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Development and Proposal of a Novel Scoring System to Classify Dry Mouth Severity

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Featured Application: We propose a dry mouth severity score to classify dry mouth patients according to severity for standardized inclusion into clinical trials, securing patient uniformity and relevant comparisons between studies.

Abstract: Dry mouth is a common complaint with unmet treatment needs, reflected by the fact that more than 500 trials are registered on ClinicalTrials.gov. Comparisons across studies, however, are difficult as inclusion criteria vary widely. Additionally, the terms xerostomia and hyposalivation are often not separated. Thus, the aim of the present work was to develop a dry mouth severity score (DMSS) that incorporates published questionnaires and measures both xerostomia and hyposalivation and proposes a grading system that can be used as a common basis for inclusion into clinical trials. The DMSS was developed through the use of data from patients in the Dry Mouth Clinic, University of Oslo, Norway. Five groups of patients (n = 131) and controls (n = 59) were included: primary Sjögren's syndrome, non-Sjögren's syndrome, radiated head and neck cancer, psychiatry, and controls. The proposed DMSS includes five parameters with corresponding cut-off values given 1 point (p) each: the General Xerostomia Question $\geq$ 2, Summated Xerostomia Inventory $\geq$ 11, Clinical Oral Dryness Score $\geq$ 6, and secretion of unstimulated and chewing-stimulated whole saliva with cut-off values at $\leq$0.1 mL/min and $\leq$0.7 mL/min, respectively. The proposed score range for DMSS is 0–3, where score 0 corresponds to 0p, score 1 to 1–2p, score 2 to 3p, and score 3 to 4–5p. In the patient group, 65% had a high DMSS of 2 or 3, while 78% of the controls scored 0. The sensitivity and specificity were high (0.93 and 0.78, respectively), and the internal reliability was satisfactory (Cronbach's alpha 0.80). The proposed DMSS represents a novel method to uniformly classify dry mouth patients for applicable comparison between clinical trials.

Keywords: xerostomia; hyposalivation; Sjögren's syndrome; head and neck cancer; psychiatry

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1. Introduction

Dry mouth is a common complaint, especially among the elderly, and refers both to xerostomia, the subjective feeling of dry mouth, and hyposalivation, an objectively measured reduction in salivary secretion, but there is often not a clear distinction between the two conditions in the literature. The most common cause of both xerostomia and hyposalivation is the anticholinergic side effects of drugs, such as antihistamines, antipsychotics, and antidepressants [1]. Other common causes are systemic diseases affecting the salivary glands like Sjögren's syndrome and connective tissue diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus), destroyed salivary secretory tissue due to radiotherapy of carcinomas in the head and neck area, and diseases causing dehydration such as diabetes mellitus and chronic renal failure [2,3].

While xerostomia is bothersome for the patient, hyposalivation may lead to diseases like caries and yeast infections. Saliva substitutes to replace saliva in patients with hyposalivation come in many forms, such as gels and sprays based on various solutions with

water, hydrophilic polymers and glycerol. Unfortunately, most of these products have short-lasting effects due to the short residence time in the oral cavity. Therefore, there is a continuous search for new remedies to relieve and treat these conditions, demonstrated by the fact that there are more than 500 clinical studies on dry mouth registered on ClinicalTrials.gov [4]. When evaluating the various studies and the way patient inclusion and testing of the products are performed, it is striking that these parameters vary to a large extent. The inclusion criteria in the clinical trials may vary from no subjective or objective assessments to single-item questions to comprehensive clinical examinations, questionnaires, and measurements of salivary gland secretion [5–7]. There is no consensus on the inclusion of dry mouth patients into clinical studies, guidelines for standardized questionnaires to be used or specified clinical examinations to be performed. Thus, the effects of the various products to alleviate dry mouth cannot easily be compared.

In the Dry Mouth Clinic at the Faculty of Dentistry, University of Oslo, established in 2015, in collaboration with the Norwegian Dry Eye Clinic, we have for years examined patients with complaints of dry mouth and dry eyes. We have reported clinical characteristics of the oral cavity and the ocular surface, as well as secretory rates and composition of saliva and tears in patients with various etiologies of dryness. During this collaborative work, it has become evident that there are far better screening tools for dryness in ophthalmology than in dentistry. A great tool for the definition and classification of dry eye disease is the dry eye severity grading scheme that grades the dry eye severity into four levels based on nine parameters [8]. No such tool exists for characterizing the severity of dry mouth. Accordingly, several systematic reviews evaluating the prevalence of dry mouth state that the diverse approaches to measure the condition may over- or underestimate the prevalence and that a standardized protocol or a consensus to diagnose dry mouth needs to be developed [9–12].

At the Dry Mouth Clinic, we have previously examined four different groups of dry mouth patients: primary Sjögren's syndrome, non-Sjögren's syndrome, patients who had received radiation therapy for head and neck cancer, and medicated psychiatric patients [13–15]. Sjögren's syndrome is a systemic autoimmune disease with dry mouth and dry eyes as some of the most common symptoms, together with fatigue and joint pain [16]. The non-Sjögren's syndrome patients in this paper refer to patients with Sjögren's syndrome-like symptoms but who do not fulfil the classification criteria for primary Sjögren's syndrome [17]. A vast set of tests was used to characterize these dry mouth patients. The tests consist of questionnaires on general and oral health-related quality of life, questionnaires on xerostomia, tests of salivary secretion and candida growth, screening for objective findings of oral dryness and pathological changes of the oral mucosa and teeth, evaluation of halitosis, dysgeusia, burning mouth, and taste and smell functions. This set of tests is useful in providing research data but is too extensive and time-consuming to be used for patient inclusion into clinical trials. Therefore, we have reevaluated these tests, together with the results from the four patient groups and a matched control group, to describe dry mouth patients in a more convenient and efficient way. Consequently, the aim of the present work was to propose a dry mouth severity score (DMSS) to facilitate uniform characterization of the dry mouth patient as such. The score may also be used as a common basis for patient inclusion in studies.

