<table>
<thead>
<tr>
<th>Plan: Aetna Better Health</th>
<th>Submission Date: 07/01/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy Number: 0302</td>
<td>Effective Date:</td>
</tr>
<tr>
<td></td>
<td>Revision Date: 05/08/2018</td>
</tr>
<tr>
<td>Policy Name: Xerostomia: Selected Treatments</td>
<td></td>
</tr>
</tbody>
</table>

**Type of Submission – Check all that apply:**
- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document. Please provide any clarifying information for the policy below:

**CPB 0302 Xerostomia: Selected Treatments**
This CPB has been revised to state that the following are considered experimental and investigational for the prevention or treatment of xerostomia: (i) acupuncture, (ii) low-level laser therapy, and (iii) transcutaneous electrical nerve stimulation (TENS).

**Name of Authorized Individual (Please type or print):**
Dr. Bernard Lewin, M.D.

**Signature of Authorized Individual:**

[Signature]

[Signature]
Xerostomia: Selected Treatments

Policy

Aetna considers electrical stimulation (e.g., the Salitron System and the Saliwell Crown device) experimental and investigational for the prevention or treatment of xerostomia (dry mouth) or for any other indications because its effectiveness has not been established.

Aetna considers the following interventions experimental and investigational for the treatment of xerostomia because their effectiveness for this indication has not been established (not an all-inclusive list):

- Acupuncture
• Fat grafting to salivary glands
• Low-level laser therapy
• Transcutaneous electrical nerve stimulation (TENS)

**Background**

Chronic xerostomia can be caused by Sjogren's syndrome, certain medications or therapeutic irradiation. It can cause difficulty in eating dry foods, swallowing and wearing dentures; and susceptibility to dental caries, oral pain and frequent infections. Proponents of electrostimulation as a treatment option postulate that stimulating the tongue and the roof of the mouth simultaneously will result in impulses to all residual salivary tissues, major and minor, in the oral and pharyngeal regions, thus causing salivation.

**Electrical Stimulation:**

Although the Food and Drug Administration (FDA) approved the Salitron System in 1988 to treat xerostomia secondary to Sjogren's syndrome, the Agency for Health Care Policy and Research (AHCPR) advised in a 1991 assessment that there were “insufficient data to determine the clinical effectiveness of this modality of salivary production, or to identify those xerostomic patients who would benefit from the procedure” (Erlichman, 1991). One published study (Weiss et al, 1986) reported some degree of response after 3 stimulation sessions of 3 minutes each in 24 patients with xerostomia related to Sjogren's, radiation therapy, drugs or unknown etiology. However, there was no control group, information on the duration of response, quantitative assessment of salivary response, or intermediate or long-term assessment of effectiveness.
Another report, a double-blind study (Steller et al, 1988) noted a statistically significant mean increase in post-stimulation whole saliva flow between subjects (n = 29) using active and placebo stimulators. However, this was due mainly to the responses of 3 subjects who showed marked increases in their whole saliva flow rate during the study. Of the active study arm, only 1 subject showed evidence of a cumulative response over the 4 weeks of the study. Further research of electrical stimulation of salivary flow is needed to ascertain its role in the treatment of Sjogren's patients with xerostomia.

Talal and colleagues (1992) reported that electrical stimulation improves salivary function of patients with Sjogren's syndrome. In this placebo controlled study, patients received three treatments (2 weeks apart, over a 4-week period) with an active device (n = 34) or a placebo device (n = 37). Patients using active devices showed a statistically greater increase in salivary production than patients using placebo devices. Moreover, patients demonstrated significant improvement in other symptoms such as difficulty in swallowing as well as burning tongue. The major shortcomings of this study were (i) it is unclear whether the control group was age-matched, (ii) lack of long-term assessment of effectiveness, and (iii) the number of patients in the active device group who did not respond to treatment was not disclosed, and the range or standard deviation for pre- and post-stimulation whole salivary flow rates was not given.

The role of electrical stimulation in the management of patients with xerostomia awaits the outcomes of randomized, double-blind, controlled clinical studies with large sample sizes and long-term follow-up. In
many reviews on the management of patients with xerostomia (Cooke, 1996; Fox, 1997; Davies, 1997; Mariette, 2002; Fox, 2003), salivary electrostimulation was not mentioned as a method to manage patients with this condition.

