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REVIEW

World Workshop on Oral Medicine VI: a systematic review of medication-induced salivary gland dysfunction: prevalence, diagnosis, and treatment

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Abstract
Objectives Medication-induced salivary gland dysfunction (MISGD) causes significant morbidity resulting in decreased quality of life. This systematic review assessed the literature on the prevalence, diagnosis, treatment, and prevention of MISGD.
Materials and methods Electronic databases were searched for articles related to MISGD through June 2013. Four independent reviewers extracted information regarding study design, study population, interventions, outcomes, and conclusions for each article. Only papers with acceptable degree of relevance, quality of methodology, and strength of evidence were retained for further analysis.
Results There were limited data on the epidemiology of MISGD. Furthermore, various methods were used to assess salivary flow rate or xerostomia. Preventive and therapeutic strategies included substitution of medications, oral, or systemic therapy with sialogogues, use of saliva substitutes or of electro-stimulating devices. Although there are promising approaches to improve salivary gland function, most studies are characterized by small numbers and heterogeneous methods.
Conclusions Physicians and dentists should identify the medications associated with xerostomia and salivary gland dysfunction through a thorough medical history. Preferably, health care providers should measure the unstimulated and stimulated whole salivary flow rates of all their patients so that these values can be used as a baseline to rate the complaints of patients who subsequently claim to experience xerostomia or salivary gland dysfunction as well as the possibilities of effectively treating this condition.

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Clinical relevance MISGD remains a major burden for the population. This systematic review provides a contemporary in-depth description of the diagnosis and treatment of MISGD.

Keywords Xerostomia · Saliva · Medications · Salivary gland dysfunction

Introduction

Saliva plays an important role in maintaining oral health and function [1]. Salivary glands secrete approximately 0.6 L/day of a complex fluid from the major salivary glands (i.e., the parotid, submandibular, and sublingual glands) which accounts for about 90 % of the saliva production (10 % derived from 600–1000 minor salivary glands) [2]. The salivary flow rate (SFR) has a circadian variation with a peak in the late afternoon. Unstimulated whole salivary flow rate (UWSF) averages 0.3–0.4 mL/min, while chewing-stimulated whole salivary flow (SWSF) is approximately 1.5–2.0 mL/min [3, 4]. Most of the unstimulated saliva during the daytime is produced by the submandibular glands (60 %) [5]. The parotid glands produce a watery, serous saliva rich in amylase and proline-rich proteins, whereas the other glands produce a mixed, more visco-elastic saliva containing greater amounts of mucin. Salivary gland dysfunction (SGD) is defined as any quantitative and/or qualitative change in the output of saliva. Thus, SGD includes either a reduction in SFR (salivary gland hypofunction), an increase in salivary output (sialorrhea), or a change in saliva composition [6]. Xerostomia, the subjective sensation of dry mouth, is often associated with SGD. However, xerostomia can also be present in patients with normal SFR [7]. In addition, patients with severely reduced SFR do not always experience xerostomia [7, 8]. Salivary gland hypofunction (SGH) disrupts the normal homeostasis of the oral cavity, causing a range of oral diseases including dental caries, oral candidiasis, taste disturbances, and difficulties with chewing, swallowing, and speaking [1]. The most common causes of persistent SGH and changes in saliva composition are intake of medications, Sjögren's syndrome, and head and neck radiotherapy [9, 10]. Hyposalivation is generally based on objective measurement of the salivary flow rates (sialometry), where the UWSF is ≤0.1 mL/min and/or the SWSF rate is ≤0.5–0.7 mL/min [11, 4, 7]. Xerostomia usually occurs when the UWSF has decreased to approximately 50 % of its normal value in any given individual, indicating that more than one major salivary gland must be affected [12]. Of interest, a large number of patients with xerostomia do not show any objectively assessed salivary hypofunction [13]; their symptoms might be related to changes in saliva composition. Xerostomia is likely to occur when the SFR is less than the rate of fluid absorption across the oral mucosa plus the rate of fluid evaporation from the mouth [14]. Xerostomia, which is a common complaint of elderly people, often remains unresolved, despite seeking medical consultation [15]. Psychological conditions such as stress, depression, and anxiety may be associated with the sensation of dry mouth [16]. Medications are widely employed for the management of chronic systemic diseases, especially in the growing geriatric population [17]. Polypharmacy may lead to SGD, presumably through the reduction of unstimulated SFR [18, 19], whereas relatively few medications are accompanied by sialorrhea [9, 20]. This systematic review represents a search and evaluation of the literature in order to explore the current state of knowledge on the prevalence, diagnosis, treatment, and prevention of medication-induced salivary gland dysfunction (MISGD) manifested as SGH and/or xerostomia and/or salivary compositional changes. In this review, xerostomia, regardless of been accompanied by proven SGD, is included as one of the manifestations of MISGD, since quantitative and/or qualitative changes in the output of saliva in relation to the use of medications are rarely reported in the literature. MISGD expressed as sialorrhea is not covered by this review.

Methods

This paper was written by members of the group on MISGD within the World Workshop on Oral Medicine 6 (WWOM VI). The group comprised five reviewers (AA, RJ, NN, YS, and AlV), six consultants (senior experts in fields related to MISGD: DA, CD, JE, AMP, GP, and ArV), one research librarian (RM), a group head (AW), and two supervisors on behalf of the WWOM VI steering committee (SBJ and ARK). The research method was based on the policies and standards set forth by a Task Force for WWOM IV [21] and by the PRISMA statement [22], adapted to the current systematic review. Different aspects related to MISGD were analyzed, including the topic of the present paper. The review process consisted of six steps (Fig. 1; this figure depicts steps 3–6):

Step 1 The following research questions were selected:

- What are the definitions of conditions related to SGD, such as xerostomia, dry mouth, hyposalivation, sialorrhea, etc.?
- Which are the accepted/validated methods for assessing SGD?
- What epidemiological data exist regarding MISGD resulting in SGH and/or xerostomia?
- Which management measures for MISGD have been described and what is their efficacy?
- Which diagnostic and/or preventive and/or therapeutic/attenuating methods of MISGD regarding SGH and/or xerostomia are under research/development?

