

Efficacy of a New Oral Lubricant Solution in the Management of Psychotropic Drug-Induced Xerostomia

A Randomized Controlled Trial

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Objective: Xerostomia is a subjective sensation of mouth dryness often occurring as an unwanted effect of psychotropic drugs.

Methods: The clinical efficacy and acceptability of a new oxygenated glycerol triester (OGT) oral spray (1 or 2 sprays up to 4 times daily) in the treatment of xerostomia was compared with those of a commercially available artificial saliva substitute (ASS [Saliveze]) in a 2-week, open-labeled, randomized, parallel-group study. Clinical assessment of xerostomia included evaluation of mouth dryness by means of a 10-cm-long visual analog scale, objective blinded assessment of the oral tissue condition by a dental hygienist by means of a 4-point ordinal scale, and subjective patient-based assessment of dry mouth symptoms by means of dichotomous responses to a questionnaire. [Day 14 – baseline] patient-based mouth dryness score was the primary end point.

Results: Seventy-four patients (41 women and 33 men, 44 ± 15 years) undergoing long-term psychotropic drug treatment were consecutively enrolled. At day 14, OGT resulted in better efficacy than ASS in mouth dryness score (mean difference, 1.2 ± 0.4 ; $P = 0.006$), speech difficulties (mean difference, 1.2 ± 0.4 ; $P = 0.005$), taste (mean difference, 1.1 ± 0.4 ; $P = 0.02$), and overall mouth condition (mean difference, 1.4 ± 0.9 ; $P = 0.005$). Taste of OGT was better than that of ASS (mean difference, 1.4 ± 0.6 ; $P = 0.04$), as was OGT acceptability (mean difference, 1.4 ± 0.9 ; $P = 0.005$).

Conclusion: Oxygenated glycerol triester lubricant oral spray was superior to a commercially available ASS in improving xerostomia and overall condition of the oral tissue.

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Saliva plays a fundamental role in the maintenance of oral health and homeostasis. Lack of saliva predisposes individuals to oral symptoms and oral disease. Xerostomia is defined as the subjective sensation of dryness of the mouth that may or may not be associated with a marked decrease in saliva secretion and may frequently occur as an unwanted effect of psychotropic drugs.^{1,2} Xerostomia is commonly associated with oral symptoms such as taste disturbances, bad breath, and mouth ulcers³ and affects oral functions such as speech, chewing, and swallowing.^{4,5} As a result, there is alteration in the microbial colonization of the oral cavity, reduction in prostheses retention, mucosal dehydration, and reduced lubrication in the oral mucosa.⁶ These complications manifest as extensive dental caries, candidiasis,⁷ mucosal atrophy and burning sensation, difficulty in denture retention,⁸ compromised speech and swallowing, and reduced or altered taste sensation, thus restricting daily activities, along with a negative impact on quality of life.⁹

Management of xerostomia includes symptomatic relief, prevention or correction of the sequelae of saliva hypofunction, and treatment of any underlying disease. Adequate hydration of the oral tissues (frequent sips of water) is the standard treatment of xerostomia. Indeed, drug-induced xerostomia can sometimes be alleviated with chewing gum or taste stimulation using gustatory substances.^{1–3} Other products available in the management of xerostomia, especially radiation-induced xerostomia or xerostomia occurring after removal of the salivary glands or in patients with Sjögren syndrome, include drugs known to stimulate the production of saliva such as pilocarpine or cevimeline.² However, in some patients with drug-induced xerostomia, it may no longer be possible to stimulate the normal saliva flow rate. In these patients, artificial saliva or saliva substitutes become the proper therapy.² The latter are usually formulated to be close to natural saliva in composition. They are typically based on aqueous electrolyte solutions and may contain animal mucins or carboxymethylcellulose. Mucin-containing saliva substitutes tend to result in slightly better improvement in xerostomia symptoms as compared with carboxymethylcellulose-containing saliva substitutes, but with poor acceptability by some patients.¹⁰