2. Materials and Methods

2.1. Study Participants

The study participants were selected among patients and controls from the Dry Mouth Clinic, who were voluntarily recruited to our previous studies through collaborations with various hospitals in Oslo. The participants were recruited from five different study groups:

(1) primary Sjögren's syndrome patients (pSS) [13].
(2) patients with non-Sjögren's syndrome (non-SS), patients with Sjögren's syndrome-like symptoms but who do not fulfil the classification criteria [13,17].
(3) patients who had received radiation therapy for head and neck cancer (HNC) [14].

(4) medicated psychiatric patients (psychiatric patients) [15].
(5) matched controls.

The patients represent groups of patients with various severities of dry mouth. The pSS and the HNC patients were the most troubled by dry mouth in terms of both xerostomia and hyposalivation, while the non-SS and psychiatric patients were more troubled by xerostomia than hyposalivation [13–15].

The control group was recruited through advertisements and had no previous complaints of oral dryness and did not use any medications that affected salivary secretory rate. All patients and controls underwent an extensive oral examination and completed the standardized questionnaires (Table 1).

Table 1. An overview of the questionnaires and clinical examinations used in the Dry Mouth Clinic, University of Oslo, Norway.

Questionnaires	**References**
The General Xerostomia Question (GXQ)	[18]
The Summated Xerostomia Inventory (SXI)	[19]
Complaints of previous oral candidiasis, bad breath (halitosis), bad taste (dysgeusia), and burning mouth	[20]
Subjective evaluation of taste and smell functions (visual analog scale)	[20]
The Oral Health Impact Profil-14 (OHIP-14)	[21]
The Short Form Health Survey-36 (SF-36)	[22]
Clinical examinations	
Clinical Oral Dryness Score (CODS)	[23,24]
Measuring unstimulated (UWS) and chewing-stimulated whole saliva (SWS)	[25]
Candida growth (swab samples)	[26]
Recording of mucosal pathology, dental plaque, tooth mobility, implants and dental caries status	[26]
Objective evaluation of taste and smell functions	[27,28]

To be included, complete sets of data on the General Xerostomia Question (GXQ), Summated Xerostomia Inventory (SXI), Clinical Oral Dryness Score (CODS), unstimulated whole saliva (UWS), and stimulated whole saliva (SWS) were needed. After reviewing the results from the patients and controls, a total of 190 subjects were included in this study (Figure 1). Two pSS patients were excluded due to missing CODS and uncertain diagnosis, one non-SS patient was excluded because CODS was missing, and two controls were excluded because SXI results were not registered.

All study protocols were approved by the Norwegian Regional Medical Ethical Committee (REK 2015/363, REK 2018/1313, and REK 2021/78549), and the studies were performed in compliance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the studies, and the data was de-identified prior to analysis.