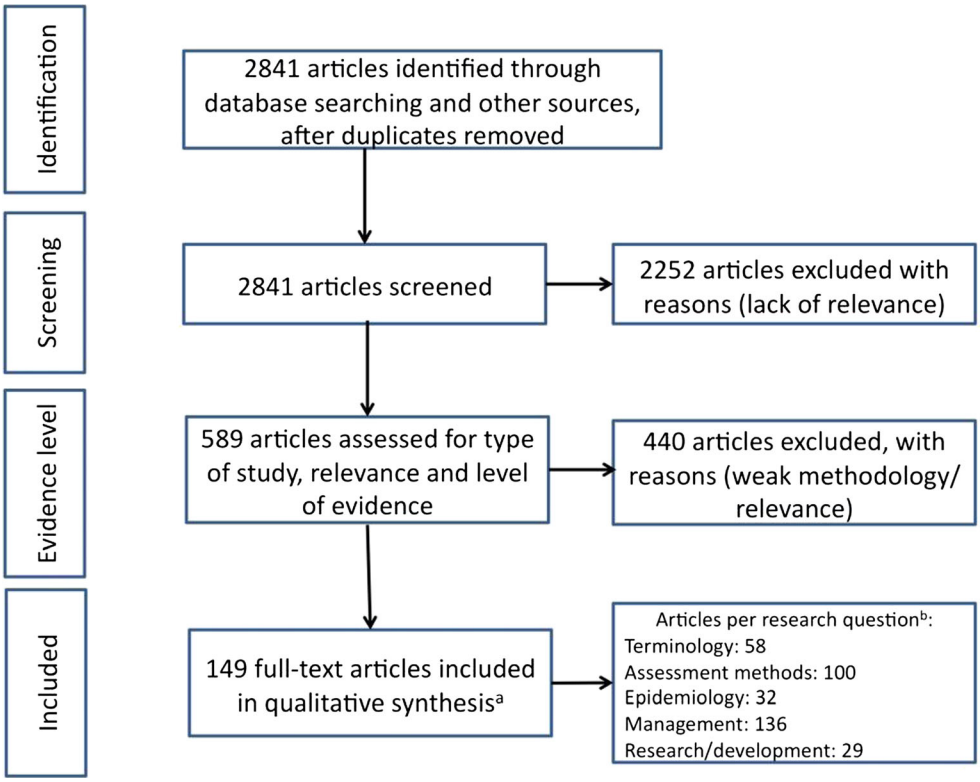

Fig. 1 Adapted PRISMA flow chart of the article selection process (steps 3–6). *a* The total number of articles found for the research questions assessed (n=149 articles) is smaller than the number obtained from summing up the articles for each question as certain articles deal with more than one question. *b* The breakdown of articles per research question was: What are the definitions of conditions related to salivary gland dysfunction and xerostomia, such as xerostomia, dry mouth, hyposalivation, sialorrhea, etc.? 58 articles. Which are the accepted/validated methods for assessing salivary gland dysfunction? 100 articles. What epidemiological data exist regarding MISGD resulting in hyposalivation and/or xerostomia? 32 articles. Which management measures for MISGD have been described and what is their efficacy? 136 articles. Which diagnostic and/or preventive and/or therapeutic/attenuating methods of MISGD regarding hyposalivation and/or xerostomia are under research/development? 29 articles

Step 2 Keyword selection: Keywords were selected for each research question (Table S1, supplementary material).

Step 3 Literature search: The literature search was conducted through June 2013, in the PubMed, Embase, and Web of Science databases, based on the chosen keywords (Step 2) and subject headings, was not limited in languages and allowed identification of potentially relevant records and development of a comprehensive library. The search was completed by a hand search of the reference lists in the eligible papers, and after duplicates were removed, a total of 2841 records were retained for Step 4.

Step 4 Record screening for eligibility: All the 2841 records were screened independently by four reviewers (AA, NN, AlV, and YS) supervised by the consultants (DA, CD, AMP) and retained for further analysis or excluded based on their relevance in regards to each of the research questions. A total of 589 sources were found to be relevant (Fig. 1).

Step 5 Paper selection for type of study, relevance, and level of evidence: After calibration papers were then divided among the reviewers, who analyzed their titles, abstracts and the materials and methods sections for a number of parameters: (a) the degree of relevance (based on whether the prevalence, diagnosis, treatment, and prevention of MISGD were the primary outcomes of the study or not), (b) the strength of methodology provided in the paper (according to the appropriateness of the study design and sample size), and (c) the level of precision by which the medications were classified, ranging from organ or system treated (lowest level), through indication (middle level) to chemical substance (highest level). The highest level of evidence was intended for papers studying MISGD as the primary outcome, reporting meta-analyses, systematic reviews, or randomized clinical trials, and focusing on chemical substances. As a result of this step, a total of 149 papers were retained for full-text analysis, of which 5 % were meta-analyses and systematic reviews, 7 % randomized controlled trials (RCTs), 44 % other types of clinical studies, 24 % narrative reviews, 3 % animal studies, 6 % epidemiological studies, and 11 % other types of

publications. The remaining papers were excluded because of weak relevance/methodology.

Step 6 In-depth analysis: This was based on expert interpretation of the evidence. Supervised by the consultants and by the group head, reviewer AlV read and analyzed all 149 selected publications and drafted the current systematic review.

Results

Epidemiology of MISGD

A recent review paper showed that the prevalence of xerostomia in the general public ranged 5–39 %, and the prevalence among community-dwelling elderly people ranged 17–40 % [23]. In other studies, the prevalence of xerostomia ranged 14–46 % [24] and differed between the genders (women had a higher prevalence) [25–27]. Furness et al. reported an estimated xerostomia incidence of between 10 and 33 % in women and between 10 and 26 % in men [28]. The prevalence of xerostomia in medicated persons was 32 % [29] and 27 % [30]. Xerostomia in the non-medicated population was found in 16 % of the persons in the Nederfors et al. study [29] and in 14 % in the study of Villa et al. [30], and the difference in medicated persons was statistically significant. The difference in xerostomia prevalence between medicated and non-medicated persons was more pronounced in a younger population of 32-year olds, being 25 and 5 %, respectively, and varied from 0 to 30 % in users of different medication categories [31]. The remaining cross-sectional studies reported prevalence data for patients on specific medication categories and varied from 8 % among patients on cardiovascular medications [32], to 35 % in patients on antiretroviral therapy [33], 50 % in patients taking antihypertensives [34], and up to 71 % in patients taking different types of antidepressants [35]. Xerostomia increases with age, probably because elderly people often take multiple medications [36, 30, 17]. During 2007–2008, half of Americans took at least one or more prescribed medications daily, with women being more likely to use medications than men. Qato et al. estimated the prevalence and patterns of medication intake over the last decade among 3005 community-residing persons, aged 57 through 85 years [37]. Results showed that 81 % of the participants took at least one prescribed medication, 42 % took at least one over-the-counter medication, and 49 % had a daily intake of dietary supplements. Twenty-nine percent took at least five prescribed medications/day, being highest among men (37 %; 95 % CI, 32–42 %) and women (36 %; 95 % CI, 30–42 %) aged 75 to 85 years. Among prescription medication users, concurrent use of dietary supplements was 52 % and concurrent use of over-the-counter medications was 46 % [37]. Intake of prescribed medication continues to increase, and as a consequence, the incidence of MISGD is assumed to increase as well. In the past decade in England, the average number of medications prescribed for each person per year has increased from 12 in 2001 to 18 in 2011 [38]. Guthrie and Makubate found that between 1995 and 2010, the proportion of patients in Scotland taking five or more drugs rose from 12 to 22 % and the proportion receiving ten or more drugs increased from 2 to 6 % [39]. Data from the Center for Disease Control in the United States showed that polypharmacy increased by 20 % and the use of five or more medications increased by 5 % from 1999–2000 to 2007–2008 [40]. Sreebny and Vissink categorized "xerogenic" medications according to the drug function and identified 58 drug categories and 71 sub-categories [7]. Smidt et al. showed that low UWSF was associated with psycholeptics, psychoanaleptics (especially selective serotonin reuptake inhibitors [SSRIs]), respiratory agents, oral antidiabetics (particularly sulfonylureas), magnesium hydroxide (typically prescribed for constipation), cardiac agents, quinine, thiazides, calcium channel blockers, statins, urinary antispasmodics, glucosamine, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and ophthalmologicals. In addition, use of antithrombotics (mainly low-dose aspirins), calcium channel blockers, or oral antidiabetics was associated with low unstimulated labial flow [17]. The methods used studies to assess the incidence and prevalence of xerostomia display large heterogeneity. The majority of the studies only registered xerostomia through a "yes" or "no" question, did not measure SFR or composition, and therefore did not assess the underlying SGD. Moreover, the majority of data came from convenience samples of institutionalized elderly with no discrimination among the etiologic factors of xerostomia [41, 42]. We are not aware of any population-based studies on the epidemiology of MISGD, despite the high-expected prevalence of this condition due to the large number of xerogenic medications consumed by a growing number of medicated persons. It is possible that the reported high prevalence of xerostomia is due to the large number of persons who receive pharmacological treatment, with a considerable likelihood that their medications are xerogenic. However, there are many other causes of xerostomia that deserve further investigation.

