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World Workshop on Oral Medicine VIII: Development of a Core Outcome Set for Dry Mouth: A Systematic Review of Outcome Domains for Salivary Hypofunction

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Abstract

Objective: To identify all outcome measures used to assess salivary gland hypofunction (i.e.: objective measures used to determine actual changes in saliva quantity or to assess response to treatment of salivary gland hypofunction) and to group these into domains.

Study Design: A systematic review including clinical trials, and prospective or retrospective observational studies involving human participants with dry mouth, with any type of intervention where objective assessment of salivary gland hypofunction was described.

Results: Five hundred fifty-three studies involving 31,507 participants were identified. The majority assessed both salivary gland hypofunction and xerostomia (68.7%), whilst 31.3% assessed salivary gland hypofunction alone. The majority of studies investigated 'amount of saliva' and the highest number of outcome measures was within the domain 'clinical/objective signs of salivary gland hypofunction'.

Conclusions: Seven domains encompassing 30 outcome measures were identified, confirming the diversity in outcomes and outcome measures used in research regarding salivary gland hypofunction. Identified items will be used in conjunction with those identified regarding xerostomia to create a COS for dry mouth quantification for use in future clinical trials, with the overall goal of improving the standardization of reporting, leading to the establishment of more robust evidence for the management of dry mouth and improving patient care.

1. Introduction

Dry mouth is a debilitating condition which can have a significant impact on quality of life. It is a ubiquitous problem worldwide, yet despite this, management options remain limited, and there is no strong evidence that treatments are effective.[1] Prevalence ranges from 5.5%- 46%[2] with a slight female preponderance[3,4] However, the precise global prevalence is difficult to determine due to differing study methodology and diagnostic or inclusion criteria used.[5-7]

The term 'dry mouth' encompasses xerostomia, salivary gland hypofunction, and hyposalivation. Xerostomia is defined as 'the subjective feeling of oral dryness',[8,9] whilst salivary gland hypofunction is objectively decreased saliva secretion, i.e. below normal secretion. Hyposalivation refers to a diagnosis when saliva secretion becomes pathologically low, as measured objectively,'[10] i.e. unstimulated whole saliva flow rate ≤0.1 mL/min, and/or stimulated whole saliva flow rate ≤0.5-0.7 mL/min.[11,12] The terms xerostomia, salivary gland hypofunction, or hyposalivation are therefore not synonymous and should not be used interchangeably. Unfortunately, however, these terms are often combined in the dry mouth literature, limiting the interpretation of study results.

Xerostomia (the subjective *feeling* of dry mouth) due to salivary gland hypofunction (an objective reduction in saliva secretion) is typically apparent once ≥50% of unstimulated salivary function has been lost.[13] Conversely, patients may experience xerostomia (*subjective* dry mouth) in the absence of objective reduction of salivary secretion. It is postulated that this may be due to mouth breathing causing evaporation of saliva[14] and/ or due to changes in the composition of saliva (a qualitative change) to a more viscous production, resulting in a *feeling of dryness*, even though the

quantity of saliva production remains unchanged.[15-17] Xerostomia has also been proposed to be psychogenic in aetiology.[3,18]

Salivary gland hypofunction may be due to a variety of reasons, including medication intake and polypharmacy (a multitude of medications, most commonly those that are anti-cholinergic, sympathomimetic, or diuretic in action), damage to salivary glands (e.g. radiation, radioactive iodine), diseases of the salivary glands (e.g. Sjögren's syndrome (also known as Sjögren's disease) either primary or secondary to connective tissue diseases), sarcoidosis, human immunodeficiency virus, hepatitis C virus, chronic graft versus host disease, primary biliary cholangitis, cystic fibrosis, amyloidosis, hemochromatosis, vasculitis), developmental abnormalities (aplasia or agenesis), diabetes mellitus, eating disorders, dehydration and/or renal failure, amongst others.[2,17,19-35] It is reported in the literature that older age does not result in salivary gland hypofunction,[12,36-38] but rather that as ageing occurs and health declines, there is an increase in polypharmacy with xerogenic medications, which often results in a reduction in saliva secretion, and/or xerostomia.[39-41] However, a previous meta-analysis has concluded that the aging process is in fact directly associated with a reduction in salivary flow rate.[42]

A range of objective special investigations can be employed to assess if there is a quantitative reduction in salivary flow rate or disease or damage to the salivary glands, including sialometry, salivary gland imaging and sialadenoscopy, amongst others. To assess the subjective feeling of dry mouth it is fundamental to obtain the patient's opinion by questioning the patient about their dry mouth, or using any number of validated scales and tools,[43-47] some of which may have direct

relation to or predictive ability for the presence of salivary gland hypofunction or even hyposalivation.[8]

Within the healthcare setting, an outcome measure reflects "a change in current or future health status that can be attributed to the antecedent intervention".[48] A plethora of outcome measures relating to the assessment of both xerostomia and salivary gland hypofunction are cited in the literature and the majority of these focus on the subjective element of dry mouth through patient-reported outcome measures (PROMS). Outcome measures for dry mouth and the definitions/terminology to which they relate are heterogeneous across the literature, which can introduce imprecision when interpreting the collective results and conclusions regarding the efficacy of interventions. Furthermore, this translates to challenges creating evidence-based guidelines and clinical decision making. With this in mind, the aim of the World Workshop on Oral Medicine Outcomes Initiative for the Direction of Research (WONDER) was to address these difficulties by creating core outcome measures for effectiveness trials. A core outcome set (COS) is an agreed *minimum* of outcome domains to be measured and reported in all trials of a particular treatment or condition.[49] As part of this process, all subjective and objective outcome measures need to be systematically reviewed, to allow consensus to be reached by a panel of experts regarding which outcomes should be part of the COS.

The purpose of this systematic review was to identify all the different outcome measures used to assess salivary gland hypofunction (i.e. the objective measures used to diagnose an actual reduction in saliva quantity or to assess response to treatment of salivary gland hypofunction) and

to group these into domains. The outcome measures relating to xerostomia are the subject of a separate systematic review.[50]

2. Materials and Methods

This systematic review was conducted as part of the World Workshop on Oral Medicine VIII (WWOM VIII). The research method was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement guidelines.[51] The protocol for this systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO), University of York Centre for Review and Disseminations, with identification number CRD42021279791 (available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021279791).

2.1. Search Strategy

The research question "what are the outcome measures used in studies for dry mouth?" was formulated to direct the search strategy. The search strategy was developed with the help of a bioinformation specialist (SvdW) according to the syntax rules of each database. On 15 September 2021, a systematic search of the scientific literature was performed for articles published from January 2000 up to September 2021 in the following bibliographic databases: MEDLINE (PubMed), EMBASE (Ovid), CINAHL (EBSCO), and Cochrane Central Register of Controlled Trials (CENTRAL). The reproducible search strategies for all databases are provided as a supplementary document (Supplement 1). A total of 34,922 citations were retrieved from the four databases. A total of 1,746 records not meeting the publication date restrictions were removed

before screening. After removal of duplicates, a total of 18,694 were retained for screening (**Figure 1**).

2.2. Eligibility Criteria

This manuscript focused on outcome measures used to assess salivary gland hypofunction. In a separate manuscript, we address outcome measures relating to xerostomia.[50] The Population, Intervention, Control, Outcome, and Study Design (PICOS) approach was adopted as follows: P – humans with a dry mouth; I – any active preventive, palliative, or curative pharmacological or non-pharmacological treatment/intervention for dry mouth administered topically or systemically; C – no restrictions to the comparison; O – all dry mouth-related outcomes (objectively and subjectively measured); S – clinical trials (randomized and non-randomized) and observational studies (descriptive, cross-sectional, cohort, case-control).

Inclusion criteria were as follows: Clinical trials and prospective or retrospective observational studies involving human participants with dry mouth and describing any types of intervention or objective assessment of dry mouth. Studies must have had at least one objective dry mouth-related outcome and/or outcome measures clearly designated in the methods section. Exclusion criteria were as follows: Animal and/or in vitro studies, publications not available in full text, conference proceedings, commentaries, editorials, study protocols, case reports, review articles, studies published before the year 2001, and records which did not have an English version. Studies using a cohort of less than ten participants were further excluded to ensure a representative sample of the general population. No age restriction was applied.

2.3. Study Selection and Data Extraction Process

Reviewer calibration was performed in two sessions on articles not included on this study prior to the initiation of the screening process. The Cohen's Kappa was 0.7 with a percentage of agreement of 85 between the various observers. The titles and abstracts obtained from the initial electronic searches were screened for relevance by the study group (AV, KD, RNR, VS, ARSS, MKS, PW, MLS, SN). Papers retained were screened by full text review by the five reviewers (ARSS, MKS, PW, MLS, SN). A total of 2,700 studies were found to be relevant and considered for comprehensive review and data extraction. Data extracted included the type of the study and the target population as well as the number of patients included. All objective outcome measures/instruments relating to dry mouth were recorded and classified within domains (paragraph 3.2; figure 2).

3. Results

A total of 553 studies assessing salivary gland hypofunction, comprising 31,507 patients met the inclusion criteria. Of these, 173 (31.3%) studies assessed salivary gland hypofunction alone, whilst 380 (68.7%) assessed both salivary gland hypofunction and xerostomia (**Table I**). Most studies (n=303, 54.8%) assessed one outcome measure for salivary gland hypofunction, with only 43 and 25 of studies assessing three and four different outcome measures, respectively. The rest of the studies assessed two outcome measures for salivary gland hypofunction, each (n=182, 32.9%).

3.1. Characteristics of Studies Included

As depicted in Table I, the proportion of studies assessing salivary gland hypofunction increased over the years, with almost double the number of studies published between the years 2011-2020

compared with 2001-2010. Most studies originated from Europe (n=206, 37.3%), followed by Asia (n=190, 34.4%) and North America (n=85, 15.4%). Cohort studies were the most represented study type (n=160; 28.9%). The most common condition studied was salivary gland hypofunction due to head and neck radiotherapy (n=123, 22.2%), closely followed by Sjögren's syndrome (n=115, 20.8%). A total of 60 studies (10.8%) did not specify the condition evaluated.

3.2. Identified Domains

Seven domains were identified (**Figure 2**). The domain most frequently explored, based on the number of studies including at least one outcome measure used for this domain, was 'Amount of Saliva,' with 481 (87.0%) studies. Domains that were less frequently studied were 'Saliva Properties,' 'Saliva Composition,' and 'Biomarkers,' with a total of 11, 11, and two studies evaluating at least one related outcome measure, respectively.

As one study could include outcome measures for more than one domain simultaneously, each study could be retrieved once per domain but also be reported in several domains.

3.3 Main Outcome Measures Within Each Domain

The highest number of outcome measures were recorded within the two subdomains of Domain 3 (Clinical/Objective Signs of Salivary Gland Hypofunction), despite there being a relative paucity of papers within this domain (**Table II)**. Domain 5 (Imaging Modalities Assessing Salivary Gland Dysfunction) and Domain 6 (Properties of Saliva) looked at five outcome measures each. Despite having the largest number of papers evaluating this domain, only four outcome measures, two in each subdomain, were identified in Domain 1 (Amount of Saliva). Only 3 outcome measures were identified for Domain 2 (Salivary Biomarkers).

3.3.1 Domain 1: Amount of Saliva

Domain 1 considered salivary gland flow rate and/or saliva weight. This was divided into two subdomains: Whole mouth saliva and gland/region specific saliva. Each subdomain included outcome measures looking at both stimulated and unstimulated saliva.

Within the outcome measure of stimulated whole saliva flow rate/weight, 276 studies used seven different instruments (**Table III**). All instruments used a scale (numerical/continuous) as the level of measurement. The most common method of assessing stimulated whole saliva flow rate/weight was stimulation by chewing (n=63). Chewing materials included paraffin wax,[52-92] gum,[93-106] rubber,[107,108] and silicone.[109-111] Other instruments to specifically assess stimulated whole saliva flow rate/weight included gustatory stimulation (n=23) with gustatory stimulants including citric acid and lime juice.[47,62,77, 85, 102,112-129] Less commonly used methods were the Saxon test; where saliva production is quantified by weighing a gauze before and after chewing it for a set time[130] (n=10),[98,131-139] biscuit test; the amount of time taken to chew and swallow a dry cracker biscuit,[140] electrostimulation,[141] and medication such as pilocarpine oral solution or tablets.[142,143] One study specifically compared the stimulated salivary flow rate induced by an alcohol-based and non-alcohol-based mouthwash.[144]

Within the outcome measure of unstimulated whole saliva flow rate/weight, 368 studies used 11 instruments (**Table III**). The most common instrument to assess unstimulated whole saliva flow rate/weight was passive drooling or spitting (n=150),[39, 57, 60, 62, 64, 67, 69, 70, 72, 77, 79, 82, 83, 85, 86, 90, 92, 93, 99, 100, 106, 107, 109, 111, 113, 114, 118-120, 122, 129, 135, 137, 141-257] followed by spitting at timed intervals (n=

30),[47, 56, 78, 87, 117, 126, 258-281] and weighing cotton balls/rolls (n=10).[116, 282-290] Other methods of measuring unstimulated whole saliva flow rate/weight included the Saxon test,[104, 291-295] Oral Schirmer's test; a strip of filter paper is placed on the floor of mouth for 5 minutes and the wetted length is measured in millimeters,[112, 296-299] Modified Schirmer's test,[283, 300, 301] and weighing gauze placed in the mouth.[302-304]

A total of 58 papers evaluated the subdomain of gland/region specific saliva (**Table III**). This included investigating specific major and/or minor glands (e.g. parotid gland, labial glands) either alone or in combination, or specific regions/locations of the oral cavity (e.g. floor of mouth, palate, labial mucosa). Outcome measures evaluated both stimulated and unstimulated saliva, and great variability was recorded in terms of the different glands and/or regions of the mouth assessed.

The most common individual gland to be investigated (i.e. not investigated in combination with any other glands) was the parotid gland. Twenty-seven studies used stimulated parotid saliva as the outcome measure[78, 305-327] with methods of stimulation of the gland including acidic sweets, 1% ascorbic acid solution, and 2%, 4% or 6% citric acid, and methods of collection including devices such as the Carlsson-Crittenden Cup, Lashley cup and the modified Crittenden-Lashley cup method. Nine studies also measured unstimulated parotid saliva alongside stimulated parotid saliva.[305, 306, 311, 315, 319, 322, 324, 325, 327]

The next most common outcome measure was unstimulated saliva from the floor of mouth (n=9)[270, 329-336] measured most frequently by the modified Schirmer's test. The submandibular and sublingual glands were assessed together, investigating both unstimulated,[236, 312, 322, 337-339] and

stimulated salivary flow rate.[317, 321, 322, 338, 340] Several papers also investigated stimulated and unstimulated saliva from the parotid and submandibular glands.[69, 341-343]

Minor glands were investigated by several authors. Some investigated these as specific, individual regions/locations of the mouth; unstimulated labial gland saliva (n=6),[100, 206, 226, 344-346] unstimulated buccal saliva,[206, 344] or unstimulated palatal saliva,[206, 347] whilst some investigated more than one individual location; palatal and upper labial glands[109] or labial and buccal glands.[73]

3.3.2 Domain 2: Salivary Biomarkers

Two studies used a total of three salivary biomarkers and the use of all these methods was ad hoc. Biomarkers recorded were inflammatory cytokines, proteins, and immunoglobulins. Specifically, chromogranin A and IgA[135] and extracellular microRNA.[348]

3.3.3 Domain 3: Clinical or Objective Signs of Hyposalivation

Domain 3 considered clinical or objective signs of hyposalivation as rated by a physician. The domain was divided into individual clinical signs of hyposalivation and multiple clinical signs of hyposalivation. Eight studies used individual clinical signs of hyposalivation as their outcome measure. The most common method used was for the physician to assess for clinical signs of dryness of the oral mucosa or specific mucosal sites such as the dorsum of the tongue[349, 350] and palate.[351] Other methods included use of the mirror test,[335, 350, 352] scoring dryness from clinical examination (giving a score between 1-10 depending on presence of clinical signs of hyposalivation e.g.: cervical caries, debris on palate),[314] and the tongue blade test.[274]

Eighteen studies used multiple clinical signs of hyposalivation as their outcome measure. The most common outcome measure used was the Clinical Oral Dryness Score (CODS) (colloquially known as the 'Challacombe Scale of Clinical Oral Dryness'),[77, 78, 85, 105, 213, 218, 255, 278, 353] followed by a physician carrying out a clinical evaluation to assess for multiple signs of dry mouth.[39, 169, 177, 261, 298, 354, 355] Other methods included scoring methods such as the Objective Oral Mucosa Scale (OOMS)[356] and a dichotomous objective dry mouth score.[353]

3.3.4 Domain 4: Mucosal Hydration

Domain 4 considered mucosal hydration, specifically moisture, wetness, and residual saliva. While most authors refer to these terms interchangeably to describe the level of mucosal hydration, some use the term 'moisture' to describe the water content of the oral mucosal surface and intramucosal layer, 'wetness' to describe the water content of the mucosal surface only, and 'residual saliva' to specifically describe the saliva remaining on mucosal surfaces after swallowing.