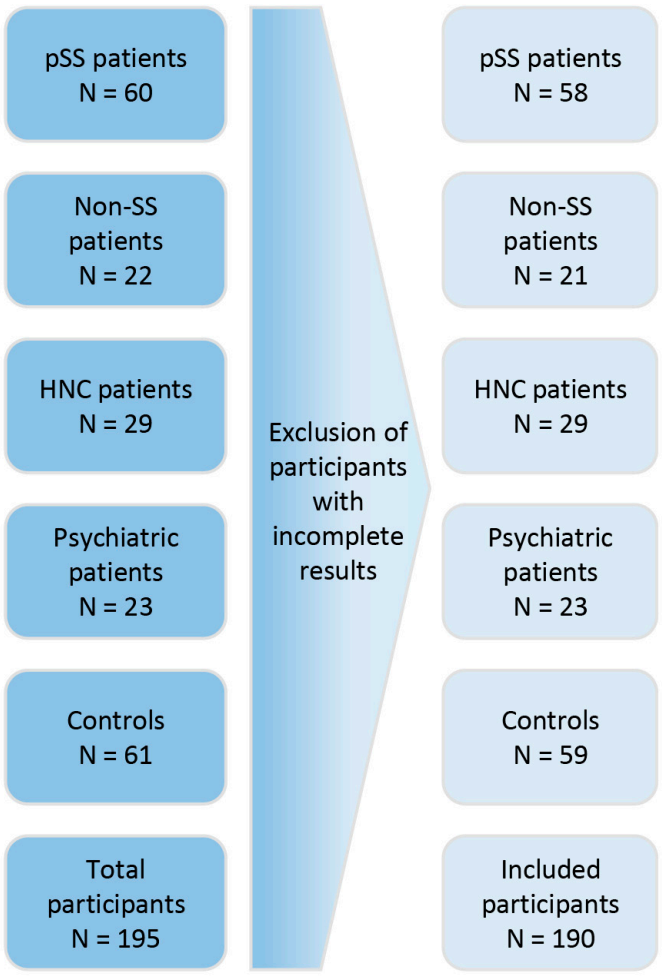
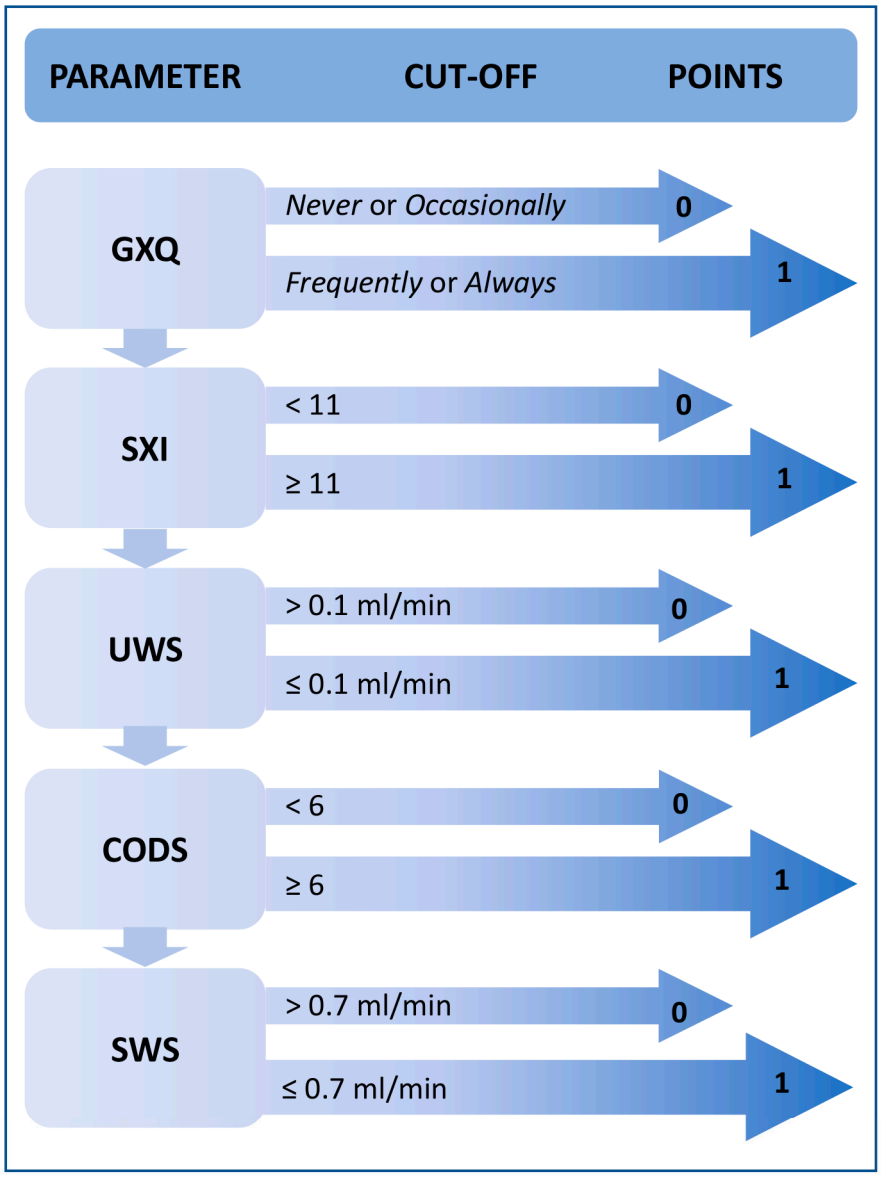


Figure 1. An overview of the selection of participants in the different study groups. pSS patients: primary Sjögren's syndrome patients, non-SS: non-Sjögren's patients (patients with Sjogren's syndrome-like symptoms but do not fulfill the classification criteria [17]), HNC patients: radiated head and neck cancer patients, psychiatric patients: patients with psychiatric disorders using at least one drug with dry mouth as known side effect, controls: healthy subjects with no dry mouth complaints.

2.2. The DMSS

To ensure a time-effective and inexpensive scoring tool for dry mouth severity, incorporating both xerostomia and hyposalivation, we excluded most of the above questionnaires and clinical examinations and only included five subjective and objective parameters in the DMSS. The subjective parameters were the GXQ and SXI, and the objective parameters were CODS and measurements of salivary secretion (UWS and SWS). Each parameter is presented with a proposed cut-off value. Results above cut-off values (below for UWS and SWS) were scored with one point each, with a total range from 0 to 5 points (5 points representing the highest severity of dry mouth). To ensure a more simple and functional scoring system for DMSS, a grading from 0 to 3 was proposed, with score 0 representing 0 points, score 1 representing 1 and 2 points, score 2 representing 3 points, and score 3 representing 4 and 5 points. In the DMSS, score 0 signifies the lowest level of dry mouth, while scores 1 and 2 signify intermediate levels, and score 3 represents the most severe degree of dry mouth. A schematic presentation of the practical step-wise approach, cut-off values and scoring table is seen in Figure 2. The considerations and reasoning of the chosen parameters and cut-off values are elaborated in the two following sections.



