KCT0001796<br>Cochrane Risk of Bias R +C!M-O?!+S+B?                            |
| Perez-Balbuena et al 2016 <sup>47</sup> | Randomized, double-masked, multi-center study            | Xanthan gum 0.09% and chondroitin sulfate 0.1%<br>PEG 400 0.4% and PG 0.3%                       | N = 76<br>N = 72                       | 49.9 ± 16.0<br>45.5 ± 12.7                               | 2 months (4x/day)                              | None  | Schirmer's, TBUT, Symptoms, Corneal & conjunctival staining                        | Schirmer's, TBUT, Symptoms  | Corneal & conjunctival staining                   | Clinical Trial NCT01657253<br>Cochrane Risk of Bias R +C!M-O?!+S+B+  |
| Pinto-Bonilla et al 2015 <sup>42</sup>  | Randomized, open-label, crossover, single-center study   | Trehalose and SH 1.5mg/mL -Thealoz Duo<br>PEG & HP-guar - Systane                                | N = 9<br>N = 8                         | 45.3 ± 11.8<br>53.8 ± 14.6                               | 1 week (5x/day)<br>(Actual 3.7±0.9 / 3.5 ±0.9) | None  | Symptoms, Corneal & conjunctival staining, Schirmer's, TBUT                        | Symptoms  | Schirmer's TBUT, Corneal & conjunctival staining  | CLINICAL TRIAL NOT REGISTERED  |
| Postorino et al 2018 <sup>53</sup>      | Randomized, investigator-masked, single-center study     | HA crosslinked + CoQ10<br>HA 0.15% crosslinked   | N = 20<br>N = 20                       | 60.2 ± 13.6<br>60.9 ± 12.5                               | 3 months (4x/day)                              | Symptoms, MGD assessment, corneal / conjunctival staining, epithelial hyperreflectivity and keratocytes with HA + CoQ10 | Symptoms, corneal aesthesiometry TBUT  | OSDI MGD assessment, corneal / conjunctival staining, epithelial hyperreflectivity and keratocytes with HA + CoQ10 only | Corneal aesthesiometry TBUT                       | Fluorescein staining only<br>Clinical Trial NCT03074344 - meibomian gland assessment and confocal additionally reported<br>Cochrane Risk of Bias R +C+M-O?!+S-B? |
| Pult et al 2021 <sup>77</sup>           | Randomized, double-masked, crossover, multi-center study | Phospholipid 0.98% - Tears Again<br>Phospholipid 0.12% - Ocuvors                                 | N=30 (all treatments)                  | 33.2±1.8   | Single application                             | Symptoms, NIBUT with high concentration lipid   | None   | Symptoms, NIBUT with high concentration lipid only  | None  | CLINICAL TRIAL NOT REGISTERED  |
| Robert et al 2016 <sup>68</sup>         | Randomized, investigator masked, multi-center study      | Cationic Emulsion (Cation Norm)<br>SH 0.18% - Vismed   | N = 37<br>N = 37<br>Moderate to severe | 60.0 ± 14.6<br>65.3 ± 11.1                               | 3 months (4x/day)                              | Symptoms at 1 month with SH   | TBUT, Schirmer's, Corneal & conjunctival staining, Osmolarity, Impression cytology | Symptoms, Corneal & conjunctival staining   | Schirmer's, TBUT, Osmolarity, Impression cytology | AEs 18% CE, 27% HS >10% drop-out<br>Clinical Trial EudraCT 2011-A00955-36<br>Cochrane Risk of Bias R +C!M-O?!+S+B?   |
| Safarzadeh et al 2017 <sup>121</sup>    | Randomized patient-masked, single-center study           | Dextran 70, 1 mg/mL and HPMC – Tears Naturale<br>Dextran 70, 0.1 mg/mL and 0.3 g HPMC – Tearlose | N = 41<br>N = 47                       | 44.1 ± 6.3<br>45.8 ± 8.4                                 | 4 weeks (2x/day)                               | None  | Symptoms, TBUT, Schirmer's Corneal & conjunctival staining                         | Symptoms, TBUT, Corneal & conjunctival staining   | Schirmer's  | Fluorescein staining only<br>CLINICAL TRIAL NOT REGISTERED   |