In total, 20 studies used outcome measures relating to this domain. The most common outcome measure was moisture, with 13 papers considering this outcome measure.[137, 204, 357-367] Five of these studies specifically investigated this via a checking device such as a Periotron™ (Pro-Flow TM Incorporated, Amityville, NY, USA). [137, 362, 364, 366, 367] Wetness was the outcome measure for four studies.[177, 190, 368, 369] Three papers used residual saliva as the outcome measure.[67, 213, 218]

3.3.5 Domain 5: Imaging Modalities Assessing Salivary Gland Dysfunction

Domain 5 considered salivary gland dysfunction (a change in quality and/or quantity of saliva)[370] assessed by a variety of different imaging modalities comprising ultrasonography, scintigraphy,

sialography, magnetic resonance imaging (MRI) and computed tomography (CT). Twenty-four studies used five individual outcomes measures involving ultrasonography of the salivary glands (parenchymal structure, colour or power doppler signal, a scoring system, tissue elasticity and not specified).[123, 293, 295, 323, 328, 371-388]

The most common outcome measure involving ultrasonography used a scoring system[123, 328, 375, 377, 379-382, 384-386, 388] such as that of Hočevar et al.[389] Six studies investigated parenchymal structure (e.g.: homogeneity, echogenicity) via ultrasonography.[293, 295, 371-373, 387] One study looked specifically at intraglandular power doppler signal.[381] Forty-four studies considered salivary gland hypofunction by scintigraphy.[134, 157, 170, 225, 268, 283, 293, 320, 355, 376, 390-423] Five studies used MRI as an outcome measure,[132, 291, 371, 403, 416] two used sialography,[371, 424] and only a single paper assessed salivary gland hypofunction by CT.[425]

3.3.6 Domain 6: Properties of Saliva

Domain 6 looked at saliva properties. The most common property considered was pH[115, 196, 221, 280] followed by buffering capacity.[196, 209, 426] Two studies used lubrication as an outcome measure, specifically looking at the level and concentration of the salivary mucin MUC5B (originally named MG1).[91, 427] Two studies used saliva stringiness (Spinnbarkeit) as an outcome measure.[213, 218] A single study looked at viscosity using the inclined plane test; the faster the velocity of the saliva on a glass slide, the less viscous ('sticky') it is.[250]

3.3.7 Domain 7: Saliva Composition

Domain 7 considered the composition of saliva. Two studies considered individual components of saliva; salivary IgA (alongside pH)[221] and calcium concentration.[427] Nine papers used multiple outcome measures regarding the composition of saliva via biochemical and sialochemical analysis.[67, 178, 195, 201, 277, 280, 311, 428, 429]

4. Discussion

Following the first of four steps outlined by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative,[430] this systematic review sought to identify domains and outcomes that have been used by clinicians from varied backgrounds and settings for the evaluation of salivary gland hypofunction (i.e., *what* to measure). Combined with Part I which reviewed the outcome domains used to assess xerostomia[50] we assessed all domains used in dry mouth research.

A total of seven domains encompassing 30 outcome measures were identified for salivary gland hypofunction based on the 553 studies included. By far, the most common domain was 'Amount of Saliva', retrieved from a total of 485 studies. This finding may indicate an overall agreement among clinicians and researchers that these are the most important, or clinically relevant outcome measures for salivary gland hypofunction. In addition, this may reflect the availability of instruments for evaluation of salivary flow rate/weight in daily practice, rendering related outcome measures feasible and relatively reproducible. Alluding to the latter is the finding that within the 'Amount of Saliva' domain, most studies (n=368, 76%) evaluated unstimulated whole saliva flow rate/weight, an outcome for which instrumentation is minimal. With the passive drooling or spitting method, the most common instrument used, all that is needed is a receptacle (e.g., cup or

a tube) and a precision scale. This may also explain why only a small number of studies investigated the domains of 'Saliva Properties', 'Saliva Composition' and 'Biomarkers'; outcome measures within these domains often require expensive laboratory equipment and appropriately trained personnel to provide and interpret results, and therefore these are less readily available. Although outcome measures within the domain 'Imaging Modalities Assessing Salivary Gland Dysfunction' require expensive imaging equipment, these are usually easily accessible in most hospital settings, reflected in the fact that this domain was the second most common to be investigated. The number of different outcomes assessed and the inconsistency in assessment methods is problematic. For example, while 'Saliva Properties' were used in only 13 of the 553 studies evaluating salivary gland hypofunction, five different outcome measures were used across the 13 studies, making comparison of studies and aggregation of results difficult.

Salivary gland hypofunction secondary to radiation to the head and neck was the most common condition/disease to be investigated (n=123). This was closely followed by Sjögren's syndrome, investigated in 115 papers, with outcome measures across a range of domains. Outcome measures included unstimulated and stimulated salivary flow rate, physician assessment of clinical dryness, including use of the CODS, ultrasonography, scintigraphy and MRI. In addition to having outcome measures within the identified domains, fourteen studies looked specifically at histological analysis of lymphocytic infiltrates (focus scores) in salivary gland biopsies.[195, 309, 371, 394, 404, 431-439] Overall, outcome measures used in studies assessing Sjögren's syndrome were relatively homogeneous, likely the results of the efforts made in recent years to move towards less invasive methods to diagnose this condition [440, 441] and to improve the understanding of the disease and to standardize the evaluation and monitoring of disease activity; starting with the 2016 International

Consensus to endorse the ACR-EULAR set of criteria for the classification of primary Sjögren's syndrome,[442] through the development of indices such as the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS),[443] addressing different aspects of the disease.

This systematic review has several limitations. By focusing on articles published after the year 2000, this study may have missed outcome measures used to assess salivary gland hypofunction before this date. We assume, however, that any clinically relevant, important outcome measures would be carried over to the evaluated time period. Additionally, with the aim to capture the diversity of outcomes and outcome measures available in the literature, included studies were not assessed on their scientific rigor. Due to the volume of results, the data extraction on outcomes was limited and information concerning the timing and implementation method(s) of the various outcome measure instruments was not retrieved. Finally, this review included English-language literature only, and relevant research published in other languages may have been left out (language bias).

The strengths of this review in our view, however, outweigh its limitations. With over 34,000 records screened, the inclusion of a large number of studies to summarize information on outcome domains and outcome measures for the evaluation of salivary gland hypofunction resulted in a comprehensive data set ranging across clinical settings, patient populations, and geographical locations. Additional strengths include the international team of reviewers, and the rigour and consistency of the screening process.

This systematic review revealed the diversity and variability in the outcomes and outcome measures used in clinical research regarding salivary gland hypofunction. The lack of standardised outcome measures for the assessment of dry mouth contributes to the heterogeneity between studies and makes it difficult to compare results, synthesize findings, or guide clinicians on management strategies. The WONDER initiative aims to address these difficulties by developing a COS for dry mouth, encompassing both the findings regarding salivary gland hypofunction as identified in this manuscript, as well as those identified for xerostomia.[50] Once available, a dry mouth COS would improve the standardization of reporting, and facilitate meta-analyses, leading to the establishment of more robust evidence for the management of dry mouth and, eventually, improved patient care. This systematic review was thus designed to identify existing outcomes and outcome measures for salivary gland hypofunction in order to inform the next steps in ranking and selecting items that would be most relevant to be included in a COS for dry mouth and to highlight potential gaps. Building on the current findings, future work is planned to further evaluate the identified outcome measures for their specific properties (i.e., *how* to measure). The next steps of the WONDER initiative are to complement the results of this systematic review with the results of focus groups regarding the most important or bothersome domains from the perspective of patients with dry mouth and to identify any gaps between priorities of clinicians/researchers and the patients' perspective.

5. Conclusion

There is considerable diversity and variability in the outcomes and outcome measures used in clinical research regarding salivary gland hypofunction. The identified seven domains, which encompass 30 outcome measures, are the first step towards development of a COS for dry mouth within the WONDER initiative.

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7. Figure Legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline flowchart detailing article selection process.

Figure 2. Identified Outcome Domains for Assessment of Salivary Gland Hypofunction.

8. References

1 Furness S, Worthington HV, Bryan G, Birchenough S, McMillan R. Interventions for the management of dry mouth: topical therapies. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD008934. DOI: 10.1002/14651858.CD008934.pub2. Accessed 22 July 2022.

2 Villa A, Connell CL, Abati S. Diagnosis and management of xerostomia and hyposalivation. Therapeutics and Clinical Risk Management 2015:11 45–51

3 Bergdahl M, Bergdahl J. Low unstimulated salivary flow and subjective oral dryness: association with medication, anxiety, depression and stress. J Dent Res 2000;79:16528

4 Niklander S, Veas L, Barrera C, Fuentes F, Chiappini G, Marshall M. Risk factors, hyposalivation and impact of xerostomia on oral health-related quality of life. Braz. Oral Res. 2017;31:e14

5 Ship JA, Pillemer SR, Baum BJ Xerostomia and the Geriatric Patient. J Am Geriatr Soc 50:535–543, 2002

6 Orellana MF, Lagravère MO, Boychuk DG, Major PW, Flores- Mir C, Ortho C. Prevalence of xerostomia in population- based samples: a systematic review. J Public Health Dent. 2006;66(2):152-8. doi:10.1111/j.1752-7325.2006.tb02572.x

7 Han P, Suarez-Durall P, Mulligan R. Dry mouth: a critical topic for older adult patients. J Prosthodont Res. 2015;59(1):6-19. doi:10.1016/j.jpor.2014.11.001

8 Fox PC, Busch KA, Baum BJ (1987). Subjective reports of xerostomia and objective measures of salivary gland performance. J Am Dent Assoc 115: 581–584.

9 Delli K, Spijkervet FK, Kroese FG, Bootsma H, Vissink A. Xerostomia. Monogr Oral Sci. 2014;24:109-25. doi: 10.1159/000358792. Epub 2014 May 23. PMID: 24862599

10 Mercadante V, Jensen SB, Smith DK, Bohlke K, Bauman J, Brennan MT, Coppes, RP, Jessen N, Malhotra NK, Murphy B, Rosenthal, DI, Vissink A, Wu J, Saunders DP, Peterson DE. 2021. Salivary Gland Hypofunction and/or Xerostomia Induced by Nonsurgical Cancer Therapies: ISOO/MASCC/ASCO Guideline. Oncol. 2021 Sep 1;39(25):2825-2843

11 Heintze U, Birkhed D, Bjørn H (1983). Secretion rate and buffer effect of resting and stimulated whole saliva as a function of age and sex. Swed Dent J7:227–238

12 Sreebny LM (2000). Saliva in health and disease: an appraisal and update. Int Dent J50:140–161

13 Dawes C (1987). Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. J Dent Res 66 (Spec Iss): 648–653.

14 Pedersen AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. Oral Dis. 2002;8:117-129.

15 Nederfors T, Dahlöf C, Twetman S (1994). Effects of the beta-adrenoceptor antagonists atenolol and propranolol on human unstimulated whole saliva flow rate and protein composition. Scand J Dent Res102:235–237

16 Guggenheimer J, Moore PA. Xerostomia: Etiology, recognition and treatment. The Journal of the American Dental Association. Volume 134, Issue 1, January 2003, Pages 61-69

17 Porter SR, Scully C, Hegarty AM. An update of the etiology and management of xerostomia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:28-46.

18 Gholami N, Hosseini Sabzvari B, Razzaghi A, Salah S. Effect of stress, anxiety and depression on unstimulated salivary flow rate and xerostomia. *J Dent Res Dent Clin Dent Prospects*. 2017;11(4):247-252. doi:10.15171/joddd.2017.043

19 Vrielinck LJ, van Parys G, van Damme B, Bossuyt M. Sicca syndrome with iron deposition in the salivary glands. Int J Oral Maxillofac Surg 1988;17:11-3.

20 Schiodt M. HIV-associated salivary gland disease: a review. Oral Surg Oral Med Oral Pathol 1992;73:164-7.

21 Mariette X, Loiseau P, Morinet F. Hepatitis C virus in saliva. Ann Intern Med 1995;122:556.

22 Epstein JB, van der Meij EH, Lunn R, Stevenson-Moore P. Effects of compliance with fluoride gel application on caries and caries risk in patients after radiation therapy for head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;82:268-75.

23 Singh N, Scully C, Joyston-Bechal S. Oral complications of cancer therapies: prevention and management. Clin Oncol (R Coll Radiol) 1996;8:15-24.A

24 Zhou Z, Lu Y, Wu L. Clinicopathological and diagnostic study of amyloidosis of oral maxillofacial area. Zhonghua Kou Qiang Yi Xue Za Zhi 1998;33:282-4.

25 Drosos AA, Voulgari PV, Psychos DN, Tsifetaki N, Bai M. Sicca syndrome in patients with sarcoidosis. Rheumatol Int 1999;18:177-80

26 Ferguson DB. The flow rate and composition of human labial gland saliva. Arch Oral Biol 1999;44:S11-4.

27 Nagler RM, Sherman Y, Nagler A. Histopathological study of the human submandibular gland in graft versus host disease. J Clin Pathol 1999;52:395-7

28 Levy S, Nagler A, Okon S, Marmary Y. Parotid salivary gland dysfunction in chronic graft-versus-host disease (cGVHD): a longitudinal study in a mouse model. Bone Marrow Transplant 2000;25:1073-8

29 Hodgson TA, Shah R, Porter SR. The investigation of major salivary gland agenesis: a case report. Pediatr Dent 2001;23: 131-4.

30 Ikuno N, Mackay IR, Jois J, Omagari K, Rowley MJ. Antimitochondrial autoantibodies in saliva and sera from patients with primary biliary cirrhosis. J Gastroenterol Hepatol 2001;16:1390-4.

31 Bowman SJ. Collaborative research into outcome measures in Sjögren' s syndrome. Update on disease assessment. Scand J Rheumatol Suppl 2002;116:23-7

32 Demarosi F, Bez C, Sardella A, Lodi G, Carrassi A. Oral involvement in chronic graft-vs-host disease following allo- genic bone marrow transplantation. Arch Dermatol 2002;138: 842-3

33 Lin CC, Sun SS, Kao A, Lee CC. Impaired salivary function in patients with noninsulin-dependent diabetes mellitus with xe- rostomia. J Diabetes Complications 2002;16:176-9.

34 Scully C. Drug effects on salivary glands: dry mouth. Oral Diseases (2003) 9, 165–176

35 Manfredi M, McCullough MJ, Vescovi P, Al-Kaarawi ZM, Porter SR. Update on diabetes mellitus and related oral diseases. Oral Diseases (2004) 10, 187–200

36 Baum BJ (1989). Salivary gland fluid secretion during aging. J Am Geriatr Soc 37:453–458

37 Atkinson JC, Fox PC (1992). Salivary gland dysfunction. Clin Ger Med 8:499–511

38 Pedersen AM, Reibel J, Nordgarden H, Bergem HO, Jensen JL, Nauntofte B (1999). Primary Sjogren's syndrome: salivary gland function and clinical oral findings. Oral Dis 5:128–138

39 Leal SC, Bittar J, Portugal A, Falcão DP, Faber J, Zanotta P. Medication in elderly people: its influence on salivary pattern, signs and symptoms of dry mouth. *Gerodontology.* 2010;27(2):129–133.

40 Villa A, Polimeni A, Strohmenger L, Cicciù D, Gherlone E, Abati S. Dental patients' self-reports of xerostomia and associated risk factors. *J Am Dent Assoc.* 2011;142(7):811–816.

41 Liu B, Dion MR, Jurasic MM, Gibson G, Jones JA. Xerostomia and salivary hypofunction in vulnerable elders: prevalence and etiol- ogy. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2012;114(1): 52–60.

42 Affoo RH, Foley N, Garrick R, Siqueira WL, Martin RE. Meta-Analysis of Salivary Flow Rates in Young and Older Adults. J Am Geriatr Soc. 2015 Oct;63(10):2142-51. doi: 10.1111/jgs.13652. Epub 2015 Oct 12. PMID: 26456531.

