Clinical Policy Bulletin: Dry Eyes

Number: 0457

Policy

I. Aetna considers punctal plugs, standard punctoplasty by electrodessication or electrocautery medically necessary for members with severe dry eyes that are not adequately treated by conservative interventions including a 2 or more week trial of artificial tears, ophthalmic cyclosporine (Restasis) where indicated, and adjustment to medications that may contribute to dry eye syndrome. Members must have a diagnosis of severe dry eyes (also known as dry eye syndrome, keratoconjunctivitis sicca, xerophthalmia, xerosis, or sicca syndrome) with documented objective evidence of lacrimal gland deficiency (e.g., Schirmer test or the tear break-up time test) or evidence of corneal decompensation on slit-lamp exam (i.e., an ocular surface dye staining pattern (rose bengal, fluorescein, or lissamine green) characteristic of dry eye syndrome).

Aetna considers punctal occlusion procedures experimental and investigational for treatment of contact lens intolerance and for all other indications because their effectiveness for indications other than the one listed above has not been established.

II. Replacement of punctal plugs:

Aetna considers repeat punctal plug procedures medically necessary for the following indications:

A. A procedure is considered medically necessary to replace temporary dissolvable punctal plugs with long-lasting semi-permanent punctal plugs. Note: Temporary punctal occlusion with a dissolvable collagen plug that lasts 1 week may be medically necessary to assess the member's response to punctal occlusion. The repeat use of temporary (collagen) plugs for ongoing therapy for dry eye syndrome has no proven value;

B. A separate procedure for occlusion of upper puncta may be medically necessary for persons with insufficient relief from occlusion of lower puncta.

C. Replacement of silicone punctal plugs or other long-lasting plugs is generally not medically necessary more frequently than every 6 months; a more frequent replacement procedure may be medically necessary if the plug does

not stay in place because the member fails to follow post-operative instructions. If punctal plugs do not stay in place because of anatomical reasons, other forms of punctal occlusion should be considered.

D. Replacement with flow controller punctal plugs is considered medically necessary for persons who experience epiphoria with standard punctal plugs.

E. Use of shorter-acting punctal plugs composed of resorbable materials that last 3 to 6 months (see background) is considered medically necessary for persons whose dry eyes are due to temporary or seasonal conditions.

III. Aetna considers the use of the laser to occlude the tear duct opening experimental and investigational because it has not been proven to be as effective as electrodessication or thermal cautery.

IV. Aetna considers measurement of tear osmolarity medically necessary for determining the severity of dry eyes.

V. Aetna considers tear film imaging (e.g., the Tear Stability Analysis System) for evaluation of dry eyes or any other indications experimental and investigational because its effectiveness has not been established.

VI. Aetna considers autologous serum tears medically necessary for the treatment of severe dry eyes.

VII. Aetna considers the following interventions for the treatment of dry eyes experimental and investigational because the effectiveness has not been established (not an all-inclusive list):

- Acupuncture
- Hydroxychloroquine
- Intense pulsed light
- Mesenchymal stem/stromal cells
- Rituximab
- Tacrolimus
- Tofacitinib
- Topical lacritin
- Topical lifitegrast ophthalmic solution

Background

Severe dry eyes (also known as dry eye syndrome, keratoconjunctivitis sicca, xerophthalmia, xerosis, or sicca syndrome) refers to chronic dryness and resultant inflammation of the cornea and conjunctiva. Dry eye syndrome can occur alone or in conjunction with immunologic disorders such as rheumatoid arthritis, systemic lupus erythematosus, or Sjogren's syndrome (SS).

There are 3 commonly used objective tests for documenting and assessing the severity of dry eyes: (i) the Schirmer test, (ii) the Rose Bengal test, and (iii) tear film break-up time

(TFBUT). All are usually performed by ophthalmologists.

Tear production may be measured using the Schirmer test. A small piece of sterile filter paper, supplied in a standard kit, is placed in the lateral third of the lower eyelid. The extent of wetting in a given time is measured. Wetting of less than 5 mm in 5 mins is considered abnormal. Use of topical anesthesia and blotting of the tear reservoir prior to the test may improve accuracy as a measure of basal tear production. The findings are typically similar in both eyes.

End-organ damage to conjunctival and corneal epithelial cells may be assessed by ocular surface staining, which stains areas of devitalized tissue. Rose bengal, lissamine green, or fluorescein dyes may be used to assess the ocular surface. To perform the Rose Bengal test, 10 microliters of 1 % Rose Bengal are instilled into the inferior fornix of the unanesthetized eye. The patient is asked to blink twice to spread the stain over the conjunctiva and cornea. Staining can then be scored by the ophthalmologist using a slit lamp. A pattern of exposure zone (interpalpebral) corneal and bulbar conjunctival staining is typically seen with aqueous tear deficiency. Lissamine green dye has a staining profile similar to that of rose bengal and may cause less ocular irritation. It is not recommended for evaluating corneal epithelial disease.

Fluorescein dye stains areas of the corneal and conjunctival epithelia where there is sufficient disruption of intercellular junctions to allow the dye to permeate into the tissue. Saline-moistened fluorescein strips or 1 % to 2 % sodium fluorescein solution is used to stain the tear film. One to 2 mins after instilling the eye, the ocular surface is examined through a biomicroscope using a cobalt blue filter. Staining is more intense when it is observed with a yellow filter. Mild fluorescein staining can be observed in normal eyes and may be more prominent in the morning. Exposure-zone punctate or blotchy fluorescein staining is observed in dry eye, and staining is more easily visualized on the cornea than on the conjunctiva.

The TFBUT (or tear clearance) provides a global assessment of the function of the lacrimal functional unit and tear exchange on the ocular surface. The test is performed by measuring break-up time and tear osmolality after instillation of fluorescein. Break-up times less than 10 seconds are considered abnormal.