|  |  |  |  |  |  |   |   |  |  |  |
|--|--|--|--|--|--|---|---|--|--|--|
| Sanchez et al 2017 <sup>39</sup>       | Randomized, investigator-masked, single-center study                           | CMC 0.5% (Viscofresh)<br>HA 0.15% (Lubristil)  | N = 7<br>N = 8   | 51.8 ± 14.1<br>71.8 ± 12.2                               | 1 month (4x/day)                                   | TBUT, corneal staining, and HLA-DR with CMC   | Schirmer's<br>Other inflammatory markers                      | HLA-DR, TBUT & corneal staining with CMC                             | Schirmer's, Tear clearance,                    | No Aes<br>CLINICAL TRIAL NOT REGISTERED  |
| Schmidl et al 2015 <sup>51</sup>       | Randomized, double-masked, single-center study                                 | Trehalose and SH<br>1.5mg/mL -Thealoz Duo<br>SH, 0.15% - Hyabak<br>NaCL 0.9% - Hydrabak  | N = 20<br>N = 20<br>N = 20                                   | 43.6 ± 13.3<br>42.9 ± 12.0<br>41.8 ± 9.9                 | 240 minutes<br>Single application                  | Tear film thickness (SH +trehalose to 240min and SH to 40min only)  | TBUT, Schirmer's  | Tear film thickness (both SH products)                               | TBUT, Schirmer's                               | CLINICAL TRIAL NOT REGISTERED  |
| Simmons and Vehige, 2007 <sup>78</sup> | Randomized, double-masked, crossover and parallel groups, multi-center studies | CMC 1.0%<br>CMC 0.5% (Refresh Tears)   | N = 43 single application<br>Parallel<br>N = 53<br>N = 50    | Mean 62<br>Not stated                                    | 60 minute (single-application)<br>1 month (4x/day) | Ocular protection index (low viscosity to 20min, high viscosity to 30min).<br>Corneal & conjunctival staining with higher viscosity | Symptoms  | Symptoms, Corneal and conjunctival staining                          | None   | Fluorescein staining only. More AEs with high viscosity – visual disturbance 23vs4%; discharge 13vs2%<br>CLINICAL TRIAL NOT REGISTERED   |
| Simmons et al 2015 <sup>79</sup>       | Randomized, investigator-masked, multi-center study                            | CMC (Refresh Optive Advanced Sensitive), unit dose<br>CMC (Refresh Optive Sensitive), unit dose<br>CMC (Refresh Optive Advanced Sensitive), multi-dose<br>CMC (Refresh Optive Sensitive), multi-dose | N = 105<br>N = 103<br>N = 51<br>N = 56                       | 54.4 ± 14.8<br>55.8 ± 14.1<br>55.2 ± 14.5<br>53.5 ± 13.9 | 30 days (2x/day +)                                 | None  | Symptoms, TBUT, Corneal & conjunctival staining<br>Schirmer's | OSDI<br>TBUT   | Corneal & conjunctival staining,<br>Schirmer's | No clinically significant differences in safety, effectiveness, and acceptability between lipid and aqueous artificial tears<br>Clinical Trial<br>NCT01459588<br>Cochrane Risk of Bias R +C?M-O?I+S+B? |
| Simmons et al 2015 <sup>49</sup>       | Randomized, double-masked, multi-center study                                  | CMC 0.5% + 0.1% HA (Optive Fusion)<br>CMC 0.5% + 0.15HA<br>CMC 0.5% (Refresh Tears)  | N = 87<br>N = 87<br>N = 90                                   | 59.6 ± 14.5<br>59.2 ± 16.3<br>60.0 ± 13.3                | 3 months (2x/day +) (actual 4.3, 3.9, 3.8x/day)    | Some symptoms with Fusion<br>Corneal staining with Fusion vs Refresh  | Conjunctival staining   | Symptoms, Corneal & Conjunctival staining                            | None   | Investigational formulations<br>Clinical Trial<br>NCT01294384<br>- visual disturbance questionnaire additionally reported<br>Cochrane Risk of Bias R +C+M+O?I+S+B?                                     |
| Szegedi et al 2018 <sup>122</sup>      | Randomized, patient-masked, single-center study                                | SH 0.18% + triglycerides, and phospholipids<br>SH 0.18% - Vismed<br>sodium chloride 0.9% - Hydrabak  | N = 20?<br>N = 20?<br>N = 20?                                | 34.6 ± 11.7<br>40.5 ± 9.9<br>39.2 ± 12.8                 | 40 minutes<br>Single-application                   | Tear film thickness 40min vs 20min vs 0min with phospholipids   | TBUT, Corneal staining, Lipid thickness                       | Tear film thickness, TBUT, Corneal staining, Lipid thickness         | None   | Clinical Trial<br>NCT03161080<br>Cochrane Risk of Bias R? C?M-O-I+S+B?   |
| Tomlison et al 2013 <sup>123</sup>     | Randomized, double-masked, crossover, single-center study                      | CMC 0.5% - Refresh Tears<br>CMC 0.5%/castor oil - Optive Plus<br>Glycerin 1%/castor oil - Refresh Ultra  | N = 18 with dry eye<br>N = 19 controls<br>For all treatments | 41 ± 14<br>30 ± 12                                       | 2 weeks<br>3x/day                                  | Evaporation for both CMCs   | Symptoms, TBUT, NIBUT (except for controls), osmolality       | Symptoms, evaporation, TBUT, NIBUT (except for controls), osmolality | Lipid thickness                                | Measures taken after adaptation to environmental centre<br>CLINICAL TRIAL NOT REGISTERED   |

