

ABSTRACT

Purpose: To present patient reported changes in oral symptoms in response to an open-label product trial conducted in patients self-identifying as having Sjögren's syndrome.

Methods: A survey was conducted in conjunction with the Sjögren's Syndrome Foundation and 151 foundation members completed a survey rating their common oral symptoms, based upon the Vanderbilt Head and Neck Symptom Survey before and after use of the trial products, including rinse, lozenges, gel, and spray.

Results: Subjects reported multiple oral symptoms with the highest rated symptoms involving dry mouth with 80% of symptoms showing statistically significant reduction from pre- to posttest. The largest symptom reductions were in dry mouth symptoms and dietary problems.

Conclusions: Symptoms of dry mouth were improved with use of MedActive® products. Increased ease of taking oral medications also was reported. Improvement in mouth/throat pain was noted. Subjects reported considerable effect of the test product upon dry mouth and oral symptoms.

KEY WORDS: Sjögren's syndrome, salivation, xerostomia, dysguesia, mouth and throat pain, quality of life

Patient reported outcomes of the clinical use of a proprietary topical dry mouth product

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Introduction

Saliva has critical biologic functions that support the health of oral tissue and supports oral function including personal and social interactions (e.g., speech) and oral intake (taste, eating, bolus formation, clearing the oral cavity, and swallowing). Saliva hydrates, maintains, and lubricates oral and oropharyngeal soft tissues, and supports remineralization of teeth. Microbial shifts may occur with hyposalivation and may result in increased cariogenic flora and fungal colonization and infection. This is in part due to the loss of antimicrobial protection afforded by the saliva through salivary antimicrobial peptides such as histatins, defensins and calprotectin, immunoglobulins and physical clearing of microbes from oral surfaces.^{1,2} Enamel demineralization and structural damage may occur due to limited buffering capacity of saliva, and lack of remineralization; that may result in rampant caries. The comfort and function of dental prostheses may be impacted by loss of mucosal wetting and hydration, dilution, and lubricating functions. Mucosal health and wound healing may be affected by loss of mucin, reduction in mucosal epithelial growth factors and reduction in salivary antibodies that may result in mucosal atrophy, fragility and delayed repair.^{3,4} Periodontal complications also may be increased.⁵ Overall, when the protective saliva functions are lost, compromised oral health and oral function may impact: oral health, diet, nutrition, and systemic health.

In people with reduced saliva production, stimulation of production may be possible, but when that stimulation is not sufficient, management should address the lost functions of saliva. One study reported that approximately one-third of SS patients do not respond significantly to sialogogues, related to the severity of gland involvement.⁴ In order to promote ongoing use, the product

should have a pleasant taste and texture and a rapid onset, ease of use, prolonged duration of effect and provide a continuum of effect over a 24-hour period.

Xerostomia is the symptom report of the sensation of dry mouth whereas hyposalivation refers to salivary gland hypofunction resulting in decreased saliva production. Up to 20% of the adult population may suffer from xerostomia.⁵

While often correlated, salivary gland hypofunction and xerostomia are not equivalent, as patients may report xerostomia while demonstrating a normal quantity of saliva and people with persisting hyposalivation may accommodate and not report dry mouth. Despite this apparent discrepancy and independently of reported symptoms, persisting hyposalivation may be profoundly deleterious to oral health.

Sjögren's syndrome (SS) is the second most common autoimmune disorder.⁶ SS is characterized by decreased exocrine gland function, primarily salivary and lacrimal gland function and may be the sole manifestation (primary SS) or be associated with other autoimmune disease presentations, including arthritis, vasculitis with organ involvement and skin and mucosal tissue damage (secondary SS).^{7,8} Oral symptoms and signs are a common consequence of hyposalivation and can impact quality of life, oral and dental health and function and, potentially, systemic health.

The purpose of this article is to present patient reported changes in symptoms using a within-subject design in response to an open-label product trial conducted in patients self-identifying as having SS.