Tear osmolarity is considered a key point in dry eye disease (DED) and its measurement is the gold standard in the diagnosis of dry eye. In a prospective, multi-site clinical study, Sullivan et al (2010) evaluated the clinical utility of commonly used tests and tear osmolarity for evaluating the severity of DED. A total of 314 consecutive subjects between the ages of 18 and 82 years were recruited from the general patient population, 299 of which qualified with complete datasets. Osmolarity testing, Schirmer test without anesthesia, TFBUT, corneal staining, meibomian dysfunction assessment, and conjunctival staining were performed bilaterally. A symptom questionnaire, the Ocular Surface Disease Index (OSDI), was also administered to each patient. Distributions of clinical signs and symptoms against a continuous composite severity index were evaluated. Osmolarity was found to have the highest correlation coefficient to disease severity ($r(2) = 0.55$), followed by conjunctival staining ($r(2) = 0.47$), corneal staining ($r(2) = 0.43$), OSDI ($r(2) = 0.41$), meibomian score ($r(2) = 0.37$), TFBUT ($r(2) = 0.30$), and Schirmer result ($r(2) = 0.17$). A comparison of standard threshold-based classification with the composite severity index revealed significant overlap between the disease severities of prospectively defined normal and dry eye groups. Fully 63 % of the subjects were found to be poorly classified by combinations of clinical thresholds. The authors concluded that tear film osmolarity was found to be the single best marker of disease severity across normal, mild/moderate, and severe categories. Other tests were found to be informative in the more severe forms of

disease; thus, clinical judgment remains an important element in the clinical assessment of dry eye severity. The results also indicate that the initiation and progression of dry eye is multi-factorial and supports the rationale for re-defining severity on the basis of a continuum of clinical signs.

Suzuki et al (2010) studied the association between tear osmolarity and dry eye severity grade, based on a modified Dry Eye Workshop (DEWS) scale, and between osmolarity and the signs and symptoms that determine dry eye disease severity. A total of 19 patients with DED were asked to complete an evaluation of dry eye signs and symptoms composed of the OSDI questionnaire, corneal staining with fluorescein, conjunctival staining with lissamine green, TFBUT, Schirmer's test with anesthesia, and tear sample collection. Tear samples were collected in 5-microL microcapillaries. Tear osmolarity was measured in the right eye with a tear osmometer. Tear osmolarity correlated significantly with dry eye severity grade (modified DEWS). Schirmer's test and tear osmolarity correlated significantly at r = -0.52, with Schirmer's test result, with adjustment for age, contributing significantly to the independent estimate of tear osmolarity. The authors concluded that tear osmolarity correlates with dry eye severity and therefore could provide a biomarker for disease severity.

Other evidence suggests that assessment of tear osmolarity provides the most objective, measurable test for determining improvement in patients with DED. Benelli et al (2010) assessed the effectiveness of 3 commercially available lubricant eye drops for the treatment of mild, dry, irritated eyes. This randomized investigator-masked study included 60 patients in which 20 subjects used carboxymethylcellulose sodium (CMC), 0.5 % (Cellufresh), Allergan Inc., Irvine, CA) (group 1); 20 subjects used a drop containing polyethylene glycol 400, 2.5 % and sodium hyaluronate (Blink Intensive Tears, Abbott Medical Optics Inc., Santa Ana, CA) (group 2); and 20 subjects used HP Guar 0.18 % (Systane, Alcon Laboratories Inc., Ft. Worth, TX) (group 3). Study visits were at baseline and 1 month. Tests performed at both visits included Schirmer, TFBUT, visual acuity, fluorescein staining, tear osmolarity and wavefront aberrometry. Osmolarity testing was performed prior to instillation of the lubricant eye drops and then a final time 5 mins after instillation of the drop at both day 1 and day 30. Tear osmolarity was performed only in the right eye and only one time before and after instillation of lubricant eye drops. At day 1, the mean reduction in osmolarity 5 mins after instillation of the lubricant eye drop was, -5.0 +/- 1.9 mOsm/L in group 1, -9.0 +/- 4.2 mOsm/L in group 2 and -5.0 +/- 2.2 mOsm/L in group 3. At day 30, the mean reduction in osmolarity 5 mins after instillation of the lubricant eye drop was, -5.6 +/- 2.3 mOsm/L in group 1; -9.9 +/- 2.8 mOsm/L in group 2 and -4.5 +/- 1.8 mOsm/L in group 3. The differences were statistically significant between groups 1 and 2, and 2 and 3. There was a reduction of osmolarity from day 1 to day 30, but the differences were not statistically significant. These researchers felt that after a 30-day treatment with the lubricant eye drops, the lower osmolarity values could indicate that the tear film is progressing towards a more normal osmolarity value. A future study could examine the tear osmolarity value after 60 or 90 days of usage. LogMAR BCVA results showed an improvement in group 2 compared with baseline with no change in BCVA in groups 1 and 3. There was no statistically significant change from day 1 to 1 month in TFBUT, while the Schirmer test showed an improvement in all groups at 1 month. The authors concluded that assessment of tear osmolarity provides the most objective, measurable test for determining improvement in patients with DED.