(Continued)

Table I (Continued).

| Paper                                  | Design   | Comparators   | Participants Completing      | Age (Years)                               | Duration (Dosing)   | Tests Showing Significant Difference  | Tests Not Differentiating Products               | Tests Showing Significant Difference                                      | Tests Showing no Change  | General Comments  |
|--|--|---|------------------------------|---|---|---|--|---|--|---|
|  |  |   |                              |   |   | Cross Comparator  |  | Compared to Baseline  |  |   |
| Troiano and Monaco, 2008 <sup>46</sup> | Randomized, patient-masked, crossover, single-center study | HA 0.4% 300mOsm/L<br>HA 0.4% 150mOsm/L  | N = 28<br>For all treatments | 55.5 ± 7.3                                | 7 days<br>4x/day  | Foreign body and dryness symptoms and ocular surface staining with 150mOsm/L          | None   | Symptoms, hyperaemia, ocular surface staining                             | None   | Reducing osmolarity effective<br>Rose Bengal staining only<br>CLINICAL TRIAL NOT REGISTERED   |
| van Setten et al 2020 <sup>124</sup>   | Substitution, open-label, multi-center study               | High molecular weight HA 0.15% - Comfort Shield<br>Over habitual controls   | N = 44<br>N = 40             | 57.7 ± 14.4<br>59.5 ± 12.5                | 8 weeks<br>Actual 8.2 vs 6.5  |   |  | Symptoms, Visual acuity, nerve fibre length with high molecular weight HA | Corneal staining, TBUT, Schirmer's, Lid wiper epitheliopathy, mucotaneous junction, osmolarity | Change from habitual optimal artificial tears. No change with controls<br>CLINICAL TRIAL NOT REGISTERED                             |
| Waduthantri et al 2012 <sup>125</sup>  | Randomized, double-masked, single-center study             | CMC 0.5% - Refresh Tears<br>PEG 400 0.4% / PG/HP-guar 0.3% - Systane Ultra  | N = 15<br>N = 15             | 54.7 ± 5.8<br>55.9 ± 5.3                  | 6 weeks<br>4x/day   | None  | Symptoms<br>Schirmer's<br>TBUT, Corneal staining | Symptoms  | Schirmer's<br>TBUT, Corneal staining   | Clinical Trial NCT00796926 - meibography, osmolarity and tear meniscus height not reported<br>Cochrane Risk of Bias R +C/M+O+I+S-B+ |
| Wang et al 2007 <sup>73</sup>          | Randomized, open label, single-center study                | Carbomer - Vidisic Ophthalmic Gel<br>Cellulose - Artelac Ophthalmic Solution<br>Mineral oil (lanolin) -Duratears Ointment | N = 22<br>N = 23<br>N = 22   | 55.9 ± 15.7<br>50.1 ± 14.3<br>60.3 ± 11.2 | 4 weeks<br>(4x/day for Carbomer and Cellulose)<br>(1x/day before sleep for mineral oil) | Schirmer's with Carbomer and Cellulose & TBUT with Carbomer                           | Schirmer's                                       | Symptoms, TBUT, Schirmer's  |  | Fluorescein staining only, but not reported in results<br>CLINICAL TRIAL NOT REGISTERED   |
| Wang et al 2010 <sup>126</sup>         | Randomized, open label, single-center study                | Carbomer + lipid gel - Liposic Ophthalmic Liquid Gel<br>HP-guar gel - Systane Lubricant Eye Drops                         | N = 15<br>N = 15             | 40.4 ± 15.0<br>49.5 ± 12.2                | 2 months (4x/day)   | Symptoms & Schirmer's with Carbomer + lipid   | TBUT   | Symptoms<br>Schirmer's<br>TBUT  | None   | Fluorescein staining only, but not analysed in results<br>CLINICAL TRIAL NOT REGISTERED   |
| Xiao et al 2008 <sup>72</sup>          | Randomized, investigator-masked, single-center study       | Carbomer-based 0.4% gel<br>CMC 1.0%   | N = 30<br>N = 30             | 46.7 ± 2.3<br>46.6 ± 2.1                  | 3 months<br>3x/day +  | Symptoms, TBUT, Schirmer's, corneal staining, ocular residence time with carbomer gel | None   | Symptoms, TBUT, Schirmer's corneal staining (but no statistics presented) | None   | Method relating to precorneal residence time missing.<br>Fluorescein staining only.<br>CLINICAL TRIAL NOT REGISTERED                |