Oxygenated glycerol triester (OGT) oral spray (Aequasyl; Eisai SAS, Paris, France) is a new oral lubricant for the treatment of dry mouth. Oxygenated glycerol triester is supplied as an oral spray and contains no pharmacological ingredients but a lubricant compound, OGT (94.4%), silicon dioxide (1.5%), and alimentary-grade flavoring agents (4.1%). Because of the presence of OGTs and silicon dioxide, OGT spray has the property of adherence to the oral mucosa, forming a lipid film that protects against mechanical trauma and may help to reduce oral tissue moisture loss and inflammation. To a lesser extent, OGT oral spray may slightly stimulate saliva production because of the presence of small amounts of flavoring agents.^{1,2,11} In the current study, we hypothesized that OGT oral spray, as an oral lubricant, may be effective in the subjective relief of dry mouth symptoms and objective signs of dry mouth in patients with xerostomia induced by long-term treatment with psychotropic drugs.

PATIENTS AND METHODS

Materials

The study was sponsored by Laboratoires Carilène (Montesson, France). Oxygenated glycerol triester oral spray was provided by the study sponsor (Laboratoires Carilène, Montesson, France). The positive control artificial saliva substitute (ASS [Saliveze]), also provided by the sponsor, is an aqueous electrolyte-containing solution (calcium chloride 0.15 mg/mL, magnesium chloride 0.05 mg/mL, sodium chloride 0.05 mg/mL, potassium chloride 1.2 mg/mL, sodium phosphate 0.28 mg/mL, and sorbitol 30 mg/mL) purchased from Wyvern Medical Limited (Herefordshire, UK). Each bottle of OGT and ASS contained 20 and 50 mL of solution, respectively.

Subjects, Aim, and Study Design

Our objective was to evaluate the clinical efficacy and acceptability of OGT oral spray in the relief of symptoms of xerostomia as compared with ASS. The latter was chosen as the reference product because it is a standard CE-marked, commercially available treatment of dry mouth and supplied as an oral spray similar to OGT.

A 2-week, randomized, parallel-group (to avoid any period, treatment, or carryover effect), open-labeled design was used. The open-labeled study design was chosen in the current trial because of the different texture of the 2 products (ASS is an aqueous solution, whereas OGT is a rather viscous oral lubricant). Patients, 18 years and older, treated with various psychotropic drugs and complaining of dry mouth, with confirmed low saliva output using a sialometer (test of saliva weight absorbed ≤ 0.5 g/5 min) at baseline and after stimulation by chewing gum (showing a mean saliva flow rate of ≤ 0.16 and ≤ 0.5 mL/min, respectively),^{9,11,12} were enrolled after written informed content was obtained and then randomly assigned to either OGT or ASS spray treatment for 2 weeks. They were not allowed to use any other products for the treatment of dry mouth but could take sips of water. They were also allowed to use other mouth care products if needed (eg,

topical analgesics, topical antiseptics, antifungal treatments). The randomization was based on a permuted blocks-of-4 design.

Demographic data and history of dry mouth were recorded, including details of the psychotropic treatment and history of psychiatric diseases. Patients completed a questionnaire to record symptoms of xerostomia at baseline (D0). Objective assessment of the oral tissue condition was recorded by a dental hygienist in a blinded fashion using a 4-point ordinal scale and included assessment of the lips, tongue, hard and soft palate, gingiva, mucobuccal fold areas, buccal mucosa, and floor of the mouth.^{9,11} Each patient was given 2 bottles of either OGT or ASS, to ensure they had adequate quantities for the entire study. They were instructed to use 1 or 2 sprays of the assigned product up to 4 times daily, as necessary. The bottles of spray were weighed before dispensing to the patients and at the end of the treatment period to assess the quantity of product used and treatment adherence. This study was conducted in accordance with the Declaration of Helsinki and approved by the research ethics committee of the Cimiez-Victor University Hospital, Nice, France. It was registered with the ClinicalTrials.gov registry (no. NCT00332618).