43 Sreebny LM, Valdini A. Xerostomia. Part I: Relationship to other oral symptoms and salivary gland hypofunction. *Oral Surg Oral Med Oral Pathol.* 1988;66(4):451–458.

44 Thomson WM, Chalmers JM, Spencer AJ, Williams SM. The Xeros- tomia Inventory: a multi-item approach to measuring dry mouth. *Com- munity Dent Health.* 1999;16(1):12–17.

45 Pai S, Ghezzi EM, Ship JA. Development of a Visual Analogue Scale questionnaire for subjective assessment of salivary dysfunction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2001;91(3):

46 Eisbruch A, Rhodus N, Rosenthal D, et al. How should we measure and report radiotherapy-induced xerostomia? *Semin Radiat Oncol.* 2003;13(3):226–234.

47 van der Putten GJ, Brand HS, Schols JM, de Baat C. The diagnostic suitability of a xerostomia questionnaire and the association between xerostomia, hyposalivation and medication use in a group of nursing home residents. *Clin Oral Investig.* 2011;15(2):185–192

48 Ni Riordain R, C McCreary (2010) The use of quality of life measures in oral medicine: a review of the literature. Oral Dis **Volume16, Issue5**. P 419-430

49 Prinsen CA, Vohra S, Rose MR, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline. *Trials.* 2016;17:449.

50 Wiriyakijja et al., 2022 – World Workshop on Oral Medicine VIII: Development of a core outcome set for dry mouth: A Systematic Review of Outcome Domains for Xerostomia [Manuscript submitted for publication]

51 Page, M.J., McKenzie, J.E., Bossuyt, P.M. *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* **10,** 89 (2021). https://doi.org/10.1186/s13643-021-01626-4

52 Brizel, D. M. and T. Wasserman (2004). "The influence of intravenous amifostine on xerostomia and survival during radiotherapy for head and neck cancer: Two year follow-up of a prospective randomized trial." Journal of Clinical Oncology **22**(14_suppl): 5536-5536.

53 Bots, C. P., et al. (2005). "The management of xerostomia in patients on haemodialysis: comparison of artificial saliva and chewing gum." Palliat Med **19**(3): 202-207.

54 Ikebe, K., et al. (2006). "Association of candidal activity with denture use and salivary flow in symptom-free adults over 60 years." J Oral Rehabil **33**(1): 36-42.

55 Gil-Montoya, J. A., et al. (2008). "Evaluation of the clinical efficacy of a mouthwash and oral gel containing the antimicrobial proteins lactoperoxidase, lysozyme and lactoferrin in elderly patients with dry mouth--a pilot study." Gerodontology **25**(1): 3-9.

56 Gomez-Moreno, G., et al. (2013a). "The efficacy of a topical sialogogue spray containing 1% malic acid in patients with antidepressant-induced dry mouth: a double-blind, randomized clinical trial." Depress Anxiety **30**(2): 137-142.

57 Gupta, V. K., et al. (2014). "The Influence of Insulin Dependent Diabetes Mellitus on Dental Caries and Salivary Flow." Int J Chronic Dis **2014**: 790898.

58 Almstahl, A., et al. (2015). "Microflora in oral ecosystems and salivary secretion rates--A 3-year follow-up after radiation therapy to the head and neck region." Arch Oral Biol **60**(9): 1187-1195.

59 Banava, S., et al. (2015). "The effect of casein phosphopeptide amorphous calcium phosphate fluoride paste (CPP-ACPF) on oral and salivary conditions of patients undergoing chemotherapy: A randomized controlled clinical trial." Electron Physician **7**(7): 1535-1541.

60 Johanson, C. N., et al. (2015). "Salivary secretion and drug treatment in four 70-year-old Swedish cohorts during a period of 30 years." Gerodontology **32**(3): 202-210.

61 Lago, M. L., et al. (2015). "The influence of hormone replacement therapy on the salivary flow of post-menopausal women." Gynecol Endocrinol **31**(2): 109-112.

62 Oyetola, E. O., et al. (2015). "Salivary Flow Rates of Nigerian Patients with Chronic Kidney Disease: A Case-control Study." J Contemp Dent Pract **16**(4): 264-269.

63 Peric, T., et al. (2015). "Efficacy of pastes containing CPP-ACP and CPP-ACFP in patients with Sjogren's syndrome." Clin Oral Investig **19**(9): 2153-2165.

64 Rahnama, M., et al. (2015). "Analysis of the influence of parenteral cancer chemotherapy on the health condition of oral mucosa." Contemp Oncol (Pozn) **19**(1): 77-82.

65 Agha-Hosseini, F., et al. (2016). "Evaluation of Xerostomia and salivary flow rate in Hashimoto's Thyroiditis." Med Oral Patol Oral Cir Bucal **21**(1): e1-5.

66 Dalodom, S., et al. (2016). "Influence of oral moisturizing jelly as a saliva substitute for the relief of xerostomia in elderly patients with hypertension and diabetes mellitus." Geriatr Nurs **37**(2): 101-109.

67 Han, G., et al. (2016). "A randomized, double-blind, placebo-controlled trial of a traditional herbal formula, Yukmijihwang-tang in elderly subjects with xerostomia." J Ethnopharmacol **182**: 160-169.

68 Iwasaki, M., et al. (2016). "Hyposalivation and dietary nutrient intake among community-based older Japanese." Geriatr Gerontol Int **16**(4): 500-507.

69 Klein Hesselink, E. N., et al. (2016). "Effects of Radioiodine Treatment on Salivary Gland Function in Patients with Differentiated Thyroid Carcinoma: A Prospective Study." J Nucl Med **57**(11): 1685-1691.

70 Marangoni-Lopes, L., et al. (2016). "Radiotherapy changes salivary properties and impacts quality of life of children with Hodgkin disease." Arch Oral Biol **72**: 99-105.

71 Singh, B., et al. (2016). "Evaluation of serum calcium and serum parathyroid levels in post-menopausal women with and without oral dryness." Gerodontology **33**(2): 240-246.

72 Al-Janaby, H., et al. (2017). "Xerostomia and Salivary Gland Hypofunction in Patients with Oral Lichen Planus Before and After Treatment with Topical Corticosteroids." Open Dent J **11**: 155-163.

73 Almstahl, A., et al. (2018). "Explorative study on mucosal and major salivary secretion rates, caries and plaque microflora in head and neck cancer patients." Int J Dent Hyg **16**(4): 450-458.

74 Barbe, A. G., et al. (2018). "Efficacy of GUM(R) Hydral versus Biotene(R) Oralbalance mouthwashes plus gels on symptoms of medication-induced xerostomia: a randomized, double-blind, crossover study." Clin Oral Investig **22**(1): 169-180.

75 Dubey, S., et al. (2018). "A comparative evaluation of dental caries status and salivary properties of children aged 5-14 years undergoing treatment for acute lymphoblastic leukemia, type I diabetes mellitus, and asthma - In vivo." J Indian Soc Pedod Prev Dent **36**(3): 283-289.

76 Iwasaki, M., et al. (2018). "Hyposalivation and 10-year all-cause mortality in an elderly Japanese population." Gerodontology **35**(2): 87-94.

77 Jager, D. H. J., et al. (2018). "Clinical oral dryness score: evaluation of a new screening method for oral dryness." Odontology **106**(4): 439-444.

78 Karagozoglu, K. H., et al. (2018). "Sialendoscopy enhances salivary gland function in Sjogren's syndrome: a 6-month follow-up, randomised and controlled, single blind study." Ann Rheum Dis **77**(7): 1025-1031.

79 Niklander, S., et al. (2018). "Impact of 1% malic acid spray on the oral health-related quality of life of patients with xerostomia." J Oral Sci **60**(2): 278-284.

80 Sherlock, S., et al. (2018). "Hyperbaric oxygen treatment for the management of radiation-induced xerostomia." J Med Imaging Radiat Oncol **62**(6): 841-846.

81 Sorensen, C. E., et al. (2018). "Hyposalivation and Poor Dental Health Status Are Potential Correlates of Age-Related Cognitive Decline in Late Midlife in Danish Men." Front Aging Neurosci **10**: 10.

82 Tiisanoja, A., et al. (2018). "Anticholinergic burden and dry mouth among Finnish, community-dwelling older adults." Gerodontology **35**(1): 3-10.

83 Wibawa, A., et al. (2018). "Low-Level Laser Therapy to the Major Salivary Glands Increases Salivary Flow and MUC5B Protein Secretion in Diabetic Patients with Hyposalivation: A Preliminary Study." Makara Journal of Health Research **22**.

84 Almstahl, A., et al. (2019). "Explorative study on quality of life in relation to salivary secretion rate in head and neck cancer patients treated with radiotherapy up to 2 years post treatment." Int J Dent Hyg **17**(1): 46-54.

85 Assy, Z., et al. (2020). "Regional differences in perceived oral dryness as determined with a newly developed questionnaire, the Regional Oral Dryness Inventory." Clin Oral Investig **24**(11): 4051-4060.

86 Goldinova, A., et al. (2020). "Oral health and salivary function in ulcerative colitis patients." United European Gastroenterol J **8**(9): 1067-1075.

87 Levrini, L., et al. (2020). "The Efficacy of a Dietary Supplement with Carnosine and Hibiscus Sabdariffa L. (AqualiefTM) in Patients with Xerostomia: a Randomized, Placebo-Controlled, Double-Blind Trial." Clin Ter **171**(4): e295-e301.

88 Serrano, J., et al. (2020). "Risk factors related to oral candidiasis in patients with primary Sjogren's syndrome." Med Oral Patol Oral Cir Bucal **25**(5): e700-e705.

89 Alvarino, C., et al. (2021). "Stimulated whole salivary flow rate: The most appropriate technique for assessing salivary flow in Sjogren syndrome." Med Oral Patol Oral Cir Bucal **26**(3): e404-e407.

90 Marin, C., et al. (2021). "Interventions for the treatment of xerostomia: A randomized controlled clinical trial." J Clin Exp Dent **13**(2): e104-e111.

91 Vinke, J., et al. (2021). "Lubricating properties of chewing stimulated whole saliva from patients suffering from xerostomia." Clin Oral Investig **25**(7): 4459-4469.

92 Ludwar, L., et al. (2022). "Oil pulling to relieve medication-induced xerostomia: A randomized, single-blind, crossover trial." Oral Dis **28**(2): 373-383.

93 Chainani-Wu, N., et al. (2006). "Assessment of the use of sialogogues in the clinical management of patients with xerostomia." Spec Care Dentist **26**(4): 164-170.

94 Maeda, M. (2006). "Dermoscopic patterns of the filiform papillae of the tongue in patients with Sjogren's syndrome." J Dermatol **33**(2): 96-102.

95 Kam, M. K., et al. (2007). "Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients." J Clin Oncol **25**(31): 4873-4879.

96 Torres, S. R., et al. (2007). "A prospective randomized trial to reduce oral Candida spp. colonization in patients with hyposalivation." Braz Oral Res **21**(2): 182-187.

97 Hayashi, Y., et al. (2014). "Terminal RFLP analysis to determine the oral microbiota with hyposalivation." Arch Microbiol **196**(7): 489-496.

98 Ryo, K., et al. (2014). "Therapeutic effects of isoflavones on impaired salivary secretion." J Clin Biochem Nutr **55**(3): 168-173.

99 Kimori, H., et al. (2015). "Factors associated with the presence of atrophic tongue in patients with dry mouth." Gerodontology **32**(1): 13-17.

100 Pendersen, C. (2015). "The EHR in the room." Nursing **45**(5): 8.

101 Tanigawa, T., et al. (2015). "Efficacy and safety of pilocarpine mouthwash in elderly patients with xerostomia." Spec Care Dentist **35**(4): 164-169.

102 Wang, Z., et al. (2016). "Minor salivary glands function is decreased in hyposalivation-related diseases." Arch Oral Biol **69**: 63-70.

103 Edens, M. H., et al. (2018). "Impact of salivary hypofunction on incidence of orofungal infections with use of topical steroids for management of oral lichen planus and xerostomia." Oral Surg Oral Med Oral Pathol Oral Radiol **126**(6): 501-505.

104 Ichiyama, T., et al. (2018). "Expression of aquaporin 3 and 5 as a potential marker for distinguishing dry mouth from Sjogren's syndrome." J Oral Sci **60**(2): 212-220.

105 Jose, A., et al. (2018). "A randomized controlled study to evaluate an experimental moisturizing mouthwash formulation in participants experiencing dry mouth symptoms." Oral Surg Oral Med Oral Pathol Oral Radiol **126**(3): 231-239 e235.

106 Choi, J. H., et al. (2021). "Oral health-related quality of life and associated factors in patients with xerostomia." Int J Dent Hyg **19**(3): 313-322.

107 Jham, B. C., et al. (2007). "A randomized phase III prospective trial of bethanechol to prevent radiotherapy-induced salivary gland damage in patients with head and neck cancer." Oral Oncol **43**(2): 137-142.

108 Marques, P. L., et al. (2015). "Hemodialysis-specific factors associated with salivary flow rates." Artif Organs **39**(2): 181-186.

109 Falcao, D. P., et al. (2014). "Sialometry of upper labial minor glands: a clinical approach by the use of weighing method Schirmer's test strips paper." ScientificWorldJournal **2014**: 268634.

110 Pereira, R. M. S., et al. (2020). "Topical pilocarpine for xerostomia in patients with head and neck cancer treated with radiotherapy." Oral Dis.

111 Xin, W., et al. (2020). "Sicca Symptoms, Oral Health Conditions, Salivary Flow and Oral Candida in Sjogren's Syndrome Patients." Int J Environ Res Public Health **17**(10).

112 Lopez-Jornet, P., et al. (2006). "A simple test for salivary gland hypofunction using Oral Schirmer's test." J Oral Pathol Med **35**(4): 244-248.

113 Chambers, M. S., et al. (2007). "Cevimeline for the treatment of post irradiation xerostomia in patients with head and neck cancer." Int J Radiat Oncol Biol Phys **68**(4): 1102-1109.

114 Scrimger, R., et al. (2007). "Correlation between saliva production and quality of life measurements in head and neck cancer patients treated with intensity-modulated radiotherapy." Am J Clin Oncol **30**(3): 271-277.

115 da Silva Marques, D. N., et al. (2011). "Effects of gustatory stimulants of salivary secretion on salivary pH and flow in patients with Sjogren's syndrome: a randomized controlled trial." J Oral Pathol Med **40**(10): 785-792.

116 Minicucci, E. M., et al. (2013). "Assessing the impact of menopause on salivary flow and xerostomia." Aust Dent J **58**(2): 230-234.

117 Knas, M., et al. (2014). "Salivary: flow and proteins of the innate and adaptive immunity in the limited and diffused systemic sclerosis." J Oral Pathol Med **43**(7): 521-529.

118 Alpoz, E., et al. (2015). "Impact of Buccotherm(R) on xerostomia: a single blind study." Spec Care Dentist **35**(1): 1-7.

119 Bhayani, M. K., et al. (2015). "Sialendoscopy for Patients with Radioiodine-Induced Sialadenitis and Xerostomia." Thyroid **25**(7): 834-838.

120 Wong, R. K., et al. (2015). "Acupuncture-Like Transcutaneous Electrical Nerve Stimulation Versus Pilocarpine in Treating Radiation-Induced Xerostomia: Results of RTOG 0537 Phase 3 Study." Int J Radiat Oncol Biol Phys **92**(2): 220-227.

121 Owosho, A. A., et al. (2017). "The role of parotid gland irradiation in the development of severe hyposalivation (xerostomia) after intensity-modulated radiation therapy for head and neck cancer: Temporal patterns, risk factors, and testing the QUANTEC guidelines." J Craniomaxillofac Surg **45**(4): 595-600.

122 Brzak, B. L., et al. (2018). "Different Protocols of Photobiomodulation Therapy of Hyposalivation." Photomed Laser Surg **36**(2): 78-82.

123 Fisher, B. A., et al. (2018). "Effect of rituximab on a salivary gland ultrasound score in primary Sjogren's syndrome: results of the TRACTISS randomised double-blind multicentre substudy." Ann Rheum Dis **77**(3): 412-416.

124 Fidelix, T., et al. (2018). "Low-level laser therapy for xerostomia in primary Sjogren's syndrome: a randomized trial." Clin Rheumatol **37**(3): 729-736.

125 Scrimger, R. A., et al. (2018). "Combination of submandibular salivary gland transfer and intensity-modulated radiotherapy to reduce dryness of mouth (xerostomia) in patients with head and neck cancer." Head Neck **40**(11): 2353-2361.

