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International Journal of Aging and Geriatric Medicine

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Vol: 1 & Iss: 1

Review

Dry Mouth and Hyposalivation: Two Common Conditions with High Burden Deserving Full Attention

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Citation: Maheu E, Reynaud-Lévy O. Dry Mouth and Hyposalivation: Two Common Conditions with High Burden Deserving Full Attention. *Int J Aging Geriatr Med 2025*, 1(1), 16-25.

Received: 06 October, 2025; **Accepted:** 21 October, 2025; **Published:** 23 October, 2025

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ABSTRACT

Dry mouth, possibly associated with salivary gland hypofunction, is a very common condition affecting up to 33% of the population and even more in the elderly. This problem is increasing with the aging of the population and the use of psychotropic drugs. The main causative factors are age, xerostomia drugs and various diseases, the best known being Sjögren's syndrome, diabetes, asthma, neurological conditions such as Parkinson's disease, cognitive disorders such as Alzheimer's disease, dehydration, head and neck cancers, as well as many local disorders associated with poor oral health. This condition, which has a high burden in terms of both oral and systemic consequences, is unfortunately under-recognized, especially in the elderly. It can affect oral perception, the ability to eat, taste and speak, as well as other functions, with a lasting impact on patients' quality of life. Few treatments are truly effective in restoring salivary function or improving dry mouth symptoms. Non-pharmacologic topical treatments including artificial saliva/saliva substitutes, chewing gum and oxygenated glycerol triester spray have been proposed, some of which have demonstrated short-term symptomatic efficacy. There is a lack of good clinical trials evaluating the efficacy of drugs, local treatments and interventions in large-scale, long-term studies. Given the condition's expected increase in prevalence and its impact on local oral and general health, more work and effort are needed to address these issues. Because treating dry mouth is such a challenge, dentists, physicians and pharmacists must work together so as to prevent it.

Keywords: Dry Mouth, Hyposalivation, Xerostomia, Salivary Glands, Elderly, Treatment

1. Introduction

Dry mouth and hyposalivation are two distinct, very common conditions that occur separately or together[1]. Because they have a significant impact on oral (especially dental) health and daily life[2,3], they are a major healthcare and economic burden[4]. Xerostomia is defined as the subjective sensation of dry mouth and is mostly diagnosed by self-report (using questionnaires or a single question)[5]. Saliva is one of the most diverse and multifunctional substances produced by the human body. It plays a major role in oral health[6]. Among its multiple functions are the formation of the food bolus, role in taste perception and lubrication of the oral mucosa, facilitation of chewing, swallowing and phonation, neutralization of ingested acids and defense and protection of the oral mucosa against microorganisms[7]. These multiple functions are due to the presence of many compounds in saliva such as bicarbonates, calcium, mucins, peroxidase, phosphates, proteins, urea, lactoferrin, immunoglobulin A, as well as histatins[8].

Hyposalivation is defined as a low salivary flow that can be objectively identified and measured[9], resulting from salivary gland hypofunction (SGH). It can be measured by collecting saliva from the salivary glands or by collecting whole saliva to assess global salivary flow. The difficulty is that there is no consensus yet on the level of flow that reflects hyposalivation. It can range from less than 0.1ml/mn of unstimulated saliva[9] to 0.8ml/mn of stimulated saliva[10].

Many different health conditions and risk factors are involved in or responsible for xerostomia or hyposalivation. The most commonly cited factors are age, iatrogenic causes due to many drugs that are especially prescribed in the elderly, diabetes, autoimmune diseases with Sjögren's syndrome (SS) being the first, stomatologic diseases, radiotherapy for head and neck cancers, as well as conditions with dehydration.

2. Diagnosis

Diagnosis is mostly clinical, based on patient history and examination. Definitions and tools for diagnosis vary depending on studies and publications.[4] For dry mouth, questionnaires were developed between 1987 and the late 1990s[11–15].

For xerostomia symptoms, a simple question about dry mouth can be sufficient. It requires a global approach from the patient, including all their experiences about dryness and how their mouth is dry. Several formulations have been proposed. The most commonly used and validated since 1993[13] asks "How often does your mouth feel dry?" with response options of "never", "sometimes", "often" or "always". Multi-item scales have been proposed and validated. However, item batteries often fail to characterize xerostomia and often perform no better than the single xerostomia item[16]. Summated multi-item rating scales allow for a better assessment and classification as dry mouth/xerostomia in patient or populations studies. The use of continuous variables allows for better perception and exploration of differences in xerostomia than binary (xerostomia: yes/no) or ordinal (xerostomia: severe/moderate/none) approaches. A specific description and accurate measurement of each aspect is needed to measure the dry mouth incidence at the patient or population level **(Table 1)**.