Materials and Methods

The design of this study is a within-subject (pretest/posttest design) that allows for subjects to serve as their own controls. This product trial was conducted in conjunction with the Sjögren's Syndrome Foundation (Bethesda, MD, USA), as previously reported.^{9,10} Briefly, an introductory letter was sent to 3,000 randomly selected members of the foundation from their mailing list from New York, Virginia, Ohio, New Jersey, Connecticut, and Pennsylvania. The letter invited the recipients to contact the study sponsor, MedActive® Pharmaceuticals, to learn more about the trial when they could volunteer to participate. Three hundred and one subjects responded to the letter and were sent study supplies that included an informed consent form, product for the treatment trial, directions for product use and a

pre- and posttrial survey. The package included: MedActive® Orange Crème Oral Relief Rinse (10 packages), Natural Spring Lozenges (60), Natural Spring Sprays (2), and Orange Crème Gels (2).

MedActive® products are based upon Ultramulsion®, an emulsion of dimethicone and oloxamer 407 designed to coat, and lubricate the surface, and Spilanthes extract a certified flavorant. The product is available in rinse, gel, spray, and lozenge form. The products are formulated to provide a means to moisten and lubricate the entire mouth continuously, day and night, as a daily self-care regime to provide relief as needed. The products have no reported side effects and no known contraindications.

One-hundred and fifty-one subjects returned signed informed consent and surveys after the trial protocol was completed. Survey results of oral symptoms and medication use have been previously reported.^{9,10}

Survey

Subjects were asked to basic demographic questions (age, gender, tobacco use), medical diagnoses, medications used (prescription and over-the-counter), and oral products used prior to the trial of study materials. Subjects rated their oral symptoms based upon the Vanderbilt Head and Neck Symptom Survey (VHNSS), which has been previously validated in oncology patients with dry mouth.^{11,12}

Symptoms queried included problems with dry mouth, saliva, weight loss, eating and swallowing, oral sores, speaking, sleeping, pain, taste, oral complications, mouth and throat lining and oral care. Ratings ranged from zero, representing absence of the problem, up to 10, representing the most severe degree of the problem. Subjects were asked to rate the symptoms for the week prior to the use of the trial products and the week after the trial products.

Data analysis

Patient characteristics, comorbid conditions, medication use, and investigational product use are reported as means ± standard deviations for

continuous variables and as percentages for dichotomous variables. Change between pre- and posttest scores were analyzed using dependent samples *t*-tests with mean differences and their corresponding 95% confidence intervals presented. Analysis was performed using SPSS 18® (SPSS Inc., Chicago, IL, USA) and statistical significance was determined at *p* < .05.

Results

Patient Characteristics, Comorbid Conditions, and Medication Use

The percentage of females in the sample was 96% with 2.6% male (1.3% of the subjects did not identify gender) and the mean age was 65.8 ± 11.5 (Table 1). Smoking was reported by 3.3% of the subjects. The mean number of oral care products used prior to the trial was 4.6 ± 1.4. This included reported use of toothpaste by 94.7% of the sample, rinse (84.8%), floss (76.2%), spray (39.7%), gum (46.4%), lozenges (39.1%), gel (37.7%), prescription saliva stimulants/sialogogue (19.2%) and other oral products (14.6%).

The mean number of comorbid conditions reported by the participants was 4.2 ± 2.9 (Table 1). The majority of subjects reported one or more comorbid conditions (94.8%). The most frequently endorsed conditions were: acid reflux (45%), arthritis (42.4%), allergies (38.4%), chronic pain (38.4%), osteoporosis (29.1%), depression/anxiety (27.8%), and insomnia (27.4%). Daily prescription medications were reported by 74.9% of subjects; the mean number of prescription medications was 4.9 ± 3.5. The most frequently endorsed medications were: blood pressure medicines (35.8%), pain relievers (33.1%), antidepressants (30.5%), antiinflammatories (29.1%), antacids (24.5%), and cholesterol medications (23.2%).

Product Use, Preference, Relief, and Duration

Majority of the sample reported having used the products as recommended in

Table 1. Demographics, comorbidity, medication and oral product use.