Strietzel et al (2007) evaluated the safety and effectiveness of a recently developed electro-stimulating device mounted on an individualized intra-oral removable appliance. The device, containing electrodes, a wetness sensor, an electronic circuit and a power source, was tested on patients with xerostomia in a cross-over, randomized, sham-controlled, double-blinded, multi-center study (n = 23; 10 with primary Sjogren's syndrome, 7 with medication-induced xerostomia, and 6 with idiopathic xerostomia). Electrical stimulation and also sham were delivered for 10 mins to the oral mucosa, in the mandibular third molar region. Oral dryness was measured by the sensor. As the primary outcome, sensor dryness and xerostomia symptom changes as a result of device wearing were assessed, and compared between active and sham modes. In addition, side-effects were recorded. Electro-stimulation resulted in a significant decrease in sensor dryness, leading to a beneficial effect on patients' subjective condition. No significant adverse events were observed. However, 30.4% patients reported the sham mode to be more effective than the active mode. The authors stated that these findings are encouraging enough to continue developing and investigating the miniature electrostimulating device mounted on a dental implant.

In a preliminary study, Ami and Wolff (2010) evaluated the effect on xerostomia of the Saliwell Crown (Saliwell Ltd., Harutzim, Israel), an innovative saliva electrostimulation device fixed on an implant, placed in the lower third molar area. A Saliwell Crown was
placed in the lower third molar area of an 81-year old female patient with complaints of dry and burning mouth. Salivary secretion was measured, and the patient was asked to fill in written satisfaction questionnaires. The patient was monitored for 1 year, comparing her salivary secretion rates and the written questionnaires. The results showed a constant slight but significant increase in the salivary secretion and in the patient's personal feelings as presented in the questionnaires. The authors concluded that the saliva stimulation device Saliwell Crown, placed on an implant in an 81-year old patient with dry and burning mouth complaints, presented promising results when both the salivary secretion tests and the self-assessment questionnaires were examined and compared. The findings of this case study need to be validated by well-designed studies.

Strietzel and colleagues (2011) evaluated the safety and effectiveness of an intra-oral electrostimulation device, consisting of stimulating electrodes, an electronic circuit, and a power source, in treating xerostomia. The device delivers electrostimulation through the oral mucosa to the lingual nerve in order to enhance the salivary reflex. The device was tested on a sample of patients with xerostomia due to Sjogren's syndrome and other sicca conditions in a 2-stage prospective, randomized, multi-center trial. Stage I was a double-blind, cross-over stage designed to compare the effects of the electrically active device with the sham device, each used for 1 month, and stage II was a 3-month open-label stage designed to assess the long-term effects of the active device. Improvement in xerostomia severity from baseline was the primary outcome measure. A total of 114 patients were randomized. In stage I, the active device performed better than the sham device for patient-reported xerostomia severity (p < 0.002), xerostomia frequency (p < 0.05), quality of life impairment (p < 0.01), and swallowing difficulty (p <
0.02). At the end of stage II, statistically significant improvements were verified for patient-reported xerostomia severity (p < 0.0001), xerostomia frequency (p < 0.0001), oral discomfort (p < 0.001), speech difficulty (p < 0.02), sleeping difficulty (p < 0.001), and resting salivary flow rate (p < 0.01). The authors concluded that the results indicated that daily use of the device alleviated oral dryness, discomfort, and some complications of xerostomia, such as speech and sleeping difficulties, and increased salivary output. These findings need to be verified by additional research.

Fedele et al (2010) noted that xerostomia is a very common condition, which not only involves dry mouth feeling, but can also lead to psychosocial distress, impaired quality of life, and complications, such as dental caries and oral candidiasis. It is generally induced by hypofunction of salivary glands, which has a wide variety of etiologies, such as Sjogren's syndrome, radiotherapy to the head and neck and side effects of medications. Current therapies rely on saliva substitutes and pharmacological stimulation of the parasympathetic system. These treatment modalities are somewhat limited by their short-term efficacy, high cost and drug interactions or other adverse effects. Local transcutaneous or per-mucosal electrostimulation in areas close to the nerves participating in the salivary autonomic reflex has been found to increase salivary secretion in animal and clinical experiments and to relieve symptoms of dry mouth in patients with salivary gland hypofunction. These investigators reviewed the current status and potential of intra-oral miniature electrostimulating devices. The authors stated that these intra-oral electrostimulating devices offer promise as an optional safe and non-chemical treatment of xerostomia.
In a phase II randomized, controlled study, Wong et al (2010) examined the potential effectiveness of xerostomia prevention using acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) delivered concomitant with radiotherapy administered to head and neck cancer patients. A total of 60 patients were randomized to either the treatment group (n = 30) that received ALTENS daily with radiotherapy or the control group (n = 26) that had standard mouth care only. Stimulated and basal unstimulated whole saliva production (WSP) plus radiation-induced xerostomia (RIX) symptoms visual analog score (RIXVAS) were assessed at specific time points. Generalized linear models and generalized estimating equations were used for analysis. RIXVAS at 3 months follow-up after therapy completion was used as the primary study endpoint. The mean RIXVAS for the ALTENS intervention at 3 months was 39.8, which was not significantly different from the control arm value of 40.5. There were no statistically significant differences between the 2 groups for their mean RIXVAS and WSP at all assessment time points. The authors concluded that there was no significant difference in mean WSP and RIXVAS between the 2 groups, so ALTENS is not recommended as a prophylactic intervention.