Table 1: Symptoms and signs of xerostomia and salivary gland hypofunction (adapted from [16]).

	Aspect of dry mouth	
	Xerostomia	Hypofunction
Domain	Symptom(s)	Sign(s)
Measurable features	Experiential aspects Behavioral aspects	Salivary flow rate
Measurement options	Single item Multi-item methods Batteries of items Summated rating scales	Stimulated flow Unstimulated flow Whole salivary flow Glandular salivary flow

An 11-item summated rating scale to identify and specify dry mouth was developed by Thomson in 1999[14] for the elderly, the Xerostomia Inventory, which is currently widely used. It was then shortened to a 5-item short-form (SXI-D) for ease of use, especially in community studies[15]. The scoring was also reduced from five possible answers to three: "never", "occasionally" and "often" (range: 1 to 3; global range of the scale: 5 to 15) **(Table 2)**.

Table 2: Short-form version of the Xerostomia Inventory (SXI-D)[15].

	Short-form version of the Xerostomia Inventory
Item content	My mouth feels dry when eating a meal My mouth feels dry I have difficulty eating dry foods I have difficulty swallowing certain foods My lips feel dry
Response options	'Never' (score 1), 'Occasionally' (2), 'Often' (3)
Possible score range	5 (no xerostomia) to 15 (worst xerostomia)

Another subjective scale for the xerostomia assessment consists of seven questions with a proposed binary response mode **(Table 3)**[11,12].

Table 3: Subjective evaluation of xerostomia[4,11,12].

Question	Answer
Do you have difficulty swallowing food?	Yes/No
Does your mouth feel dry when you eat a meal?	Yes/No
Do you sip liquids to help you swallow dry foods?	Yes/No
Does the amount of saliva in your mouth seem low?	Yes/No
Does the amount of saliva in your mouth seem excessive?	Yes/No
Dryness of lips	Present/Absent
Dryness of buccal mucosa	Present/Absent

Thomson recommends measuring both xerostomia and salivary flow[15], as diagnosis of SGH requires salivary flow measurement. The flow rate must then be compared to a reference or threshold value. Individuals with a salivary flow rate below this threshold are considered to have SGH. The diagnosis of xerostomia is based on the patient's answers to one or more questions about their "dry mouth" symptoms.

Salivary flow can be assessed by measuring unstimulated salivary flow rate or stimulated salivary flow rate, with unstimulated salivary flow rate being measured first. Salivary flow can be measured by collecting saliva from the entire mouth or by collecting saliva from a salivary gland, which is painful or at least uncomfortable. In practice, the test is usually performed on whole saliva, which better reflects the clinical reality.

3. Prevalence

A systematic literature review by Agostini et al., conducted in 2018[17], found a prevalence of 23% (95% confidence interval [95%CI]: 0.18-0.28) for xerostomia, of 20% (95%CI: 0.15-0.25) for hyposalivation and of 22% (95%CI: 0.17-0.26) for dry mouth overall. This review was based on 29 studies for dry mouth, 14 studies for hyposalivation and 26 studies for xerostomia **(Figure 1)**. Studies were included in the meta-analysis if they were population-based with representative samples, but not samples of a specific disease (asthma, cancer, depression or SS). Case reports, retrospective studies and literature reviews were excluded from the meta-analysis.

A recent study investigated the prevalence of hyposalivation in the elderly[18]. The authors performed a review and meta-analysis of five databases, including all observational studies that evaluated hyposalivation in patients aged 60 years and older using either unstimulated or stimulated salivary flow methods. They excluded specific studies in patients with SS, diabetes, cancer or radiation therapy, as well as studies in animal models, ex-vivo or in-vivo, reviews, letters, book chapters and abstracts.