126 Asif, M., et al. (2020). "The effect of radiotherapy on taste sensation in head and neck cancer patients - a prospective study." Radiat Oncol **15**(1): 144.

127 Lan, X., et al. (2020). "Saliva electrolyte analysis and xerostomia-related quality of life in nasopharyngeal carcinoma patients following intensity-modulated radiation therapy." Radiother Oncol **150**: 97-103.

128 Wilkie, J. R., et al. (2020). "Predicting late radiation-induced xerostomia with parotid gland PET biomarkers and dose metrics." Radiother Oncol **148**: 30-37.

129 Basakci Calik, B., et al. (2021). "Translation and validation of a Turkish version of the Xerostomia Inventory XI in patients with primary Sjogren's syndrome." Turk J Med Sci **51**(5): 2477-2484.

130 Kohler, P.F. and Winter, M.E., 1985. A quantitative test for xerostomia. The Saxon test, an oral equivalent of the Schirmer test. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *28*(10), pp.1128-1132.

131 Gornitsky, M., et al. (2004). "Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **98**(1): 45-52.

132 Kamishima, T. (2005). "Chemical shift MR images of the parotid gland in Sjogren's syndrome utilizing low-field MR system comparison with MR sialography and salivary secretion function." Radiat Med **23**(4): 277-282.

133 Kovacs, L., et al. (2005). "Clinical associations of autoantibodies to human muscarinic acetylcholine receptor 3(213-228) in primary Sjogren's syndrome." Rheumatology (Oxford) **44**(8): 1021-1025.

134 Nishiyama, S., et al. (2006). "A study to standardize quantitative evaluation of parotid gland scintigraphy in patients with Sjogren's syndrome." J Rheumatol **33**(12): 2470-2474.

135 Ohyama, K., et al. (2015). "Saliva as a potential tool for diagnosis of dry mouth including Sjogren's syndrome." Oral Dis **21**(2): 224-231.

136 Rogus-Pulia, N. M., et al. (2016). "Effects of Change in Tongue Pressure and Salivary Flow Rate on Swallow Efficiency Following Chemoradiation Treatment for Head and Neck Cancer." Dysphagia **31**(5): 687-696.

137 Saleem, M., et al. (2019). "Improvement of salivary flow and oral wetness by a lip trainer device and sonic toothbrush in older Japanese men and women with dry mouth." J Oral Sci **61**(2): 221-228.

138 Ushikoshi-Nakayama, R., et al. (2019). "Effect of gummy candy containing ubiquinol on secretion of saliva: A randomized, double-blind, placebo-controlled parallel-group comparative study and an in vitro study." PLoS One **14**(4): e0214495.

139 Ono Minagi, H., et al. (2020). "Evaluation of the Saxon test for patients with hyposalivation without Sjögren's syndrome." J Oral Rehabil **47**(12): 1550-1556.

140 Springborg, L. K. and M. N. Moller (2013). "Submandibular gland excision: long-term clinical outcome in 139 patients operated in a single institution." Eur Arch Otorhinolaryngol **270**(4): 1441-1446.

141 Lakshman, A. R., et al. (2015). "Evaluation of effect of transcutaneous electrical nerve stimulation on salivary flow rate in radiation induced xerostomia patients: a pilot study." J Cancer Res Ther **11**(1): 229-233.

142 Sung, J. M., et al. (2005). "Decreased salivary flow rate as a dipsogenic factor in hemodialysis patients: evidence from an observational study and a pilocarpine clinical trial." J Am Soc Nephrol **16**(11): 3418-3429.

143 St Clair, E. W., et al. (2013). "Rituximab therapy for primary Sjogren's syndrome: an open-label clinical trial and mechanistic analysis." Arthritis Rheum **65**(4): 1097-1106.

144 Kerr, A. R., et al. (2007). "A comparison of the effects of 2 commercially available nonprescription mouthrinses on salivary flow rates and xerostomia." Quintessence Int **38**(8): e440-447.

145 Fox, P. C., et al. (2001). "Use of orally administered anhydrous crystalline maltose for relief of dry mouth." J Altern Complement Med **7**(1): 33-43.

146 Frydrych, A. M., et al. (2002). "An investigation into the use of pilocarpine as a sialagogue in patients with radiation induced xerostomia." Aust Dent J **47**(3): 249-253.

147 Eguia Del Valle, A., et al. (2003). "Burning mouth syndrome in the Basque Country: a preliminary study of 30 cases." Med Oral **8**(2): 84-90.

148 Navazesh, M., et al. (2003). "A 4-year longitudinal evaluation of xerostomia and salivary gland hypofunction in the Women's Interagency HIV Study participants." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **95**(6): 693-698.

149 Dawes, C. and O. Odlum (2004). "Salivary status in patients treated for head and neck cancer." J Can Dent Assoc **70**(6): 397-400.

150 Gorsky, M., et al. (2004). "The efficacy of pilocarpine and bethanechol upon saliva production in cancer patients with hyposalivation following radiation therapy." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **97**(2): 190-195.

151 Flink, H., et al. (2005). "Influence of the time of measurement of unstimulated human whole saliva on the diagnosis of hyposalivation." Arch Oral Biol **50**(6): 553-559.

152 Nagler, R. M. and O. Hershkovich (2005). "Age-related changes in unstimulated salivary function and composition and its relations to medications and oral sensorial complaints." Aging Clin Exp Res **17**(5): 358-366.

153 Yalcin, F., et al. (2005). "The effect of menopause, hormone replacement therapy (HRT), alendronate (ALN), and calcium supplements on saliva." J Contemp Dent Pract **6**(2): 10-17.

154 Baker, S. R., et al. (2006). "Utility of two oral health-related quality-of-life measures in patients with xerostomia." Community Dent Oral Epidemiol **34**(5): 351-362.

155 Flink, H., et al. (2006). "Effect of oral iron supplementation on unstimulated salivary flow rate: a randomized, double-blind, placebo-controlled trial." J Oral Pathol Med **35**(9): 540-547.

156 Taweechaisupapong, S., et al. (2006). "Efficacy of pilocarpine lozenge for post-radiation xerostomia in patients with head and neck cancer." Aust Dent J **51**(4): 333-337.

157 Veerasarn, V., et al. (2006). "Effect of Amifostine to prevent radiotherapy-induced acute and late toxicity in head and neck cancer patients who had normal or mild impaired salivary gland function." J Med Assoc Thai **89**(12): 2056-2067.

158 Aframian, D. J., et al. (2007). "Pilocarpine treatment in a mixed cohort of xerostomic patients." Oral Dis **13**(1): 88-92.

159 Baker, S. R., et al. (2007). "Testing relationships between clinical and non-clinical variables in xerostomia: a structural equation model of oral health-related quality of life." Qual Life Res **16**(2): 297-308.

160 Gibson, J., et al. (2007). "A controlled release pilocarpine buccal insert in the treatment of Sjogren's syndrome." Br Dent J **202**(7): E17; discussion 404-405.

161 Nagy, K., et al. (2007). "Controlled study of lactoperoxidase gel on oral flora and saliva in irradiated patients with oral cancer." J Craniofac Surg **18**(5): 1157-1164..

162 Suh, K. I., et al. (2007). "Relationship between salivary flow rate and clinical symptoms and behaviours in patients with dry mouth." J Oral Rehabil **34**(10): 739-744.

163 Blazer, T., et al. (2008). "Salivary and gustatory alterations among bulimia nervosa patients." Eur J Clin Nutr **62**(7): 916-922.

164 Oh, D. J., et al. (2008). "Effects of carboxymethylcellulose (CMC)-based artificial saliva in patients with xerostomia." Int J Oral Maxillofac Surg **37**(11): 1027-1031.

165 Khosravani, N., et al. (2009). "The cholinesterase inhibitor physostigmine for the local treatment of dry mouth: a randomized study." Eur J Oral Sci **117**(3): 209-217.

166 Aliko, A., et al. (2010). "Sicca symptoms, and lacrimal and salivary flow in Albanian patients with rheumatoid arthritis." J Oral Pathol Med **39**(8): 651-656.

167 Borges, B. C., et al. (2010). "Xerostomia and hyposalivation: a preliminary report of their prevalence and associated factors in Brazilian elderly diabetic patients." Oral Health Prev Dent **8**(2): 153-158.

168 Cho, M. A., et al. (2010). "Salivary flow rate and clinical characteristics of patients with xerostomia according to its aetiology." J Oral Rehabil **37**(3): 185-193.

169 Wiener, R. C., et al. (2010). "Hyposalivation and xerostomia in dentate older adults." J Am Dent Assoc **141**(3): 279-284.

170 Jaguar, G. C., et al. (2010). "Impact of submandibular gland excision on salivary gland function in head and neck cancer patients." Oral Oncol **46**(5): 349-354.

171 Lofgren, C. D., et al. (2010). "Screening for oral dryness in relation to salivary flow rate addresses the need for functional tests of saliva." Oral Health Prev Dent **8**(3): 243-252.

172 Singh, M., et al. (2010). "Effect of omega-3 and vitamin E supplementation on dry mouth in patients with Sjogren's syndrome." Spec Care Dentist **30**(6): 225-229.

173 Scelza, M. F., et al. (2010). "The influence of medication on salivary flow of the elderly: preliminary study." Gerodontology **27**(4): 278-282.

174 Braga, F. P., et al. (2011). "Acupuncture for the prevention of radiation-induced xerostomia in patients with head and neck cancer." Braz Oral Res **25**(2): 180-185.

175 Femiano, F., et al. (2011). "A comparison of salivary substitutes versus a natural sialogogue (citric acid) in patients complaining of dry mouth as an adverse drug reaction: a clinical, randomized controlled study." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **112**(1): e15-20.

176 Lopez-Jornet, M. P., et al. (2011). "Clinical and antimicrobial evaluation of a mouthwash and toothpaste for xerostomia: a randomized, double-blind, crossover study." J Dent **39**(11): 757-763.

177 Osailan, S., et al. (2011). "Investigating the relationship between hyposalivation and mucosal wetness." Oral Dis **17**(1): 109-114.

178 Tiwana, M. S., et al. (2011). "Whole saliva physico-biochemical changes and quality of life in head and neck cancer patients following conventional radiation therapy: a prospective longitudinal study." Indian J Cancer **48**(3): 289-295.

179 Agha-Hosseini, F. and I. Mirzaii-Dizgah (2012a). "Unstimulated saliva 17beta-estradiol and xerostomia in menopause." Gynecol Endocrinol **28**(3): 199-202.

180 Agha-Hosseini, F. and I. Mirzaii-Dizgah (2012b). "Serum and saliva magnesium in postmenopausal women with xerostomia." Climacteric **15**(5): 496-499.

181 Aliko, A., et al. (2012). "Evaluation of the clinical efficacy of Biotene Oral Balance in patients with secondary Sjogren's syndrome: a pilot study." Rheumatol Int **32**(9): 2877-2881.

182 Alajbeg, I., et al. (2012). "Intraoral electrostimulator for xerostomia relief: a long-term, multicenter, open-label, uncontrolled, clinical trial." Oral Surg Oral Med Oral Pathol Oral Radiol **113**(6): 773-781.

183 da Mata, A. D., et al. (2012). "Translation, validation, and construct reliability of a Portuguese version of the Xerostomia Inventory." Oral Dis **18**(3): 293-298.

184 Marucci, L., et al. (2012). "Influence of intensity-modulated radiation therapy technique on xerostomia and related quality of life in patients treated with intensity-modulated radiation therapy for nasopharyngeal cancer." Head Neck **34**(3): 328-335.

185 Meng, Z., et al. (2012). "Randomized controlled trial of acupuncture for prevention of radiation-induced xerostomia among patients with nasopharyngeal carcinoma." Cancer **118**(13): 3337-3344.

186 Morales-Bozo, I., et al. (2012). "Evaluation of the efficacy of two mouthrinses formulated for the relief of xerostomia of diverse origin in adult subjects." Gerodontology **29**(2): e1103-1112.

187 Abbasi, F., et al. (2013). "Efficacy of Pilocarpine and Bromhexine in Improving Radiotherapy-induced Xerostomia." J Dent Res Dent Clin Dent Prospects **7**(2): 86-90.

188 Agha-Hosseini, F., et al. (2013a). "Unstimulated whole saliva 25-hydroxycholecalciferol in patients with xerostomia in menopausal women." Aging Clin Exp Res **25**(2): 147-151.

189 Agha-Hosseini, F., et al. (2013b). "Salivary flow, testosterone, and femur bone mineral density in menopausal women with oral dryness feeling." Oral Surg Oral Med Oral Pathol Oral Radiol **115**(5): 612-616.

190 Altarawneh, S., et al. (2013). "Clinical and histological findings of denture stomatitis as related to intraoral colonization patterns of Candida albicans, salivary flow, and dry mouth." J Prosthodont **22**(1): 13-22.

191 Brimhall, J., et al. (2013). "Efficacy of cevimeline vs. pilocarpine in the secretion of saliva: a pilot study." Spec Care Dentist **33**(3): 123-127.

192 Cho, H. J., et al. (2013). "The EULAR Sjogren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjogren's syndrome patients: in comparison with non-Sjogren's sicca patients." Rheumatology (Oxford) **52**(12): 2208-2217.

193 Daikeler, T., et al. (2013). "Sicca symptoms and their impact on quality of life among very long-term survivors after hematopoietic SCT." Bone Marrow Transplant **48**(7): 988-993.

194 Fan, W. F., et al. (2013). "Study on the clinical significance and related factors of thirst and xerostomia in maintenance hemodialysis patients." Kidney Blood Press Res **37**(4-5): 464-474.

195 Juusela, P., et al. (2013). "Xerostomia in hereditary gelsolin amyloidosis." Amyloid **20**(1): 39-44.

196 Kaushik, A., et al. (2013). "Oral and salivary changes among renal patients undergoing hemodialysis: A cross-sectional study." Indian J Nephrol **23**(2): 125-129.

197 Mortensen, H. R., et al. (2013). "Late dysphagia after IMRT for head and neck cancer and correlation with dose-volume parameters." Radiother Oncol **107**(3): 288-294.

198 Nittayananta, W., et al. (2013). "Relationship between xerostomia and salivary flow rates in HIV-infected individuals." J Investig Clin Dent **4**(3): 164-171.

199 Oton-Leite, A. F., et al. (2013). "Effect of low level laser therapy in the reduction of oral complications in patients with cancer of the head and neck submitted to radiotherapy." Spec Care Dentist **33**(6): 294-300.

200 Pavithra, S., et al. (2013). "Impact of highly active antiretroviral therapy on salivary flow in patients with human-immuno deficiency virus disease in Southern India." J Oral Maxillofac Pathol **17**(1): 17-22.

201 Zalewska, A., et al. (2013). "Rheumatoid arthritis patients with xerostomia have reduced production of key salivary constituents." Oral Surg Oral Med Oral Pathol Oral Radiol **115**(4): 483-490.

202 Artico, G., et al. (2014). "Prevalence of Candida spp., xerostomia, and hyposalivation in oral lichen planus--a controlled study." Oral Dis **20**(3): e36-41.

203 De Rossi, S. S., et al. (2014). "A phase II clinical trial of a natural formulation containing tea catechins for xerostomia." Oral Surg Oral Med Oral Pathol Oral Radiol **118**(4): 447-454.e443.

204 Fujimaki, Y., et al. (2014). "Non-invasive objective evaluation of radiotherapy-induced dry mouth." J Oral Pathol Med **43**(2): 97-102.

205 Gomes, A. O. F., et al. (2014). "Early and late oral features of chronic graft-versus-host disease." Revista Brasileira de Hematologia e Hemoterapia **36**(1): 43-49.

206 Kim, J. H., et al. (2014). "Effect of 0.1% pilocarpine mouthwash on xerostomia: double-blind, randomised controlled trial." J Oral Rehabil **41**(3): 226-235.

207 Kolnick, L., et al. (2014). "Associations of oral health items of the Vanderbilt Head and Neck Symptom Survey with a dental health assessment." Oral Oncol **50**(2): 135-140.

208 Malicka, B., et al. (2014). "Prevalence of xerostomia and the salivary flow rate in diabetic patients." Adv Clin Exp Med **23**(2): 225-233.

209 Nemeth, O., et al. (2014). "Late effects of multiagent chemotherapy on salivary secretion in children cancer survivors." J Am Coll Nutr **33**(3): 186-191.

210 Saleh, J., et al. (2014). "Effect of low-level laser therapy on radiotherapy-induced hyposalivation and xerostomia: a pilot study." Photomed Laser Surg **32**(10): 546-552.