In a phase II component of a multi-institutional, phase II/III, randomized trial, Wong et al (2012) evaluated the feasibility and preliminary effectiveness of ALTENS in reducing radiation-induced xerostomia. Patients with cancer of the head and neck who were 3 to 24 months from completing radiotherapy with or without chemotherapy (RT +/- C) and who were experiencing xerostomia symptoms with basal whole saliva production greater than or equal to 0.1 ml/min and were without recurrence were eligible. Patients received twice-weekly ALTENS sessions (24 sessions over 12 weeks) using a proprietary electrical stimulation unit.
The primary study objective was to assess the feasibility of ALTENS treatment. Patients were considered compliant if 19 of 24 ALTENS sessions were delivered, and the targeted compliance rate was 85%. Secondary objectives measured treatment-related toxicities and the effect of ALTENS on overall radiation-induced xerostomia burden using the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS). Of 48 accrued patients, 47 were evaluable. The median age was 60 years, 84% of patients were men, 70% completed RT +/- C for greater than 12 months, and 21% had previously received pilocarpine. Thirty-four patients completed all 24 ALTENS sessions, 9 patients completed 20 to 23 sessions, and 1 patient completed 19 sessions, representing a 94% total compliance rate. Six-month XeQOLS scores were available for 35 patients and indicated that 30 patients (86%) achieved a positive treatment response with a mean +/- standard deviation reduction of 35.9% +/- 36.1%. Five patients developed grade 1 or 2 gastro-intestinal toxicity, and 1 had a grade 1 pain event. The authors concluded that the current results indicated that ALTENS treatment for radiation-induced xerostomia can be delivered uniformly in a cooperative, multi-center setting and produced possible beneficial treatment response. They noted that given these results, the phase III component of this study was initiated.