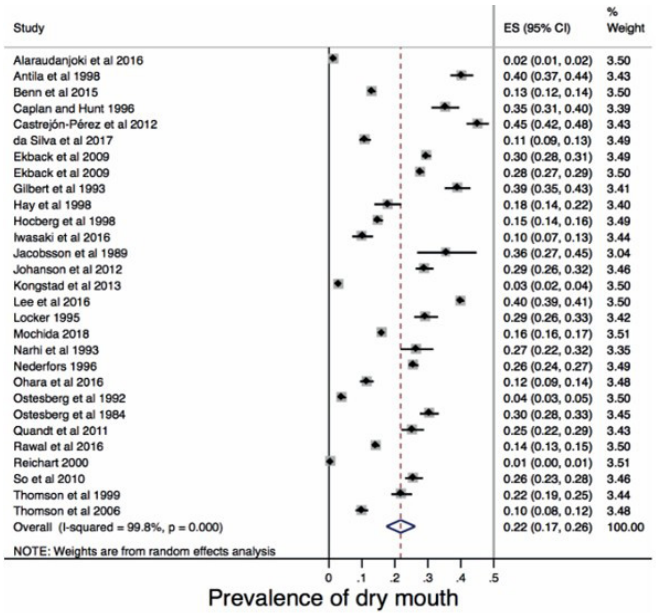

Figure 1: Overall prevalence of dry mouth and xerostomia based on 29 specific studies[17].

Out of 72 eligible full-text articles, 13 studies were retained, after a double-check by two investigators. The primary outcome was hyposalivation as measured in adults aged 60 years or older. The studies reported on 28 to 800 participants. Ten studies used the unstimulated method of salivary flow rate measurement. There was heterogeneity and inconsistency among the studies and assessment methods. The overall prevalence of hyposalivation was 33.37%. The prevalence with unstimulated versus stimulated salivary flow was 33.39% and 30.47%, respectively. However, the clinical relevance of hyposalivation in older adults remains unknown. Lower salivary flow is not necessarily associated with a dry mouth symptom nor does it have an impact on patients' lives. This is in agreement with Thomson, who states that both the saliva measurement and the clinical assessment of xerostomia by means of a questionnaire should be used to diagnose dry mouth[16].

However, the prevalence of dry mouth is difficult to assess because the definitions and methods used to diagnose xerostomia or SGH vary widely, as do the characteristics of the study samples. In the current literature, estimates of xerostomia range from 12% to 39% in elderly populations, with a mean estimate of 21%. Prevalence estimates of SGH in the elderly range from 5% to 47%, again reflecting the discrepancies in case definitions. In addition, the prevalence of dry mouth in the elderly is estimated to be around 20%. Based on only two reports conducted in younger adults, the observed prevalence was approximately half that of older adults[19,20]. Similar findings were reported by Benn[21] in a nationally representative sample from New Zealand, where xerostomia affected 5% of 18-24-year-olds compared to 26% of those aged 75 years and older. A higher prevalence is often reported in post-menopaused women[22], whatever the cause.

One of the most common diseases responsible for xerostomia is SS, including SS associated with other autoimmune diseases (SS+AID). Demographic and epidemiologic studies on SS+AID are lacking, in contrast to primary SS (pSS), which is known to predominantly affect females (female: male ratio = 9:1) at a mean age of 52-56 years.[23–25] Although the true pSS prevalence in the general population is not well defined, epidemiologic reports indicate a prevalence range from 0.1 to 3 per 1000 persons[24–27]. A systematic review and meta-analysis estimated an overall global prevalence rate of 61 per 100,000 persons (0.06%), with considerable geographic variations[25]. Seror et al. reported a slight increase in the overall prevalence of pSS (23-32 per 100,000) and of SS+AID (16-20 per 100,000) from 2011 to 2018, with females accounting for 90%-91% and 92%-93% of cases, respectively[28]. The incidence of SS per 100,000 persons decreased from 2012 (pSS: 4.3; SS+AID: 2.0) to 2017 (pSS: 0.7; SS+AID: 0.3).

In an Australian population study, Jamieson asked dentate individuals aged 15 years and older "How often does your mouth feel dry?" (response options "never", "occasionally", "frequently" or "always")[29]. Individuals who responded "frequently" or "always" were classified as xerostomic. The prevalence of xerostomia was 13.2% (95%CI: 12.4-14.0), ranging from 9.3% (95%CI: 7.9-10.8) in those aged 15-34 years to 26.5% (95%CI: 23.3-30.0) in those aged 75 years and older. Prevalence was higher in the lowest income tertiles (24.5%) (95%CI: 22.6-26.5), those without dental insurance (16.6%) (95%CI: 15.4-17.8) and those with unfavorable dental visit patterns (18.1%) (95%CI: 16.2-20.1). This study shows that even younger adults are likely to suffer from xerostomia/dry mouth and its consequences. In another cross-sectional population study conducted in New Zealand by Thomson on 923 participants (48.9% female) with a mean age of 32 years, one in 10 participants was classified as 'xerostomic', with no apparent gender difference[30]. There was a strong association between xerostomia and poorer oral health-related quality of life (across all Oral Health Impact Profile-14 domains). This association persisted after a multivariate analysis controlling for clinical characteristics, gender, smoking status and personality characteristics (negative emotionality and positive emotionality).