	Mean	SD
Age	65.8	11.5
Number of comorbidities	4.2	2.9
Number of prescription medications	4.9	3.5
Number of current oral products used	4.6	1.4
	N	Percentage
Gender (female)	145	96.0
Current smoker	5	3.3
Most frequently endorsed comorbidities		
Acid reflux	68	45.0
Arthritis	64	42.4
Allergies	58	38.4
Chronic pain	58	38.4
Osteoporosis		29.1
Depression/anxiety		27.8
Insomnia		27.4
Most frequently endorsed medications		
Antihypertensives	54	35.8
Pain relievers	50	33.1
Antidepressants	46	30.5
Antiinflammatories		29.1
Antacids		24.5
Cholesterol medications		23.2
Current oral products used		
Toothpaste	143	94.7
Rinse	128	84.8
Floss	115	76.2
Spray	60	39.7
Gum	70	46.4
Lozenges	59	39.1
Gel	57	37.7
Prescription saliva stimulants/sialogogue	29	19.2
Other oral products	22	14.6

the instruction packet (86.8%). They reported that the symptom questionnaire was not difficult to complete (87.4%) and indicated the instructions were easy to follow (93.4%). The investigational products were rated as easy to use in daily activities by 82.1% and optimal relief from symptoms was reported by 60.9% of the sample (Figure 1). To

determine if correct use of the product was related to symptom relief, subjects were divided into groups based on their reported product use as recommended and whether they reported the product was easy to use and group differences for key symptoms at posttest (dry mouth, average pain over the last week, worst pain over the last week) were evaluated.

There were no statistically significant symptom differences between the groups for either comparison (data not shown). Age and gender also did not differ between groups (data not shown).

The participants stated they would use the products again with the spray (82.8%), lozenges (75.5%), rinse (60.3%), and gel (53.6%). Lozenges were ranked highest with 41.1% of subjects ranking this product first (Figure 2). Symptom relief for more than 30 minutes was highest for lozenges (67.6%) while more than half of the subjects reported this duration of relief for all formulations. Product duration for more than 30 minutes was highest for gel (58.9%) followed by rinse (53.5%), spray (53.5%), and lozenges (40.5%).

Pre- and Posttest Oral Symptoms

Subjects reported multiple oral symptoms, 80% of which had a statistically significant reduction from pre- to posttest (Figures 3A to E). At pretest, the highest rated symptoms involved problems with dry mouth (Figure 3A, $x = 7.6 \pm 2.1$), dry mouth making chewing and swallowing hard ($x = 5.7 \pm 2.9$), dry mouth affecting ability to talk ($x = 5.3 \pm 3.1$), dry mouth affecting sleep ($x = 4.8 \pm 3.3$) and some subjects rated medications hard to take due to dry mouth ($x = 2.7 \pm 3.1$). The dry mouth symptom reduction shown in Figure 3A represent statistically significant reductions in symptoms, with trouble wetting/softening food due to dry mouth showing the smallest reduction (mean difference = 0.56, 95%CI = 0.19 to 0.93, $p = .003$) and problems with dry mouth having the largest reduction (mean difference = 1.44, 95%CI = 1.13 to 1.75, $p < .001$).

All questions related to pain showed statistically significant reduction from pre- to posttest (Figure 3B). Painful sores in the mouth or throat that were moderately problematic at pretest ($x = 3.0 \pm 3.4$) had the largest symptom reduction (mean difference = 0.75, 95%CI = 0.43 to 1.07, $p < .001$). The mean worst pain over the prior week was rated 3.3 ± 3.3 and the average pain over the last week was 2.9 ± 2.8 . Symptom reduction was similar for both worst pain (mean difference = 0.52,