211 Aitken-Saavedra, J., et al. (2015). "Salivary gland dysfunction markers in type 2 diabetes mellitus patients." J Clin Exp Dent **7**(4): e501-505.

212 Cafaro, A., et al. (2015). "Effect of laser acupuncture on salivary flow rate in patients with Sjogren's syndrome." Lasers Med Sci **30**(6): 1805-1809.

213 Chaudhury, N. M., et al. (2015). "Changes in Saliva Rheological Properties and Mucin Glycosylation in Dry Mouth." J Dent Res **94**(12): 1660-1667.

214 Cunha, K. S., et al. (2015). "High prevalence of hyposalivation in individuals with neurofibromatosis 1: a case-control study." Orphanet J Rare Dis **10**: 24.

215 Jeppesen, J., et al. (2015). "Changes in salivary secretion and sense of taste following cochlear implantation: a prospective study." Acta Otolaryngol **135**(6): 578-585.

216 Leite, C. A., et al. (2015). "Prevalence of hyposalivation in patients with systemic lupus erythematosus in a brazilian subpopulation." Int J Rheumatol **2015**: 730285.

217 Ohara, Y., et al. (2015). "Effectiveness of an oral health educational program on community-dwelling older people with xerostomia." Geriatr Gerontol Int **15**(4): 481-489.

218 Chaudhury, N. M., et al. (2016). "Reduced Mucin-7 (Muc7) Sialylation and Altered Saliva Rheology in Sjogren's Syndrome Associated Oral Dryness." Mol Cell Proteomics **15**(3): 1048-1059.

219 Dabić, D., et al. (2016). "The Effectiveness of Acupuncture in Drug-Induced Hyposalivation." Research Journal of Pharmaceutical, Biological and Chemical Sciences **7**: 543.

220 Glazar, I., et al. (2016). "Salivary Flow Rate, Oral Yeast Colonization and Dental Status in Institutionalized and Non-Institutionalized Elderly." Acta Clin Croat **55**(3): 390-395.

221 Gueimonde, L., et al. (2016). "Supplementation of xylitol-containing chewing gum with probiotics: a double blind, randomised pilot study focusing on saliva flow and saliva properties." Food Funct **7**(3): 1601-1609.

222 Hajiabbasi A, S. M. I., Alizadeh Y, Banikarimi AS, Ghavidel Parsa P. (2016). "Secondary Sjogren's Syndrome in 83 Patients With Rheumatoid Arthritis." Acta Med Iran **54**: 448-453.

223 Imura, H., et al. (2016). "Characteristic changes of saliva and taste in burning mouth syndrome patients." J Oral Pathol Med **45**(3): 231-236.

224 Kaae, J. K., et al. (2016). "Xerostomia after Radiotherapy for Oral and Oropharyngeal Cancer: Increasing Salivary Flow with Tasteless Sugar-free Chewing Gum." Front Oncol **6**: 111.

225 Kim, Y. M., et al. (2016). "Salivary gland function after sialendoscopy for treatment of chronic radioiodine-induced sialadenitis." Head Neck **38**(1): 51-58.

226 Kogawa, E. M., et al. (2016). "Salivary function impairment in type 2 Diabetes patients associated with concentration and genetic polymorphisms of chromogranin A." Clin Oral Investig **20**(8): 2083-2095.

227 Lopez-Jornet, P., et al. (2016). "Sleep quality in patients with xerostomia: a prospective and randomized case-control study." Acta Odontol Scand **74**(3): 224-228.

228 Terlevic Dabic, D., et al. (2016). "The Effectiveness of Low-Level Laser Therapy in Patients with Drug-Induced Hyposalivation: A Pilot Study." Photomed Laser Surg **34**(9): 389-393.

229 Ahmad, M. S., et al. (2017). "The Impact of Hyposalivation on Quality of Life (QoL) and Oral Health in the Aging Population of Al Madinah Al Munawarrah." Int J Environ Res Public Health **14**(4).

230 Cotomacio, C., et al. (2017). "Influence of bethanechol on salivary parameters in irradiated patients." Med Oral Patol Oral Cir Bucal **22**(1): e76-e83.

231 Epstein, J. B., et al. (2017). "Management of dry mouth: assessment of oral symptoms after use of a polysaccharide-based oral rinse." Oral Surg Oral Med Oral Pathol Oral Radiol **123**(1): 76-83.

232 Martin, M., et al. (2017). "Products based on olive oil, betaine, and xylitol in the post-radiotherapy xerostomia." Rep Pract Oncol Radiother **22**(1): 71-76.

233 Morales-Bozo, I., et al. (2017). "Evaluation of the effectiveness of a chamomile (Matricaria chamomilla) and linseed (Linum usitatissimum) saliva substitute in the relief of xerostomia in elders." Gerodontology **34**(1): 42-48.

234 Navarro Morante, A., et al. (2017). "Natural products for the management of xerostomia: a randomized, double-blinded, placebo-controlled clinical trial." J Oral Pathol Med **46**(2): 154-160.

235 Palma, L. F., et al. (2017). "Impact of low-level laser therapy on hyposalivation, salivary pH, and quality of life in head and neck cancer patients post-radiotherapy." Lasers Med Sci **32**(4): 827-832.

236 Gronhoj, C., et al. (2018). "Safety and Efficacy of Mesenchymal Stem Cells for Radiation-Induced Xerostomia: A Randomized, Placebo-Controlled Phase 1/2 Trial (MESRIX)." Int J Radiat Oncol Biol Phys **101**(3): 581-592.

237 Kimura-Hayama, E., et al. (2018). "Elastographic ultrasound: an additional image tool in Sjogren's syndrome." Int J Rheum Dis **21**(6): 1293-1300.

238 Muralidharan, J., et al. (2018). "Comparison of pilocarpine and bethanechol as effective sialogogue agents in xerostomic completely edentulous patients." Drug Invention Today **10**: 958-961.

239 Palma, L. F., et al. (2018). "A novel method to evaluate salivary flow rates of head and neck cancer patients after radiotherapy: a pilot study." Braz J Otorhinolaryngol **84**(2): 227-231.

240 St Clair, E. W., et al. (2018). "Clinical Efficacy and Safety of Baminercept, a Lymphotoxin beta Receptor Fusion Protein, in Primary Sjogren's Syndrome: Results From a Phase II Randomized, Double-Blind, Placebo-Controlled Trial." Arthritis Rheumatol **70**(9): 1470-1480.

241 Takesh, T., et al. (2018). "Effects of a Novel Formulation on Oral Biofilm, pH Buffering, and Gingival Health in Patients with Dry Mouth." Int J Dent **2018**: 2748274.

242 Wolff, A., et al. (2018). "Electrostimulation of the lingual nerve by an intraoral device may lead to salivary gland regeneration: A case series study." Med Oral Patol Oral Cir Bucal **23**(5): e552-e559.

243 Aframian, D. J., et al. (2019). "Improvement of dry mouth following intraductal irrigation of salivary glands." Oral Dis **25**(7): 1735-1743.

244 Barbe, A. G., et al. (2019). "Efficacy of a newly developed mouth gel for xerostomia relief-A randomized double-blind trial." Oral Dis **25**(6): 1519-1529.

245 Farag, A. M., et al. (2019). "Comparing the effectiveness and adverse effects of pilocarpine and cevimeline in patients with hyposalivation." Oral Dis **25**(8): 1937-1944.

246 Lopez-Pintor, R. M., et al. (2019). "Effects of Xerostom((R)) products on xerostomia in primary Sjogren's syndrome: A randomized clinical trial." Oral Dis **25**(3): 772-780.

247 Teng, F., et al. (2019). "Reducing Xerostomia by Comprehensive Protection of Salivary Glands in Intensity-Modulated Radiation Therapy with Helical Tomotherapy Technique for Head-and-Neck Cancer Patients: A Prospective Observational Study." Biomed Res Int **2019**: 2401743.

248 Fernandez-Martinez, G., et al. (2020). "Oral health-related quality of life in primary Sjogren's syndrome." Reumatol Clin (Engl Ed) **16**(2 Pt 1): 92-96.

249 Flink, H., et al. (2020). "Self-reported oral and general health related to xerostomia, hyposalivation, and quality of life among caries active younger adults." Acta Odontol Scand **78**(3): 229-235.

250 Kaae, J. K., et al. (2020). "A randomized phase III trial for alleviating radiation-induced xerostomia with chewing gum." Radiother Oncol **142**: 72-78.

251 Lacombe, V., et al. (2020). "Unstimulated whole saliva flow for diagnosis of primary Sjogren's syndrome: time to revisit the threshold?" Arthritis Res Ther **22**(1): 38.

252 Martinez, A. C., et al. (2020). "Late Oral Complications Caused by Head and Neck Radiotherapy: Clinical and Laboratory Study." J Oral Maxillofac Res **11**(3): e3.

253 Riabushko, N. A. (2020). "Methods of salivation reduction assessment at a dental appointment." Wiad Lek **73**(6): 1264-1266.

254 Fallon, B. S., et al. (2021). "The use of BokaFlo instrument to measure salivary flow." BMC Oral Health **21**(1): 191.

255 Karagozoglu, K. H., et al. (2021). "Sialendoscopy increases saliva secretion and reduces xerostomia up to 60 weeks in Sjogren's syndrome patients: a randomized controlled study." Rheumatology (Oxford) **60**(3): 1353-1363.

256 Menezes, A., et al. (2021). "The combination of traditional and auricular acupuncture to prevent xerostomia and anxiety in irradiated patients with HNSCC: a preventive, parallel, single-blind, 2-arm controlled study." Oral Surg Oral Med Oral Pathol Oral Radiol **131**(6): 675-683.

257 Ozen, N., et al. (2021). "The effect of chewing gum on dry mouth, interdialytic weight gain, and intradialytic symptoms: A prospective, randomized controlled trial." Hemodial Int **25**(1): 94-103.

258 Bots, C. P., et al. (2005). "Chewing gum and a saliva substitute alleviate thirst and xerostomia in patients on haemodialysis." Nephrol Dial Transplant **20**(3): 578-584.

259 Sanchez-Guerrero, J., et al. (2005). "Prevalence of Sjogren's syndrome in ambulatory patients according to the American-European Consensus Group criteria." Rheumatology (Oxford) **44**(2): 235-240.

260 Jen, Y. M., et al. (2006). "Dramatic and prolonged decrease of whole salivary secretion in nasopharyngeal carcinoma patients treated with radiotherapy." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **101**(3): 322-327.

261 Cankaya, H., et al. (2010). "Effects of hydroxychloroquine on salivary flow rates and oral complaints of Sjogren patients: a prospective sample study." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **110**(1): 62-67.

262 Vidovic Juras, D., et al. (2010). "Effects of low-level laser treatment on mouth dryness." Coll Antropol **34**(3): 1039-1043.

263 Jae-Woo Park, B.-J. L., Youngmin Bu, Inkwon Yeo, Jinsung Kim, and Bongha Ryu (2010). "Effects of Korean Red Ginseng on Dry Mouth: A Randomized, Double- Blind, Placebo-Controlled Trial." J. Ginseng Res. **34**(3): 183-191.

264 Gunes, Z., et al. (2012). "The risk factors effecting the dry mouth in inpatients in Hospital in west Anatolia." J Clin Nurs **21**(3-4): 408-414.

265 Kakoei, S., et al. (2012). "Xerostomia after radiotherapy and its effect on quality of life in head and neck cancer patients." Arch Iran Med **15**(4): 214-218.

266 Gomez-Moreno, G., et al. (2013b). "Effectiveness of malic acid 1% in patients with xerostomia induced by antihypertensive drugs." Med Oral Patol Oral Cir Bucal **18**(1): e49-55.

267 Bruzda-Zwiech, A., et al. (2014). "Sodium gradient, xerostomia, thirst and inter-dialytic excessive weight gain: a possible relationship with hyposalivation in patients on maintenance hemodialysis." Int Urol Nephrol **46**(7): 1411-1417.

268 Dugonjić, S., et al. (2014). "Evaluation of diagnostic parameters from parotid and submandibular dynamic salivary glands scintigraphy and unstimulated sialometry in Sjögren's syndrome." Hell J Nucl Med **17**(2): 116-122.

269 Gomez-Moreno, G., et al. (2014). "Evaluation of the efficacy of a topical sialogogue spray containing malic acid 1% in elderly people with xerostomia: a double-blind, randomized clinical trial." Gerodontology **31**(4): 274-280.

270 Kumar, N. N., et al. (2014). "Modified schirmer test--a screening tool for xerostomia among subjects on antidepressants." Arch Oral Biol **59**(8): 829-834.

271 Annette Milton, B., et al. (2015). "Evaluation of Sialometric Analysis of Patients Suffering from Depressive Disorders." Kathmandu Univ Med J (KUMJ) **13**(50): 134-139.

272 Bassim, C. W., et al. (2015). "Oral disease profiles in chronic graft versus host disease." J Dent Res **94**(4): 547-554.

273 Djukic, L. J., et al. (2015). "The effects of anti-hypertensives and type 2 diabetes on salivary flow and total antioxidant capacity." Oral Dis **21**(5): 619-625.

274 Konidena, A., et al. (2016). "Effect of TENS on stimulation of saliva in postmenopausal women with or without oral dryness - An interventional study." J Oral Biol Craniofac Res **6**(Suppl 1): S44-S50.

275 Yu, I. C., et al. (2016). "Effects of mouthwash interventions on xerostomia and unstimulated whole saliva flow rate among hemodialysis patients: A randomized controlled study." Int J Nurs Stud **63**: 9-17.

276 Gonnelli, F. A., et al. (2016). "Low-Level Laser for Mitigation of Low Salivary Flow Rate in Head and Neck Cancer Patients Undergoing Radiochemotherapy: A Prospective Longitudinal Study." Photomed Laser Surg **34**(8): 326-330.

277 Jager, D. J., et al. (2016). "Sialendoscopy of Salivary Glands Affected by Sjogren Syndrome: A Randomized Controlled Pilot Study." J Oral Maxillofac Surg **74**(6): 1167-1174.

278 Chengappa, R. K., et al. (2016). "Utility of two methodologies in the clinical assessment of oral dryness in postmenopausal women." J Midlife Health **7**(3): 114-118.

279 Apperley, O., et al. (2017). "A clinical trial of a novel emulsion for potential use as a saliva substitute in patients with radiation-induced xerostomia." J Oral Rehabil **44**(11): 889-895.

280 Kavitha, M., et al. (2017). "A study on Evaluation of efficacy of bethanechol in the management of chemoradiation-induced xerostomia in oral cancer patients." J Oral Maxillofac Pathol **21**(3): 459-460.

281 Bardellini, E., et al. (2019). "Effectiveness of a spray containing 1% malic acid in patients with xerostomia induced by graft-versus-host disease." Med Oral Patol Oral Cir Bucal **24**(2): e190-e194.

282 Gerdin, E. W., et al. (2005). "Impact of dry mouth conditions on oral health-related quality of life in older people." Gerodontology **22**(4): 219-226.

283 Liquidato, B. M., et al. (2006). "Evaluation of the concordance of sialometry and salivary glands scintigraphy in dry mouth patients." Braz J Otorhinolaryngol **72**(1): 116-119.

284 Simcock, R., et al. (2009). "Group acupuncture to relieve radiation induced xerostomia: a feasibility study." Acupunct Med **27**(3): 109-113.

285 Silva, L. A., et al. (2014). "The role of xerostomia in burning mouth syndrome: a case-control study." Arq Neuropsiquiatr **72**(2): 91-98.

286 Hira, D., et al. (2015). "Dry mouth as a novel indicator of hoarseness caused by inhalation therapy." J Asthma **52**(3): 296-300.

287 Ohara, Y., et al. (2016). "Prevalence and factors associated with xerostomia and hyposalivation among community-dwelling older people in Japan." Gerodontology **33**(1): 20-27.

288 Watanabe, M., et al. (2018). "New low-dose liquid pilocarpine formulation for treating dry mouth in Sjogren's syndrome: clinical efficacy, symptom relief, and improvement in quality of life." J Pharm Health Care Sci **4**: 4.

289 Yang, L. Y., et al. (2019). "The effect of transcutaneous electrical nerve stimulation on increasing salivary flow rate in hemodialysis patients." Oral Dis **25**(1): 133-141.

290 Marimuthu, D., et al. (2021). "Saliva substitute mouthwash in nasopharyngeal cancer survivors with xerostomia: a randomized controlled trial." Clin Oral Investig **25**(5): 3105-3115.

291 Habu, M., et al. (2010). "Significance of dynamic magnetic resonance sialography in prognostic evaluation of saline solution irrigation of the parotid gland for the treatment of xerostomia." J Oral Maxillofac Surg **68**(4): 768-776.