In a Cochrane review, Furness et al (2013) evaluated the effects of non-pharmacological interventions administered to stimulate saliva production for the relief of dry mouth/xerostomia. These investigators searched the Cochrane Oral Health Group's Trials Register (to April 16, 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 3), MEDLINE via OVID (1948 to April 16, 2013), EMBASE via
OVID (1980 to April 16, 2013), AMED via OVID (1985 to April 16, 2013), CINAHL via EBSCO (1981 to April 16, 2013), and CANCERLIT via PubMed (1950 to April 16, 2013). The metaRegister of Controlled Clinical Trials and ClinicalTrials.gov were also searched to identify ongoing and completed trials. References lists of included studies and relevant reviews were also searched. There were no restrictions on the language of publication or publication status. These researchers included parallel group randomized controlled trials of non-pharmacological interventions to treat dry mouth, where participants had dry mouth symptoms at baseline. At least 2 review authors assessed each of the included studies to confirm eligibility, assess risk of bias and extract data using a piloted data extraction form. They calculated mean difference (MD) and 95 % confidence intervals (CI) for continuous outcomes or where different scales were used to assess outcome, they calculated standardized mean differences (SMD) together with 95 % CIs. These investigators attempted to extract data on adverse effects of interventions. Where data were missing or unclear, they attempted to contact study authors to obtain further information. There were 9 studies (total 366 participants randomized) included in this review of non-pharmacological interventions for dry mouth, which were divided into 3 comparisons: (i) 8 studies were assessed at high-risk of bias in at least one domain and the remaining study was at unclear risk of bias, (ii) 5 small studies (total 153 participants, with dry mouth following radiotherapy treatment) compared acupuncture with placebo, and 4 were assessed at high-risk and 1 at unclear risk of bias, (iii) 2 trials reported
outcome data for dry mouth in a form suitable for meta-analysis. The pooled estimate of these 2 trials (70 participants, low-quality evidence) showed no difference between acupuncture and control in dry mouth symptoms (SMD -0.34, 95% CI: -0.81 to 0.14, p value 0.17, I(2) = 39%) with the CIs including both a possible reduction or a possible increase in dry mouth symptoms. Acupuncture was associated with more adverse effects (tiny bruises and tiredness that were mild and temporary). There was a very small increase in unstimulated whole saliva (UWS) at the end of 4 to 6 weeks of treatment (3 trials, 71 participants, low-quality evidence) (MD 0.02 ml/min, 95% CI: 0 to 0.04, p value 0.04, I(2) = 57%), and this benefit persisted at the 12-month follow-up evaluation (2 trials, 54 participants, low-quality evidence) (UWS, MD 0.06 ml/min, 95% CI: 0.01 to 0.11, p value 0.03, I(2) = 10%). For the outcome of stimulated whole saliva (SWS, 3 trials, 71 participants, low-quality evidence) there was a benefit favoring acupuncture (MD 0.19 ml/min, 95% CI: 0.07 to 0.31, p value 0.002, I(2) = 1%) an effect which also persisted at the 12-month follow-up evaluation (SWS MD 0.28 ml/min, 95% CI: 0.09 to 0.47, p value 0.004, I(2) = 0%) (2 trials, 54 participants, low-quality evidence). Two small studies, both at high-risk of bias, compared the use of an electro-stimulation device with a placebo device in participants with Sjogren's syndrome (total 101 participants). A further study, also at high-risk of bias, compared acupuncture-like electro-stimulation of different sets of points in participants who had previously been treated with radiotherapy. None of these studies reported the outcome of dry mouth. There was no difference between electro-stimulation and placebo in the outcomes of UWS.
or SWS at the end of the 4-week treatment period in the 1 study (very low that provided data for these outcomes). No adverse effects were reported. A single study at high-risk of bias, compared the stimulatory effect of powered versus manual tooth-brushing and found no difference for the outcomes of UWS or SWS. The authors concluded that there is low-quality evidence that acupuncture is no different from placebo acupuncture with regard to dry mouth symptoms, which is the most important outcome. This may be because there were insufficient participants included in the 2 trials to show a possible effect or it may be that there was some benefit due to “placebo” acupuncture that could have biased the effect to the null. There is insufficient evidence to determine the effects of electro-stimulation devices on dry mouth symptoms. It is well-known that dry mouth symptoms may be problematic even when saliva production is increased, yet only 2 of the trials that evaluated acupuncture reported dry mouth symptoms, a worrying reporting bias. There is some low-quality evidence that acupuncture results in a small increase in saliva production in patients with dry mouth following radiotherapy. There is insufficient evidence to determine the effects of electro-stimulation devices on dry mouth symptoms or saliva production in patients with Sjogren's syndrome. Reported adverse effects of acupuncture are mild and of short duration, and there were no reported adverse effects from electro-stimulation.

In a phase II clinical trial, Vijayan et al (2014) evaluated the effectiveness of TENS delivered using an extra-oral device in patients with radiation-induced xerostomia. A total of 30 oral cavity and oropharyngeal cancer patients
post-adjuvant (n = 26) or definitive radiotherapy (n = 4) were enrolled in this study. The TENS electrode pads were placed externally on the skin overlying the parotid glands. Un-stimulated whole saliva was collected for 5 mins into graduated tubes using the low forced spitting method. The TENS unit was then activated and stimulated saliva was collected for an additional 5 mins. The difference between un-stimulated and stimulated saliva output was measured using the paired t-test. Linear regression was used to determine factors significantly influencing the improvement in salivary output. Twenty-nine (96.7%) of 30 patients showed increased saliva flow during stimulation. A statistically significant improvement in saliva production (p < 0.05) during stimulation was noted. The mean un-stimulated saliva flow was 0.056 ml/min and the mean stimulated saliva flow was 0.12 ml/min with a median increase of 0.06 ml/min. The interval to the application of TENS after radiotherapy significantly influenced the improvement in salivary flow. The authors concluded that extra-oral application of TENS is effective in increasing the whole salivary flow in most of the post-radiated oral cavity/oropharyngeal cancer patients with xerostomia. They stated that TENS therapy may be useful as an effective supportive treatment modality in post-radiated oral cancer patients. These preliminary findings from a small (n = 30) phase II study need to be validated by well-designed studies.