Tear osmolarity can be measured in the clinical setting. Versura and colleagues (2010) evaluated tear osmolarity in patients with DED versus a control group to assess its diagnostic performance compared to clinical and laboratory tests performed in either clinical or research settings. Tear osmolarity was measured with the TearLab Osmolarity System (OcuSense) in 25 normal subjects and 105 DED patients (severity score 1 to 4,

DEWS). The following tests were also performed: OSDI symptoms questionnaire, Schirmer I test, TFBUT, ferning test, lissamine green staining, tear clearance, corneal esthesiometry, and conjunctival cytology by scraping and imprint. Statistical evaluation was performed by un-paired Student's t and Mann-Whitney tests, the Spearman's rho and the Pearson's r correlation coefficients (significance $p < 0.05$); all variables were also analyzed for sensitivity, specificity, Receiver Operating Characteristics (ROC) curves, likelihood ratio LR+, and positive predictive value (PPV). Tear osmolarity normal values were 296.5 +/- 9.8 mOsm/L, increasing values were shown stepwise DED severity (mild to moderate to severe dry eye, respectively: 298.1 +/- 10.6 versus 306.7 +/- 9.5 versus 314.4 +/- 10.1, $p < 0.05$). A progressive worsening occurred in all the parameters with DED severity increase. Tear osmolarity exhibited the larger correlation strength versus tear clearance, TFBUT and clinical score, strength increased with DED severity, mainly to inflammatory score and corneal sensitivity. Tear osmolarity 305 mOsm/L was selected as cut-off value for dry eye, 309 mOsm/L for moderate dry eye, 318 mOsm/L for severe dry eye (Area-under-the-curve was 0.737, 0.759, and 0.711, respectively). The authors concluded that tear osmolarity can now be considered a test suitable to be performed in a clinical setting. It showed a good performance in the diagnosis of DED, higher than the other tests considered, mainly in severe dry eye. Tear osmolarity values should be interpreted as an indicator of DED evolutionary process to severity.

The American Academy of Ophthalmology (AAO) recommends the following conservative interventions for dry-eye syndrome: elimination of exacerbating medications where feasible; ocular environmental interventions; computer work site interventions; aqueous tear enhancement with topical agents or external means; and medications. In addition, any lid abnormalities should be corrected. Punctal occlusion or tarsorrhaphy are indicated in severe cases of dry eye syndrome that are refractory to conservative management.

Cyclosporine ophthalmic emulsion (Restasis) has been approved by the Food and Drug Administration (FDA) to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator.

Guidelines from the American Optometric Association (AOA, 2002) state that punctal occlusion may be necessary for persons with severe dry eyes. In its position statement on punctal occlusion for dry eye, the AAO affirmed that punctal occlusion is a surgical procedure, and that it is considered only in patients with moderately severe to severe dry eye when symptoms and signs of dry eye are not adequately controlled by artificial tears and adjustment of medications that may contribute to dry eye symptoms. The AAO position statement explained that patients with mild dry eye frequently do not respond to punctal occlusion, and that failure of response to artificial tears and punctal occlusion suggests other problems, such as blepharitis.

Punctal plugs provide a temporary or semi-permanent means of occluding the punctum (tear duct opening) in patients with severe dry eyes. Temporary occlusion can be performed using collagen plugs, which dissolve within 1 week, to determine if punctal occlusion results in epiphoria. If a trial of temporary punctual occlusion proves successful, patients may then be offered semi-permanent or permanent forms of occlusion. There is little chance that permanent occlusion would be helpful if the plugs did not decrease symptoms of dry eye syndrome.

The opening of the tear ducts (the puncta) can be permanently occluded to retain tears, although it occasionally leads to excess tearing (epiphoria). Semi-permanent (reversible)

punctual occlusion can be achieved by non-dissolvable silicone punctual plugs. Less commonly, semi-permanent occlusion may be achieved by suturing the punctum. If the semi-permanent plugs help but do not remain in position, then permanent surgical punctal occlusion can be performed.

The most typical usage of plugs is in the lower two puncta, but some people have plugs in all 4 ducts (2 lower, 2 upper). Punctal plugs are generally made of silicone; silicone punctal plugs last for 6 or more months. More recently, plugs for long-term (6 or more month) punctal occlusion made of thermodynamic acrylic polymer (SmartPlug) and hydrogel (Oasis FormFit plug) have been developed.

Short-term punctal plugs, composed of absorbable synthetic materials, have been developed that last less than 6 months have been developed for persons with seasonal symptoms or whose dry eyes are caused by a temporary condition. Examples of short-term punctal plugs include those composed of PCL (e.g., Duraplug Extended Temporary Canalicular Inserts), which last 3 to 6 months; absorbable copolymer of glycolic and trimethylene carbonate (ProLong long term absorbable plugs), which last 3 or more months; synthetic polydioxanone (Dissolvable VisiPlug Lacrimal Plugs), which last approximately 3 months; and synthetic collagen (Oasis extended duration absorbable, Oddesy Extend absorbable implants), which last up to 3 months.

Flow controller plugs that allow partial punctal plug occlusion may be used for persons with epiphoria from standard punctal plugs. Examples of these plugs include the FCI Perforated Plugs, and Eagle Vision Flow Controller Plugs.

Surgical punctal occlusion (occlusive punctoplasty) may be achieved by cautery, electrodessication, simple excision, or argon laser surgery. In its position statement, the AAO affirmed its earlier conclusion that the preferred surgical methods of permanent punctal occlusion are electrodessication or thermal cautery, and that laser punctal occlusion should be discouraged because it is less effective and more expensive than other methods.

In a randomized, controlled, double-masked, single-center clinical trial, Geldis and Nichols (2008) described the impact of punctal occlusion in symptomatic dry eye contact lens wearers and the relation between subjective and objective outcomes. A previously described dry-eye questionnaire was used to determine subject eligibility. Tear interferometry was performed to evaluate pre-lens tear film thickness, contact lens center thickness, and post-lens tear film thickness. Each subject was randomly assigned to receive the punctal plugs or a sham procedure. At the outcome examination, the subject completed the dry-eye questionnaire and answered 1 question rating the efficacy of the punctal plug treatment in addition to undergoing tear interferometry using an identical protocol as the first visit. A total of 19 subjects completed both visits of this study. There was a significant improvement in the dry-eye questionnaire scores from baseline to the outcome visit for both the plug ($z = -2.52$, $p = 0.01$) and sham groups ($z = -2.93$, $p = 0.003$). A significant increase in pre-lens tear film thickness occurred within the sham group from baseline to the outcome visit ($z = -1.96$, $p = 0.05$), but not for the punctal plug group. No other layers measured by interferometry were shown to change significantly for either group. The authors concluded that results comparing the sham and plug groups were not significantly different from each other with regards to the questionnaire score and treatment benefit assessment, indicating either the treatment effect was not detected, although present, or punctal occlusion had no treatment effect at all.