**Notes:** Grey box = no statistical comparison made; ? = not certain from paper. Cochrane Risk of Bias Tool Rating:<sup>35</sup> "+" : low risk; "-" : high risk; "?" : unclear risk; for Random sequence generation (selection bias), allocation Concealment (selection bias); Masking of participants/researchers (performance bias), masking of Outcome assessment (detection bias), Incomplete outcome data (attrition bias), Selective reporting (reporting bias), other Biases (respectively). CLINICAL TRIAL NOT REGISTERED - based on a search of the main registries and paper. © Aston University.

**Abbreviations:** CoQ10, coenzyme Q10; CMC, carboxymethylcellulose/ carmellose sodium; HA, hyaluronic acid/ hyaluronan; HPMC, Hydroxypropyl methylcellulose; HP-Guar, Hydroxypropyl guar; NaCl, sodium chloride; NIBUT, non-invasive tear breakup time; PEG, polyethylene glycol; PG, propylene glycol; PVA, polyvinyl alcohol; SH, sodium hyaluronate; TBUT, fluorescein tear breakup time; TMH, tear meniscus height; LIPCOF, Lid parallel conjunctival folds.

- Long-term compliance is needed to improve ocular surface signs rather than just symptoms<sup>4</sup> and symptoms benefit from 4x/day compared to “as needed” dosing.<sup>75</sup>
- Higher liposomal concentration increases effectiveness.<sup>76,77</sup>
- Lower osmolarity drops increase the effectiveness of an artificial tear drop.<sup>46</sup>
- Higher concentration (viscosity) CMC is more effective in reducing corneal and conjunctival staining, but caused more reports of visual disturbance.<sup>78</sup>
- While drops targeting individual layers of the tear film seem equally effective,<sup>41,79</sup> studies have shown that the most effective drop for an individual can be predicted from their baseline classification; drops containing phospholipids are more effective in those with evaporative dry eye<sup>3,4</sup> and osmoprotectants benefit those with high tear film osmolarity.<sup>3</sup>
- Artificial tears may not be effective for as much as one-third of patients, but this can be predicted by one month of compliant use.<sup>4</sup>

These findings can inform clinical dry eye practice; in summary: non-preserved or soft preserved artificial tears being appropriate to prescribe to patients, regardless of the severity of their DED; patients with evaporative dry eye should be prescribed artificial tears containing a high concentration of liposomes; one month’s compliant use 4x/day is recommended to determine whether an artificial tear can manage the patients’ symptoms in the longer-term; signs of ocular surface disease typically take up to 4 months to start improving so patience is needed; artificial tears with multiple active ingredients (especially with PEG) seem to outperform more basic previous generation drops; ability to use different types of artificial tear bottles/sprays varies<sup>9</sup> and should be part of the prescribing consideration. While the efficacy of artificial tears is well established for managing DED, its use in ocular surface disease without symptoms to improve post-surgical symptomology and to reduce refractive ‘surprises’ from poor ocular biometry<sup>80</sup> is less well established. The data available as reviewed in this study is limited by the definition of dry eye disease applied in published studies being variable as well as the disease severity examined and compliance with artificial tears being rarely quantified.

## Other Therapeutic Functions of Artificial Tears

As well as being a management option for dry eye disease and the ocular surface, artificial tears can also be utilised for a wide range of therapeutic functions such as in the treatment of anterior eye trauma, infection, inflammation and disease as well as contact lens management.