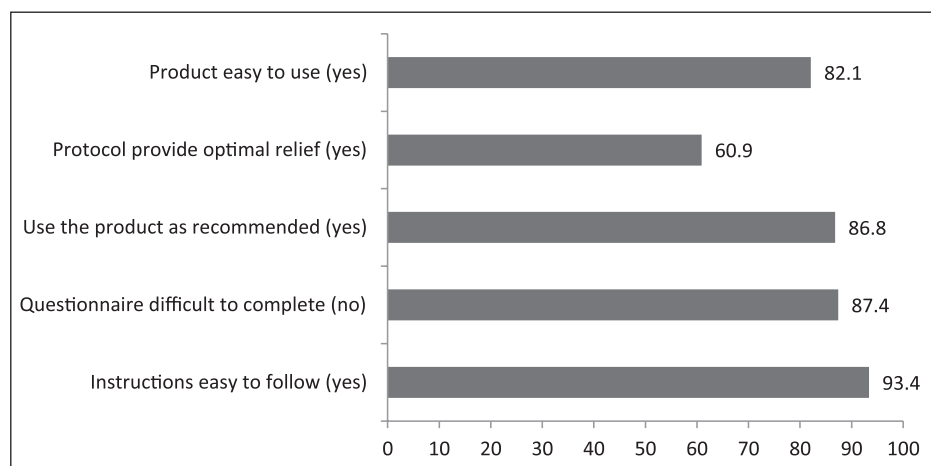


Figure 1. Trial product use information. Note: Values represent the percentage of subjects who endorsed the item indicated in the vertical axis.

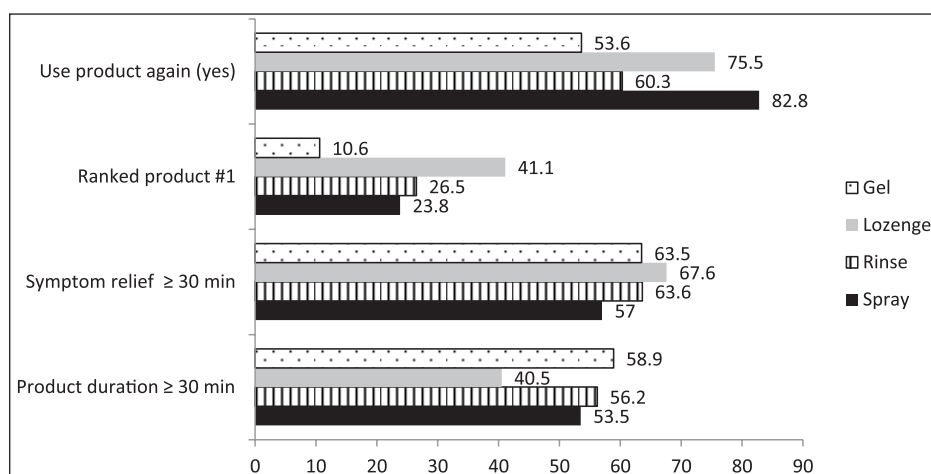


Figure 2. Trial product preference, relief, and duration. Note: Values represent the percentage of subjects who endorsed the item indicated in the vertical axis.

95%CI = 0.15 to 0.88, $p = .006$) and average pain (mean difference = 0.52, 95%CI = 0.24 to 0.81, $p < .001$).

Taste/diet changes and dietary problems were frequently reported while others were less problematic at pretest. Product use resulted in a statistically significant reduction for the majority of symptoms (Figures 3C and 3D). Sensitivity of the lining of mouth and throat due to dryness (pretest $x = 6.6 \pm 3.0$), trouble eating certain solid foods (pretest $x = 6.0 \pm 3.4$), food sticking in mouth due to dryness (pretest $x = 5.9 \pm 3.4$), sensitivity in the lining of mouth

and throat to spicy/hot/acidic foods (pretest $x = 5.9 \pm 3.5$) were more problematic while symptoms such as less desire to eat due to taste change (pretest $x = 2.3 \pm 3.1$) and decrease in food eaten due to taste changes (pretest $x = 2.2 \pm 3.1$) were less problematic.