Clinical Measurements and Questionnaires

The primary outcome variable was patient-based dry mouth score as evaluated by means of self-rated 10-cm-long visual analog scale (VAS) scores recorded at day (D) 0 and D14.^{9,11} Anchor points of the VAS score were 0, representing normal (ie, no dry mouth symptoms), and 10, representing “the worst imaginable” dry mouth symptoms. The latter was chosen as the primary end point because it was a specific, sensitive, and reproducible criterion, consistent with the main objective of the current clinical trial.¹¹ Secondary outcome variables included subjective perception of changes in other dry mouth symptoms (ie, chewing, swallowing, and speech difficulties as well as taste and burning sensations) using self-rated 10-cm-long VAS. In addition, oral tissue condition was recorded by the dental hygienist in a blinded fashion at D14 (redness and dryness of the tissues, degree of inflammation) using a 4-point ordinal scale, as previously described.^{9,11} The scale was calibrated as follows: 0 = none, 1 = mild, 2 = moderate, and 3 = severe defect. The dental hygienist who evaluated each patient was blind to the treatment. Results were expressed as mean score $\pm$ standard deviation (SD) obtained in the respective treatment groups.

Subjective assessment of xerostomia was performed at baseline and at D14 using dichotomous responses to a previously validated questionnaire¹ and included several criteria such as diurnal and nocturnal mouth dryness, sleep disturbances due to mouth dryness, bad taste sensation, and use of saliva substitute, as well as questions indicating social life restrictions, that is, “Do you avoid speaking to people because of your dry mouth?” and “Do you stay home because of your dry mouth?”

Evaluation of Treatment Tolerance and Acceptability

Treatment tolerance, acceptability, and taste were evaluated by means of a self-rated 10-cm-long VAS. Adverse events were recorded by the investigator.

Statistical Analysis

Statistical analysis was implemented in SPSS v.12.0 for Windows (SPSS Inc, Chicago, Ill). Data were presented as mean $\pm$ SD of the [D14 – baseline] differences for VAS scores and 4-point ordinal scales, respectively. Two-tailed comparisons of [D14 – baseline] differences in primary and secondary end points were made between treatments with respect to demographic and efficacy parameters, according to the intent-to-treat principle. Because of the lack of any published data regarding the efficacy of OGT oral spray, the power calculation was estimated based on data derived from previously published studies of treatments for xerostomia.^{11,12} Hence, assuming a within-group SD of 1 cm in the VAS score, a power of 85%, and a type 1 error rate of 0.05, a sample size of 33 patients in each treatment arm was required to demonstrate an effect size of 0.75. Allowing for a dropout rate of approximately 10%, the target was set for 74 patients to be recruited in the current study. To compare the effectiveness of one product against the other with respect to continuous variables relating to effectiveness of spray at D14, the [D14 – baseline] differences in primary and secondary end points were compared using a 2-tailed, unpaired Student *t* test; χ^2 or Fisher exact tests were used to determine the significance of differences (if any) between dichotomous response variables between the 2 treatment groups, where appropriate. A 2-tailed, independent Mann-Whitney *U* test was used to determine the significance of differences (if any) in the objective assessments of oral status between the 2 groups. Given that some of the objective assessments of oral status were related to each other and to increase the number of patients per item, a further analysis was performed, combining related data, that is, assessment of overall dryness of mouth that included assessment of dryness, inflammation, redness, stickiness, dullness of oral mucosa, and severity of mucositis. This combination

was assessed using Cronbach α internal reliability scale. A *P* value of 0.05 was set as the level of statistical significance for each comparison performed.