292 Baron, M., et al. (2014). "The Canadian systemic sclerosis oral health study: orofacial manifestations and oral health-related quality of life in systemic sclerosis compared with the general population." Rheumatology (Oxford) **53**(8): 1386-1394.

293 Dejaco C, D. Z. T., Heber D, Hartung W, Lipp R, Lutfi A, Magyar M, Zauner D, Lackner A, Duftner C, Horwath-Winter J, Graninger WB, Hermann J. (2014). "Real-time sonoelastography of salivary glands for diagnosis and functional assessment of primary Sjögren's syndrome." Ultrasound Med Biol **40**(12): 2759-2767.

294 Baron, M., et al. (2015). "Relationship between disease characteristics and orofacial manifestations in systemic sclerosis: Canadian Systemic Sclerosis Oral Health Study III." Arthritis Care Res (Hoboken) **67**(5): 681-690.

295 Takagi, Y., et al. (2016). "Salivary gland ultrasonography as a primary imaging tool for predicting efficacy of xerostomia treatment in patients with Sjogren's syndrome." Rheumatology (Oxford) **55**(2): 237-245.

296 López-Jornet P, Bermejo-Fenoll A, Bagan-Sebastian JV, Pascual-Gomez E. Comparison of a new test for the measurement of resting whole saliva with the draining and the swab techniques. Braz Dent J. 1996;7(2):81-6. PMID: 9206358.

297 Mardani, H., et al. (2017). "The Effect of ginger herbal spray on reducing xerostomia in patients with type II diabetes." Avicenna J Phytomed **7**(4): 308-316.

298 Chen, C. C., et al. (2018). "Bedside screen for oral cavity structure, salivary flow, and vocal production over the 14days following endotracheal extubation." J Crit Care **45**: 1-6.

299 Cifuentes, M., et al. (2018). "Pilocarpine and artificial saliva for the treatment of xerostomia and xerophthalmia in Sjogren syndrome: a double-blind randomized controlled trial." Br J Dermatol **179**(5): 1056-1061.

300 Chen, A., et al. (2005). "Using the modified Schirmer test to measure mouth dryness: a preliminary study." J Am Dent Assoc **136**(2): 164-170; quiz 229-130.

301 Crogan, N. L. (2011). "Managing xerostomia in nursing homes: pilot testing of the Sorbet Increases Salivation intervention." J Am Med Dir Assoc **12**(3): 212-216.

302 Dietsch, A. M., et al. (2018). "Saliva Production and Enjoyment of Real-Food Flavors in People with and Without Dysphagia and/or Xerostomia." Dysphagia **33**(6): 803-808.

303 Lim, R. J., et al. (2019). "Effects of herbal medicine for xerostomia in head and neck cancer patients: an observational study in a tertiary cancer hospital." Support Care Cancer **27**(9): 3491-3498.

304 Rakha, A., et al. (2021). "Salivary flow rate and radioactivity in saliva, blood and serum of benign and malignant thyroid patients after 131I therapy." International Journal of Radiation Research **19**: 197-203.

305 Chavez, E. M., et al. (2001). "A longitudinal analysis of salivary flow in control subjects and older adults with type 2 diabetes." Oral Surg Oral Med Oral Pathol Oral Radiol Endod **91**(2): 166-173.

306 Eisbruch, A., et al. (2001). "Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer." Int J Radiat Oncol Biol Phys **50**(3): 695-704.

307 Patel, P. S., et al. (2001). "Xerostomic complaints induced by an anti-sialogogue in healthy young vs. older adults." Spec Care Dentist **21**(5): 176-181.

308 Burlage, F. R., et al. (2005). "Variability of flow rate when collecting stimulated human parotid saliva." Eur J Oral Sci **113**(5): 386-390.

309 Gescuk, B., et al. (2005). "Lamivudine is not effective in primary Sjogren's syndrome." Ann Rheum Dis **64**(9): 1326-1330.

310 Hammi, A. R., et al. (2005). "Assessment of SS-A and SS-B in parotid saliva of patients with Sjogren's syndrome." J Oral Pathol Med **34**(4): 198-203.

311 Pedersen, A. M., et al. (2005). "Salivary changes and dental caries as potential oral markers of autoimmune salivary gland dysfunction in primary Sjogren's syndrome." BMC Clin Pathol **5**(1): 4.

312 Pijpe, J., et al. (2005). "Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study." Arthritis Rheum **52**(9): 2740-2750.

313 Braam, P. M., et al. (2006). "Intensity-modulated radiotherapy significantly reduces xerostomia compared with conventional radiotherapy." Int J Radiat Oncol Biol Phys **66**(4): 975-980.

314 Frost, P. M., et al. (2006). "Impact of wearing an intra-oral lubricating device on oral health in dry mouth patients." Oral Dis **12**(1): 57-62.

315 Meirovitz, A., et al. (2006). "Grading xerostomia by physicians or by patients after intensity-modulated radiotherapy of head-and-neck cancer." Int J Radiat Oncol Biol Phys **66**(2): 445-453.

316 Pow, E. H., et al. (2006). "Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial." Int J Radiat Oncol Biol Phys **66**(4): 981-991.

317 Astreinidou, E., et al. (2007). "3D MR sialography as a tool to investigate radiation-induced xerostomia: feasibility study." Int J Radiat Oncol Biol Phys **68**(5): 1310-1319.

318 Deming, F. P., et al. (2007). "Comparison of salivary calmodulin binding proteins in Sjogren's syndrome and healthy individuals." J Oral Pathol Med **36**(3): 132-135.

319 Li, Y., et al. (2007). "The impact of dose on parotid salivary recovery in head and neck cancer patients treated with radiation therapy." Int J Radiat Oncol Biol Phys **67**(3): 660-669.

320 Baum, B. J., et al. (2012). "Early responses to adenoviral-mediated transfer of the aquaporin-1 cDNA for radiation-induced salivary hypofunction." Proc Natl Acad Sci U S A **109**(47): 19403-19407.

321 Dijkema, T., et al. (2012). "Xerostomia: a day and night difference." Radiother Oncol **104**(2): 219-223.

322 Little, M., et al. (2012). "Reducing xerostomia after chemo-IMRT for head-and-neck cancer: beyond sparing the parotid glands." Int J Radiat Oncol Biol Phys **83**(3): 1007-1014.

323 Osterhus, I. N., et al. (2012). "Salivary gland pathology as a new finding in Treacher Collins syndrome." Am J Med Genet A **158A**(6): 1320-1325.

324 Miah, A. B., et al. (2013a). "The effect of concomitant chemotherapy on parotid gland function following head and neck IMRT." Radiother Oncol **106**(3): 346-351.

325 Miah, A. B., et al. (2013b). "Dose-response analysis of parotid gland function: what is the best measure of xerostomia?" Radiother Oncol **106**(3): 341-345.

326 Zhang, Y., et al. (2013). "Diffusion-weighted MR imaging of salivary glands with gustatory stimulation: comparison before and after radiotherapy." Acta Radiol **54**(8): 928-933.

327 Aparna, P. V., et al. (2017). "Effect of Transcutaneous Electrical Nerve Stimulation on Parotid Saliva Flow in Patients with Hyposalivation." J Pharm Bioallied Sci **9**(Suppl 1): S142-S146.

328 Wang, X., et al. (2020). "Progenitor cell niche senescence reflects pathology of the parotid salivary gland in primary Sjogren's syndrome." Rheumatology (Oxford) **59**(10): 3003-3013.

329 Nonzee, V., et al. (2012). "Xerostomia, hyposalivation and oral microbiota in patients using antihypertensive medications." J Med Assoc Thai **95**(1): 96-104.

330 Maeshima, E., et al. (2013). "Hyposalivation in autoimmune diseases." Rheumatol Int **33**(12): 3079-3082.

331 Dyasanoor, S. and S. C. Saddu (2014). "Association of Xerostomia and Assessment of Salivary Flow Using Modified Schirmer Test among Smokers and Healthy Individuals: A Preliminutesary Study." J Clin Diagn Res **8**(1): 211-213.

332 Homb, K. A., et al. (2014). "Improvement of radiation-induced xerostomia with acupuncture: A retrospective analysis." Acupuncture and Related Therapies **2**(2): 34-38.

333 Abdul Khader, N. F. and S. Dyasanoor (2015). "Assessment of Salivary Flow Rate and pH Among Areca Nut Chewers and Oral Submucous Fibrosis Subjects: A Comparative Study." J Cancer Prev **20**(3): 208-215.

334 Kim DH, P. J. (2020). "The Effect of Saline Gargling on Dry Mouth and Sore Throat in Patients with Thyroidectomy." Asian Oncol Nurs **20**(4): 160-170.

335 Wrobel-Dudzinska, D., et al. (2021). "The use of Schirmer strips to measure salivary and lacrimal flow in non-Sjogren patients." Clin Oral Investig **25**(6): 4107-4114.

336 Huang, S. H., et al. (2021). "Short-term and long-term unstimulated saliva flow following unilateral vs bilateral radiotherapy for oropharyngeal carcinoma." Head Neck **43**(2): 456-466.

337 Pathak, K. A., et al. (2004). "Upfront submandibular salivary gland transfer in pharyngeal cancers." Oral Oncol **40**(9): 960-963.

338 Zhang, Y., et al. (2012). "Prevention of radiation-induced xerostomia by submandibular gland transfer." Head Neck **34**(7): 937-942.

339 Meiners, P. M., et al. (2014). "Abatacept treatment reduces disease activity in early primary Sjogren's syndrome (open-label proof of concept ASAP study)." Ann Rheum Dis **73**(7): 1393-1396.

340 Hasegawa, Y., et al. (2016). "Enhanced salivary secretion by interferential current stimulation in patients with dry mouth: a pilot study." Oral Surg Oral Med Oral Pathol Oral Radiol **121**(5): 481-489.

341 Vermaire, J. A., et al. (2021). "Mastication, swallowing, and salivary flow in patients with head and neck cancer: objective tests versus patient-reported outcomes." Support Care Cancer **29**(12): 7793-7803.

342 Vainshtein, J. M., et al. (2016). "Impact of xerostomia on dysphagia after chemotherapy-intensity-modulated radiotherapy for oropharyngeal cancer: Prospective longitudinal study." Head Neck **38 Suppl 1**: E1605-1612.

343 Buchholzer, S., et al. (2022). "Novel Multidisciplinary Salivary Gland Society (MSGS) Questionnaire: An International Consensus." Laryngoscope **132**(2): 322-331.

344 Eliasson, L., et al. (2005). "Minor gland saliva flow rate and proteins in subjects with hyposalivation due to Sjogren's syndrome and radiation therapy." Arch Oral Biol **50**(3): 293-299.

345 Satoh-Kuriwada, S., et al. (2012). "Diagnostic performance of labial minor salivary gland flow measurement for assessment of xerostomia." Arch Oral Biol **57**(8): 1121-1126.

346 Ramsay, D. S., et al. (2015). "Tooth wear and the role of salivary measures in general practice patients." Clin Oral Investig **19**(1): 85-95.

347 Marton, K., et al. (2006). "Evaluation of palatal saliva flow rate and oral manifestations in patients with Sjogren's syndrome." Oral Dis **12**(5): 480-486.

348 Tomasik, B., et al. (2021). "Serum MicroRNAs as Xerostomia Biomarkers in Patients With Oropharyngeal Cancer Undergoing Radiation Therapy." Int J Radiat Oncol Biol Phys **111**(5): 1237-1249.

349 Mori, Y., et al. (2010). "Trehalose inhibits oral dryness by protecting the cell membrane." Int J Oral Maxillofac Surg **39**(9): 916-921.

350 Solemdal, K., et al. (2012). "The impact of oral health on taste ability in acutely hospitalized elderly." PLoS One **7**(5): e36557.

351 Kunin, A., et al. (2018). ""Dry mouth" and "Flammer" syndromes-neglected risks in adolescents and new concepts by predictive, preventive and personalised approach." EPMA J **9**(3): 307-317.

352 Strömberg, E., et al. (2013). "Oral health-related quality-of-life in homebound elderly dependent on moderate and substantial supportive care for daily living." Acta Odontol Scand **71**(3-4): 771-777.

353 Al-Ezzi, M., et al. (2020). "Is the taste acuity affected by oral dryness in primary Sjogren's syndrome patients?" Oral Dis **26**(3): 688-695.

354 Gil-Montoya, J. A., et al. (2016). "Prevalence of Drug-Induced Xerostomia in Older Adults with Cognitive Impairment or Dementia: An Observational Study." Drugs Aging **33**(8): 611-618.

355 Yildirim, O. A., et al. (2021). "Nivolumab-Related Dry Mouth and Dry Eye: Cross-Sectional Study." Cancer Invest **39**(10): 797-807.

356 Zhang, W., et al. (2022). "Symptom management to alleviate thirst and dry mouth in critically ill patients: A randomised controlled trial." Aust Crit Care **35**(2): 123-129.

357 Kakinoki, Y., et al. (2004). "Usefulness of new wetness tester for diagnosis of dry mouth in disabled patients." Gerodontology **21**(4): 229-231.

358 Yamada, H., et al. (2005). "Preliminary results of moisture checker for Mucus in diagnosing dry mouth." Oral Dis **11**(6): 405-407.

359 Kakudate, N., et al. (2014). "Factors associated with dry mouth in dependent Japanese elderly." Gerodontology **31**(1): 11-18.

360 Nishii, M., et al. (2014). "Sequential changes in oral dryness evaluated by a moisture-checking device in patients with oropharyngeal cancer during chemoradiotherapy: a pilot study." Oral Health Dent Manag **13**(2): 507-511.

361 Murakami, M., et al. (2015). "Dry mouth and denture plaque microflora in complete denture and palatal obturator prosthesis wearers." Gerodontology **32**(3): 188-194.

362 Ihara, Y., et al. (2018). "Dysphagia and Oral Morbidities in Chemoradiation-Treated Head and Neck Cancer Patients." Dysphagia **33**(6): 739-748.

363 Shimazaki, Y., et al. (2020). "Oral hypofunction and its association with frailty in community-dwelling older people." Geriatr Gerontol Int **20**(10): 917-926.

364 Choi, E. and D. Jung (2021). "Factors Influencing Oral Health-Related Quality of Life in Older Adults in Rural Areas: Oral Dryness and Oral Health Knowledge and Behavior." Int J Environ Res Public Health **18**(8).

365 Iwasaki, M., et al. (2022). "Oral hypofunction and malnutrition among community-dwelling older adults: Evidence from the Otassha study." Gerodontology **39**(1): 17-25.

366 Onuki, W., et al. (2021). "Survey of oral hypofunction in older outpatients at a dental hospital." J Oral Rehabil **48**(10): 1173-1182.

367 Shimosato, M., et al. (2021). "Diagnostic accuracy of patient-reported dry mouth as a predictor for oral dryness in terminally ill cancer patients." Support Care Cancer **29**(5): 2743-2748.

368 Duong, S., et al. (2012). "An imaging-based approach to the evaluation of xerostomia." Lasers Surg Med **44**(6): 482-489.

369 Jang, C. S. and Y. S. Shin (2016). "Effects of combination oral care on oral health, dry mouth and salivary pH of intubated patients: A randomized controlled trial." Int J Nurs Pract **22**(5): 503-511.

370 Villa A, Wolff A, Narayana N, Dawes C, Aframian DJ, Lynge Pedersen AM, Vissink A, Aliko A, Sia YW, Joshi RK, McGowan R, Jensen SB, Kerr AR, Ekström J, Proctor G. World Workshop on Oral Medicine VI: a systematic review of medication-induced salivary gland dysfunction. Oral Dis. 2016 Jul;22(5):365-82. doi: 10.1111/odi.12402. Epub 2016 Jan 20. PMID: 26602059.

371 El Miedany, Y. M., et al. (2004). "Quantitative ultrasonography and magnetic resonance imaging of the parotid gland: can they replace the histopathologic studies in patients with Sjogren's syndrome?" Joint Bone Spine **71**(1): 29-38.

372 Brozzi, F., et al. (2013). "Salivary glands ultrasound examination after radioiodine-131 treatment for differentiated thyroid cancer." J Endocrinol Invest **36**(3): 153-156.

373 Theander, E. and T. Mandl (2014). "Primary Sjogren's syndrome: diagnostic and prognostic value of salivary gland ultrasonography using a simplified scoring system." Arthritis Care Res (Hoboken) **66**(7): 1102-1107.