In a pilot study, Hadassah et al (2010) evaluated the effectiveness of succinylated collagen punctal plugs (SCPP) in the treatment of patients with dry eye syndrome (DES). Succinylated collagen punctal plugs were prepared from succinylated collagen with the

exact dimensions of the punctum (length 1.5 to 2.5 mm, diameter 0.2 to 0.5 mm, water content between 50 and 55 %). Subjects were evaluated for best corrected visual acuity (BCVA), tear fluid levels (TFL), protein content (PC), tear fluid osmolarity (TFO), fluorescence staining of the cornea and TFBUT before and after punctal occlusion with SCPP. Tear fluid levels improved among all the patients after punctal occlusion with SCPP; BCVA showed improvement in case 4 (right eye/left eye), case 5 (left eye) and case 6 (right eye), who had developed dry eyes due to environmental conditions. Protein content increased on day 7 in all the patients and gradually decreased. Tear fluid levels decreased on days 3 and 5 in all patients after punctal occlusion with SCPP, and showed the same levels on day 14; TFL, PC, TFO and TFBUT showed significant improvement in all the patients after punctal occlusion with SCPP. The authors concluded that all patients experienced symptomatic relief after punctal occlusion with SCPP. There was no discomfort, foreign body sensation, plug extrusion, corneal aberration, infection, or formation of pyogenic granuloma with SCPP. They stated that SCPP is a promising alternative to other punctal plugs in the treatment of DES.

In a randomized, patient-assessor blinded, sham acupuncture controlled trial, Shin et al (2010) assessed the safety and effectiveness of acupuncture for ocular symptoms, tear film stability and tear secretion in dry eye patients. A total of 42 subjects with defined moderate to severe dry eye underwent acupuncture treatment 3 times a week for 3 weeks. Seventeen standard points (GV23; bilateral BL2, GB14, TE23, Ex1, ST1 and GB20; and unilateral SP3, LU9, LU10 and HT8 on the left for men and right for women) with "de qi" manipulation for the verum acupuncture group and 17 sham points of shallow penetration without other manipulation for the sham group were applied during the acupuncture treatment. Differences were measured using the ocular surface disease index (OSDI), the visual analog scale (VAS) of ocular discomfort, the TFBUT and the Schimer I test with anesthesia. In addition, adverse events were recorded. There were no statistically significant differences between results on the OSDI, VAS, TFBUT or Schimer I tests from baseline between the verum and sham acupuncture groups. However, results from the within-group analysis showed that the OSDI and VAS in both groups and the TFBUT in the verum acupuncture group were significantly improved after 3 weeks of treatment. No adverse events were reported during this trial. The authors concluded that both types of acupuncture improved signs and symptoms in dry-eye patients after a 4-week treatment. However, verum acupuncture did not result in better outcomes than sham acupuncture.

Lee and colleagues (2011) evaluated the effectiveness of acupuncture as a treatment option for treating the condition of dry eye. These investigators searched the literature using 14 databases from their inceptions to December 3, 2009, without language restrictions. They included randomized clinical trials (RCTs) comparing acupuncture with conventional treatment. Their risk of bias was assessed using Cochrane criteria. A total of 6 RCTs met all the inclusion criteria. Three RCTs compared the effects of acupuncture with artificial tears in patients with xerophthalmia or Sjögren syndrome. A meta-analysis of these data showed that acupuncture improved tear break-up times ($p < 0.0001$), Schirmer test scores ($p < 0.00001$), response rates ($p = 0.002$) and the region of cornea fluorescent staining ($p = 0.0001$) significantly more than artificial tears did. The other 3 RCTs compared the effects of acupuncture plus artificial tears with artificial tears alone -- 2 of these studies failed to show significant effects of acupuncture, while 1 reported significant effects. For Schirmer test scores and frequency of artificial tear usage, 2 RCTs reported superior effects of acupuncture plus artificial tears, while 1 RCT failed to do so. The authors concluded that these findings provide limited evidence for the effectiveness of acupuncture for treating dry eye. However, the total number of RCTs, the total sample size and the methodological quality were too low to draw firm conclusions.

Akpek and colleagues (2011) performed an outcomes-based review of reported treatment

options for patients with dry eye secondary to SS. A search strategy was developed to identify prospective, interventional studies of treatments for SS-associated dry eye from electronic databases. Eligible references were restricted to English-language articles published after 1975. These sources were augmented by hand searches of reference lists from accessed articles. Study selection, data extraction, and grading of evidence were completed independently by 4 or more review authors. The searches identified 3,559 references as of August 10, 2010. After duplicate review of the titles and abstracts, 245 full-text papers were assessed, 62 of which were relevant for inclusion in the review. The authors concluded that in the current literature on SS-associated dry eye, there is a paucity of rigorous clinical trials to support therapy recommendations. Nonetheless, the recommended treatments include topical lubricants, topical anti-inflammatory therapy, and tear-conserving strategies. The effectiveness of oral secretagogues seems greater in the treatment of oral dryness than ocular dryness. Although oral hydroxychloroquine is commonly prescribed to patients with SS to alleviate fatigue and arthralgias, the literature lacks strong evidence for the efficacy of this treatment for dry eye. The authors also noted that "[s]everal studies demonstrate subjective symptom improvement after the use of serum tears, but there is a paucity of objective evidence that the treatment is beneficial in patients with SS".