For dietary problems, food sticking in the mouth due to dryness was improved during the product trial (mean difference = 0.06, 95%CI = 0.70 to 1.43, $p < .001$) while, choking or strangling on liquids did not have a statistically significant change (mean difference = 0.22, 95%CI = -0.04 to 0.49, $p = .095$). For

taste/diet changes, sensitivity in the lining of mouth and throat to spicy/hot/acidic foods had the largest symptom reduction (mean difference = 0.70, 95%CI = 0.37 to 1.03, $p < .001$). Decreased dietary intake due to taste changes and altered foods choices due to taste changes did not show a statistically significant change (mean difference = 0.27, 95%CI = -0.02 to 0.56, $p = .071$ and mean difference = 0.16, 95%CI = -0.21 to 0.54, $p = .383$, respectively).

Similar to taste and diet changes/problems, some oral complaints were reduced at posttest (Figure 3E). Reduction occurred in mouth/throat sensitivity due to dryness (pretest mean = 6.6 ± 3.0 ; mean difference = 1.08, 95%CI = 0.71 to 1.45, $p < .001$), burning sensation in lining of mouth/throat (pretest $x = 4.1 \pm 3.4$; mean difference = 0.64, 95%CI = 0.28 to 1.0, $p = .001$) and tooth sensitivity to hot/cold/sweet foods (pretest $x = 4.3 \pm 3.7$; mean difference = 0.81, 95%CI = 0.42 to 1.21, $p < .001$). Burning pain in lining of the mouth/throat that prevented brushing of teeth, trouble with dentures and teeth cracking/chipping did not have statistically significant reductions (p values range from 0.08 to 0.747). Trouble with dentures was rated as moderately problematic at pretest ($x = 3.8 \pm 3.8$) and was one of the few symptoms to increase at posttest, although the difference was small (mean difference increase = 0.087) and not statistically significant ($p = .75$).

Discussion

In this study, we tested different formulations of MedActive® products in a within subject design to assess ease of use, subject preference of product, level and duration of symptom relief and duration of product effect. The MedActive® products in this study were well received by the subjects with 82.1% rating the products as easy to use in daily activities and 60.9% of the subjects reported relief from symptoms when using the products. It is likely that this report of relief is based on participants' prior experience and in contrast to previously used products. Patient preference for a product is