Diagnosis of MISGD

The diagnosis of MISGD requires a careful and systematic evaluation of the patient (Fig. 2). Initially, the clinician should review the patient's subjective complaints (oral dryness, difficulty swallowing, problems speaking; sensitivity to acidic or spicy food, taste disturbances, or difficulty tolerating dentures) [43]. These symptoms may have occurred shortly after the initiation of a new pharmacological treatment, or increased (or decreased), when drugs are taken for a long period of time. Several methods have been used for diagnosis of MISGD. In

general, they are similar to those used for assessment of SGD occurring in relation to Sjögren's syndrome, radiation therapy, or psychological conditions [44]. In this systematic review, we identified a total of 23 studies that assessed MISGD through different methods (Table 1).

Questionnaires for assessment of xerostomia

Several questionnaires have been proposed for investigation of SGD-related symptoms. Fox et al. attempted to identify questions with a good degree of reliability, which may therefore predict true SGD [45]. They developed a simple test for xerostomia that correlates well with major salivary gland output and consists of asking the following questions: (1) does the amount of saliva in your mouth seem to be too little, too much or you do not notice it?; (2) do you have any difficulty swallowing?; (3) does your mouth feel dry when eating a meal?; (4) do you sip liquids to aid in swallowing dry food? A positive answer to all four was found to be associated with salivary gland hypofunction. Sreebny and Valdini used a questionnaire on dry mouth-related symptoms and compared the results with those obtained from measurement of the SFR [46]. The question "does your mouth usually feel dry" had a sensitivity of 93 %, specificity of 68 %, positive predictive value of 54 %, and a negative predictive value of 98 % for salivary gland hypofunction. When other symptoms were taken into consideration (trying to keep the mouth moist, difficulty with speech, and getting out of bed to drink), the positive predictive value increased to 75 % and the specificity to 91 %. Thomson et al. proposed an 11-item summated rating scale which combines the responses to 11 items into a single continuous scale score for the severity of xerostomia (Xerostomia Inventory) [47]. Patients are asked to choose one of five responses ("never," scoring 1; "hardly ever," 2; "occasionally," 3; "fairly often," 4; and "very often," 5) to the following statements referring to the previous 4 weeks: "My mouth feels dry"; "I have difficulty in eating dry foods"; "I get up at night to drink"; "My mouth feels dry when eating a meal"; "I sip liquids to aid in swallowing food"; "I suck sweets or cough lollies to relieve dry mouth"; "I have difficulties swallowing certain foods"; "The skin of my face feels dry"; "My eyes feel dry"; "My lips feel dry"; and "The inside of my nose feels dry". Each patient's responses are then scored and summed to give a single Xerostomia Inventory score. This system showed a statistically significant correlation between the total number of medications taken and the Xerostomia Inventory score [48, 36]. Another study developed an 8-item visual analog scale to assess xerostomia [49]. Patients were asked to rate: (1) the difficulty they experience in speaking due to dryness, (2) the difficulty they experience in swallowing due to dryness, (3) how much saliva is in their mouth, (4) the dryness of their mouth, (5) the dryness in the throat, (6) the dryness of the lips, (7) the dryness of the tongue, and (8) the level of their thirst. Eisbruch et al. evaluated the grade of xerostomia through a validated scale: subjective grade 1: no disability; grade 2: dryness requiring additional fluids for swallowing; and grade 3: dryness causing dietary alterations, interference with sleep, speaking, or other activities [50]. Van der Putten et al. proposed a shorter version of the Xerostomia Inventory: the Summated Xerostomia Inventory-Dutch. In this questionnaire, five items ("My mouth feels dry when eating a meal"; "My mouth feels dry"; "I have difficulty in eating dry foods"; "I have difficulties swallowing certain foods"; and "My lips feel dry") were used, with the patient asked to choose one of three response options ("Never," scoring 1; "Occasionally," 2; and "Ever," 3) [13]. The only questionnaire that correlated xerostomia with medications was the Xerostomia Inventory, and therefore, it is probably the best one for the purpose of research on MISGD. However, it is quite long and therefore difficult to use in busy medical/dental practices. In addition, it was tested in non-institutionalized elderly and may not be generally applicable to the whole population. Finally, the questionnaire was sent to patients by mail prior to the clinical examination. This may have introduced a bias as family members could have helped participants. All the other questionnaires on xerostomia were used to assess the prevalence of dry mouth in the population, especially the elderly. However, they could be employed in future studies to test a possible relationship between xerostomia and medication intake. Positive answers to the xerostomia questionnaire may be predictive of true SGH and be a useful tool for the clinician to identify patients at risk. The Fox questionnaire and the Summated XI-Dutch are the shortest to administer to patients and may be employed in daily practice.

Medical history

A detailed history of present symptoms, type and number of medications, systemic and oral diseases, and previous therapies is important. A comprehensive medical history should be taken to exclude other known causes of SGD such as Sjögren's syndrome, radiation treatment of the head and neck region, and other systemic diseases, although SGD in these patients might be worsened by the medicaments they use (Fig. 2). Recording medication intake is fundamental to identifying MISGD. Particular attention should be paid to the mechanism of drug action, prescription source, dosage, duration of exposure, and drug interactions (being particularly common in relation to polypharmacy), bioavailability, and underlying influence of diseases like psychiatric and cardiovascular diseases, urinary incontinence, Parkinson's

Table 1 Methods used to assess MISGD

Authors	Type	Assessment methodology	Definition of MISGD patients	Definition of patients for comparison	Main findings/conclusions
Wu and Ship (1993) [54]	Observational study prospective	SSMLSF USMLSF USPF SPSF	Prescription medications	No medications	- Decrease in all flow rates with increasing numbers of medications and systemic diseases - Statistical significance ($p<0.05$) only for SSMLSF and USMLSF
Hunter et al. (1995) [35]	Observational study prospective	SPSF Salivary qualitative analyses	Amitriptyline, dothiepin, fluoxetine, or paroxetine	No medications	- Reduction among users of amitriptyline, $p<0.01$ and dothiepin, $p<0.05$ - Consequent decrease in [Na+] and increase in [K+]
Navazesh et al. (1996) [130]	Non-RCT	UWSF SWSF SPSF	Any medication (unspecified)	No medications	- All flow rates reduced - Medication intake for >2 years: significantly lower UWSF and SWSF than for intake for 1 to 2 years
Nordgarden et al. (1996) [131]	Non-RCT	UWSF SWSF SSMLSF USMLSF USPF SPSF Salivary qualitative analyses	Central stimulant treatment for narcolepsy	No medications	- Lower whole salivary flow rates - Lower buffering effect - Higher *Candida albicans* scores
Billings et al. (1996) [132]	Observational study retrospective	UWSF SWSF Xerostomia Questionnaire	Any medication (unspecified)	n/a	Xerostomia was significantly associated with use of medications, difficulty with dry foods, cracked lips, dry eyes, difficulty swallowing, and, among men, current cigarette smoking
Pajukoski et al. (1997) [133]	Epidemiological study	SWSF Salivary qualitative analyses	Any medication (unspecified)	n/a	- Endocrinological diseases, ophthalmologic and respiratory drugs, and potassium chloride reduced the salivary flow rate - IgA, IgM, lysozyme, and amylase concentrations: higher in older patients taking multiple drugs
Persson et al. (1998) [134]	Non-RCT	SWSF	Any medication (unspecified)	n/a	- Low SWSF (<0.01 mL/min) in 1/3 of patients using xerogenic medications - Hypothyroidism associated with low SWSF
Meurman et al. (1998) [135]	Observational study prospective	UWSF SWSF	Non-insulin-dependent diabetes mellitus (NIDDM)	No NIDDM	Number of medications correlated with salivary flow rates ($p<0.001$) only among controls
Thomson et al. (2000) [48]	Observational study prospective	UWSF Xerostomia Questionnaire	Any medication	No medications	- UWSF lower among females or users of antidepressants - UWSF higher among smokers or users of hypolipidemic drugs - Xerostomia severity higher among: - Females - Users of antianginal, antidepressant, or antiasthma agents at baseline and at 5-year follow-up - Users of antianginals without concomitant beta-blockers, thyroxine, and diuretics at 5-year follow-up
Moore et al. (2001) [136]	Epidemiological study	UWSF SWSF Xerostomia Questionnaire	Diabetes mellitus type I; patients on xerogenic drugs (anticholinergics, amphetamines, antidepressants, antihistamines, diuretics, and antihypertensive)	No diabetes	Xerogenic medications and elevated fasting blood glucose concentrations were significantly associated with decreased salivary flow rates
		UWSF	Patients on any medication (unspecified)	n/a	