RESULTS

Demographic Characteristics at Baseline

Among the 96 patients approached to participate in the study, 74 (41 women and 33 men) signed the written informed consent before being enrolled. All but two completed the study. Mean age (44 ± 15 years; range, 18–88 years), weight (66 ± 14 kg; range, 32–110 kg), and height (167 ± 9 cm; range, 140–186 cm) did not differ between treatment groups (respectively, $P > 0.1$, 2-tailed, unpaired Student *t* test). Likewise, sex ratio did not differ between groups ($P = 0.64$, χ^2 test). Bipolar disorder was noted in 50% of patients. Remaining psychiatric disorders for which patients received psychotropic drugs included depression in 26% of cases, schizophrenia in 7% of cases, social anxiety disorders and obsessive-compulsive disorders in 7% of cases, and major anxiety in 3% of cases. Fifty-three drugs, totaling 221 prescriptions (ie, 2.99 drugs per patient), were taken by the 74 patients at the time of the study. These included antidepressants in 59 cases (citalopram, clomipramine, paroxetine, sertraline), benzodiazepines in 55 cases (bromazepam, dipotassium clorazepate, prazepam), antipsychotics including neuroleptics in 47 cases (cyamemazine, olanzapine, risperidone), hypnotics in 36 cases (zolpidem, zopiclone), meprobamate in 11 cases, anticonvulsants and lithium carbonate in 8 cases (carbamazepine, lithium carbonate, valpromide), and levodopa in 5 cases. Medical history was otherwise unremarkable except for alcohol abuse in as much as 10% of patients. Hyposalivation was objectively confirmed upon enrollment by measurement of saliva output (in milliliters per minute) using a sialometer, showing a mean saliva flow rate less than the normal border of 0.16 mL/min (see Patients and Methods), and did not differ between treatment groups (0.04 ± 0.2 vs. 0.03 ± 0.2 mL/min). Eleven patients (15%) were using a saliva substitute at the time of the study. Seven of these used anetholtrithione (Sulfarlem S25), whereas the 4 remaining patients preferred chewing gum.

TABLE 1. Mean [D14 – Baseline] Differences in Primary and Secondary End Points, as Determined Using Self-rated 10-cm VAS for Assessment of Dry Mouth Symptoms, According to Treatments

Items*	[D14 – Baseline] Difference, cm		Mean Between-Treatment Difference, cm
	OGT (n = 37)	ASS (n = 37)	
Mouth dryness	-5.8 ± 2.8	-4.6 ± 2.3	$1.2 \pm 0.4^{\dagger}$
Chewing difficulties	-4.3 ± 3.5	-3.3 ± 2.7	0.5 ± 0.8
Swallowing difficulties	-4.8 ± 2.9	-4.0 ± 2.8	0.5 ± 0.1
Speech difficulties	-5.7 ± 2.7	-4.5 ± 2.3	$1.2 \pm 0.4^{\dagger}$
Taste	-4.5 ± 3.4	-3.1 ± 2.8	$1.1 \pm 0.4^{\dagger}$
Burning sensation	-2.7 ± 2.6	-2.9 ± 3.2	0.1 ± 0.3

*[D14 – baseline] differences and between-treatment difference scores are presented as mean $\pm$ SD.

[†] $P = 0.006$ for mouth dryness, $P = 0.005$ for speech difficulties, and $P = 0.02$ for taste (2-tailed unpaired Student *t* test).