TOTAL POINTS	DMSS
0	0
1 – 2	1
3	2
4 – 5	3

Figure 2. The practical step-wise approach, cut-off values, and scoring table to determine the Dry Mouth Severity Score. DMSS: The Dry Mouth Severity Score; GXQ: The General Xerostomia Question; SXI: Summated Xerostomia Inventory; UWS: Unstimulated Whole Saliva; CODS: Clinical Oral Dryness Score; SWS: Stimulated Whole Saliva.

2.3. Description of Selected Parameters for DMSS

The GXQ is a single-item question to evaluate the frequency of dry mouth: How often does your mouth feel dry? It has four alternative responses: never, occasionally, frequently

or always, scoring 0, 1, 2 and 3, respectively. Thomson et al. recommended that the GXQ be used together with SXI as a validity check, therefore, we decided to follow this advice [19].

The SXI is an assessment of the subjective severity of xerostomia where the patient evaluates the frequency of complaints regarding five statements, as listed in Table 2 [19]. Each statement has three possible replies: never, occasionally, or often, scoring 1, 2, and 3, respectively. The SXI has a score range from 5 to 15, where a maximum score indicates severe problems related to dry mouth [19]. If SXI was excluded as a parameter, three of the controls (5%) received a DMSS of 2, which seemed incorrect. Thus, SXI was included as a parameter.

Table 2. The five questions of the Summated Xerostomia Inventory (SXI) and the ten clinical features of the Clinical Oral Dryness Score (CODS) [19,23,24].

SXI	CODS
1. My mouth feels dry when eating a meal 2. My mouth feels dry 3. I have difficulties eating dry foods 4. I have difficulties swallowing certain foods 5. My lips feel dry	1. Mirror sticks to buccal mucosa 2. Mirror sticks to tongue 3. Frothy saliva 4. No saliva pool in floor of mouth 5. Tongue shows loss of papillae 6. Altered/smooth gingival architecture 7. Glassy appearance of other oral mucosa, especially palate 8. Tongue lobulated/fissured 9. Active or recent (<6 months) restored cervical caries (>2 teeth) 10. Debris on palate (excluding under dentures)

CODS is a semi-quantitative score of clinical oral dryness; the score ranges from 0 to 10, where each clinical feature of oral dryness scores one point [23,24]. The ten features are listed in Table 2. An attempt was made in the present study to shorten the CODS by including only the most frequent features reported in our Dry Mouth Clinic, but as the DMSS results of the dataset showed no improvement, it was decided to preserve all the features of CODS.

UWS was collected by instructing the participants to allow all saliva produced for 15 min (5 min for the psychiatric patients) to drip passively into a plastic cup. For SWS, the participants chewed on a paraffin wax tablet (Paraffin pellets, Ivoclar Vivadent, Shaan, Lichenstein) for approximately 30 s first, then they were instructed to swallow any saliva in the mouth before starting the collection of SWS for 5 min into the plastic cup. The saliva samples were weighed, and saliva secretion rates were calculated for both UWS and SWS (g/min = mL/min) [25]. The patients were instructed not to have anything in their mouth the last hour before the appointment. To make the clinical examination less time-consuming, an attempt was made to exclude SWS from the DMSS. The major changes were seen in the two highest scores: DMSS 2 now increased from 29 patients (22%) to 46 patients (35%), and DMSS 3 decreased from 56 patients (43%) to 35 patients (27%). To ensure that the majority of these dry mouth patients received a high score of dry mouth severity, SWS was kept as a parameter.

2.4. Proposed Cut-Off Values for DMSS

A cut-off at $\geq$2 (frequently or always) for GXQ was suggested in this paper. This is in accordance with recommendations from Putten et al., and a lower prevalence seemed unreasonable [29].

Through the validation of SXI (score range 5–15), a score of 8 was suggested as typical in the general population, though a SXI score of 10 was observed in one of the New Zealand samples [19]. In our control group, the mean SXI was 6.0 $\pm$ 0.9, but the control group

consisted only of subjects with no dry mouth complaints. Thus, these subjects may not be comparable to the general population as such. A cross-sectional study on a 65-year-old population in Norway had a SXI median of 6, and 95% of the participants had a SXI < 11 [30]. The psychiatric patients demonstrated the lowest SXI mean (10.4 ± 2.7) of the patient groups in our dataset; subsequently, a cut-off at ≥11 was proposed to separate the patient groups [15].

A CODS cut-off value of ≥6 was proposed, both because this was the mean value for the patients (6.0 ± 1.6) when CODS was developed by Jager et al. and because it was the median value in our patient group [31]. In this study, we therefore decided to use a CODS cut-off of ≥6.

Hyposalivation is defined as a salivary secretion rate of ≤0.1 mL/min for UWS and of ≤0.7 mL/min for SWS, and these values were kept as cut-off values for the DMSS [25].

2.5. Distribution and Correlations of DMSS

The distribution of the DMSS was evaluated by comparing the scores from the patient group with the control group. Additionally, the mean values of the five included parameters (GXQ, SXI, CODS, UWS, and SWS) were plotted across the DMSS results to evaluate their relationship and their distribution across the scores. Furthermore, results from the Oral Health Impact Profile-14 (OHIP-14) and the Short Form Health Survey-36 (SF-36) were applied to investigate potential correlations between the DMSS and oral health-related quality of life (OHRQoL) and general health-related quality of life, respectively [21,22].