Table 1 (continued)

Authors	Type	Assessment methodology	Definition of MISGD patients	Definition of patients for comparison	Main findings/conclusions
Last Pollak et al. (2002) [137]	Observational study prospective	SWSF			No statistically significant correlations were found with age, medications, diagnoses, or number of teeth
Fure (2003) [138]	Observational study prospective	UWSF SWSF	Any medication (unspecified)	n/a	Daily intake of ≥4 drugs significantly lowered salivary flow rates
van der Putten et al. (2003) [139]	Observational study prospective	UWSF SWSF	Any medication (unspecified)	n/a	Salivary flow rates decreased significantly with age ($p<0.05$). The number of prescribed medications was significantly higher in patients over the age of 70 and also in women
Lin et al. (2003) [140]	Non-RCT	UWSF SSMLSF USMLSF USPF SPSF Sialochemistry	HIV+ patients taking xerostomic drugs	Healthy individuals not taking any medication; HIV(+) not on xerogenic medications	All flow rates for HIV(+) were significantly lower as compared with those for control. The flow rates for the HIV(+) patients taking xerogenic medications did not differ from those of patients who did not
Vucićević Boras et al. (2006) [67]	Non-RCT	UWSF Salivary qualitative analyses	Patients with medication-induced xerostomia	Healthy individuals not taking any medication	No significant differences in salivary IL-6 and TNF-alpha
Scelza et al. (2009) [141]	Observational study prospective	UWSF SWSF	Elderly men and women; individuals taking any drug	n/a	Reduction of SWSF among users of cardiovascular agents
Cho et al. (2010) [83]	Epidemiologic study	Xerostomia Questionnaire UWSF SWSF	Antipsychotic medications (hypnotics, antidepressants, anxiolytics) or systemic diseases or medications affecting salivary flow rate (except for antipsychotics)	Sjögren's syndrome or post-radiation therapy in the head and neck region	- Burning sensation in the mouth: most prevalent in patients with systemic diseases or users of medications - Altered taste perception: most prevalent in patients taking antipsychotics
Smidt et al. (2010) [17]	Non-RCT	ULSF UWSF SWSF	Any medication (unspecified)	n/a	- Low UWSF, SWSF, and ULSF: associated with specific and high number of diseases and medications, among older patients - Low UWSF: associated with psychiatric and respiratory disorders, type 2 diabetes mellitus, and intake of psycholeptics, psychoanaleptics, respiratory agents, oral antidiabetics, magnesium hydroxide, cardiac agents, quinine, thiazides, calcium channel blockers, statins, urinary antispasmodics, glucosamine, NSAIDs, opioids, and ophthalmologicals - Low SWSF: associated with ophthalmological disorders, antiglaucoma agents and miotics, antidepressants, cardiac agents (mostly digitalis glycosides), and calcium channel blockers - Low ULSF: associated with cardiovascular diseases, antithrombotics, calcium channel blockers, and oral antidiabetics
Leal et al. (2010) [19]	Non-RCT	UWSF SWSF Salivary qualitative analyses Oral mucosa	Any medication	No medications	- Dry and cracked lips and fissured tongue among individuals direct relationship with consumption of xerogenic medication - Buffering capacity and UWSF: negative relationship with drug consumption
Ohara et al. (2011) [142]	Non-RCT	Xerostomia Questionnaire Oral mucosal moisture	Individuals on medications and xerostomia	Individuals with no xerostomia	Heart disease, the use of anti-inflammatory drugs and analgesics, a social role, difficulty in mastication, and

Table 1 (continued)

Authors	Type	Assessment methodology	Definition of MISGD patients	Definition of patients for comparison	Main findings/conclusions
					difficulty in swallowing were significantly associated with xerostomia
van der Putten et al. (2011) [13]	Observational study prospective	Xerostomia Inventory UWSF SWSF	Nursing home patients with no cognitive impairment, fever, dehydration, Sjögren's syndrome, or previously received radiotherapy in the head and neck region	n/a	- 44 % of all medications used were hyposalivation-related and women used significantly more medications than men - Salivary secretion rates not correlated with number of hyposalivation-related medications
Nonzee et al. (2012) [34]	Non-RCT	UWSF Salivary qualitative analyses	Patients with hypertension on antihypertensive medications	Healthy individuals taking no medications	Higher prevalence of xerostomia, lower mean stimulated salivary flow rate, and increasing numbers of salivary mutans streptococci, *Lactobacilli spp.* and *Candida spp.*
Gomez-Moreno et al. (2013) [94]	RCT	UWSF SWSF	Patients with antidepressant-induced xerostomia	n/a	Xerostomia in patients on antidepressants improved after 1 % malic acid topical spray application ($p < 0.05$) UWSF and SWSF increased after 2 weeks of 1 % malic acid application

Abbreviations: *IL* interleukin, *LSST* labial saliva starch test, *MW* mucosal wetness, *NSAID* non-steroidal anti-inflammatory drug, *RCT* randomized controlled trial, *SPSF* stimulated parotid saliva flow rate, *SS* Sjögren's syndrome, *SSMLSF* stimulated submandibular and sublingual saliva flow rate, *SWSF* stimulated whole saliva flow rate, *TNF* tumor necrosis factor, *ULSF* unstimulated labial saliva flow rate, *UPASF* unstimulated palatal saliva flow rate, *UPSF* stimulated parotid saliva flow rate, *USMLSF* unstimulated submandibular and sublingual saliva flow rate, *UWSF* unstimulated whole saliva flow rate

disease, Alzheimer's disease, HIV infection, and others [43, 30].

Extra- and intraoral examination

The dental and medical history should be followed by a thorough facial and intraoral examination including inspection and palpation of the salivary glands, expulsion ("milking") of saliva from the major salivary duct orifices (at rest and after a stimulus), and inspection of the oral mucosa and the dentition. However, there are no specific clinical signs that make it possible to discriminate among various causes of xerostomia and salivary gland hypofunction. A clear response to a stimulus, though, makes MISGD more plausible than no or hardly any secretory response on applying a stimulus as usually happens in cases of irreversible damage to glandular structures. Even salivary gland swelling is not always indicative of Sjögren's syndrome and may be related to sialoadenosis secondary to medication intake, a number of chronic diseases, sodium retention syndrome, malignancies, or parotitis [51]. Regardless of the etiology, patients may suffer from SGH without having xerostomia, but often display other signs and symptoms such as rampant dental decay (in particular cervical caries and smooth surfaces caries), bad breath, or burning mouth [4, 30]. Osailan et al. recorded oral dryness with a scoring system that is composed of ten features: (1) mirror sticks to buccal mucosa, (2) mirror sticks to tongue, (3) saliva frothy, (4) no saliva pooling in floor of mouth, (5) tongue shows loss of papillae, (6) altered gingival architecture/smooth (especially anterior), (7) glassy appearance to oral mucosa (especially palate), (8) tongue lobulated/deeply fissured, (9) cervical caries (more than two teeth), (10) mucosal debris on palate (excluding under dentures) [52]. Each item was assigned a score of 1 with 1 being the least and 10 being the most severe.