The Tear Stability Analysis System (TSAS) is a computerized tear film imaging device that is designed to observe the tear film integrity and evaluate ocular surface deficiency. The instrument utilities an advanced laser to capture and analyze the tear quality of the eye. There is insufficient evidence that the TSAS is effective for the evaluation of patients with dry eyes.

In a prospective case-control study, Gumus et al (2011) evaluated tear film stability in patients with tear dysfunction and an asymptomatic control group by using the novel, non-invasive Tear Stability Analysis System (TSAS). A total of 45 patients with dysfunctional tear syndrome (DTS) were stratified into 3 groups (1, 2, and 3/4) based on clinical severity, with higher scores indicating more severe symptoms; 25 asymptomatic control subjects were evaluated. Tear Stability Analysis System measurements were performed with the RT-7000 Auto Refractor-Keratometer (Tomey Corporation, Nagoya, Japan). Images of ring mires projected onto the cornea every second for 6 seconds were captured and analyzed. Focal changes in brightness were calculated as numerical ring break-up (RBU) values, and the elapsed time when the cumulative values (RBU sum) exceeded a threshold was defined as the ring break-up time (RBUT). RBUTs in the DTS groups were all significantly lower than those in the control subjects, with the lowest values found in DTS 3/4. RBUT was significantly shorter in DTS 3/4 than in DTS 1 ($p < 0.001$). The change in RBU sum over a 6-second period in the DTS groups combined or between the individual groups was statistically significant ($p < 0.001$), as was the difference between the 1- and 6-second values. For distinguishing between asymptomatic controls and DTS, the sensitivity and specificity of a 5.0-second RBUT cutoff were 82.0 % and 60.0 %, respectively. The authors concluded that the TSAS may be a useful, non-invasive instrument for evaluating tear stability and for classifying DTS severity. The findings from this small case-control study need to be validated by well-designed studies.

In a pilot study, Abelson et al (2012) examined (i) the use of an improved ocular tear film analysis protocol (OPI 2.0) in the Controlled Adverse Environment (CAE(SM)) model of dry eye disease, and (ii) the utility of new metrics in the identification of subpopulations of dry eye patients. A total of 33 dry eye subjects completed a single-center, single-visit, pilot CAE study. The primary end-point was mean break-up area (MBA) as assessed by the OPI 2.0 system. Secondary end-points included corneal fluorescein staining, tear film break-up time, and OPI 2.0 system measurements. Subjects were also asked to rate their ocular discomfort throughout the CAE. Dry eye end-points were measured at baseline,

immediately following a 90-min CAE exposure, and again 30 mins after exposure. The post-CAE measurements of MBA showed a statistically significant decrease from the baseline measurements. The decrease was relatively specific to those patients with moderate-to-severe dry eye, as measured by baseline MBA. Secondary end-points including palpebral fissure size, corneal staining, and redness, also showed significant changes when pre- and post-CAE measurements were compared. A correlation analysis identified specific associations between MBA, blink rate, and palpebral fissure size. Comparison of MBA responses allowed clinicians to identify subpopulations of subjects who exhibited different compensatory mechanisms in response to CAE challenge. Of note, none of the measures of tear film break-up time showed statistically significant changes or correlations in pre-, versus post-CAE measures. The authors concluded that these findings confirmed that the tear film metric MBA can detect changes in the ocular surface induced by a CAE, and that these changes are correlated with other, established measures of dry eye disease. The observed decrease in MBA following CAE exposure demonstrated that compensatory mechanisms are initiated during the CAE exposure, and that this compensation may provide the means to identify and characterize clinically relevant subpopulations of dry eye patients. The findings from this small pilot study need to be validated by well-designed studies.

McGinnigle et al (2012) stated that dry eye is a common yet complex condition. Intrinsic and extrinsic factors can cause dysfunction of the lids, lacrimal glands, meibomian glands, ocular surface cells, or neural network. These problems would ultimately be expressed at the tear film-ocular surface interface. The manifestations of these problems are experienced as symptoms such as grittiness, discomfort, burning sensation, hyperemia, and secondary epiphora in some cases. Accurate investigation of dry eye is crucial to correct management of the condition. Techniques can be classed according to their investigation of tear production, tear stability, and surface damage (including histological tests). The application, validity, reliability, compatibility, protocols, and indications for these are important. The use of a diagnostic algorithm may lead to more accurate diagnosis and management. The lack of correlation between signs and symptoms seems to favor tear film osmolarity, an objective biomarker, as the best current clue to correct diagnosis.

Furthermore, he American Academy of Ophthalmology's guideline on "Dry eye syndrome" (AAO, 2011) as well as the AAO's "Dry eye syndrome summary benchmark" (AAO, 2012) did not mention the use of the Tear Stability Analysis System.

In a review on "Emerging drugs for the treatment of dry eye disease", Gadaria-Rathod et al (2013) noted that recently discovered pathophysiology of DED has prompted investigators to explore new molecules that target the core mechanisms that drive DED. These include anti-inflammatory/immune-modulatory drugs, lubricant, hormones, secretagogues, and autologous serum.

An American Academy of Ophthalmology Dry Eyes Preferred Practice Pattern (AAO, 2013) states that autologous serum drops have been reported to improve ocular irritation symptoms as well as conjunctival and corneal dye staining in patients with severe dry eyes from Sjogren syndrome and GVHD.