374 Soo Roh, S., et al. (2016). "Association of Xerostomia and Ultrasonographic Features of the Major Salivary Glands After Radioactive Iodine Ablation for Papillary Thyroid Carcinoma." AJR Am J Roentgenol **207**(5): 1077-1081.

375 Mossel, E., et al. (2017). "Ultrasonography of major salivary glands compared with parotid and labial gland biopsy and classification criteria in patients with clinically suspected primary Sjogren's syndrome." Ann Rheum Dis **76**(11): 1883-1889.

376 Lee, K. A., et al. (2018). "Diagnostic and predictive evaluation using salivary gland ultrasonography in primary Sjogren's syndrome." Clin Exp Rheumatol **36 Suppl 112**(3): 165-172.

377 Notarstefano, C., et al. (2018). "A clinical and histopathological analysis of the anti-centromere antibody positive subset of primary Sjögren's syndrome." Clin Exp Rheumatol **36 Suppl 112**(3): 145-149.

378 Ferro, F., et al. (2020). "Ultra-high frequency ultrasonography of labial glands is a highly sensitive tool for the diagnosis of Sjogren's syndrome: a preliminary study." Clin Exp Rheumatol **38 Suppl 126**(4): 210-215.

379 Jousse-Joulin, S., et al. (2020). "Weight of salivary gland ultrasonography compared to other items of the 2016 ACR/EULAR classification criteria for Primary Sjogren's syndrome." J Intern Med **287**(2): 180-188.

380 La Paglia, G. M. C., et al. (2020). "Ultrasound salivary gland involvement in Sjogren's syndrome vs. other connective tissue diseases: is it autoantibody and gland dependent?" Clin Rheumatol **39**(4): 1207-1215.

381 Lee, K. A., et al. (2020). "Ultrasonographic Changes of Major Salivary Glands in Primary Sjogren's Syndrome." J Clin Med **9**(3).

382 Nieto-Gonzalez, J. C., et al. (2020). "Salivary gland ultrasound is linked to the autoimmunity profile in patients with primary Sjogren's syndrome." J Int Med Res **48**(1): 300060518767031.

382 Sinjari, B., et al. (2020). "Artificial Saliva in Diabetic Xerostomia (ASDIX): Double Blind Trial of Aldiamed((R)) Versus Placebo." J Clin Med **9**(7).

384 Zandonella Callegher, S., et al. (2020). "Normal-Appearing Salivary Gland Ultrasonography Identifies a Milder Phenotype of Primary Sjogren's Syndrome." Front Med (Lausanne) **7**: 602354.

385 Al Tabaa, O., et al. (2021). "Normal salivary gland ultrasonography could rule out the diagnosis of Sjögren's syndrome in anti-SSA-negative patients with sicca syndrome." RMD Open **7**(1).

386 Bukhari, A. F., et al. (2021). "Salivary glands ultrasonography as a diagnostic aid in Sjogren syndrome: A prospective pilot investigation." Oral Surg Oral Med Oral Pathol Oral Radiol **132**(2): 172-181.

387 Mo, Y. Q., et al. (2021). "Ultrasonography predicts the results of labial salivary gland biopsy in patients with suspected Sjogren's syndrome: a matrix risk model." Ther Adv Musculoskelet Dis **13**: 1759720X211010592.

388 Sebastian, A., et al. (2021). "Is it possible to not perform salivary gland biopsy in targeted patients according to unstimulated salivary flow results in patients with suspected Sjogren's syndrome?" Rheumatol Int **41**(6): 1125-1131.

389 Hočevar A., et al. (2021). Development of a new ultrasound scoring system to evaluate glandular inflammation in Sjögren's syndrome: an OMERACT reliability exercise. Rheumatology (Oxford). doi: 10.1093/rheumatology/keab876. Epub ahead of print. PMID: 34849616.

390 Mateos, J. J., et al. (2001). "Salivary scintigraphy for assessing the protective effect of pilocarpine in head and neck irradiated tumours." Nucl Med Commun **22**(6): 651-656.

391 Solans, R., et al. (2001). "Salivary and lacrimal gland dysfunction (sicca syndrome) after radioiodine therapy." J Nucl Med **42**(5): 738-743.

392 Esfahani, A. F., et al. (2004). "Semi-quantitative assessment of salivary gland function in patients with differentiated thyroid carcinoma after radioiodine-131 treatment." Hell J Nucl Med **7**(3): 206-209.

393 Negoro, A., et al. (2004). "Taste function in Sjogren's syndrome patients with special reference to clinical tests." Auris Nasus Larynx **31**(2): 141-147.

394 Zhao, Y., et al. (2005). "Evaluation of international classification criteria (2002) for primary Sjogren's syndrome in Chinese patients." Chin Med Sci J **20**(3): 190-193.

395 Anand, A. K., et al. (2006). "Can dose reduction to one parotid gland prevent xerostomia?--A feasibility study for locally advanced head and neck cancer patients treated with intensity-modulated radiotherapy." Clin Oncol (R Coll Radiol) **18**(6): 497-504.

396 Coracin, F. L., et al. (2006). "Major salivary gland damage in allogeneic hematopoietic progenitor cell transplantation assessed by scintigraphic methods." Bone Marrow Transplant **37**(10): 955-959.

397 Novljan, M. P., et al. (2006). "Comparison of the different classification criteria sets for primary Sjogren's syndrome." Scand J Rheumatol **35**(6): 463-467.

398 Goleń, M., et al. (2007). "The influence of radiation technique on xerostomia in head and neck cancer patients – prospective study." Reports of Practical Oncology & Radiotherapy **12**(5): 253-260.

399 Munter, M. W., et al. (2007). "Changes in salivary gland function after radiotherapy of head and neck tumors measured by quantitative pertechnetate scintigraphy: comparison of intensity-modulated radiotherapy and conventional radiation therapy with and without Amifostine." Int J Radiat Oncol Biol Phys **67**(3): 651-659.

400 Nin, T., et al. (2008). "Nizatidine enhances salivary secretion in patients with dry mouth." Auris Nasus Larynx **35**(2): 224-229.

401 Voordeckers, M., et al. (2008). "Longitudinal assessment of parotid function in patients receiving tomotherapy for head-and-neck cancer." Strahlenther Onkol **184**(8): 400-405.

402 Gune, S., et al. (2010). "Quantitative and visual evaluation of salivary and thyroid glands in patients with primary Sjogren's syndrome using salivary gland scintigraphy: relationship with clinicopathological features of salivary, lacrimal and thyroid glands." Nucl Med Commun **31**(7): 666-672.

403 Kato, H., et al. (2011). "Salivary gland function evaluated by diffusion-weighted MR imaging with gustatory stimulation: preliminary results." J Magn Reson Imaging **34**(4): 904-909.

404 Zou, Q., et al. (2012). "Semi-quantitative evaluation of salivary gland function in Sjogren's syndrome using salivary gland scintigraphy." Clin Rheumatol **31**(12): 1699-1705.

405 Chen, J. Z., et al. (2013). "Results of a phase 2 study examining the effects of omitting elective neck irradiation to nodal levels IV and Vb in patients with N(0-1) nasopharyngeal carcinoma." Int J Radiat Oncol Biol Phys **85**(4): 929-934.

406 Fallahi, B., et al. (2013). "Does vitamin E protect salivary glands from I-131 radiation damage in patients with thyroid cancer?" Nucl Med Commun **34**(8): 777-786.

407 Jeong, S. Y., et al. (2013). "Salivary gland function 5 years after radioactive iodine ablation in patients with differentiated thyroid cancer: direct comparison of pre- and postablation scintigraphies and their relation to xerostomia symptoms." Thyroid **23**(5): 609-616.

408 Ayan, A., et al. (2014). "The effect of antiallergic treatment with desloratadine-montelukast on salivary glands function in allergic rhinitis." Hell J Nucl Med **17**(3): 190-193.

409 Jonklaas, J., et al. (2015). "Salivary Function after Radioiodine Therapy: Poor Correlation between Symptoms and Salivary Scintigraphy." Front Endocrinol (Lausanne) **6**: 100.

410 Orsal, E., et al. (2015). "Evaluation of the effect of isotretinoin on salivary gland function by Tc-99m pertechnetate imaging in acne vulgaris patients." Turk J Med Sci **45**(3): 674-677.

411 Wu, J. Q., et al. (2015). "Systematic evaluation of salivary gland damage following I-131 therapy in differentiated thyroid cancer patients by quantitative scintigraphy and clinical follow-up." Nucl Med Commun **36**(8): 819-826.

412 Badam, R. K., et al. (2016). "Assessment of Salivary Gland Function Using Salivary Scintigraphy in Pre and Post Radioactive Iodine Therapy in Diagnosed Thyroid Carcinoma Patients." J Clin Diagn Res **10**(1): ZC60-62.

413 Chung, M. K., et al. (2016). "Randomized Trial of Vitamin C/E Complex for Prevention of Radiation-Induced Xerostomia in Patients with Head and Neck Cancer." Otolaryngol Head Neck Surg **155**(3): 423-430.

414 Kreps, S., et al. (2016). "Salivary gland-sparing helical tomotherapy for head and neck cancer: Preserved salivary function on quantitative salivary gland scintigraphy after tomotherapy." Eur Ann Otorhinolaryngol Head Neck Dis **133**(4): 257-262.

415 Teymoortash, A., et al. (2016). "Safety and Efficacy of Botulinum Toxin to Preserve Gland Function after Radiotherapy in Patients with Head and Neck Cancer: A Prospective, Randomized, Placebo-Controlled, Double-Blinded Phase I Clinical Trial." PLoS One **11**(3): e0151316.

416 Ogura, I., et al. (2018). "Magnetic Resonance Sialography and Salivary Gland Scintigraphy of Parotid Glands in Sjogren's Syndrome." Chin J Dent Res **21**(1): 63-68.

417 Acar-Denizli, N., et al. (2020). "Systemic phenotype related to primary Sjögren's syndrome in 279 patients carrying isolated anti-La/SSB antibodies." Clin Exp Rheumatol **38 Suppl 126**(4): 85-94.

418 Huang, J., et al. (2020). "Quantitative evaluation of salivary gland scintigraphy in Sjogren's syndrome: comparison of diagnostic efficacy and relationship with pathological features of the salivary glands." Ann Nucl Med **34**(4): 289-298.

419 Zhu, G. W., et al. (2020). "Quantitative analysis for modified Schall's classification by stimulation test with dynamic scintigraphy in Sjogren's syndrome." Int J Rheum Dis **23**(3): 381-391.

420 Chen, Y. C., et al. (2021). "Office-based salivary gland ductal irrigation in patients with chronic sialoadenitis: A preliminary study." J Formos Med Assoc **120**(1 Pt 2): 318-326.

421 Garcia-Gonzalez, M., et al. (2021). "The validity of salivary gland scintigraphy in Sjogren's syndrome diagnosis: comparison of visual and excretion fraction analyses." Clin Rheumatol **40**(5): 1923-1931.

422 Lopes, A. I., et al. (2021). "The role of minor salivary glands' biopsy in the diagnosis of Sjogren's syndrome and other systemic diseases." Eur J Intern Med **94**: 69-72.

423 Pascoto, G. R., et al. (2021). "Sialendoscopy for Improvement of Salivary Flow in Patients with Sjogren Syndrome - Comparative Analysis of Intraglandular Washing Solutions." Int Arch Otorhinolaryngol **25**(1): e1-e7.

424 Ou, D., et al. (2013). "Magnetic resonance sialography for investigating major salivary gland duct system after intensity-modulated radiotherapy of nasopharyngeal carcinoma." Int J Clin Oncol **18**(5): 801-807.

425 Obinata, K., et al. (2014). "Changes in parotid gland morphology and function in patients treated with intensity-modulated radiotherapy for nasopharyngeal and oropharyngeal tumors." Oral Radiol **30**: 135-141.

426 Saes Busato, I. M., et al. (2016). "Salivary flow rate, buffer capacity, and urea concentration in adolescents with type 1 diabetes mellitus." J Pediatr Endocrinol Metab **29**(12): 1359-1363.

427 Randall, K., et al. (2013). "Analysis of factors influencing the development of xerostomia during intensity-modulated radiotherapy." Oral Surg Oral Med Oral Pathol Oral Radiol **115**(6): 772-779.

428 Carda, C., et al. (2006). "Structural and functional salivary disorders in type 2 diabetic patients." Med Oral Patol Oral Cir Bucal **11**(4): E309-314.

429 Agha-Hosseini, F., et al. (2007). "Stimulated whole salivary flow rate and composition in menopausal women with oral dryness feeling." Oral Dis **13**(3): 320-323.

430 Williamson, P.R., Altman, D.G., Bagley, H. *et al.* The COMET Handbook: version 1.0. *Trials* **18,** 280 (2017).

431 Helenius, L. M., et al. (2005). "Oral and salivary parameters in patients with rheumatic diseases." Acta Odontol Scand **63**(5): 284-293.

432 Avouac, J., et al. (2006). "Systemic sclerosis-associated Sjogren's syndrome and relationship to the limited cutaneous subtype: results of a prospective study of sicca syndrome in 133 consecutive patients." Arthritis Rheum **54**(7): 2243-2249.

433 Champey, J., et al. (2006). "Quality of life and psychological status in patients with primary Sjogren's syndrome and sicca symptoms without autoimmune features." Arthritis Rheum **55**(3): 451-457.

434 Imanguli, M. M., et al. (2010). "Salivary gland involvement in chronic graft-versus-host disease: prevalence, clinical significance, and recommendations for evaluation." Biol Blood Marrow Transplant **16**(10): 1362-1369.

435 Antero, D. C., et al. (2011). "Secondary Sjogren's syndrome and disease activity of rheumatoid arthritis." Rev Assoc Med Bras (1992) **57**(3): 319-322.

436 Devauchelle-Pensec, V., et al. (2011). "Effects of rituximab therapy on quality of life in patients with primary Sjögren's syndrome." Clin Exp Rheumatol **29**(1): 6-12.

437 Adler, S., et al. (2013). "Evaluation of histologic, serologic, and clinical changes in response to abatacept treatment of primary Sjogren's syndrome: a pilot study." Arthritis Care Res (Hoboken) **65**(11): 1862-1868.

438 Carubbi, F., et al. (2013). "Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study." Arthritis Res Ther **15**(5): R172.

439 Mariette, X., et al. (2015). "Efficacy and safety of belimumab in primary Sjogren's syndrome: results of the BELISS open-label phase II study." Ann Rheum Dis **74**(3): 526-531.

440 Kalk WW., et al. (2001). "Sialometry and sialochemistry: diagnostic tools for Sjögren's syndrome." Ann Rheum Dis. 60(12):1110-6.

441 Kalk WW,. et al. (2002) "Sialometry and sialochemistry: a non-invasive approach for diagnosing Sjögren's syndrome. " Ann Rheum Dis. 61(2):137-44.

442 Shiboski, C.H., Shiboski, S.C., Seror, R., Criswell, L.A., Labetoulle, M., Lietman, T.M., Rasmussen, A., Scofield, H., Vitali, C., Bowman, S.J. and Mariette, X., 2017. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Annals of the rheumatic diseases*, *76*(1), pp.9-16.