Measurement of salivary flow rates

The clinical examination of a patient with presumed MISGD should be followed by the measurement of salivary flow rates. In most studies on MISGD, salivary flow rates have been determined by collection of unstimulated and stimulated whole saliva or selective secretions from the salivary glands by various methods. Whole saliva is a mixture of salivary gland secretions, food debris, crevicular fluid, microorganisms, oral epithelial cells, neutrophils, and bronchoalveolar and nasal secretions. Consequently, the term "oral fluids" was suggested instead of whole saliva [53]. In cases of MISGD, the UWSF is usually markedly reduced, whereas the chewing-stimulated flow rate is often within the normal range [17, 54]. However, intake and/or prolonged use of drugs with anticholinergic effects and centrally acting analgesics

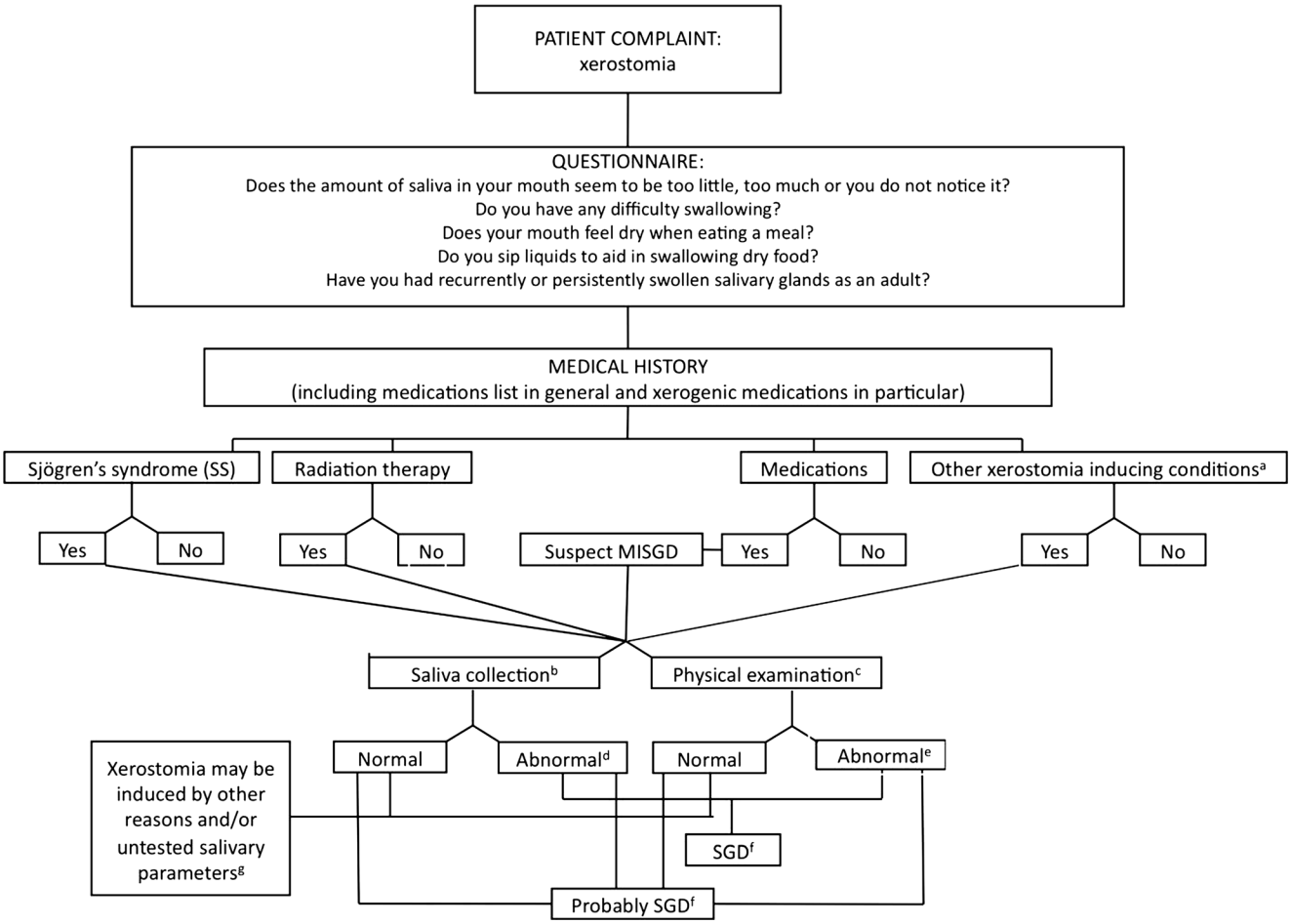

Fig. 2 Diagnostic algorithm for MISGD in patients with xerostomia. *a* e.g., congenital aplasia, graft-versus-host disease, Alzheimer's disease, Parkinson's disease, not identified. *b* Please refer to "Diagnosis of MISGD" in the manuscript. *c* Investigation of caries, candidiasis, mucosal changes [52], or salivary gland swelling. *d* Decreased unstimulated whole saliva flow rate and normal stimulated whole saliva flow rate may indicate the presence of MISGD. *e* Consider sialadenosis or medication-induced parotitis in case of salivary gland swelling. *f* Depending on the medical background, SGD is induced by SS, radiation therapy, medications, or other conditions. *g* Untested quantitative and/or qualitative salivary parameters may be abnormal. *Abbreviations*: *SGD* salivary gland dysfunction. Types of xerostomia by their etiology are not mutually exclusive

often cause diminution of both UWSF and SWSF [18]. There are several methods for assessment of the UWSF as well as various stimulation techniques (Table 1). Most of these methods rely on the patient's cooperation and are painless. The secretion and/or composition of saliva are influenced by many factors, including patient's gender, and the time of day and duration of collection. Saliva is typically collected in morning hours for at least 5 min. Too long (>15 min) or too short (<1 min) collection periods may produce unreliable values of the salivary flow rates. Patient should avoid eating, drinking, smoking, and tooth brushing 2 h prior to assessment of salivary gland function [55, 56]. The flow rate of whole saliva/major salivary gland secretion is expressed as milliliters per minute (the density of 1.0 g/mL is assumed).

Measurement of unstimulated whole saliva flow rate Methods for collecting UWSF include draining, spitting, swab (absorbent), and suction methods. The "draining method" can easily be conducted in the dental office. UWSF is collected with the patient in an upright position. The individual is instructed to swallow and then tilt the head forward so that saliva moves anteriorly in the mouth. After the initial swallow, the patient allows saliva to drain continuously from the lower lip through a funnel into a graduated or preweighted cylinder for 15 min, at the end of which residual saliva in the mouth is spat out [57]. When using the spitting method, saliva is allowed to accumulate in the floor of the mouth with the mouth closed and the patient spits it out into a test tube every 60 s or when they experience the urge to swallow the accumulated fluid. The tube can be fitted with a funnel to ease collection of saliva [57]. This spitting method may cause a stimulatory effect on saliva secretion and may not reflect reliable values of UWSF. However, it may be a valuable method in patients with severely reduced SFRs, since the

degree of evaporation of saliva is less compared with the draining method. In the suction method, saliva is suctioned from the floor of the mouth into a graduated test tube by a saliva aspirator or ejector. The amount of saliva is determined by weighing or reading off the level in a graduated tube [19]. Finally, relatively unstimulated whole saliva can be collected by pre-weighed cotton rolls, swabs, or gauze sponges which are placed in the oral cavity at the orifices of the ducts of the major salivary glands and these are reweighed at the end of the collection period [19]. Van den Berg et al. used the UWSF draining method during a 15-min time period to differentiate between patients with Sjögren's syndrome, patients with salivary gland disease related to metabolic or cardiovascular disorders, and patients suffering from MISGD [58]. However, the results did not provide any new insights to differentiate between the different causes of SGD. Chen et al. proposed using a graduated absorbent strip on the floor of the mouth to take readings at 1, 2, and 3 min [59]. This is an easy-to-perform and well-tolerated test for measuring unstimulated whole saliva secretion.