At baseline, most patients complained of severe dry mouth (>8 cm), as measured by a 10-cm-long VAS (Table 1). Fifty-five percent (41/74) of them were wearing a denture (21 in the OGT group and 20 in the control group). Denture retention was affected by mouth dryness in only 28.6% (6/21) and 20% (4/20) of patients in the OGT and ASS groups, respectively ($P = 0.72$, Fisher exact test). Ninety-nine percent of patients presented with moderate to severe dry mouth according to the dental hygienist's objective assessment at baseline. Likewise, 96% of patients presented with oral mucosal inflammation, more than half of them being moderate to severe. Thirty-three percent (24/74) of patients presented with severe mucositis, and 51% of patients presented with at least 1 abrasion of the oral mucosa. Overall, only 4 patients in each treatment group had moderate ($n = 3$) to severe ($n = 1$) oral abrasions. Seventy-eight percent (55/74) of patients presented with damaged lips and/or thickened tongue. Almost 50% of patients treated with OGT oral spray had mild lip damage as compared with only 19% of patients treated with ASS. Conversely, 48.6% of patients in the control group had moderate or severe lip damage as compared with 32.4% in the OGT group ($P = 0.02$, Fisher exact test). Sixty-one percent (45/74) of patients presented with viscous saliva. Moderate or severe viscous saliva, however, was noted in less than 25% of patients and did not differ between treatment groups (Table 2). In addition, 73% (54/74) of patients had moderate to severe speech difficulties related to dry mouth.

Efficacy of OGT Oral Spray Based on the Primary and Secondary End Points at D14

All but 2 patients (72/74) completed the study. Data were lacking for 1 patient (ASS group) at D14. Another

patient (OGT oral spray group) was excluded because of protocol violation. These patients, however, were included in the final analysis according to the intent-to-treat principle. Data regarding these patients were estimated based on the mean (continuous variables) or median (nominal variables) of the respective treatment group. Of the 6 symptoms self-rated on a 10-cm-long VAS at D14, OGT resulted in significantly better efficacy than ASS in 3 items, that is, mouth dryness ($P = 0.006$), defined as primary end point, speech difficulties ($P = 0.005$), and taste improvement ($P = 0.02$), after adjustment for differences at baseline (Table 1). The sensation of improvement started on the second day of treatment in 55% and 83% of patients in the ASS and OGT groups, respectively, and lasted up to 4 hours after each oral spray for the majority of patients.

D14 Patient-Based Assessment of Symptoms

At baseline, 99% and 66% of patients complained of diurnal and nocturnal mouth dryness, respectively. Almost 45% of them woke up because of mouth dryness. Likewise, 65% of patients had a bad taste in their mouth. No difference was noted between treatment arms at baseline ($P > 0.2$, Fisher exact test). At D14, OGT spray improved chewing, swallowing, and speech in 73%, 65%, and 60% of cases, respectively, as compared with 53%, 47%, and 58% of patients treated with ASS ($P = 0.08$, $P = 0.18$, and $P = 0.55$, respectively, Fisher exact test). Taste, burning sensation, and social life items, that is, dichotomous responses to questions such as "Do you stay at home more because of your dry mouth?" and "Do you avoid speaking to people because of your dry mouth?" which were mentioned by up to 56% of patients at baseline, were improved overall by either oral

TABLE 2. Mean [D14 – Baseline] Differences in the Oral Condition Parameters Recorded by the Blinded Dental Hygienist Using 4-Point Ordinal Scale

Items*	[D14 – Baseline] Difference		Between-Treatment Difference†
	OGT (n = 37)	ASS (n = 37)	
Overall dryness of mouth	-1.7 ± 0.8	-1.6 ± 0.8	0.1 ± 0.2
Dryness of oral mucosa	-1.2 ± 0.4	-1.2 ± 0.7	0.1 ± 0.1
Inflammation of oral mucosa	-1.1 ± 0.8	-1.2 ± 0.9	0.1 ± 0.2
Redness of oral mucosa	-1.0 ± 0.5	-1.2 ± 1.0	0.2 ± 0.3
Stickiness of oral mucosa	-1.1 ± 0.6	-1.2 ± 0.9	0.1 ± 0.3
Dullness of oral mucosa	-1.3 ± 0.8	-1.0 ± 0.8	0.3 ± 0.1
Severity of mucositis	-0.3 ± 0.6	-0.5 ± 0.8	0.2 ± 0.2
Oral mucosal abrasion and ulcerations	-0.6 ± 0.8	-0.9 ± 0.9	0.2 ± 0.1
Damaged lips	-1.1 ± 0.8	-1.1 ± 0.9	0.05 ± 0.1
Thickened tongue	-0.7 ± 0.7	-0.8 ± 0.9	0.1 ± 0.2
Deficiency of saliva	-1.3 ± 0.5	-1.3 ± 0.9	0.1 ± 0.1
Viscosity of saliva	-0.6 ± 0.7	-0.7 ± 0.8	0.1 ± 0.3
Foamy quality of saliva	-0.5 ± 0.7	-0.6 ± 0.9	0.1 ± 0.3
Halitosis	-0.8 ± 1.1	-0.9 ± 0.8	0.1 ± 0.2
Speech difficulties	-1.0 ± 1.0	-1.1 ± 1.3	0.05 ± 0.1
Saliva and crusting at corners of mouth	-0.4 ± 0.7	-0.5 ± 0.9	0.05 ± 0.1