443 Arends, S, Wolff, L, de Nimwegen, JF, et al. Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS): development and validation of a novel outcome measure. Lancet Rheumatol 2021; 3: e553–562

Table I. Characteristics of the Included Studies

Study characteristics	Number (%)
Year published	***Total n=553***
2001-2010	180 (32.5)
2011-2020	331 (59.9)
2021	42 (7.8)
Origin of the article	
Europe	206 (37.3)
Asia	190 (34.4)
North America	85 (15.4)
South America	51 (9.2)
Multiple	15 (2.7)
Oceania	4 (0.7)
Africa	2 (0.4)
Types of studies	
Cohort	160 (28.9)
Randomized controlled trials (RCTs)	119 (21.5)
Case-control studies	50 (9.0)
Case series	8 (1.4)
Other types of study Cross-sectional Clinical trial Comparative Randomized crossover Qualitative (questionnaire/survey) Validation Crossover Observational Chart review	216 (39.1) 140 30 16 12 6 5 3 3 1
Number of patients	31,507
Range of age (years)	5 – 99
Conditions associated with dry mouth	
Salivary gland hypofunction secondary to radiation to the head and neck	123 (22.2)
Sjögren's syndrome	115 (20.8)
Other conditions	112 (20.3)
Several disease groups	89 (16.1)
Unknown etiology of dry mouth	60 (10.8)
Older age	32 (5.8)
Polypharmacy	22 (4.0)
What is the article assessing	

Salivary gland hypofunction and xerostomia	380 (68.7)
Salivary gland hypofunction only	173 (31.3)

Table II: Outcome Measures Represented Within Each Domain

DOMAIN	SUBDOMAINS	OUTCOME MEASURES
DOMAIN 1: AMOUNT OF SALIVA (please also see Table III)	**Whole-mouth saliva**	a) Stimulated whole saliva flow rate/weight b) Unstimulated whole saliva flow rate/weight
	Gland/region-specific saliva	a) Stimulated gland/region-specific saliva b) Unstimulated gland/region-specific saliva
DOMAIN 2: SALIVARY BIOMARKERS	**Laboratory biomarkers**	a) Inflammatory cytokines b) Protein and immunoglobulins c) Extracellular microRNA
DOMAIN 3: CLINICAL/OBJECTIVE SIGNS OF HYPOSALIVATION	**Individual physician-rated signs of hyposalivation**	a) Physician-assessment of individual clinical signs of dryness of the oral mucosa or specific mucosal sites b) Mirror test c) Scoring oral dryness d) Tongue blade test
	Multiple physician-rated signs of hyposalivation	a) Clinical Oral Dryness Score (CODS) b) Physician-assessment of multiple clinical signs of dryness of the oral mucosa or specific mucosal sites c) Scoring oral dryness
DOMAIN 4: MUCOSAL HYDRATION	**N/A**	a) Moisture b) Wetness c) Residual saliva
DOMAIN 5: IMAGING MODALITIES ASSESSING SALIVARY GLAND DYSFUNCTION	**Salivary gland imaging**	Outcome measures per imaging modality: a) Salivary gland ultrasonography b) Salivary gland scintigraphy c) Sialography d) Salivary gland MRI (Magnetic Resonance Imaging) e) Salivary gland CT (Computerized Tomography)
DOMAIN 6: SALIVA PROPERTIES	**N/A**	a) Lubrication b) Stringiness c) pH d) Viscosity e) Buffering
DOMAIN 7: SALIVA COMPOSITION	**Individual components of saliva**	Salivary proteins Inorganic components
	Multiple components of saliva	Biochemical and sialochemical analysis

Table III: Domain 1: Amount of Saliva

DOMAIN	SUBDOMAIN	OUTCOME MEASURES	INSTRUMENTS/METHODS
DOMAIN 1: AMOUNT OF SALIVA	**Whole-mouth saliva**	Stimulated whole saliva flow rate/weight	1. Biscuit 2. Chewing 3. Electrostimulation 4. Gustatory stimulant 5. Medication 6. Mouthwash 7. Saxon test 8. Not specified
		Unstimulated whole saliva flow rate/weight	1. Biscuit test 2. Blotting mucosa 3. Frequency of swallow (by electromyography) 4. Modified Schirmer's test 5. Passive drooling or spitting 6. Saxon test 7. Schirmer's test 8. Spitting at timed intervals 9. Wafer test 10. Weight of cotton balls/roll 11. Weight of gauze 12. Not specified
	Gland/region-specific saliva	**OUTCOME MEASURES**	**ANATOMICAL LOCATION**
		a) Stimulated gland/region-specific saliva	1. Parotid 2. Parotid and submandibular 3. Submandibular and sublingual saliva 4. Floor of mouth
		b) Unstimulated gland/region-specific saliva	1. Parotid 2. Parotid and submandibular 3. Submandibular and sublingual 4. Labial mucosa 5. Buccal mucosa 6. Palate 7. Floor of mouth 8. Labial and buccal minor glands 9. Palatal and upper labial glands

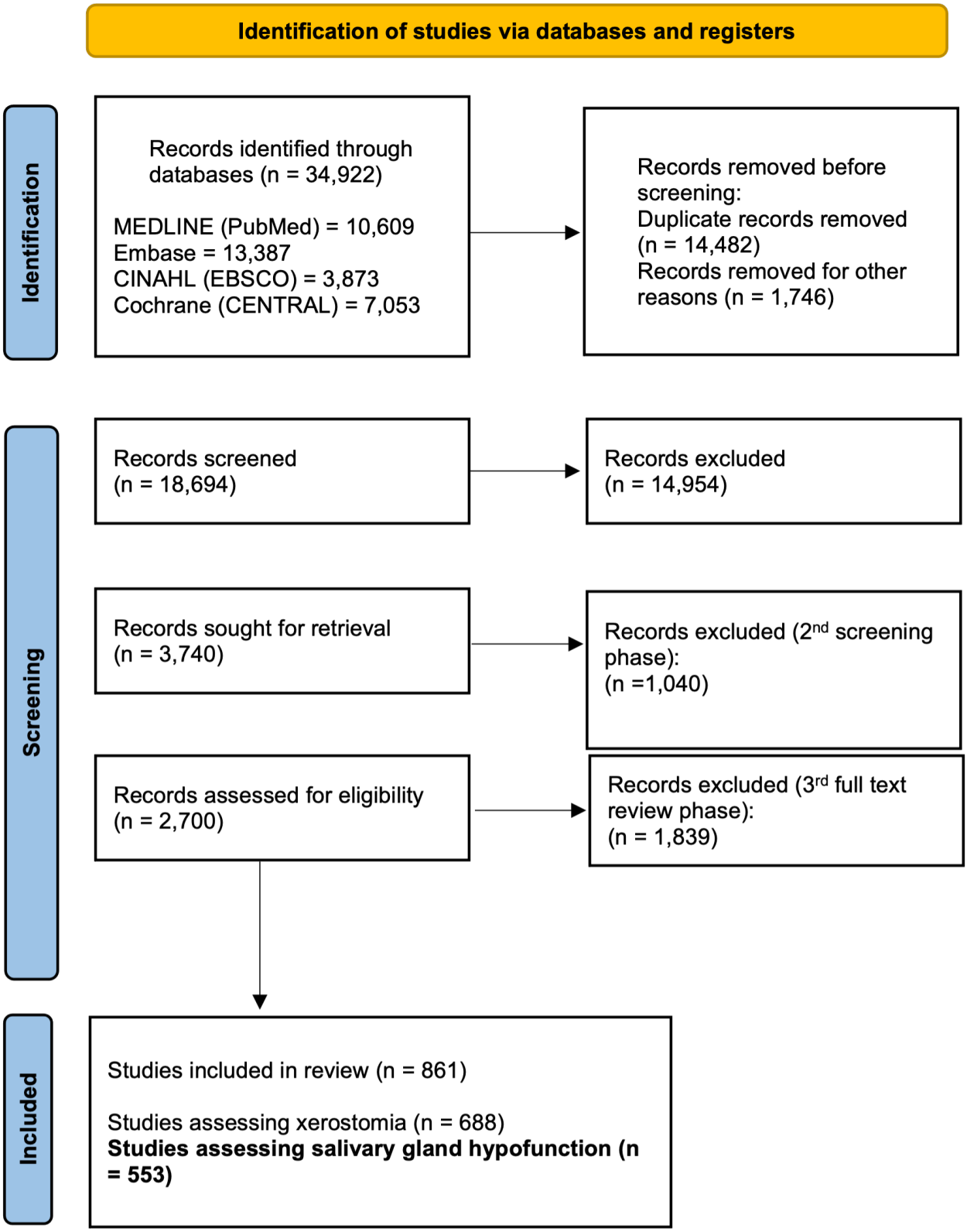
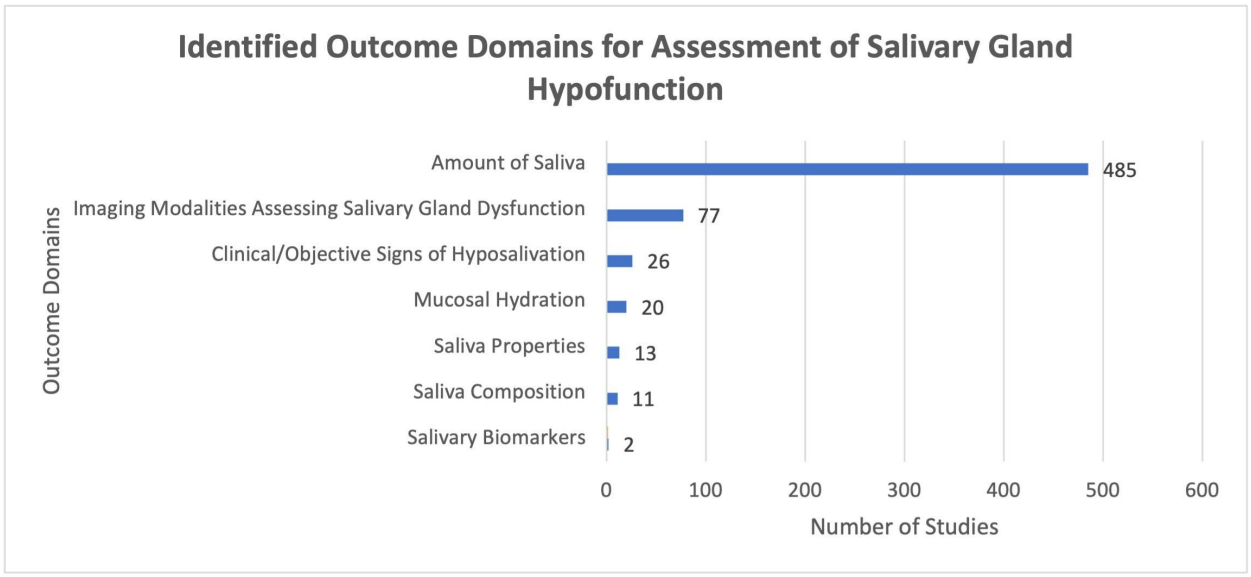

Identification of studies via databases and registers
Identification
Records identified through databases (n = 34,922)
MEDLINE (PubMed) = 10,609
Embase = 13,387
CINAHL (EBSCO) = 3,873
Cochrane (CENTRAL) = 7,053
Records removed before screening:
Duplicate records removed (n = 14,482)
Records removed for other reasons (n = 1,746)
Screening
Records screened (n = 18,694)
Records excluded (n = 14,954)
Records sought for retrieval (n = 3,740)
Records excluded (2nd screening phase): (n =1,040)
Records assessed for eligibility (n = 2,700)
Records excluded (3rd full text review phase): (n = 1,839)
Included
Studies included in review (n = 861)
Studies assessing xerostomia (n = 688)
Studies assessing salivary gland hypofunction (n = 553)

Figure 1


Identified Outcome Domains for Assessment of Salivary Gland Hypofunction
Outcome Domains
Amount of Saliva
Imaging Modalities Assessing Salivary Gland Dysfunction
Clinical/Objective Signs of Hyposalivation
Mucosal Hydration
Saliva Properties
Saliva Composition
Salivary Biomarkers
485
77
26
20
13
11
2
0
100
200
300
400
500
600
Number of Studies

Supplementary Material

MEDLINE (PubMed) 8-9-2021

("Xerostomia"[Mesh] OR xerostomia*[tiab] OR hyposaliv*[tiab] OR dry-mouth[tiab] OR mouth-dryness[tiab] OR oral-dryness[tiab] OR sjogren*[tiab] OR hyposiali*[tiab] OR salivary-gland-dysfunct*[tiab] OR salivary-gland-hypofunct*[tiab] OR reduced-saliv*[tiab])
AND
("Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR "Outcome Assessment, Health Care"[Mesh] OR "Quality of Life"[Mesh] OR "Visual Analog Scale"[Mesh] OR "Biomarkers"[Mesh] OR intervention*[ti] OR treatment*[ti] OR therap*[ti] OR management*[ti] OR study[ti] OR random*[tiab] OR trial*[tiab] OR controlled-study[tiab] OR clinical-study[tiab] OR cohort[tiab] OR case-control[tiab] OR prospectiv*[tiab] OR follow-up[tiab] OR followed-up[tiab] OR retrospectiv*[tiab] OR crosssectional*[tiab] OR cross-sectional*[tiab] OR questionnair*[tiab] OR inventory[tiab] OR patient-reported[tiab] OR outcome*[tiab] OR survey*[tiab] OR tool[tiab] OR tools[tiab] OR tooling[tiab] OR scale*[tiab] OR scaling[tiab] OR index[tiab] OR "Visual Analog Scale"[tiab] OR VAS-scale[tiab] OR clinician-reported[tiab] OR marker*[tiab] OR biomarker*[tiab] OR indicator*[tiab])
NOT
(("Animals"[Mesh] NOT "Humans"[Mesh]) OR "Review" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type])
AND
("2000/01/01"[pdat] : "3000"[pdat])
10,588 results 8-9-2021

Embase (embase.com) *n.b. copy/paste the search in 'Advanced'. Clear selections.*
('xerostomia'/exp/mj OR (xerostomia* OR hyposaliv* OR 'dry mouth' OR 'mouth dryness' OR 'oral dryness' OR sjogren* OR hyposiali* OR 'salivary gland dysfunct*' OR 'salivary gland hypofunct*' OR 'reduced saliv*'):ab,ti)
AND
('clinical study'/exp OR 'questionnaire'/exp OR 'quality of life'/exp OR 'treatment outcome'/exp OR 'visual analog scale'/exp OR 'biological marker'/exp OR (intervention* OR treatment* OR therap* OR management* OR study):ti OR (random* OR trial* OR 'controlled study' OR 'clinical study' OR cohort OR 'case control' OR prospectiv* OR 'follow-up' OR 'followed up' OR retrospectiv* OR crosssectional* OR 'cross-sectional*' OR questionnair* OR inventory OR 'patient reported' OR outcome* OR survey* OR tool OR tools OR tooling OR scale* OR scaling OR index OR 'Visual Analog Scale' OR 'VAS-scale' OR 'clinician-reported' OR marker* OR biomarker* OR indicator*):ab,ti)
NOT
((('animal'/exp OR 'in vitro study'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp) OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'review'/it)
AND
[2000-2021]/py

13,371 titles 8-9-2021

CINAHL (EBSCO)
((MH "Xerostomia+") OR TI (xerostomia* OR hyposaliv* OR “dry mouth” OR “mouth dryness” OR “oral dryness” OR sjogren* OR hyposiali* OR “salivary gland dysfunct*” OR “salivary gland hypofunct*” OR “reduced saliv*”) OR AB (xerostomia* OR hyposaliv* OR “dry mouth” OR “mouth dryness” OR “oral dryness” OR sjogren* OR hyposiali* OR “salivary gland dysfunct*” OR “salivary gland hypofunct*” OR “reduced saliv*”))
AND
((MH "Nonexperimental Studies+") OR (MH "Experimental Studies+") OR (MH "Quasi-Experimental Studies+") OR (MH "Questionnaires+") OR (MH "Visual Analog Scaling") OR (MH "Outcomes (Health Care)+") OR (MH "Biological Markers+") OR (MH "Quality of Life+") OR **TI** (intervention* OR treatment* OR therap* OR management* OR study OR random* OR trial* OR “controlled study” OR “clinical study” OR cohort OR “case control” OR prospectiv* OR “follow-up” OR “followed up” OR retrospectiv* OR crosssectional* OR “cross-sectional*” OR questionnair* OR inventory OR “patient reported” OR outcome* OR survey* OR tool OR tools OR tooling OR scale* OR scaling OR index OR “Visual Analog Scale” OR “VAS-scale” OR “clinician-reported” OR marker* OR biomarker* OR indicator*) OR **AB** (random* OR trial* OR “controlled study” OR “clinical study” OR cohort OR “case control” OR prospectiv* OR “follow-up” OR “followed up” OR retrospectiv* OR crosssectional* OR “cross-sectional*” OR questionnair* OR inventory OR “patient reported” OR outcome* OR survey* OR tool OR tools OR tooling OR scale* OR scaling OR index OR “Visual Analog Scale” OR “VAS-scale” OR “clinician-reported” OR marker* OR biomarker* OR indicator*))
AND
PT (Letter OR Masters-Thesis OR Meta-analysis OR Review OR Editorial OR Commentary OR Book OR Book-chapter OR Book-review)
Published Date: 20000101-30001231

3,866 titles 8-9-2021

Cochrane Library, CENTRAL (Trials)
([mh Xerostomia] OR xerostomia*:ti,ab OR hyposaliv*:ti,ab OR dry-mouth:ti,ab OR mouth-dryness:ti,ab OR oral-dryness:ti,ab OR sjogren*:ti,ab OR hyposiali*:ti,ab OR salivary-gland-dysfunct*:ti,ab OR salivary-gland-hypofunct*:ti,ab OR reduced-saliv*:ti,ab)
4451 Trials 8-9-2021 (total result 4547 titles: 93 Cochrane reviews, 2 Protocols, 4451 Trials, 1 Editorial)