Measurement of stimulated whole saliva flow rate For stimulated saliva, the patient is instructed to chew a standard piece (1–2 g) of paraffin wax or unflavored gum base at a fixed rate (e.g., 70 chews/min) [60]. Another method uses a solution of citric acid at a concentration of 2 % applied to the sides of the tongue every 30 s. The saliva is then collected into a graduated cylinder, usually at fixed intervals (over a period of 5 min). Of note, the use of a gustatory stimulus may interfere with subsequent assays of salivary composition.

Measurement of selective glandular secretion To measure the parotid SFR, the clinician may place a modified Lashley or Carlson-Crittenden cup over the orifice of the parotid/Stensen's duct [61]. It is relatively simple to apply these cups, but the method is primarily used in research settings or dry mouth clinics. The outer chamber is attached to a suction device via plastic tubing, and the inner chamber is placed over Stensen's duct. Unstimulated parotid salivary flow rates are often very low or even absent, and consequently, parotid saliva is usually collected under stimulated conditions. The salivary flow of a submandibular gland can be measured through the use of a cannula entering the appropriate Wharton's duct. Schneyer proposed the use of a segregator, a custom-made device with two lateral chambers for the collection of saliva from the sublingual glands and a central chamber for the saliva from both submandibular glands [62]. Another simple method to collect the mixed saliva from the sublingual and submandibular glands is to block Stensen's ducts and then isolate the Wharton's, Bartholin's, and other ducts. Afterwards, the saliva can be collected with a syringe from the floor of the mouth. Finally, Wolff et al. developed a saliva collection system for both sublingual and submandibular glands. This system has tubing for collection, a buffering chamber, a storage tube, and a suction device [63]. Minor salivary gland secretions can be collected by various techniques including micropipette and absorbent filter paper. Secretion volumes may also be determined by the Periotron® method (ProFlow™ Inc., Amityville, NY, USA). For the latter, the oral mucosa is initially dried with cotton gauze and a filter paper of known area is placed over a small region of the oral mucosa. Fluid is collected on the filter paper over a given time period and the volume determined using the change in conductance in the Periotron® [64]. Flow rates can be calculated in units of μL/min/cm^2 of mucosal area [18].

Analyses of salivary composition

Assay of the organic and inorganic constituents in saliva may be a valuable diagnostic tool for many diseases. However, most salivary constituents display large variations even for healthy persons and the concentrations of various constituents are strongly dependent on the flow rate and consequently on the type and intensity of the stimulus applied during collection of saliva. Consequently, in order to determine changes in saliva composition, e.g., electrolytes and proteins, it is important to know at least the rate at which the saliva is secreted. Compositional changes of saliva may reflect disturbances of acinar cell secretion of electrolytes, water, and proteins, as well as functional disturbances of the salivary duct cells. The literature on compositional changes in saliva in relation to medication intake is very limited and still not sufficient to be used in the diagnosis of MISGD. It has been shown that patients undergoing chemotherapy for breast cancer had compositional changes reflected by a small increase in salivary sodium and chloride concentrations as well as a decrease in inorganic phosphate concentration, in spite of lower or unchanged flow rates. These findings suggest that acinar and ductal cell functions are affected by chemotherapy [65]. Bardow et al. showed that patients on daily medication use reporting xerostomia with lower stimulated whole saliva flow rates had lower unstimulated and stimulated outputs of bicarbonate, calcium, phosphate, and protein, and higher levels of *Lactobacillus species* [66]. Sialochemical changes have also been observed in patients taking antihistamines and antidepressants as they reduce the salivary secretion by inhibition of the muscarinic cholinergic receptors [35], and β-blockers may lead to impaired protein secretion [41]. However, none of these medications caused specific changes in the inorganic salivary composition. Vucićević Boras et al. did not find any significant differences in salivary tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 levels in patients with medication-induced xerostomia compared with controls [67]. Interestingly, in the last decade, the field of saliva proteomics has developed extensively, resulting in the discovery of numerous potential salivary biomarkers [68, 69]. These have been used or are currently being tested for diagnosis of SGD related to diseases, but not for MISGD [70–73]. To date, there

is no consensus for MISGD evaluation and further studies on the organic and inorganic components of saliva in MISGD are needed.

Investigation of structural salivary gland changes

There are no systematic studies on how the various medications may influence human salivary gland morphology. Studies on rodents have shown that quinolone-based antibiotics may alter the secretory function of the parotid glands and inhibit cell regeneration and proliferation [74]. Bedi showed that the nonselective β-agonist isoproterenol or β1-selective agonists increased the level of proline-rich proteins in the parotid glands of rats and caused an increase in size of the glands within days [75]. They also caused induction of salivary cystatin in submandibular glands in rats but did not affect the parotid amylase concentration. A study by Schneyer investigated the effect of dobutamine and the β2 adrenergic agonist, terbutaline on rat submandibular, and parotid glands [76]. Dobutamine is an adrenergic agonist usually incorrectly presented in the literature as a selective β1 receptor stimulant; it is, however, noteworthy that dobutamine also acts on β2 and α1 receptors [77]. Results showed that both medications caused an increase in gland size, which was greater with dobutamine. Of note, terbutaline acts also on β1 receptors at higher doses. The selective β1 antagonist metoprolol has been shown to prevent the terbutaline-produced gland enlargement in rats [78]. Bloom et al. showed that administration of isoproterenol in rats caused both hypertrophy as well as hyperplasia of the parotid and submandibular glands with an associated increase in weight [79]. Importantly, animal experiments show the gland weight to be unaffected by prolonged treatment with parasympatholytics in contrast to parasympathetic denervation, which results in a marked weight loss [80]. It may be that parasympathetic non-adrenergic, non-cholinergic transmission mechanisms are those that regulate the gland weight rather than acetylcholine [81].

Use of diagnostic methods to compare patients with MISGD and patients with other types of SGD

Different studies compared MISGD with other types of SGD. Kaplan et al. performed major gland sialometry (unstimulated and stimulated parotid saliva flow rates [82]; unstimulated and stimulated submandibular and sublingual saliva flow rates) and complementary tests in patients with SGH due to: (1) medication, (2) Sjögren's syndrome, (3) radiotherapy to the head and neck region, (4) idiopathic salivary gland hypofunction, (5) xerostomia without SGH, and (6) no xerostomia and no intake of xerogenic medications (controls). The lowest unstimulated and stimulated flow rates were reported in patients who had received radiotherapy, whereas there were no statistically significant differences among the patients with intake of medications, Sjögren's syndrome and idiopathic salivary gland hypofunction. Van den Berg et al. collected data on salivary gland function, saliva composition, sialographic imaging, Schirmer's tear test, and level of subjective complaints in patients with primary and secondary Sjögren's syndrome, sialadenosis, sodium retention syndrome, medication-induced xerostomia (use of xerogenic medications, but no evident salivary gland pathology), and on patients with no disease directly related to salivary gland pathology [58]. Unstimulated and stimulated submandibular/sublingual salivary flow rates were significantly lower in Sjögren's syndrome patients than in the other groups. Patients with sialadenosis, Sjögren's syndrome, and medication-induced xerostomia had significantly lower UWSF than patients without salivary gland pathology and patients with sodium retention syndrome. SWSF rates were significantly lower in patients with Sjögren's syndrome and sialadenosis compared with the other groups. Cho et al. measured the UWSF and SWSF in five groups of patients [83]. The patients also completed a questionnaire on xerostomia. The groups included patients with: (1) Sjögren's syndrome, (2) a history of radiotherapy of the head and neck area, (3) intake of antipsychotics, (4) systemic diseases or intake of medications, except for antipsychotics, and (5) dry mouth of unknown etiology. Patients with dry mouth of unknown etiology had the highest flow rates, and patients with a history of radiotherapy had the lowest UWSF and SWSF rates. Patients with a history of radiotherapy also had the most severe dry mouth-related symptoms and behaviors. The consequences of medication-induced SGH are comparable with those seen in patients with Sjögren's syndrome or patients who had received radiotherapy, although in some cases less severe. In conclusion, the methods that are common to the evaluation of the different types of SGD are useful for quantitative comparisons among them. However, at present, none of them is considered to be a gold standard procedure for the diagnosis of MISGD. New methods are needed to provide better understanding of the mechanism of action of many of the xerogenic medications.