OHIP-14 is a short form of the original OHIP-49 questionnaire and provides a comprehensive measurement of self-reported dysfunction, discomfort and disability attributed to oral conditions [21]. The range score is from 0–56, where a high score indicates poor OHRQoL [32]. Two questions (Q) in the 14-item questionnaire represent a dimension that each addresses various aspects of oral health: functional limitations (Q1 + Q2), physical pain (Q3 + Q4), psychological discomfort (Q5 + Q6), physical disability (Q7 + Q8), psychological disability (Q9 + Q10), social disability (Q11 + Q12), and handicap (Q13 + Q14) [32].

SF-36 is a generic, 36-item questionnaire that measures general health-related quality of life [22]. Eight separate dimensions are evaluated with individual scores: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health [22].

2.6. Statistical Analyses

The data was analysed using Stata Statistical Software, version 17 (StataCorp LLC, College Station, TX, USA). The results are presented as mean ± standard deviation (SD). The non-parametric Wilcoxon Rank Sum Test was used for the intergroup comparisons. One-way ANOVA was used in the intergroup comparisons of three or more variables. Spearman's rho was applied for correlations between variables, and the chi-square test and Fisher exact test were used for binary outcomes. Sensitivity and specificity were calculated by dividing the number of patients with DMSS 1, 2, or 3 by the number of all the patients and dividing the number of controls with DMSS 0 by the number of all the controls, respectively. Cronbach's alpha coefficient was used to measure the internal consistency of the DMSS parameters and for the binary outcome of the parameters (above or below cut-off values). An alpha coefficient of 0.7 to 0.8 was regarded as satisfactory [33]. Statistical values were considered significant when $p < 0.05$.

3. Results

3.1. Study Group

Data from 131 patients (mean age 52 ± 15 years) and 59 age- and gender-matched controls (mean age 51 ± 17) were included in the study. The demographic data and characteristics of the subjects are presented in Table 3. Most participants were female as all pSS patients were females, which also is reflected in the control group. The patient and

control group differed significantly for three parameters: education level, occupation and smoking status.

Table 3. Demographic data and characteristics of the patients and controls. Values are presented as the mean ± SD or number (percent) of participants.

	Patients (*n* = 131)	**Controls (*n* = 59)**	***p*-Value**
Age (years)	52 ± 15	51 ± 17	0.438
Gender			0.192
Male	26 (20%)	17 (29%)	
Female	105 (80%)	42 (71%)	
Ethnicity			0.056
Scandinavian	119 (91%)	49 (83%)	
European	8 (6%)	6 (10%)	
Other	4 (3%)	4 (7%)	
Educational level			0.029 *
Basic (7–10 years)	9 (7%)	2 (3%)	
Secondary (10–13 years)	39 (30%) [a]	6 (10%)	
Higher (>13 years)	83 (63%) [a]	51 (86%)	
Occupation			<0.001 *
Working	56 (43%) [b]	41 (69%)	
Sick leave/rehabilitation/disabled	40 (31%) [b,c]	1 (2%)	
Unemployed	8 (6%) [e]	1 (2%)	
Student	3 (2%) [c,d,e]	8 (14%)	
Retired	24 (18%) [d]	8 (14%)	
Smoking status	16 (12%)	1 (2%)	0.025 *

* p-value < 0.05. Intergroup difference ($p < 0.05$): [a] = secondary vs. higher $p = 0.005$, [b] = working vs. sick leave $p < 0.001$, [c] = sick leave vs. student $p < 0.001$, [d] = retired vs. student $p = 0.016$, [e] = student vs. unemployed $p = 0.016$.

3.2. Parameters Included in DMSS

All results from the individual parameters of DMSS (GXQ, SXI, CODS, UWS, and SWS) were significantly different between the patient and control group, as shown in Table 4. Additionally, 40 to 79% of the patients showed values above the cut-off values (below for UWS and SWS) for each parameter. Corresponding percentages were significantly lower for the controls for all parameters (0–21%).

3.3. Distribution, Sensitivity, Specificity and Reliability of DMSS

As each result above cut-off values (below for UWS and SWS) for each parameter generated one point with a maximum total value of five possible points, most patients gained two points or more (85%), while none in the control group gained more than two points, as seen in Table 5. When the DMSS was calculated (scores 0–3), the patients were represented with all scores, with the highest score of 3 being the most frequent (43%). In contrast, the controls were represented with only the two lowest scores, with 0 being the most frequent score (78%).

Table 4. Results from the Dry Mouth Severity Score parameters and cut-off values for patients and controls. DMSS: The Dry Mouth Severity Score; GXQ: The General Xerostomia Question; SXI: Summated Xerostomia Inventory; CODS: Clinical Oral Dryness Score; UWS: Unstimulated Whole Saliva; SWS: Stimulated Whole Saliva. Patients n = 131, controls n = 59. Values are presented as mean ± SD or number of participants (percentage).

DMSS Parameter	Patients Mean ± SD	Controls Mean ± SD	*p*-Value
GXQ	2.2 ± 0.9	0.1 ± 0.2	<0.001 *
SXI	11.7 ± 2.5	6.0 ± 0.9	<0.001 *
CODS	5.2 ± 1.9	1.1 ± 1.4	<0.001 *
UWS	0.13 ± 0.13	0.31 ± 0.18	<0.001 *
SWS	0.95 ± 0.68	1.70 ± 0.76	<0.001 *
	Patients *n* (%)	**Controls *n* (%)**	***p*-Value**
GXQ ≥ 2	103 (79%)	0	
SXI ≥ 11	93 (71%)	0	
CODS ≥ 6	65 (50%)	1 (2%)	<0.001 *
UWS ≤ 0.1 mL/min	85 (65%)	13 (21%)	<0.001 *
SWS ≤ 0.7 mL/min	57 (44%)	3 (5%)	<0.001 *

* p-value < 0.05.