*[D14 – baseline] differences and between-treatment difference scores are presented as mean ± SD.

† $P > 0.14$ for all comparisons between treatments (2-tailed, unpaired Mann-Whitney U test).

spray, according to patient-based assessment of symptoms. Fifty-six percent of patients treated with ASS and 76% treated with OGT declared that their oral spray was as effective during the day as during the night ($P = 0.2$, Fisher exact test).

Objective Assessment of Oral Condition at D14 by Means of a 4-Point Ordinal Scale

Table 2 presents assessment of oral condition as recorded by the dental hygienist at D14 with respect to treatment. The oral condition was significantly improved by both oral sprays, as shown by a mean 65% decrease in the score of each item as compared with baseline. No significant differences between the 2 treatment options were found. Nevertheless, some interesting clinically relevant differences between the two were observed during the 2-week treatment period, for example, overall dryness of mouth and mucosa, inflammation, redness, stickiness, dullness of oral mucosa, deficiency of saliva, and improvement in speech difficulties (Table 2). Given that some of the objective assessments of oral status were related to each other and to increase the number of patients per item, further analysis was performed combining related data, that is, assessment of overall dryness of mouth, dryness, inflammation, redness, stickiness, dullness of oral mucosa, and severity of mucositis, to produce a scale that had high internal reliability, as ascribed by a Cronbach α coefficient of 0.85. Even when combining these variables into a single model, the difference between treatment groups remained nonsignificant at D14 after adjusting for baseline value ($P = 0.62$). The remaining items assessing saliva as well as the presence of halitosis, mucosal abrasion, damaged lips, and speech difficulties (Table 2) were not strongly correlated and could not be added to the model to build a scale that was internally consistent (Cronbach $\alpha = 0.07$).

Treatment Tolerance and Acceptability

No serious adverse event was reported during the study. Minor adverse events were noted in 4 patients (4.6% of cases) and included nausea ($n = 1$, ASS group) and unpleasant taste ($n = 1$, ASS group; $n = 2$, OGT group). Both oral sprays were qualified as easy to use by 90% of patients. More than 85% of patients were willing to continue their spray after the end of the study, although the taste of OGT was preferred to that of ASS (7.2 ± 2.2 vs. 5.8 ± 2.9 ; mean difference, 1.4 ± 0.6 ; $P = 0.04$, Mann-Whitney U test). Global treatment acceptability at D14 was significantly better for OGT, as assessed by global mouth sensation after each spray administration using the self-rated 10-cm-long VAS (6.3 ± 2.6 vs. 7.7 ± 1.6 in the ASS and OGT groups, respectively; mean difference, 1.4 ± 0.9 ; $P = 0.005$, Mann-Whitney U test).