In a Cochrane review, Pan and colleagues (2013) evaluated the safety and effectiveness of autologous serum eye drops (AS) compared to artificial tears for treating dry eye. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2013, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, (January 1950 to April 2013), EMBASE (January 1980 to April 2013), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to April 2013),

The meta Register of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov(www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). They also searched the Science Citation Index Expanded database (September 2013) and reference lists of included studies. They did not use any date or language restrictions in the electronic searches for trials. They last searched the electronic databases on April 15, 2013. These researchers included RCTs in which AS was compared to artificial tears in the treatment of dry eye in adults. Two review authors independently screened all titles and abstracts and assessed full-text articles of potentially eligible trials. Two review authors extracted data and assessed the methodological quality and characteristics of the included trials. They contacted investigators for missing data. For both primary and secondary outcomes, they reported mean differences with corresponding 95 % confidence intervals (CIs) for continuous outcomes. These investigators identified 4 eligible RCTs in which AS was compared with artificial tear treatment or saline in individuals (n = 72 participants) with dry eye of various etiologies (Sjogren's syndrome-related dry eye, non-Sjogren's syndrome dry eye and post-operative dry eye induced by laser-assisted in situ keratomileusis (LASIK)). The quality of the evidence provided by these trials was variable. A majority of the risk of bias domains were judged to have an unclear risk of bias in 2 trials owing to insufficient reporting of trial characteristics. One trial was considered to have a low risk of bias for most domains while another was considered to have a high risk of bias for most domains. Incomplete outcome reporting and heterogeneity in the participant populations and follow-up periods prevented the inclusion of these trials in a summary meta-analysis. For the primary outcome, improvement in participant-reported symptoms at 1 month, 1 trial (12 participants) showed no difference in participant-reported symptoms between 20 % AS and artificial tears. Based on the results of 2 trials in 32 participants, 20 % AS may provide some improvement in participant-reported symptoms compared to traditional artificial tears after 2 weeks of treatment. One trial also showed positive results with a mean difference in TBUT of 2.00 seconds (95 % CI: 0.99 to 3.01 seconds) between 20 % AS and artificial tears after 2 weeks, which were not similar to findings from the other trials. Based on all other objective clinical assessments included in this review, AS was not associated with improvements in aqueous tear production measured by Schirmer's test (2 trials, 33 participants), ocular surface condition with fluorescein (4 trials, 72 participants) or Rose Bengal staining (3 trials, 60 participants), and epithelial metaplasia by impression cytology compared to artificial tears (1 trial, 12 participants). Data on adverse effects were not reported by 3 of the included studies. In one study, there were no serious adverse events reported with the collection of and treatment with AS. The authors concluded that overall there was inconsistency in the possible benefits of AS in improving participant-reported symptoms and TBUT and lack of effect based on other objective clinical measures. Moreover, they stated that well-planned, large, high-quality RCTs are warranted, in different severities of dry eye and using standardized questionnaires to measure participant-reported outcomes and objective clinical tests as well as objective biomarkers to assess the benefit of AS therapy for dry eye.

Gottenberg and colleagues (2014) stated that primary SS is a systemic autoimmune disease characterized by mouth and eye dryness, pain, and fatigue. Hydroxychloroquine is the most frequently prescribed immunosuppressant for the syndrome. However, evidence regarding its effectiveness is limited. These investigators evaluated the effectiveness of hydroxychloroquine for the main symptoms of primary SS: dryness, pain, and fatigue. From April 2008 to May 2011, a total of 120 patients with primary SS according to American-European Consensus Group Criteria from 15 university hospitals in France were randomized in a double-blind, parallel-group, placebo-controlled trial. Participants were assessed at baseline, week 12, week 24 (primary outcome), and week 48. The last follow-up date for the last patient was May 15, 2012. Patients were

randomized (1:1) to receive hydroxychloroquine (400 mg/day) or placebo until week 24. All patients were prescribed hydroxychloroquine between weeks 24 and 48. The primary end-point was the proportion of patients with a 30 % or greater reduction between weeks 0 and 24 in scores on 2 of 3 numeric analog scales (from 0 [best] to 10 [worst]) evaluating dryness, pain, and fatigue. At 24 weeks, the proportion of patients meeting the primary end-point was 17.9 % (10/56) in the hydroxychloroquine group and 17.2 % (11/64) in the placebo group (odds ratio [OR], 1.01; 95 % CI: 0.37 to 2.78; p = 0.98). Between weeks 0 and 24, the mean (SD) numeric analog scale score for dryness changed from 6.38 (2.14) to 5.85 (2.57) in the placebo group and 6.53 (1.97) to 6.22 (1.87) in the hydroxychloroquine group. The mean (SD) numeric analog scale score for pain changed from 4.92 (2.94) to 5.08 (2.48) in the placebo group and 5.09 (3.06) to 4.59 (2.90) in the hydroxychloroquine group. The mean (SD) numeric analog scale for fatigue changed from 6.26 (2.27) to 5.72 (2.38) in the placebo group and 6.00 (2.52) to 5.94 (2.40) in the hydroxychloroquine group. All but 1 patient in the hydroxychloroquine group had detectable blood levels of the drug. Hydroxychloroquine had no efficacy in patients with anti-SSA autoantibodies, high IgG levels, or systemic involvement. During the first 24 weeks, there were 2 serious adverse events in the hydroxychloroquine group and 3 in the placebo group; in the last 24 weeks, there were 3 serious adverse events in the hydroxychloroquine group and 4 in the placebo group. The authors concluded that among patients with primary SS, the use of hydroxychloroquine compared with placebo did not improve symptoms during 24 weeks of treatment. They stated that further studies are needed to evaluate longer-term outcomes.