In a case-series study, Zadik et al (2014) investigated the safety of an intra-oral electrostimulator (GenNarino) in symptomatic chronic graft-versus-host disease (cGVHD) patients. The secondary objective was to study the impact on the salivary gland involvement of cGVHD patients. The study included patients treated for 4 weeks, randomly assigned to the active device and then crossed-over to a sham-device or vice versa. The patients and clinicians were blind to the treatment
delivered. Data regarding oral mucosal and salivary gland involvement were collected. A total of 6 patients were included in this study. Most of the intra-oral areas with manifestations of cGVHD were not in contact with the GenNarino device. Two patients developed mild mucosal lesions in areas in contact with the GenNarino during the study. However, only 1 of them had a change in the National Institutes of Health (NIH) score for oral cGVHD. The un-stimulated and stimulated salivary flow rate increased in 4 out of the 5 patients included in this analysis. Symptoms of dry mouth and general oral comfort improved. The authors concluded that the findings of this study suggested that GenNarino is safe in cGVHD patients with respect to oral tissues. Furthermore the use of GenNarino resulted in subjective and objective improvements in dry mouth symptoms. Moreover, they stated that a large scale study is needed to confirm the impact and safety of GenNarino on systemic cGVHD.

Bakarman and Keenan (2014) examined the evidence of non-pharmacological treatments for patients with dry mouth. Study assessment and data extraction were carried out independently by at least 2 reviewers. Mean difference and SMD together with 95% CIs were calculated where appropriate. A total of 9 studies (366 participants) were included in this review, 8 were assessed at high risk of bias and 1 at unclear risk of bias. Five small studies (153 participants), with dry mouth following radiotherapy treatment compared acupuncture with placebo. Four were at high risk and 1 at unclear risk of bias. Two trials reported outcome data for dry mouth in a form suitable for meta-analysis. The pooled estimate of these 2 trials (70 participants, low quality evidence) showed no difference between acupuncture and control in dry mouth symptoms (SMD -0.34, 95% CI: -0.81 to 0.14, p value 0.17, I² = 39%) with the CIs including a possible reduction or a possible
increase in dry mouth symptoms. Acupuncture was associated with more adverse effects (tiny bruises and tiredness which were mild and temporary). There was a very small increase in unstimulated whole saliva (UWS) at the end of 4 to 6 weeks of treatment (3 trials, 71 participants, low quality evidence) (MD 0.02 ml/minute, 95 % CI: 0 to 0.04, p value 0.04, I² = 57 %), and this benefit persisted at the 12-month follow-up evaluation (2 trials, 54 participants, low quality evidence) (UWS, MD 0.06 ml/minute, 95 % CI: 0.01 to 0.11, p value 0.03, I² = 10 %). For the outcome of stimulated whole saliva (SWS, 3 trials, 71 participants, low quality evidence) there was a benefit favoring acupuncture (MD 0.19 ml/minute, 95 % CI: 0.07 to 0.31, p value 0.002, I² = 1 %) an effect which also persisted at the 12-month follow-up evaluation (SWS MD 0.28 ml/minute, 95 % CI: 0.09 to 0.47, p value 0.004, I² = 0 %) (2 trials, 54 participants, low quality evidence). Two small studies, both at high risk of bias, compared the use of an electrostimulation device with a placebo device in participants with Sjogren's syndrome (total 101 participants). A further study, also at high risk of bias, compared acupuncture-like electrostimulation. None of these studies reported the outcome of dry mouth. A single study at high risk of bias compared the stimulatory effect of powered versus manual toothbrushing and found no difference for the outcomes of UWS or SWS. The authors concluded that there is low quality evidence that acupuncture is no different from placebo acupuncture with regard to dry mouth symptoms, which is the most important outcome. This may be because there were insufficient participants included in the 2 trials to show a possible effect or it may be that there was some benefit due to “placebo” acupuncture, which could have biased the effect to the null. There is insufficient evidence to determine the effects of electrostimulation devices on dry mouth symptoms. It is well-known that dry mouth symptoms
may be problematic even when saliva production is increased, yet only 2 of the trials that evaluated acupuncture reported dry mouth symptoms, a worrying reporting bias. There is some low quality evidence that acupuncture results in a small increase in saliva production in patients with dry mouth following radiotherapy. There is insufficient evidence to determine the effects of electrostimulation devices on dry mouth symptoms or saliva production in patients with Sjogren's syndrome. Reported adverse effects of acupuncture are mild and of short duration, and there were no reported adverse effects from electrostimulation.