### Corneal Abrasion and Wound Healing

Corneal abrasions can be caused by foreign bodies, trauma, and trichiasis, and may result in pain, redness, lacrimation, and photophobia. Artificial tears improve epithelial healing.<sup>81</sup> Ideally, preservative free drops are used as they tend to be associated with better ocular surface health and tolerability.<sup>82</sup> The most common treatment for perioperative corneal abrasions is artificial tears followed by a combination of artificial tears and antibiotic ointment.<sup>83</sup> Most artificial tears contain hydrogels; these are known to activate the epidermal growth factor (EGF) receptor which promotes the healing of corneal epithelial wounds.<sup>84</sup>

### Pain and Inflammation Management

Artificial tears are commonly used in the management of ocular pain and inflammation. In the treatment of episcleritis, the combination of artificial tears and cold compresses provide symptomatic relief.<sup>85</sup> No significant differences have been observed in the signs or symptoms of idiopathic episcleritis when either artificial tears or topical ketorolac (NSAID) is used.<sup>86</sup> Following photorefractive keratectomy (PRK) surgery, the application of preservative-free artificial tears reduces postoperative ocular discomfort and increases visual recovery.<sup>87</sup> Cooled artificial tears have been shown to reduce corneal and conjunctival sensation, with 4°C being the most comfortable temperature.<sup>88</sup> In contrast to this, Bitton et al found no improvement in perceived patient comfort when refrigerated Systane Ultra artificial tears were used for mild to moderate dry eye sufferers.<sup>89</sup> It is also worth noting that pain complaints can be associated with contrasting subjective responses,<sup>90</sup> and in some patients artificial tears are not effective in relieving uncomfortable symptoms.<sup>91</sup>

## Conjunctivitis

Allergic conjunctivitis causes ocular itching, watery discharge, lid oedema and conjunctival chemosis. Bilkhu et al exposed 18 participants (who had a known allergy to grass pollen) to grass pollen, and found that artificial tears and cold compresses improved the signs of allergic conjunctivitis and provided symptomatic relief.<sup>92</sup> However, if symptoms are persistent, short-term use of topical antihistamines and mast cell stabiliser drops is recommended.<sup>93</sup>

Viral (non-herpetic) conjunctivitis causes redness, discomfort, and watering. Follicles on the palpebral conjunctiva and punctate epithelial lesions on the cornea may also be observed. It has been shown that 0.5% topical ketorolac,<sup>94</sup> 0.45% ketorolac tromethamine,<sup>95</sup> and 1% prednisolone acetate<sup>96</sup> are no better in relieving signs or symptoms of viral conjunctivitis compared to artificial tears.

Bacterial conjunctivitis causes redness, discomfort, and produces a sticky discharge with crusting of the eyelids. Bacterial conjunctivitis usually self-resolves, but the application of artificial tears and eye bathing aids ocular comfort and hygiene. If bacterial conjunctivitis persists after 3–4 days, the application of topical antibiotics is usually recommended.<sup>97</sup>

## Keratitis

Keratitis is an inflammation of the cornea and has several different aetiologies including viral (Herpes Simplex), bacterial (marginal keratitis), fungal, contact-lens associated and unprotected exposure to ultraviolet radiation (photokeratitis). In dry eye and photokeratitis,<sup>98</sup> the application of artificial tears has been recommended. In herpetic keratitis, marginal keratitis, fungal keratitis, and contact-lens associated keratitis, artificial tears are advised (for lubrication and symptomatic relief) alongside additional treatment such as topical antivirals, topical and/or oral antibiotics, and antifungals.

## Contact Lens Rewetting and Removal

Contact lens wearers commonly use preservative free artificial tears for ocular lubrication, comfort and contact lens rehydration.<sup>99–101</sup> Towards the end of wear, contact lenses become drier and fit tighter. The application of artificial tears reduces friction against the cornea and can facilitate safe lens removal.

## Foreign Body Removal

Corneal foreign bodies can cause irritation, lacrimation, blurred vision, and redness. Loose foreign bodies can be irrigated away with normal saline or artificial tears. Upon successful removal of a foreign body, prophylactic antibiotics,<sup>102</sup> analgesia and artificial tears are advised.<sup>103</sup>

## Summary

Artificial tears are the mainstay of DED management, but also have a role in corneal abrasion and wound healing, pain and inflammation management, conjunctivitis, keratitis, contact lens rewetting and removal, and foreign body removal. A review of randomized controlled trials comparing artificial tears identified 64 papers. There is good evidence that artificial tears improve symptoms of DED within a month of regular use, applied ~4x a day, but signs generally take several months. Not all patients with DED benefit from artificial tears, so if there is no benefit over a month, alternative management should be considered. Combination formulations are more effective than single active ingredient artificial tears. PEG containing artificial tears are more effective than those containing CMC and HPMC. Those classified as having evaporative DED, benefit from artificial tears with liposomes, especially of higher concentration.

## Disclosure

JSW is on the executive of the Tear Film and Ocular Surface Society and the Aston University Optometry Research Group have received research funding from Alcon, the Eye Doctor, Scope Ophthalmic and Thea Pharmaceuticals. No funding was received to conduct this review. The authors report no other conflicts of interest in this work.

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