Sacchetti et al (2014) noted that topical cyclosporine A (CsA) is a therapeutic option for DED to control ocular surface inflammation and improve tear function. These investigators reviewed data from RCTs evaluating safety and effectiveness of topical CsA treatment for DED. Articles published up to December 2012 were identified from Medline, Embase and the Cochrane Controlled Trials Register. A total of 18 RCTs that evaluated the safety and effectiveness of different topical CsA formulations for the treatment of DED were selected according to the set criteria. The Jadad score was calculated to assess RCT quality. The mean Jadad score of the included RCTs was 2.8 ± 0.6. All CsA formulations proved safe for the treatment of DED. Symptoms improved in 100 % (9/9) RCTs, tear function improved in 72 % (13/18) RCTs and ocular surface damage was ameliorated in 53 % (9/17) RCTs in patients with DED. No improvements with CsA treatment versus control were observed in DED resulting from surgical procedures, contact lens use and thyroid orbitopathy. Statistical comparison of CsA efficacy through a meta-analysis of data was not possible due to a lack of standardized criteria and comparable outcomes among studies. The authors concluded that although topical CsA appears to be a safe treatment for DED, evidence emerging from RCTs is limited, and this affected the strength of recommendations to healthcare providers and policymakers for optimal management. They stated that standardized diagnostic criteria to assess the efficacy of topical CsA are recommended to improve the design of future RCTs in DED.

Colligris et al (2014) noted that the vast majority of new compounds under development for the treatment of dry eye disease are anti-inflammatories, steroids, non-steroids and antibiotics; however, there are also some novel lubricating drops and mucin-tear secretagogues. A future aggressive therapy for dry eye, depending on the severity of the symptoms, would include combinations of soft steroids, anti-inflammatories, such as cyclosporine A, with the addition of the new polyvalent mucin and tear secretagogues.

Zhou and Wei (2014) conducted a systematic review and meta-analysis of RCTs on CsA versus placebo in treating DES to evaluate the treatment safety and effectiveness of CsA. These investigators searched for RCTs published after 1990, in MEDLINE, EMBASE, the Cochrane library, and ClinicalTrials.gov. The RCTs that were included compared topical CsA and placebo for DES treatment by evaluating scores of ocular surface disease index,

tear break-up time, or Schirmer test. Cochrane risk of bias tool was used for assessing the risk of bias. These researchers included 12 RCTs involving 3,034 eyes of 1,660 participants. They observed statistically significant improvements on scores of break-up time (standardized mean difference [SMD], 0.80; 95 % CI: 0.13 to 1.46; I = 95 %) and scores of Schirmer test with anesthesia (SMD, 0.78; 95 % CI: 0.09 to 1.46; I = 97 %) after treatment with topical CsA. Scores of ocular surface disease index (SMD, 0.77; 95 % CI: -1.05 to 2.58; I = 98 %) and scores of Schirmer test without anesthesia (SMD, 0.08; 95 % CI: -0.11 to 0.27; I = 0 %) were not improved. Adverse events (odds ratio [OR], 1.61; 95 % CI: 1.28 to 2.02; I = 21 %) were observed. The authors concluded that topical CsA could be an effective treatment for DES, especially for DES associated with conjunctival injury. Moreover, they stated that further RCTs with larger sample sizes for different clinical types of DES are needed to determine the effectiveness and limitation for different clinical types of DES.

Vijmasi et al (2014) stated that lacritin is a tear glycoprotein with pro-secretory, pro-survival, and mitogenic properties. These researchers examined lacritin levels in the tears of SS patients and explored the therapeutic potential of topical lacritin for the treatment of keratoconjunctivitis sicca. Tears from healthy controls (n = 14) and SS patients (n = 15) were assayed for lacritin using a C-terminal antibody. In a paired-eye study, autoimmune regulator (Aire) knockout (KO) mice (n = 7) were treated 3 times daily for 21 days with 10 µL of 4 µM lacritin (left eye) or vehicle (PBS) control (right eye). Tear secretion and ocular surface integrity were assessed at baseline and after treatment. Immunohistochemical staining of CD4+ T cells, cytokeratin-10 (K10), and cytokeratin-12 (K12) expression in the cornea and CD4+ T cell infiltration in the lacrimal glands were assessed. Lacritin monomer (421.8 ± 65.3 ng [SS] versus 655.8 ± 118.9 ng [controls]; p = 0.05) and C-terminal fragment protein (125 ± 34.1 ng [SS] versus 399.5 ± 84.3 ng [controls]; p = 0.008) per 100 µL of tear eluate were significantly lower in SS patients. In Aire KO mice treated with lacritin, tear secretion increased by 46 % (13.0 ± 3.5 mm versus 8.9 ± 2.9 mm; p = 0.01) and lissamine green staining score significantly decreased relative to baseline (-0.417 ± 0.06 versus 0.125 ± 0.07; p = 0.02). Expression of K10 but not K12 in the cornea was significantly decreased in lacritin-treated eyes. Focal CD4+ T cell infiltration of the lacrimal glands was significantly reduced on the lacritin-treated side versus the untreated side. The authors concluded that lacritin is significantly reduced in the tears of SS patients; topically administered lacritin has therapeutic potential for the treatment of aqueous-deficient dry eye disease.

Devauchelle-Pensec et al (2014) noted that primary SS (pSS) is an autoimmune disorder characterized by ocular and oral dryness or systemic manifestations. In a randomized, placebo-controlled, parallel-group trial, these researchers evaluated the effectiveness and harms of rituximab in adults with recent-onset or systemic pSS. Study personnel (except pharmacists), investigators, and patients were blinded to treatment group. A total of 120 patients with scores of 50 mm or greater on at least 2 of 4 visual analogue scales (VASs) (global disease, pain, fatigue, and dryness) and recent-onset (< 10 years) biologically active or systemic pSS were included in this study. Participants were randomized (1:1 ratio) to rituximab (1 g at weeks 0 and 2) or placebo. Primary end-point was improvement of at least 30 mm in 2 of 4 VASs by week 24. No significant difference between groups in the primary end-point was found (difference, 1.0 % [95 % CI: -16.7 % to 18.7 %]). The proportion of patients with at least 30-mm decreases in at least 2 of the 4 VAS scores was higher in the rituximab group at week 6 (22.4 % versus 9.1 %; p = 0.036). An improvement of at least 30 mm in VAS fatigue score was more common with rituximab at weeks 6 (p < 0.001) and 16 (p = 0.012), and improvement in fatigue from baseline to week 24 was greater with rituximab. Adverse events were similar between groups except for a higher rate of infusion reactions with rituximab. The authors conclude that rituximab did not

alleviate symptoms or disease activity in patients with pSS at week 24, although it alleviated some symptoms at earlier time points.