In a pilot study, Lakshman et al (2015) evaluated the effectiveness of a TENS unit in stimulating the whole salivary flow rate in radiation-induced xerostomia patients. A total of 40 subjects were included in the study. The study group consisted of 30 individuals and was divided into Group S1 (n = 20), which was further subdivided into Group S1A (n = 10) subjects complaining of dry mouth who were undergoing head and neck radiotherapy with TENS stimulation during the commencement of radiotherapy, on the 3rd, 6th week and after a month of completion of radiotherapy and Group S1B (n = 10) with TENS stimulation daily during the full course of radiotherapy and Group S2 (n = 10) subjects complaining of dry mouth who had undergone head and neck radiotherapy that ended 1 month prior to their entry into the study. The control group (n = 10) consisted of healthy individuals not complaining of dry mouth and who have not undergone head and neck radiotherapy. Whole saliva was collected without stimulation for 10 mins and after electrostimulation with TENS unit for additional 10 mins in a graduated test tube. The results were statistically analyzed using Mann-Whitney U-test and Kruskal-Wallis's test. The data analysis revealed that control and S1B group
showed increased salivary flow rate after stimulation by TENS therapy compared with the unstimulated salivary flow, whereas in S1A and S2 group it was found to be statistically non-significant. The authors concluded that the findings of this study provided an insight about the effectiveness of TENS therapy in stimulating salivary flow in healthy subjects and it is very effective when used in conjunction with radiation therapy by reducing the side-effects of radiation therapy. They stated that TENS therapy can be used as an adjunctive method for the treatment of xerostomia along with other treatment modalities. These preliminary findings need to be validated by well-designed studies.

Wong et al (2015) presented the results of the phase III clinical trial, RTOG 0537, which compared ALTENS with pilocarpine (PC) for relieving radiation-induced xerostomia. Eligible patients were randomized to twice-weekly 20-min ALTENS sessions for 24 sessions during 12 weeks or PC (5 mg 3 times daily for 12 weeks). The primary end-point was the change in the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) scores from baseline to 9 months from randomization (MFR). Secondary end-points included basal and citric acid primed whole salivary production (WSP), ratios of positive responders (defined as patients with greater than or equal to 20 % reduction in overall radiation-induced xerostomia symptom burden), and the presence of adverse events based on the Common Terminology Criteria for Adverse Events version 3. An intention-to-treat analysis was conducted. A total of 148 patients were randomized. Only 96 patients completed the required XeQOLS and were evaluable at 9 MFR (representing merely 68.6 % statistical power); 76 patients were evaluable at 15 MFR. The median change in the overall XeQOLS in ALTENS and PC groups at 9 and 15 MFR were -0.53 and -0.27 (p = 0.45) and -0.6 and -0.47 (p = 0.21). The corresponding
percentages of positive responders were 81% and 72% (p = 0.34) and 83% and 63% (p = 0.04). Changes in WSP were not significantly different between the groups. Grade 3 or less adverse events, mostly consisting of grade 1, developed in 20.8% of patients in the ALTENS group and in 61.6% of the PC group. The authors concluded that the observed effect size was smaller than hypothesized, and statistical power was limited because only 64.8% (96 of 148) of the recruited were evaluable. The primary end-point -- the change in radiation-induced xerostomia symptom burden at 9 MFR-was not significantly different between the ALTENS and PC groups. There was significantly less toxicity in patients receiving ALTENS.

Patient (a medical information and support organization from England and Wales)’s webpage on “Dry Mouth (Xerostomia)” (last updated 12/23/2015) stated that “A technique called acupuncture-like transelectrical nerve stimulation is currently being investigated”.

Furthermore, an UpToDate review on “Management of late complications of head and neck cancer and its treatment” (Galloway and Amdur, 2016) states that “Neuromuscular electrical stimulation (NMSE) is a potentially promising improvement to traditional therapy (for dysphagia)”. It does not mention electrical stimulation as a therapeutic option for xerostomia.

**Fat Grafting to Salivary Glands:**

Kawakami and colleagues (2016) stated that atrophy or hypo-function of the salivary gland because of aging or disease leads to hypo-salivation that affects patient quality of life by causing dry mouth, deterioration of mastication/deglutition, and poor oral hygiene status. Current therapy for atrophy or hypo-function of the salivary gland in clinical practice focuses on symptom
relief using drugs and artificial saliva; therefore, there is still a need to develop new therapies. To investigate potential novel therapeutic targets, these researchers induced the differentiation of salivary gland cells by coculturing human adipose-derived stem cells isolated from buccal fat pads (hBFP-ASCs) with human salivary-gland-derived fibroblasts (hSG-fibros). They examined their potential for transplantation and tissue neogenesis. Following the culture of hBFP-ASCs and hSG-fibros, differentiated cells were transplanted into the submandibular glands of SCID mice, and their degree of differentiation in tissues was determined. These investigators also examined their potential for functional tissue reconstitution using a three-dimensional (3D) culture system. Co-cultured cells expressed salivary gland-related markers and generated new tissues following transplantation in-vivo. Moreover, cell reconstituted glandular structures in the 3D culture system. The authors concluded that co-culture of hSG-fibros with hBFP-ASCs led to successful differentiation into salivary gland cells that could be transplanted to generate new tissues.