4. Burden and Consequences

Given the high prevalence of xerostomia in the general population, which increases with age and the many common medical conditions, the burden of xerostomia/dry mouth in terms of buccal health and quality of life is high. The consequences of xerostomia are listed in **(Table 4)**.

Table 4: Consequences of xerostomia[4].

Consequences of xerostomia
Dry mouth
Thirst
Difficulties with oral function
Dysphagia
Changes in speech
Difficulty with dentures
Nocturnal oral discomfort
Oropharyngeal infections
Oropharyngeal burning
Mucus accumulation
Food retention in the mouth
Plaque accumulation
Changes in oral microbial flora
Mucosal changes
Hyposalivation-related caries
Taste disturbances

The impact of dry mouth on sufferers has been shown to be significant, whether studied in older[31-33] or younger adults[30]. Interestingly, a strong association between dry mouth and reduced quality of life observed in elderly Japanese[34] was seen with both xerostomia and SGH, suggesting that both aspects of dry mouth affect quality of life.

Hyposalivation contributes to a large number of health problems and negatively impacts the patient's overall quality of life by affecting dietary habits, nutritional status, speech, taste and tolerance to dentures **(Table 4)**. It may also affect the risk of oral infection, including candidiasis and susceptibility to dental caries, periodontal disease and tooth loss. People with xerostomia may have difficulty eating, speaking, swallowing and wearing dentures. People with hyposalivation may find it particularly difficult to eat dry foods (cookies, crackers). These people have difficulty chewing and swallowing and may need to sip liquids while eating. There may also be changes in taste, as saliva is a key component in the taste process[35]. A lack of saliva at the denture-mucosa interface can cause denture sores and make it difficult to wear prosthesis. This can affect food choices. Denture wearers may experience problems with denture retention, denture sores and the tongue sticking to the palate. The halitosis, burning sensation of the mouth and tongue and intolerance of acidic and spicy foods observed in people with dry mouth[36] may lead to changes in food and drink intake, which in turn may adversely affect nutritional status and quality of life. Xerostomia symptoms are more common at night because the salivary production decreases during sleep (lowest circadian level) and the problem may be exacerbated by mouth breathing. These difficulties likely affect social interactions and may be responsible for avoiding social engagements in some individuals[37].

While speech and eating difficulties are perhaps most obvious in people who have undergone radiation therapy for head and neck cancer[38], they are also seen in less severely affected people with dry mouth. Chewing food can be uncomfortable or even painful; eating requires frequent sips of water and swallowing is difficult.

5. Common Causes

5.1. Age

One of the main etiologic factors is aging according to all epidemiologic studies on the prevalence and incidence of xerostomia/dry mouth, whether associated with salivary gland hypofunction or not. Many studies[4,16-18] have reported a high rate of xerostomia/dry mouth in the elderly, up to 33.4% in the systematic review by Pina, et al.

The high prevalence is obviously due to a physiological decrease in salivary flow, but is increased by comorbidities that may themselves cause or increase xerostomia and by the frequent use of medications, including those with a high incidence of inducing dry mouth as an adverse effect[39]. These drugs mainly consist of anticholinergic, sympathomimetic, sedative-hypnotic, opiate, antihistamine and muscle relaxant medications[40]. The prevalence of xerostomia increases dramatically with the number of medications taken[16,41]. In a cohort study of elderly people from New Zealand and Australia, the prevalence of xerostomia increased from 8.3% in those taking no medication to 15.6 % in those taking one medication taken and to 24,7% in those taking two or more medications **(Figure 2)**[41].