DISCUSSION

In clinical practice, xerostomia is often underestimated by clinicians and patients themselves, presumably because the efficacy of currently available therapeutic options is highly unpredictable.¹³ Based on extensive evaluation of clinically relevant symptoms of xerostomia,^{1,11,12,14,15} the

current prospective randomized controlled study conducted in patients under real conditions of treatment by psychotropic drugs for various psychiatric and neuropsychiatric disorders, with drug-induced xerostomia and confirmed severe hyposalivation,^{16–18} demonstrated that a 14-day treatment with OGT oral spray was significantly more effective than ASS, specifically in improving mouth dryness, speech difficulties, and taste, as assessed by means of VAS. The 2 oral sprays were equally effective in significantly improving mouth condition, especially oral mucosa status and dryness of mouth and oral mucosa (Table 2).

It is difficult to make the initial clinical decision as to whether a given patient has salivary gland hypofunction with symptoms of xerostomia and hence requires additional salivary gland evaluation and whether he or she may be eligible for treatment. In this regard, and apart from the use of a previously validated questionnaire¹ rather than the recently published xerostomia inventory,¹⁹ we used validated tools (eg, 10-cm-long VAS and 4-point ordinal scale) and a validated cutoff of salivary flow rate to relevantly identify and enroll patients with dry mouth for the purpose of the current clinical trial.^{9,11,12,20} Despite the clinical relevance of the enrolled population and the observed treatment efficacy, the current study has several limitations, partly related to the difficulty in evaluating treatments in such a subjective condition as xerostomia. The short-term parallel design of the trial requires further evidence of continued efficacy of OGT oral spray in the relief of dry mouth symptoms. A longer, crossover clinical study would have been helpful to demonstrate the efficacy of OGT oral spray over time in psychiatric patients with drug-induced xerostomia caused by long-term treatments.²¹ The open-labeled study design chosen in the current trial because of the different texture and taste of the 2 products (ASS is an aqueous solution, whereas OGT is a rather viscous oral lubricant containing alimentary-grade flavoring agents) may limit the reliability of the results and require further confirmation in a future, double-blind, randomized controlled trial conducted in a larger cohort of patients. In addition, although OGT may have slightly enhanced saliva production because of the presence of small amounts of a flavor,²¹ neither oral spray stimulated saliva production, and saliva output was therefore only measured upon patient enrollment to confirm hyposalivation but not upon treatment completion at D14. Finally, the purpose of the current study was to compare OGT oral spray with a currently marketed saliva substitute (and not with pilocarpine hydrochloride, the reference treatment of dry mouth²) in the relief of symptoms of xerostomia, but not to correlate treatment efficacy to the decrease in saliva output in our patients, the latter not being established to the best of our knowledge.^{2,12,14,20}

There are more than 500 medications that report dry mouth as a side effect, but only a small number, however, have been shown to result in actual reduced salivation. These include tricyclic antidepressants, antihistamines, antihypertensives, and diuretics.^{15–18,22–24} Salivation is dependent on parasympathetic, especially muscarinic-dependent, stimulation that induces dilation of the oral

mucosal blood vessels and myoepithelial cell contraction.^{25,26} In addition, the central nervous system controls saliva secretion in response to several common stimuli, for example, taste or smell. β -Adrenergic-dependent sympathetic stimulation, but also serotonin, may enhance glycoprotein secretion in the saliva, which in turn enhances oral cavity lubrication.^{25,26} Numerous drugs, including psychotropic drugs,^{3,15–18,22} directly act on the sympathetic and parasympathetic pathways, thus decreasing salivary output and modifying the quality of saliva without directly structurally affecting salivary glands, with effects in the oral cavity.^{24–26} Moreover, an additive effect has been previously observed when several psychotropic agents are associated in the same patient, which was the case in the current study, with a mean of almost 3 concomitant psychotropic drugs per patient.³ Drug-induced, especially psychotropic drug-induced, xerostomia is often neglected by physicians as it has long-term, especially severe dental, rather than immediate consequences on the oral condition.^{3,13} In some instances, eating as well as social life may be severely impaired in some patients, especially in the elderly who frequently take numerous concomitant medications.^{3,13,15,16} In psychiatric patients, the prevalence of severe xerostomia with restriction of daily activity may be as high as 29%,¹⁶ consistent with our patients.