Treatment and prevention of MISGD

Treatment of MISGD resulting in SGH aims to relieve symptoms and to stimulate salivary secretion (Table 2). Therapeutic strategies include improved hydration, humidifiers, avoidance of irritating dentifrices and crunchy/hard foods, use of saliva stimulants, such as sugar-free chewing gums or sugar-free candy and/or medications, and saliva substitutes/mucosal lubricants [84].

Pharmacological stimulants

The most commonly used medications for stimulation of salivary glands and to alleviate xerostomia include pilocarpine

Table 2 Treatment modalities for medication-induced salivary gland hypofunction and/or xerostomia

Authors	Type	Diagnosis	Product	Main findings/conclusions
Bagheri et al. (1997) [143]	RCT	Tricyclic antidepressants or neuroleptics induced xerostomia	Yohimbine and anetholtrithion	Increased the UWSF
Hooper et al. (1997) [144]	Observational study prospective	Xerostomia secondary to oxybutynin therapy	Salivix	The frequency of xerostomia was unchanged but there was a significant decrease in median severity
Götrick et al. (2004) [145]	Non-RCT	Tramadol-induced xerostomia	Pilocarpine	Increased the UWSF
Masters (2005) [146]	Other	Xerostomia secondary to clozapine and olanzapine; benztropine; tricyclic antidepressants and mirtazapine	Pilocarpine	Good response
Papas et al. (2006) [147]	RCT	Medication-induced xerostomia	Powered toothbrush	Beneficial
Aframian et al. (2007) [93]	Non-RCT	Medication-induced xerostomia (unspecified)	Pilocarpine	Good response
Ship et al. (2007) [103]	Non-RCT	Medication-induced xerostomia (unspecified)	Olive oil, betaine, xylitol	Relieved xerostomia and increased unstimulated whole salivary flow rate
Kharevich et al. (2011) [148]	Case study	Medication-induced xerostomia (unspecified)	Salese lozenges	Salivary pH shift to a more neutral level in patients with xerostomia secondary to medication use
Loosström et al. (2011) [149]	RCT	Tramadol-induced xerostomia	Pilocarpine	Increased the UWSF with well-preserved protein concentration but decreased IgA concentration
Gomez-Moreno et al. (2013) [95]	RCT	Antihypertensive-induced xerostomia	Malic acid 1 %	Improved the UWSF and SWSF

Abbreviations: RCT randomized controlled trial, *SWSF* stimulated whole saliva flow rate, *UWSF* unstimulated whole saliva flow rate

and cevimeline [85, 86]. Pilocarpine is a parasympathomimetic agent with potent muscarinic, cholinergic stimulating properties. The stimulatory effect of pilocarpine requires the presence of functional residual glandular tissue. This agent exerts a broad spectrum of pharmacological effects with predominant muscarinic action via M3 and M1 receptors [85–87]. In addition to the stimulation of muscarinic receptors in the salivary gland tissue, the superior cervical ganglion is stimulated and leads to the release of norepinephrine and subsequent stimulation of α and β1-adrenoceptors [88]. A closely related sialogogue, cevimeline, is a quinuclidine analog with a 40-fold greater affinity for M3 receptors compared with pilocarpine (in animal studies) [89, 85, 90, 88, 91]. Despite the greater affinity/selectivity, the response/adverse effect profiles of the two agents are very similar [92]. The most commonly used and studied formulation is pilocarpine tablets 5 mg up to three times a day for at least 3 months before the treatment effect can be evaluated and cevimeline tablets 30 mg up to three times a day for at least 3 months [93]. Systemic sialogogues usually provide a longer effect than topical therapies. Cholinergic adverse effects other than hypersalivation include nausea, emesis, diarrhea, singultus, hypersudoration, cutaneous vasodilatation, bronchoconstriction, pollakiuria, bradycardia, hypotension, and difficulty in visual accommodation. In addition, they should be used with prudence in patients with cardiovascular diseases, asthma, and chronic pulmonary disease. Pilocarpine is contraindicated in acute asthma attack, narrow-angle glaucoma, and iritis [91, 86]. As stated in the label of Evoxac® (Daiichi Pharmaceutical Corporation; Montvale, NJ), cevimeline is contraindicated in patients suffering from these conditions, as well. Patients affected by MISGD may be taking medications that interact with pilocarpine or cevimeline. Specifically, attention should be paid in patients taking anticholinergic xerogenic medications [86]. Parasympathomimetics, due to their muscarinic receptor stimulation, may antagonize the anticholinergic effects of certain drugs. Such medications include diphenhydramine, promethazine, and trimeprazine, phenothiazines (e.g., mesoridazine, promazine, thioridazine, and trifluprom azine), some antidepressants (e.g., amitriptyline, amoxapine, bupropion, clomipramine, doxepin, maprotiline, and protriptyline) as well as clozapine, cyclobenzaprine, and disopyramide. Pilocarpine should also be given with caution to individuals taking β-adrenergic antagonists because of possible cardiac conduction disturbance. As a general rule, before prescribing a pharmacologic saliva stimulant, it is recommended that the relevant treating physician(s) be consulted. In addition, before prescribing any medication, it is recommended to check whether non-pharmacological stimulants, such as chewing gum, have any effect, to ensure gland functionality.

Intraoral topical agents

There are several other over-the-counter products (either saliva stimulants or substitutes) available for the management of SGH. Two recent studies demonstrated the efficacy of a topical sialogogue spray containing 1 % malic acid in patients with antidepressant or antihypertensive-induced xerostomia [94, 95], although a malic acid-containing spray can potentially lead to enamel erosion. Other options for the treatment of SGH include the use of sugar-free chewing gums or candy to stimulate salivary secretion, and the use of non-alcoholic oral care products (including mouthwash, gel, toothpaste, and oral spray) [96]. Saliva substitutes help to moisten and lubricate the oral cavity by mimicking natural saliva [97]. They contain agents to increase viscosity, such as hydroxyethylcellulose, carboxymethylcellulose, mucin or xanthan gum, minerals such as calcium and phosphate ions and fluoride, preservatives such as methyl- or propylparaben, and flavoring and related agents [84].

Mucin spray for management of xerostomia was tested in four placebo-controlled trials [98, 97, 99, 100]. Overall, results were controversial with little evidence that mucin spray saliva substitute was more effective than placebo [96]. However, a study in which mucin-containing lozenges were compared with placebo lozenges in patients affected by Sjögren's syndrome showed highly statistically significant differences between mucin and placebo for the treatment of xerostomia [101].

Mouly et al. proposed a new oxygenated glycerol triester (OGT) oral spray (1 or 2 doses up to 4 times daily) for the treatment of xerostomia which was reported to be more efficacious when compared with another commercially available oral saliva substitute (ASS [Saliveze]) [102]. Ship et al. evaluated the efficacy of topical dry mouth products (toothpaste, mouth rinse, mouth spray, and gel) containing olive oil, betaine, and xylitol in a single-blinded, open-label, cross-over clinical study on 39 patients and found them to be safe and effective in relieving xerostomia in patients with MISGD [103].