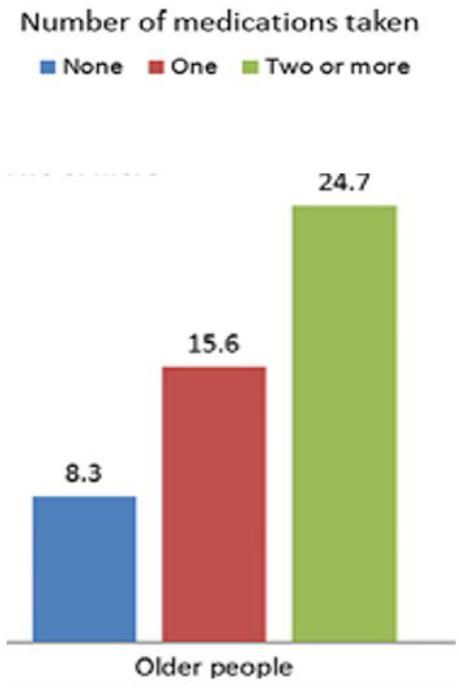

Figure 2: Prevalence of xerostomia (data, percentages) by number of medications taken in elderly people from New Zealand and Australia[16].

5.2. Medications

Medication use is certainly at the top of the list of causes responsible for dry mouth/xerostomia[4,16-18,39-42]. Many drugs can induce or increase mouth dryness. The main drugs associated with xerostomia are listed in **(Table 5)**.

Table 5: Drugs associated with dry mouth[4,44].

Xerostomic drug class
Drugs that directly damage salivary glands
Cytotoxic drugs
Drugs with anticholinergic activity
Anticholinergic agents: atropine, atropinics and hyoscine
Antireflux agents: proton-pump inhibitors (e.g., omeprazole)
Central-acting psychoactive agents
Antidepressants, including tricyclic compounds
Phenothiazines
Benzodiazepines
Antihistamines
Bupropion
Opioids
Drugs acting on sympathetic system
Drugs with sympathomimetic activity (e.g., ephedrine)
Antihypertensive agents: alpha-1 antagonists (e.g., terazosin and prazosin); alpha-2 agonists (e.g., clonidine); beta-blockers (e.g., atenolol, propanolol), which also alter salivary protein levels
Drugs that deplete fluid
Diuretics

The relationship between specific drug intake and mouth dryness must be questioned and is not so easy to assess[45]. Thomson identified three approaches to address this issue. For the first approach, some authors have looked at the relationship between xerostomia/dry mouth and the total number of medications

taken, regardless of drug class or potential xerogenicity[19,31]. This approach provides an overview of the true relationship between medication use and xerostomia.

In the second approach, researchers have used lists of purported xerogenic medications[46-48] to count the total number of xerogenic medications taken by each participant. However, such classifications lack specificity because of their inclusivity, their variation and their lack of specificity regarding which aspect of dry mouth is concerned. The results of studies using such lists do not tell which medications are actually responsible for the effect.

In the third approach, associations were examined by therapeutic drug classes (or even individual compounds) without assuming xerogenicity. Assessing xerogenicity is the most sensitive approach, as it also allows the issue of polypharmacy to be addressed, but it is analytically challenging. If someone taking an antidepressant is experiencing SGH, the first consideration should be whether the side effect is due to other drugs that are being taken. A complication is that, after controlling for other factors, the more medications a person takes, the more likely they are to experience dry mouth, most probably because of their overall anticholinergic burden[49]. Of the three studies that addressed the issue of polypharmacy, two were conducted in the elderly. The main study analyzed the relationship between long-term medication use (baseline and after 5 years) and dry mouth (diagnosed by Xerostomia Inventory score and unstimulated whole saliva flow rate)[50]. Dry mouth was more severe in women and patients taking an anti-anginal drug, thyroxine and a diuretic at 5 years, as well as antidepressants or anti-asthma drugs at baseline and 5 years. Unstimulated flow was found to be higher in smokers and patients on statins.

It has been reported that 80% of the most commonly prescribed drugs can cause xerostomia. Xerostomic features affect 42 drug classes and 56 subclasses[48,51]. Polypharmacy increases with age. Therefore, the prevalence of drug-related xerostomia is much higher in the elderly. The most common medications causing hyposalivation are those with anticholinergic activity. Although cancer chemotherapy has been associated with decreased salivary function, these changes appear to be transient in most patients[51,52]. Radioactive iodine used to treat thyroid cancer may affect parotid function in a dose-dependent fashion[53].