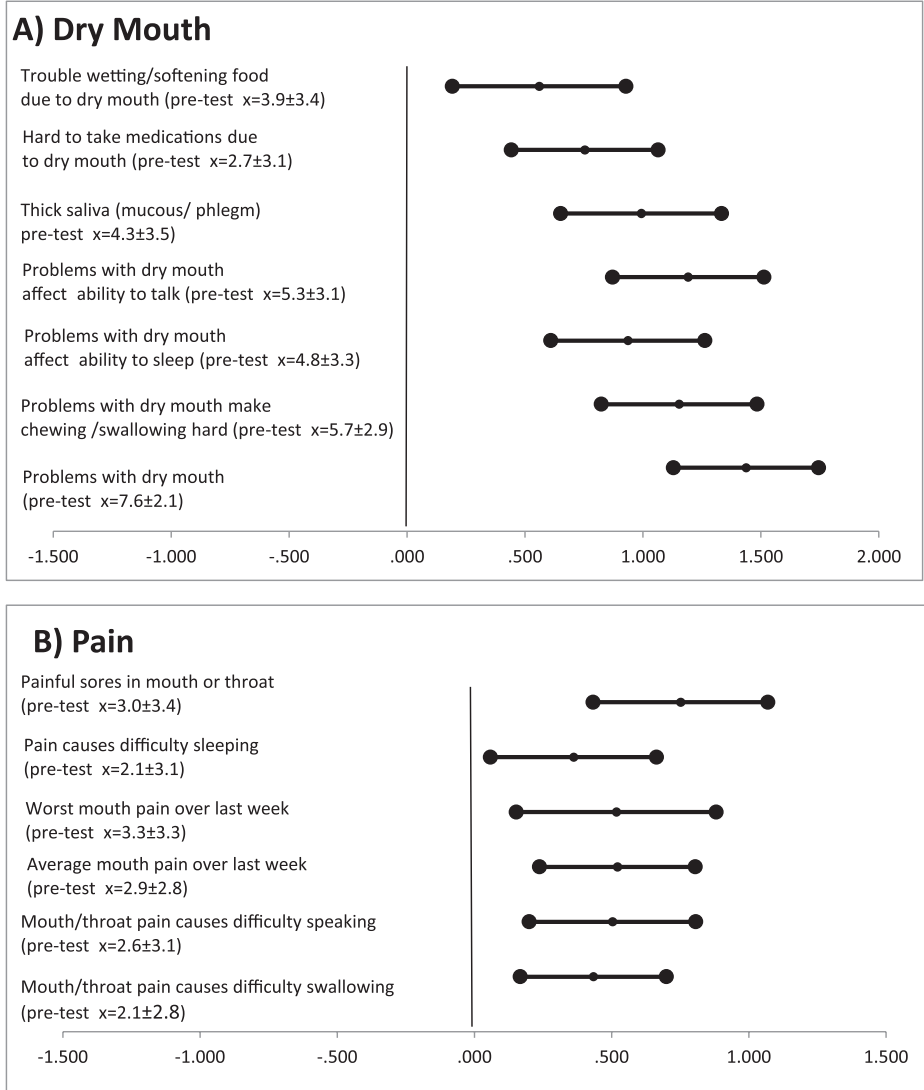


Figure 3. Mean symptom difference and 95% confidence intervals between pre- and posttest scores. Note: Mean difference and 95% confidence intervals for symptom difference are statistically significant if the confidence does not include zero. Positive mean differences represent an improvement in symptoms at posttest after using the investigational product(s). Pretest scores are represented as mean ± SD. Rating scale ranges from 0, indicating the least amount of problems with a symptom, to 10, indicating the most amount of problems with a symptom. Values represent mean ± standard deviation.

essential for protocol adherence and patient comfort to avoid patient discontinuation of treatment.¹³

Perhaps the best indicator of patient preference was that the subjects stating a willingness to use the product again with ranking of products as follow: the spray (82.8%), the lozenges (75.5%), the rinse (60.3%), and the gel (53.6%). Although the spray received the highest endorsement for use in the future, the lozenges

were the highest ranked product for preference possibly due to ease of use and longer symptom relief as reported by the subjects.

Overall, the products were effective in symptom relief with 80% of symptoms having statistically significant reduction after product use. Importantly, all dry mouth and pain symptoms had a statistically significant reduction and the majority of dietary problems and taste/

diet changes also had a statistically significant reduction. Given that these symptoms may be the most severe symptoms for patients with SS and can have the largest impact on overall health and quality of life,^{7,8} the findings support the utility of use of the MedActive®, Ultramulsion®-based products for these dry mouth patients. This study examined changes in symptoms within a one week period, and long-term efficacy of the products was not assessed. The performance evaluations and relief evaluations demonstrate a statistically significant reduction within 1 week of product use indicating benefit for patients.

In this study, subjects self-identified as having SS and medical confirmation was not obtained. This is comparable to diagnosis of SS in the private dental practice setting, where medical status is generally based on patient report. While some subjects may not have a medically confirmed diagnosis, the mean reported dry mouth symptom score was 7.6 with the upper limit of scoring being a 10 indicating the sample was experiencing moderate to severe dry mouth symptoms. Additionally, this recruitment format allowed from a broad regional sample which may reduce sampling biases that are inherent to sampling from a specific area or clinic. Similarly, symptoms were self-reported via questionnaire without objective measures of the symptoms reported; however, this analogous to clinical practice as well. Potential limitations include those common to all survey and self-reported data.