Table 5. The distribution of points and Dry Mouth Severity Score for patients and controls. DMSS: The Dry Mouth Severity Score. Values are presented as number (percentage) of participants. Patients n = 131, controls n = 59.

Points	Patients	Controls	DMSS	Patients	Controls	*p*-Value
0	9 (7%)	46 (78%)	0	9 (7%)	46 (78%)	<0.001 *
1	10 (8%)	10 (17%)	1	37 (28%)	13 (22%)	0.555
2	27 (21%)	3 (5%)				
3	29 (22%)	0%	2	29 (22%)	0%	
4	28 (21%)	0%	3	56 (43%)	0%	
5	28 (21%)	0%				

* p-value < 0.05.

The distribution of the mean values of GXQ, SXI and CODS showed a clearly ascending gradient and a descending gradient in the means of UWS and SWS across the scores of the DMSS, as shown in Figure 3.

An ascending distribution across the scores of DMSS was seen when the number of patients presenting with results above cut-off values (below for UWS and SWS) were plotted against the DMSS results, as seen in Figure 4.

The sensitivity and specificity of the DMSS were 0.93 and 0.78, respectively. The Cronbach's alpha coefficient was 0.74 for the included parameters in DMSS and 0.80 for the binary outcomes of the parameters (values above the cut-off for GXQ, SXI and CODS, and values below the cut-off for UWS and SWS).

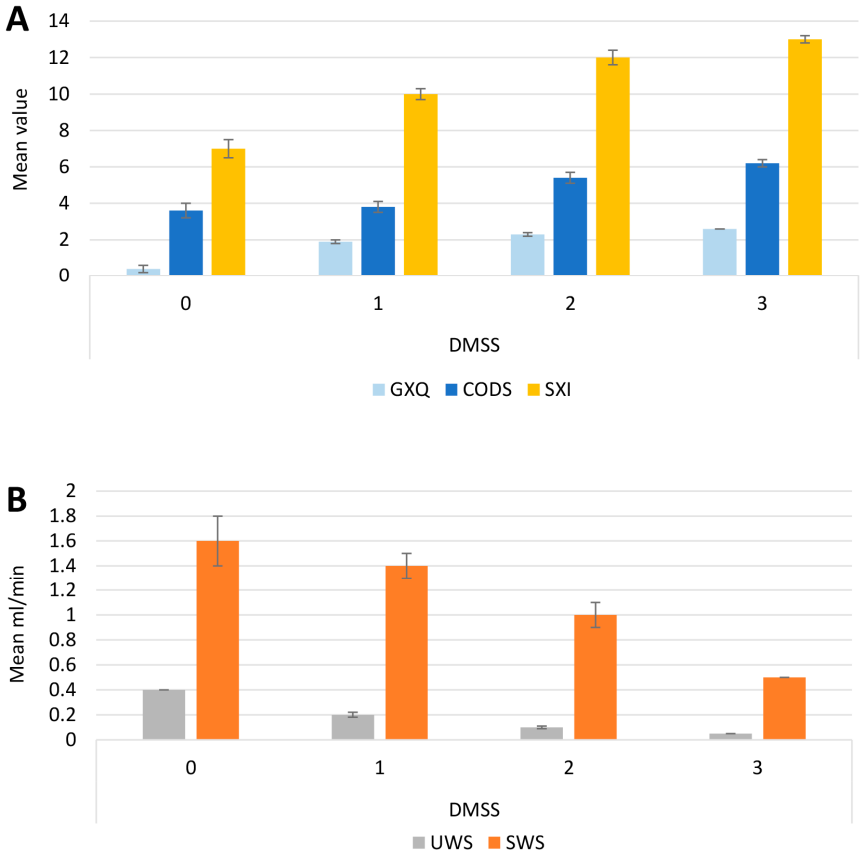


Figure 3. The distribution of mean values of the parameters included in the Dry Mouth Severity Score for the patient group, across the scores. DMSS: The Dry Mouth Severity Score. (**A**) GXQ: The General Xerostomia Question; CODS: Clinical Oral Dryness Score; SXI: Summated Xerostomia Inventory. (**B**) UWS: Unstimulated Whole Saliva; SWS: Stimulated Whole Saliva. Error bars ± 1 SD. n = 131.