Aframian et al. introduced a mucoadhesive lipid-based bioerodable tablet applied to the hard palate for the treatment of xerostomia [104]. Kerr et al. compared the efficacy of a similar mucoadhesive disk containing lubricating agents (carbomer homopolymer and triglycerides), flavoring and taste agents, and antimicrobial agents (glucose oxidase, lysozyme, and lactoferrin) with a placebo disk [105]. Both the active agent and the placebo were associated with an increased sense of oral moistness. Finally, other studies tested a saliva substitute spray containing carboxymethylcellulose [106], xanthan gum-containing spray [107] or buffered "Prophylin" gel [108] with limited benefit for the patient. Of interest, Regelink et al. reported that saliva substitutes are not thought to be effective in patients with reasonable stimulated SFR [109]. In summary, saliva substitutes are widely used, even with medically compromised patients. However, as of to date, evidence supporting topical treatment for relieving xerostomia secondary to medication use is controversial. Moreover, certain preparations are acidic and therefore should not be prescribed to dentate patients, in which hyposalivation implies an added risk for dental caries.

Changes in medication intake

Other management options for medication-induced SGH include a possible reduction in the number or dosage of the medications taken by the patients or replacement with medications or formulations with fewer xerogenic effects [110]. Little evidence is available on this important topic.

Changes in medication dosage Azodo et al., for example, managed xerostomia among psychiatric patients by reducing the medication dose in 41 % of patients [111]. However, no controlled data are available on the true benefit secondary to the medication dose reduction. Several studies showed a medication dose-related increase in xerostomia. Bray et al. showed that sibutramine, a medication for weight loss, caused xerostomia with a dose-related increase (1 mg: 9/149 (6 %); 5 mg: 20/169 (12 %); 10 mg: 34/203 (17 %); 15 mg: 50/196 (26 %); 20 mg: 47/146 (32 %); 30 mg: 48/151 (32 %)) [112]. Similarly, Johnston et al. showed that xerostomia secondary to bupropion for smoking cessation increased with increasing dose [113]. Bauer et al. compared two groups of patients taking once-daily quetiapine extended-release (XR) adjunctive to ongoing antidepressant therapy [114]. Those taking 300 mg/day quetiapine XR reported higher rates of xerostomia compared with the group of patients taking quetiapine XR 150 mg/day (40 vs. 27 %). Kane et al. in a double-blind, placebo-controlled study on armodafinil for treatment of schizophrenia reported higher frequency of xerostomia in patients taking higher doses (150 mg: 2/71 (3 %); 200 mg: 3/69 (4 %); 250 mg: 6/71 (8 %)) [115].

Changes in number of medications The severity of xerostomia has been also associated with increasing number of medications [56]. In a cross-sectional study, Bardow et al. showed that both the total number of daily medications and the number of xerogenic medications were significantly associated with xerostomia (p=0.50 and p=0.52, respectively, p=0.01) [66]. Similarly, Villa and Abati showed that dental patients taking more than three medications/day were at a higher risk of having xerostomia compared with patients taking only one medication daily (OR=2.9, 95% CI 1.4–6.2, p<0.01) [116]. Brooks et al. found that xerostomia was more prevalent in individuals with bipolar disorder taking more than one second-generation antipsychotic (84/162 (52 %)) compared with patients taking only one

antipsychotic (503/1796 (28 %)) [117]. Helenius-Hietala et al. (2013) showed that recipients of liver transplantation taking eight medications or more had higher odds of reporting xerostomia in comparison with those taking less than four medications (OR=4.8, 95% CI 0.16–0.81, p= 0.005) [118]. Two additional randomized controlled studies showed that the incidence of xerostomia in patients receiving two medications was higher compared with patients receiving one medication plus placebo. Specifically, Vulink et al. showed that patients with non-refractory obsessive-compulsive disorder taking citalopram and quetiapine had more xerostomia compared with patients taking citalopram and a placebo (13/39 (33 %) vs. 5/37 (14 %), p=0.026) [119]. Houston et al. found that patients with bipolar mixed episodes taking divalproex and olanzapine reported higher rates of xerostomia compared with patients taking divalproex and placebo (3/101 (3 %) vs. 13/101 (13 %), p=0.017) [120]. We conclude that the severity of xerostomia with increasing number of medications may be due to the fact that taking an additional xerogenic drug increases and/or potentiates the xerogenic effect of the original medication.

Changes in medication formulation and type Different classes of medications and different formulations may be associated with fewer adverse effects. A meta-analysis by Wilson et al. showed that xerostomia was more prevalent in patients taking tricyclic antidepressants (28 %) when compared with patients taking selective serotonin reuptake inhibitors (7 %) [121]. Thus, in agreement with the patient's psychiatrist, patients taking tricyclic antidepressants may be switched to a different antidepressant known to impart a lesser xerogenic effect. Another example comes from the treatment of overactive bladder which has been associated with xerostomia and often leads to treatment discontinuation [122]. Different formulations may cause less xerostomia. For example, Drutz et al. showed that tolterodine immediate-release is better tolerated than oxybutynin immediate-release in terms of frequency and severity of xerostomia [123]. In addition, extended-release formulations of these medications are administered only once per day and have more consistent pharmacokinetics, which may help to decrease the frequency and severity of adverse events compared with immediate-release formulations.

Others

Another interesting method to increase the SFR is intraoral electrostimulation [124, 125]. Intraoral appliances (e.g., "GenNarino" and "Saliwell Crown") have been reported to reduce xerostomia and to increase production of saliva [126]. Khosravani et al. showed that topical application of the anticholinesterase, physostigmine, on the oral mucosa for the treatment of xerostomia was a successful alternative to systemic treatment [127]. The drug diffused through the mucosal barrier and the underlying mucin-producing minor glands were stimulated to secrete saliva, with few or no systemic adverse effects.

Conclusions

SGD is a clinically significant adverse effect, mainly from medication use, and occurs frequently. The overall prevalence of xerostomia ranges from 1–65 % [128] in the population with limited data on the epidemiology and cost of MISGD. Large prospective studies are needed to determine the true epidemiology of MISGD. This systematic review found that most of the studies on xerostomia secondary to medication were small and used a heterogeneous number of methods to assess the SFR or xerostomia. Although there are promising approaches to improve salivary gland function, data are still limited. The majority of treatment options focused on SGD in general rather than specifically on MISGD. Moreover, no randomized controlled studies evaluating diagnostic and therapeutic options for MISGD were available.

Of interest, there may be patients with asymptomatic SGH, i.e., patients who do not complain of xerostomia although their UWSF are at a low level. Clinicians may diagnose these patients with MISGD through signs and symptoms that are surrogates for SGH such as rampant tooth decay, mucosal changes, oral candidiasis, difficulty talking or eating certain foods, halitosis, or an oral burning sensation. Adding these signs and symptoms to the anamnesis and history of medication intake may result in identifying a larger number of patients suffering from MISGD. Also, health care providers should be aware of the underlying disease for which patients are taking medications that may induce SGD. Patients with poorly controlled psychiatric disorders, who are taking xerogenic medication, may have a higher rate of complications secondary to SGD due to a lower rate of adherence to preventive recommendations by oral health care providers [129]. In addition, this group of patients may have a lack of motivation and poor self-care, which are barriers to good oral hygiene practice [111].

Healthcare professionals have a responsibility to take an active role in the diagnosis and management of MISG D. Both physicians and dentists should identify the medications associated with SGH and xerostomia through a thorough medical history collection. In addition, ideally, oral health providers should measure the UWSF rate of all their patients, at least at their first appointment, as a baseline for the patient who later in his or her life develops SGH and/or xerostomia.

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