Dry mouth evaluation should be carried out in a systematic fashion, as performed in the current study. In clinical practice, the goals are to document salivary function and to determine the cause for any dysfunction found. The results of such evaluation may help provide guidance for the development of a rational, comprehensive management plan.¹ The adoption of 1 treatment option from among the different options available depends on the cause underlying xerostomia and on the functionality of the saliva glands.² In any event, the goals are to relieve symptoms, prevent or correct the sequelae of salivary dysfunction, and treat any underlying disease. Given the mechanisms involved in psychotropic drug-induced xerostomia, adequate hydration of the oral mucosa to moisten and cleanse the mucosal surface and to hydrate the oral tissue is essential. As mentioned above, many saliva substitutes are currently available on the market.^{1,2,7,10,12,14} The majority of dry mouth patients do not use saliva substitutes regularly. In some authors' experience,²⁴ most patients find that frequent sipping of fluids is superior and more esthetically acceptable than applications of saliva substitutes. The current study does not confirm these observations. Indeed, 90% of patients, most of them with severe depression and/or psychosis, endorsed both oral sprays as easy to use, and acceptability of the 2 products was high, as assessed by means of a self-rated VAS. More than 85% of patients were willing to continue using oral sprays after the end of the study.

To date, only a few randomized controlled trials have addressed the problem of relief of psychotropic-drug induced xerostomia. In a previous randomized controlled trial enrolling 94 patients with symptomatic hyposalivation caused by senile hypofunction, medications, or oral cancer therapy and comparing the bile secretion-stimulating drug, anethole trithione, to a commercially available saliva

substitute, the cholagogue significantly increased saliva flow rate in all 49 patients, especially those with drug-induced xerostomia, as compared with those treated with the saliva substitute, and there was significant relief of oral discomfort and inflammation.¹² In another randomized, open-labeled, placebo-controlled trial conducted in healthy volunteers treated with the opioid analgesic, tramadol, to induce hyposalivation, oral pilocarpine significantly restored saliva flow rate as compared with placebo.¹⁴ However, except for a self-based assessment of the sensation of a decrease in saliva production, no evaluation of dry mouth symptoms or oral cavity was performed in this study.¹⁴ Finally, in a more recent randomized controlled crossover study comparing 3 mildly flavored sodium lauryl sulfate-containing and detergent-free toothpastes with or without betaine in 27 patients with xerostomia and 18 healthy controls using VAS score for patient evaluation, the authors observed that the betaine-containing toothpaste relieved dry mouth symptoms in 44% of patients, which is close to the observed 55% of patients treated with ASS who mentioned symptom relief, but much lower than the observed 83% of patients with symptom relief after the second day of treatment with OGT.²¹

In conclusion, using a systematic approach and aggressive management, most patients with dry mouth can achieve oral comfort and adequate oral function.^{20–24} In this regard, the current study showed that OGT oral spray was more effective than a currently marketed ASS containing electrolytes in improving some but not all evaluated symptoms of psychotropic drug-induced xerostomia, such as oral mouth dryness, speech difficulties, taste, and overall mouth condition. Given the limited efficacy of some treatments such as gustatory substances²¹ and chewing gum, we believe that OGT oral spray may be proposed in the management of psychotropic-drug induced xerostomia, especially when sialogogues such as pilocarpine may be hard to use because of increased risk of cardiovascular side effects.^{2,14–16} Further studies will be needed to determine whether the efficacy of OGT oral spray may be prolonged over time in the clinical setting. Increasing numbers of isolated or concomitant prescriptions of antidepressants and benzodiazepines in primary and specialty care settings should warn physicians on the risk of invalidating xerostomia with or without hyposalivation and its consequences on oral health, daily activity, and maybe adherence to long-term psychotropic treatments.

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