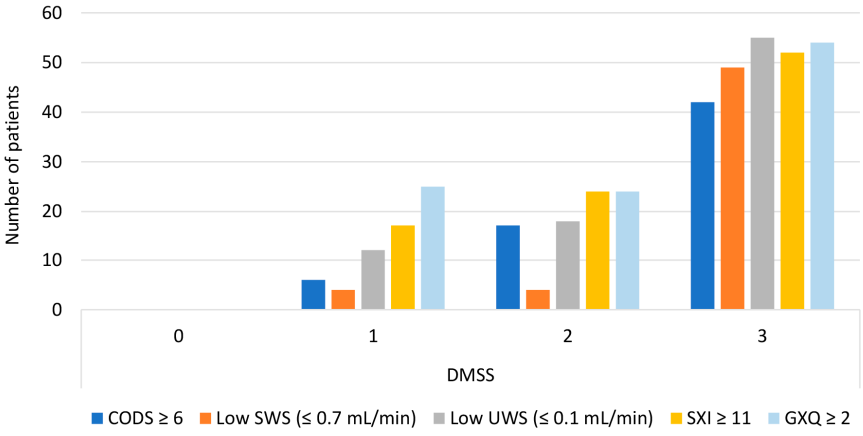


Figure 4. The number of patients with results above cut-off values (below for UWS and SWS) across the scores of the Dry Mouth Severity Score. DMSS: The Dry Mouth Severity Score; CODS: Clinical Oral Dryness Score; SWS: Stimulated Whole Saliva; UWS: Unstimulated Whole Saliva; SXI: Summated Xerostomia Inventory; GXQ: The General Xerostomia Question. n = 131.

3.4. Correlations with OHIP-14 and SF-36

A weak positive correlation was seen for DMSS of the patient group and OHIP-14 (r = 0.22, p = 0.013). The HNC group showed a moderate positive correlation with OHIP-14 (r = 0.51, p = 0.005). No significant correlations were found between DMSS for the patient

group and any of the dimensions of OHIP-14. For the psychiatric patient group, a moderate correlation with the dimension functional limitations was demonstrated (r = 0.47, $p = 0.026$).

For the patient group, no significant correlations were found between DMSS and SF-36. In the psychiatric patient group, moderate negative correlations with the dimensions: vitality (r = −0.42, $p = 0.047$), social functioning (r = −0.47, $p = 0.023$), and role emotional (r = −0.46, $p = 0.029$), were observed.

4. Discussion

4.1. Gaps in the Literature

There is no consensus or gold standard for the inclusion of dry mouth patients into clinical studies; thus, comparing different clinical trials on dry mouth products is challenging or even impossible. In the present study, we have proposed a dry mouth severity score, the DMSS, to classify the severity of dry mouth based on five objective and subjective parameters that may be used as a common basis for patient inclusion in studies.

Several examples from the literature show that the inclusion criteria vary extensively in clinical trials concerning dry mouth. Asakawa et al. tested a commercial dry mouth product on two groups with different age categories solely [5]. Epstein et al. tested four different commercial dry mouth products on members from the Sjogren's Syndrome Foundation (Bethesda, MD, USA) with self-identified disease [34]. Another study from Epstein et al. tested an experimental moisturizing mouthwash on subjects answering at least 3 on a 0 to 10 scale on the question I have dry mouth, while the inclusion criteria in a study from Barbe et al. was a minimum of 4 on the same scale [6,35]. Salom et al. included patients with a mean salivary flow rate of $\leq$0.16 g/min or any medical condition or treatment associated with xerostomia when testing the efficacy of a new oral saliva equivalent [7]. Other studies have included specific patient groups, such as the study of Warde et al. that included HNC patients and excluded patients using drugs associated with anticholinergic side effects or other medical conditions associated with xerostomia [36]. Furthermore, Jose et al. used wider inclusion criteria when including patients with pSS, non-SS, and others who answered at least agree a little to two out of four questions from the Xerostomia Inventory when testing an experimental moisturizing mouthwash [37,38]. Taken together, these examples clearly demonstrate a need for standardized inclusion for dry mouth patients.

4.2. Application of the DMSS

The proposed DMSS is fairly easy to use and encompasses a four-point scale from 0 to 3, where a higher score represents a more severe degree of dry mouth. A high DMSS indicates that several dry mouth parameters received 1 point. Thus, one can assume that the dry mouth is of high severity. On the contrary, a lower DMSS may not necessarily indicate that the severity of dry mouth is mild or moderate because one or more dry mouth parameters still received 1 point. In fact, as the cut-off values were set relatively high, a mild degree of dry mouth will likely receive a DMSS of 0. It can be argued that the cut-off values are set too high.

A proposed DMSS of 1 for inclusion into clinical studies may be reasonable. On the other hand, it also means that patients answering frequently or always on GXQ as the only parameter above cut-off (below for UWS and SWS) are included. A DMSS of >1 may be considered if the latter is unacceptable. Another approach could be to select one or more of the parameters to be crucial, depending on the nature of the clinical study in question. An example is the inclusion of patients in studies exploring saliva-stimulating agents, where one point for the SWS parameter may be crucial. By setting one or several parameters as crucial or mandatory, one can ensure that appropriate patients for a given output are included in the study. Comparisons between studies still require that the patients are categorized according to the DMSS.

For the classification of pSS, a 15 min collection time for UWS is mandatory and was used in our studies, but is too time-consuming to be recommended for the DMSS [17]. In an effort to adapt the DMSS to a clinical setting, we suggest measuring UWS and SWS for five

minutes each. These time intervals were, for instance, used in the OsloMunn65 study [30]. We recommend starting with GXQ and SXI, and then continuing with the collection of UWS before executing CODS and finishing with the collection of SWS. A work-flow to expedite the application of the DMSS in clinical settings is suggested in Supplementary Figure S1. The estimated time used for this approach is about 15 min, including ten minutes of saliva collection.