Impaired salivary function can result in compromised oral health that may lead to maladaptive changes in diet and nutrition that may affect oral and systemic health. Dry mouth patients benefit from stimulation of residual secretory capacity; however, replacing the lost functions of saliva should be addressed if the salivary glands cannot be adequately stimulated. Salivary replacement can not only improve the symptoms but also may help in maintaining or reconstituting a normal oral flora including yeast colonization.^{14,15}

When saliva stimulation is not possible, symptom management and oral

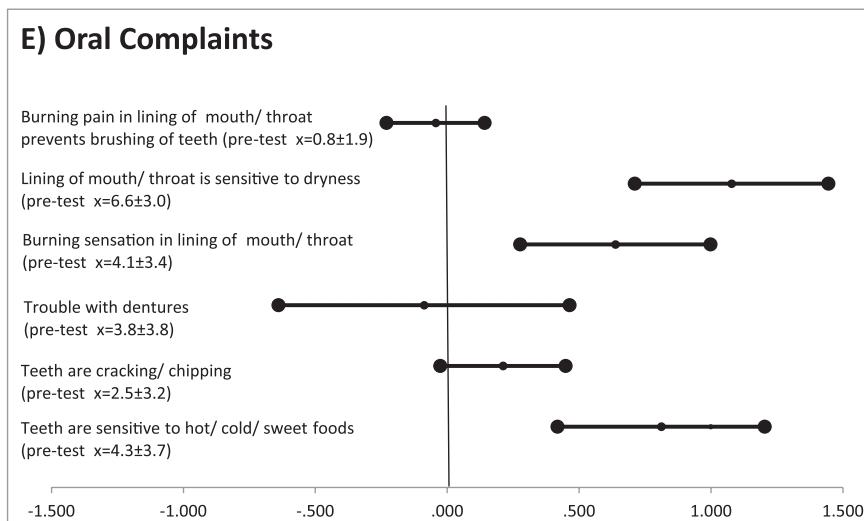
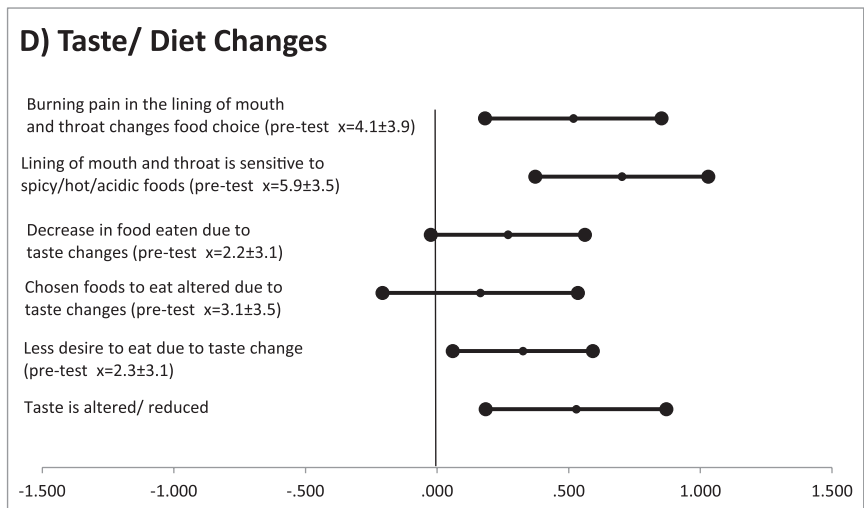
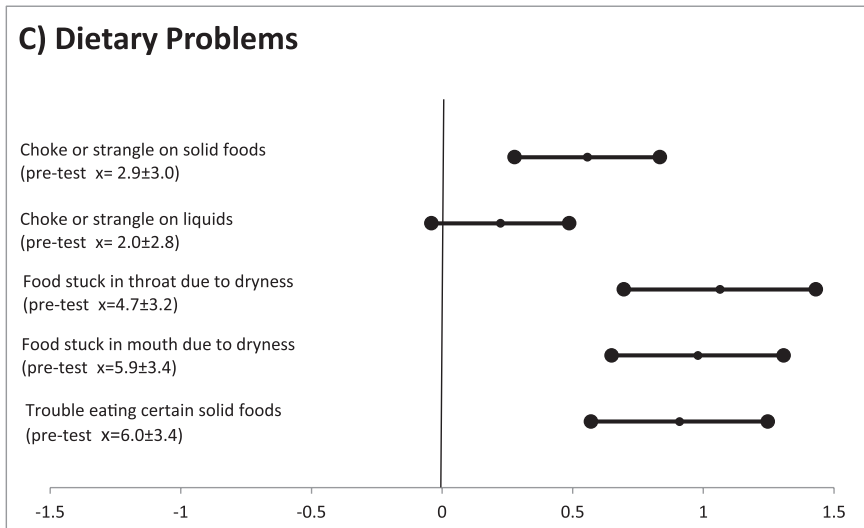