Furthermore, a systematic review on “Treatment of xerostomia and hyposalivation in the elderly” (Gil-Montoya et al, 2016) and an UpToDate review on “Treatment of dry mouth and other non-ocular sicca symptoms in Sjogren's syndrome” (Baer, 2016) does not mention fat grafting as a therapeutic option.

Acupuncture:

 Assy and Brand (2018) noted that several studies have suggested a positive effect of acupuncture on oral dryness. These investigators carried out a systematic review of the effects of acupuncture on xerostomia and hypo-salivation. PubMed and Web of Science were electronically searched.
Reference lists of the included studies and relevant reviews were manually searched. Studies that met the inclusion criteria were systematically evaluated; 2 reviewers assessed each of the included studies to confirm eligibility and assessing the risk of bias. A total of 10 randomized controlled trials (RCTs) investigating the effect of acupuncture were included; 5 trials compared acupuncture to sham/placebo acupuncture; 4 trials compared acupuncture to oral hygiene/usual care. Only 1 clinical trial used oral care sessions as control group. For all the included studies, the quality for all the main outcomes had been rated as low. Although some publications suggested a positive effect of acupuncture on either salivary flow rate or subjective dry mouth feeling, the studies were inconclusive about the potential effects of acupuncture. The authors concluded that insufficient evidence was available to conclude whether acupuncture is an evidence-based therapeutic option for xerostomia/hypo-salivation. They stated that further well-designed, larger, double-blinded trials are needed to determine the potential benefit of acupuncture. Sample size calculations should be performed before initiating these studies.

Artificial Saliva:

Apperley and co-workers (2017) noted that researchers have recently developed a novel oily formulation for potential use as a saliva substitute for the treatment of dry mouth. In a randomized, cross-over study, these researchers compared this new formulation to a currently available saliva substitute and a control of water on measures of mastication, subjective feeling of
oral dryness and product acceptability. A total of 40 participants treated with radiotherapy to the head and neck and experiencing xerostomia were invited to participate in the trial. Each participant tried all 3 products in a randomized order. The effect of each product was measured using the Test of Masticating and Swallowing Solids (TOMASS), the Shortened Xerostomia Inventory (SXI) and a questionnaire designed to test patient acceptability of each product. Outcome data were gathered in a single session after the 1st administration of each product to evaluate immediate effects and after 7 days of use to evaluate longer-term effects. Statistical analyses consisted of repeated-measures analysis of variance and mixed models. There was no evidence that application of the 3 formulations had an effect on any of the TOMASS measures, either immediately or after 1 week of use ($p > 0.05$). There was a significant main effect of formulation on the SXI score ($p = 0.02$). Application of the novel emulsion resulted in a clinically small but significant improvement in SXI score ($p < 0.01$); however, application of methylcellulose ($p = 0.21$) and water ($p = 0.81$) resulted in no significant difference. There was no difference in participant acceptability between the 3 products ($p = 0.32$). The novel oily emulsion showed no clinically significant benefit over 2 existing products for relief of xerostomia; in fact, none of the 3e products demonstrated significant change in patient outcomes.

In a double-blind, randomized, controlled study, Cifuentes and colleagues (2018) compared the efficacy of pilocarpine and artificial saliva as symptomatic treatments for xerostomia and xerophthalmia in patients with Sjogren's
Syndrome (SS). A total of 72 patients with SS were assigned randomly to receive 10 drops of pilocarpine (5 mg) or 10 drops of artificial saliva, orally, t.i.d. for 12 weeks. Patients were evaluated at baseline and periodically throughout the study by whole saliva and tear flow for global assessment of their dryness as well as for any adverse effects. Patients receiving pilocarpine had a statistically significant improvement in their salivary flow (p < 0.0001), lachrymal flow (p < 0.0001), and their subjective global assessment (p < 0.0001), compared with patients on artificial saliva. The most common side effects were sialorrhea and nausea. The authors concluded that pilocarpine was more effective than artificial saliva for enhancing salivary and lachrymal secretion in patients with SS. They noted that this was the first study comparing the efficacy of pilocarpine and artificial saliva as treatments for xerostomia and xerophthalmia in SS.