4.3. Selection of Dry Mouth Parameters

The SXI has been validated as a measure for research as a shortening of the original Xerostomia Inventory (XI) [19,38]. The XI was originally developed because instruments to compare xerostomia across patient groups were missing, the XI and SXI have been translated and validated into several languages and are much-used tools in research [39–41]. Additionally, Thomson et al. argued that single-item approaches like the GXQ were insufficient due to different interpretations of a single-item question [38,42,43]. Accordingly, 11 items were included in the XI for a more comprehensive investigation (score range 11–55) [38]. Van der Putten et al. reduced the number of responses, resulting in a score range from 11 to 33 (the modified XI-Dutch version) [29]. Furthermore, Putten et al. proposed a shortened version of the modified XI-Dutch version, with a score range from 5 to 15. As a different number of questions and response points for XI and SXI exists, care must be taken to verify that the number of questions and response points are the same if the comparison of total scores is planned. The SXI score range in the data set used in the present study was 5–15 and was kept as the score range of the SXI parameter of the DMSS.

When CODS was evaluated by Jager et al., they recommended using it in combination with a subjective measure (XI or "bother index") [23]. This was taken into account in the present proposal of DMSS as CODS is used together with SXI and GXQ when the DMSS is calculated. Pathological changes of the oral mucosa were one of the clinical examinations from our Dry Mouth Clinic. Mucosal pathology should naturally be notified when examining dry mouth patients but was not regarded as a principal parameter in this context. It can be discussed if pathological changes of the teeth associated with hyposalivation are assessed sufficiently in feature nine of CODS ("active or recent restored cervical caries"), but to narrow the number of parameters of the DMSS, it was not included as a separate parameter [31].

Disturbances in taste and smell functions were also tested in the Dry Mouth Clinic and have been found to correlate with hyposalivation, but were not included in the DMSS because proper evaluation requires expensive equipment and is too time-consuming in this context [44]. Lastly, candida growth was also one of our previous tests and was shown to correlate with several measures of dry mouth in pSS and HNC patients, but because of the need for resources and time, evaluation of candida growth was not included as a parameter in the DMSS [13,14].

4.4. Sensitivity, Specificity and Reliability of DMSS

The relatively high sensitivity and specificity of the DMSS indicate that the score may be a useful and sensitive tool for the inclusion of patients in clinical studies. The internal reliability of the DMSS, as measured with Cronbach's alpha, was satisfactory and showed that the DMSS measures the same characteristics satisfactorily [33]. The study also demonstrated that the majority of patients received a DMSS of 3, which was anticipated as the patient group consisted of a majority of patients with severe complaints of dry mouth.

For verification, the OsloMunn65 study was used to calculate the mean DMSS of the study participants that included a random sample of 460 65-year-olds living in Oslo, Norway [30]. The participants of the OsloMunn65 study underwent the same protocol as in the studies used for the development of DMSS. The study showed that xerostomia and hyposalivation were not prevalent conditions in the general population of 65 year olds [30]. None of the parameters of DMSS in that study had median values above cut-off values (or below for UWS and SWS). Accordingly, a DMSS calculation of 0 is in agreement with the

results from the OsloMunn65 study [30]. The ranges of the parameters of DMSS, however, showed that some of the participants would have received a higher DMSS and that those participants used more than four medications daily or were previously radiated to the head and neck area.

4.5. Correlations with Quality of Life Measurements

As the DMSS is not mainly directed towards OHRQoL, the OHIP-14 was not included in the score but rather used to investigate possible associations between the DMSS and OHRQoL. A weak positive correlation was seen between DMSS for all patients and OHIP-14. This is in accordance with other studies showing a positive correlation between dry mouth and OHRQoL using OHIP-14 [45–47].

No significant correlations were seen between the DMSS of all patients and the selected measure for general health-related quality of life, SF-36. This may indicate that DMSS specifically describes dry mouth, as intended, and that general and oral health-related quality of life should be investigated with other specified tools when needed. Our results are in accordance with other studies showing no significant correlation between dry mouth and SF-36 [48–50].

4.6. Strengths and Limitations of the Study

To our knowledge, this is the first study to incorporate parameters for both xerostomia and hyposalivation into the same score. As patient-reported data on xerostomia often do not correspond with objective measures of hyposalivation, such a combination must be considered as a strength [51]. Another strength of the study is that all participants were examined according to a standardized predefined protocol and that the patient group consisted of patients with several dry mouth complaints with different etiologies. However, the major limitations of the study were the relatively low number of participants and the lack of a "gold standard" for dry mouth measurement to verify an association with the DMSS. As the most common dry mouth parameters were already included in the DMSS, a validation of the DMSS by calculating the association with one of those parameters is not suitable.

To investigate optimization and validation of this dry mouth severity score, it would be beneficial to investigate the DMSS in larger patient samples and in other patient groups to evaluate the distribution of scores within additional patient samples than those included in the present paper, i.e., elderly with polypharmacy. For the evaluation of the usability of the DMSS in a clinical trial, it would probably be most beneficial to test the DMSS in a small feasibility study.

5. Conclusions

By combining two subjective and three objective dry mouth parameters from previous studies in our Dry Mouth Clinic, we have proposed a method to classify dry mouth patients according to severity. We established cut-off values and points for the calculation of the dry mouth severity score (DMSS) based on previously defined dry mouth parameters. The sensitivity and specificity of the DMSS were high, and the internal reliability was satisfactory. However, the proposed scoring method for dry mouth should be explored in other patient groups and in a clinical study for optimization and validation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app132111758/s1, Figure S1: DMSS appendix.

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Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to restrictions in the ethical approvement.

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