Figure 3. Continued.

health should be addressed. The complex biologic functions of saliva may be maintained by addressing components of the secretion. This includes surface wetting, lubrication, and tissue hydration. The product should be pleasant, rapidly active, with prolonged duration of effect and provide a continuum of effect over a 24-hour period. While the principle goal of management for xerostomia is symptomatic management on a continuing basis, it is important to address loss of biologic functions of decreased saliva. The product trial showed impact upon oral symptoms affecting mucosal sensitivity and pain and a high level of patient satisfaction.

The majority of “saliva substitutes” or mouth wetting agents are based upon carboxymethylcellulose or mucin (Europe), while other formulas have been explored hydroxymethylpropylcellulose, polyglycerylmethacrylate, polyethylenoxide, xanthan gum, linseed extract, aloe vera, olive and a variety of oils. Some may include antibacterial products and inorganic molecules with a goal of affecting dental mineralization, although often evidence of efficacy is often not assessed in clinical trials.¹⁶ The major disadvantages of the saliva substitutes is the generally short duration of relief and the lack of biologic constituents, and when some are incorporated, limited evidence of effect of the product on oral comfort and oral/dental disease.¹⁶

The ideal management protocols may vary with the cause and magnitude of salivary gland hypofunction, time of day and activity, and patient preferences of application, texture, and flavor. The ideal product also will provide a continuum of care throughout the day and night. Some advocate the use of salivary stimulating gum combined with a salivary substitute.¹⁷ It has been reported that the patient with more severe hyposalivation may be more responsive to salivary substitutes or wetting agents.¹⁸ An additional strategy advocated and tested by some in ameliorating xerostomia is the construction of a wetting-agent reservoir that would slowly release a lubricant into the oral cavity.¹⁹ While reports may suggest this strategy is feasible, its high cost and

potential risks have significantly impacted the enthusiasm for such an approach. Thus, different products or formulations may be helpful.

In severe hyposalivation, the texture and viscosity of the palliative product may be poorly tolerated compared to people with some saliva production, and different characteristics of products may be of importance. Care of patients with hyposalivation may be best managed by preventive (regular schedule) surface wetting, cellular hydration, with “break-through” use of convenient product when dry mouth is increased (e.g., oral spray, gel product, lozenge, chewing gum). Products with extended duration of effect may be helpful at night.

A hurdle in clinical evaluation and comparison of salivary substitute is the lack of uniform tools to measure the outcomes. Some have relied on nonvalidated questionnaires.^{18–22} In this study, we used a validated tool, the VHNS which provides detailed evaluation of the impact of xerostomia and has utility in assessing the impact of management of xerostomia on key symptoms and oral function associated with dry mouth, including comfort, pain, taste that impact quality of life. The majority of prior studies on dry mouth products assessment were limited to use, convenience and duration of effect but do not assess details on oral function and impact upon key characteristics of effect that are possible by employing tools such as the VHNS.^{23–27} The impact of the test products upon validated patient reported outcomes with dry mouth showed positive impact in important domains of convenience, and effect upon oral symptoms and function.

Future studies in patients with hyposalivation should employ validated measures assessing symptoms and function as well as biologic effects of dry mouth agents. Study design should consider stratifying patients with mild and severe xerostomia as well as etiology of dry mouth in order to inform future management. The impact of xerostomia on quality of life mandates that evaluation of the use of saliva substitutes must assess symptoms and QoL.

Conclusion

The current open-label trial in patients reporting SS evaluated changes in symptoms in a within-subject design in response to an open-label product trial, with good results upon significant dry mouth symptoms. This study is limited by several factors as discussed above. None the less, the symptomatic responses to the MedActive® products support consideration for use in management of patients with SS.

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