Low-Level Laser Therapy:

In a randomized trial, Fidelix and associates (2017) evaluated the effectiveness of low-level laser therapy (LLLT) in the treatment of xerostomia in primary SS. Patients with dry mouth symptoms associated with primary SS receiving care at a university hospital were eligible for enrollment in the study. A total of 66 patients were randomly assigned with a 1:1 allocation ratio to receive LLLT (laser group, n = 33) or placebo treatment (placebo group, n = 33). Patients in the laser group received LLLT twice-weekly for 6 weeks, for a total of 12 treatment sessions. Laser irradiation was performed with an aluminum-gallium-arsenide
laser diode at a wavelength of 808 nm, 100-mW output power, and energy density of 4.0 J/cm² per irradiation point per session. Placebo treatment was performed following the same protocol used for irradiated patients and using the same laser device to mimic a real irradiation, but with no active laser emission and the tip of the laser probe covered with aluminum foil. The outcomes of interest were xerostomia inventory scores, salivary flow rate, salivary beta-2 microglobulin levels, and salivary sodium and chlorine concentrations. Patients in both groups showed no improvement in xerostomia. Likewise, there was no significant improvement in xerostomia inventory scores (p = 0.301) or salivary flow rate (p = 0.643) in either group. There was no difference in salivary beta-2 microglobulin levels, sodium concentration, and chlorine concentration before and after intervention or between the 2 groups. The authors concluded that the LLLT protocol used in this study effected no improvement in xerostomia or salivary flow rate in patients with primary SS.

Transcutaneous Electrical Nerve Stimulation (TENS):

Sivaramakrishnan and Sridharan (2017) stated that the use of transcutaneous electrical nerve stimulation (TENS) has been contemplated on by various researchers for treatment of xerostomia. These researchers performed a systematic compilation and quantitative synthesis of the existing evidence related to the utility of TENS in patients with xerostomia. A total of 6 RCTs were identified from databases for inclusion and analyzed using non-Cochrane
mode in RevMan 5.0 software. The heterogeneity between the studies were assessed using Forest plot, I2 statistics wherein more than 50% was considered to have moderate-to-severe heterogeneity and Chi-square test with a statistical p-value of less than 0.10 to indicate statistical significance. Results show that the effect of TENS on salivary flow rate in 369 participants with SMD [95% CI] was 0.63 [-0.03 to 1.29] and was not statistically significant. The authors concluded that the available evidence did not support the use of TENS in patients with xerostomia and may be considered as a salivary substitute for symptomatic improvement. However the type, frequency and amplitude of current used needs to be studied in detail. They stated that high quality RCTs with adequate power are needed, either to support or refute the use of TENS in xerostomia.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>20926</td>
<td>Tissue grafts, other (eg, paratenon, fat, dermis)</td>
</tr>
<tr>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
<td></td>
</tr>
<tr>
<td>E0755</td>
<td>Electronic salivary reflex stimulator (intraoral/noninvasive)</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>K02.3</td>
<td>Dental caries and other specified diseases of hard tissues of teeth</td>
</tr>
<tr>
<td>K02.9</td>
<td></td>
</tr>
<tr>
<td>K03.89</td>
<td></td>
</tr>
<tr>
<td>K11.7</td>
<td>Disturbance of salivary secretion (xerostomia)</td>
</tr>
<tr>
<td>K12.1</td>
<td>Other and unspecified diseases of oral soft tissues</td>
</tr>
<tr>
<td>K13.1</td>
<td></td>
</tr>
<tr>
<td>K13.4</td>
<td></td>
</tr>
<tr>
<td>K13.6</td>
<td></td>
</tr>
<tr>
<td>K13.79</td>
<td></td>
</tr>
<tr>
<td>M35.00</td>
<td>Sicca syndrome [Sjögren]</td>
</tr>
<tr>
<td>M35.09</td>
<td></td>
</tr>
<tr>
<td>R13.10</td>
<td>Dysphagia</td>
</tr>
<tr>
<td>R13.19</td>
<td></td>
</tr>
<tr>
<td>R68.2</td>
<td>Dry mouth, unspecified</td>
</tr>
<tr>
<td>T66.xx+</td>
<td>Effects of radiation, unspecified [radiation-induced xerostomia]</td>
</tr>
<tr>
<td>Z92.3</td>
<td>Personal history of irradiation</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


Amendment to
Aetna Clinical Policy Bulletin Number: 0302 Xerostomia: Selected Treatments

There are no amendments for Medicaid.