Valim et al (2014) noted that DED is a multi-factorial disease of the tears and ocular surface that causes tear film instability with potential damage to the ocular surface. The prevalence of dry eye in the world population ranges from 6 to 34 %. It is more common in those aged over 50, and affects mainly women. Since the introduction of the Schirmer's test in 1903, other tests have been developed to evaluate dry eye, such as biomicroscopy, TBUT, vital dyes (lissamine green and rose bengal), fluorescein, leaf fern test, corneal sensitivity test, conjunctiva impression cytology, optical coherence tomography (OCT), and tear osmolarity measurement. Although there is no gold standard, it is advisable to combine at least 2 tests. Strategies for treating DED have recently been modified and include patient education, tear substitute, corticosteroids, secretagogues, fatty acids, immunomodulators, occlusion of lacrimal puncta surgery and, tarsorrhaphy. Biological therapy and new topical immunomodulators such as tacrolimus, tofacitinib and IL-1 receptor inhibitor are being tested.

In a retrospective non-comparative interventional case-series study, Toyos et al (2015) examined the clinical benefits of intense-pulsed-light therapy for the treatment of dry-eye disease caused by meibomian gland dysfunction (MGD). A total of 91 patients presenting with severe dry eye syndrome were included in this study. Treatment included intense-pulsed-light therapy and gland expression at a single out-patient clinic over a 30-month study. Pre/post tear breakup time data were available for a subset of 78 patients. For all patients, a specially developed technique for the treatment of dry eye syndrome was applied as a series of monthly treatments until there was adequate improvement in dry eye syndrome symptoms by physician judgment, or until patient discontinuation. Primary outcomes included change in TBUT, self-reported patient satisfaction, and adverse events. Physician-judged improvement in dry eye TBUT was found for 68 of 78 patients (87 %) with 7 treatment visits and 4 maintenance visits on average (medians), and 93 % of patients reported post-treatment satisfaction with degree of dry eye syndrome symptoms. Adverse events, most typically redness or swelling, were found for 13 % of patients. No serious adverse events were found. The authors concluded that although preliminary, study results of intense-pulsed-light therapy treatment for dry eye syndrome caused by meibomian gland dysfunction are promising. They stated that a multi-center clinical trial with a larger sample, treatment comparison groups, and randomized controlled trials is currently underway.

Lee and colleagues (2015) stated that DES is one of the most common ocular diseases affecting nearly 10 % of the U.S. population. Most of the currently available treatments are palliative, and few therapeutic agents target biological pathway of DES. Although DES is a multi-factorial disease, it is well-known that inflammation in the ocular surface plays an important role in the pathogenesis of DES. Mesenchymal stem/stromal cells (MSCs) have been shown to repair tissues by modulating excessive immune responses in various diseases. Thus, these investigators examined the therapeutic potential of MSCs in a murine model of an inflammation-mediated dry eye that was induced by an intra-orbital injection of concanavalin A. They found that a peri-orbital administration of MSCs reduced the infiltration of CD4(+) T cells and the levels of inflammatory cytokines in the intra-orbital gland and ocular surface. Also, MSCs significantly increased aqueous tear production and the number of conjunctival goblet cells. Subsequently, corneal epithelial integrity was well-preserved by MSCs. The authors concluded that the results demonstrated that MSCs protect the ocular surface by suppressing inflammation in DES, and suggested that MSCs may offer a therapy for a number of ocular surface diseases where inflammation plays a key role.

An UpToDate review on “Dry eyes” (Shtein, 2015) states that “A 2013 systematic review of 18 randomized trials concluded that topical cyclosporine was a safe treatment for dry eyes. While meta-analysis was not possible because of lack of standardized criteria and outcome measures, 9 of 9 trials that evaluated symptoms and 13 of 18 trials that evaluated tear function found improvement. No improvements were found in patients with dry eyes from surgical procedures, contact lens use, or thyroid orbitopathy. Despite the available evidence, we have not seen such a degree of beneficial results in our practice. There appears to be a subset of patients who do respond favorably to this treatment, but there are no good predictive models available to guide clinical decision-making at this time …. Investigational -- In a phase III randomized trial, twice daily topical use of an integrin antagonist (Lifitegrast ophthalmic solution) that decreases inflammation by blocking lymphocyte-endothelial adhesion led to improvement in symptoms and signs of dry eye disease, compared to placebo

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:

68760	Closure of the lacrimal punctum; by thermocauterization, ligation, or laser surgery
68761	by plug, each
68801	Dilation of lacrimal punctum, with or without irrigation
83861	Microfluidic analysis utilizing an integrated collection and analysis device, tear osmolarity

CPT codes not covered for indications listed in the CPB:

97810 - 97814	Acupuncture

HCPCS codes covered if selection criteria are met:

A4262	Temporary, absorbable lacrimal duct implant, each
A4263	Permanent, long-term, non-dissolvable lacrimal duct implant, each

ICD-9 codes covered if selection criteria are met:

370.33	Keratoconjunctivitis sicca, not specified as Sjögren's
375.52	Stenosis of lacrimal punctum
372.53	Conjunctival xerosis
375.15	Tear film insufficiency, unspecified
710.2	Sicca syndrome

Tear Film Imaging:

CPT codes not covered for indications listed in the CPB:

0330T	Monitoring of intraocular pressure, imaging, screening of visual acuity, sacroiliac joint stabilization

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