Substitution of xerostomia-causing drugs with similar types of medication with fewer xerostomic side effects should be considered whenever possible. For example, selective serotonin reuptake inhibitor has been reported to cause less dry mouth than tricyclic antidepressants[54]. Milnacipran, used in combination with norepinephrine-serotonin reuptake inhibitor for depression, has been shown to improve outcome and is associated with fewer dry mouth symptoms than clomipramine[55]. The use of anticholinergic drugs during the day may minimize symptoms at night. Dividing daily doses can also eliminate or reduce the side effects associated with a single large dose.

A recent systematic review and meta-analysis of medications responsible for dry mouth as an adverse effect in the elderly (defined as people aged ≥ 60 years) selected and analyzed 52 observational studies or placebo-controlled trials.[39] The meta-analysis included 22 placebo-controlled randomized trials. Drugs used for urinary frequency and incontinence were the most studied (13 trials) and likely to cause xerostomia, followed by the group of antidepressants (6 trials) and psycholeptics (3 trials). Urinary drugs most associated with dry mouth were tolterodine, oxybutynin and fesoterodine. Darifenacin and solifenacin were less commonly associated with dry mouth and mirabegron was similar to placebo. Among antidepressants, duloxetine (selective serotonin and norepinephrine reuptake inhibitor) was most associated with dry mouth, followed by escitalopram (selective serotonin reuptake inhibitor) and doxepin (tricyclic). The psycholeptics found to be xerostomic in randomized controlled trials were eszopiclone and quetiapine (two trials). Other drugs commonly responsible for dry mouth include opioids, benzodiazepines, proton pump inhibitors, some hypotensive and beta-blocker drugs and some diuretics.

In addition to medications, another treatment commonly reported to be associated with xerostomia as an adverse effect is the fractionated radiation therapy for head and neck cancer[38,56-59]. Acute hyposalivation may be related to an acute inflammatory reaction. Conversely, chronic and late xerostomia is caused by salivary gland fibrosis, reduced blood flow and acinar cell loss. Intensity-modulated radiation therapy and three-dimensional treatment planning and dose delivery techniques can minimize radiation exposure to the salivary glands, sparing salivary function and improving xerostomia-related quality of life[60,61]. The degree of salivary gland damage depends on the number of salivary glands exposed to radiation and on the dose. Radiation doses of 23 and 25 Gy are the threshold above which permanent salivary gland destruction occurs[4]. The use of amifostatine, a radioprotectant, was shown to reduce radiotherapy-induced hyposalivation[62].

5.3. Diseases

5.3.1. Sjögren syndrome: SS is one of the most common and well-known diseases responsible for xerostomia[4,16,28,63]. SS is an auto-immune inflammatory chronic disease, predominantly affecting women. The most common presentation combines dry syndrome (involving the mouth and eyes) with polyarthritis. It is often associated with a serological signature involving anti-RO/SSA and/or anti-LA/SSB antibodies and rheumatoid factor. The disease is characterized by lymphocyte infiltration of the salivary and lacrimal glands responsible for hypofunction. SS may be primary (pSS), involving the salivary glands or secondary, associated with another autoimmune disorder (SS+AID), most often rheumatoid arthritis. The prevalence and incidence of SS are low. In a French national study, Seror et al. identified 23,848 patients with pSS and 14,809 with SS+AID in the national Health database[28]. From 2011 to 2018, the prevalence of pSS (23-32 per 100,000) and SS+AID (16-20 per 100,000) increased slightly, with women accounting for 90%-91% and 92%-93% of cases, respectively. The incidence of SS per 100,000 persons decreased from 2012 (pSS: 4.3; SS+AID: 2.0) to 2017 (pSS: 0.7; SS+AID: 0.3). In an Italian study, the prevalence of pSS in 2018 was calculated based on the Fondazione Ricerca e Salute's database (approximately 5 million inhabitants/year)[63]. In 2018, 3.8/10,000 inhabitants were identified as affected by pSS (1746 cases; 1746 controls). Given this low prevalence, SS is considered a rare disease and even an orphan disease in terms of treatment and research. In the French national survey, rheumatoid arthritis was the most common associated autoimmune disorder in patients with SS (9070 patients; 53%), followed by systemic lupus erythematosus (4731 patients; 28%), systemic sclerosis (2309 patients; 13%), overlap syndromes (882 patients; 5%) and juvenile arthritis (180 patients; 1%).

5.3.2. Other diseases: Diabetes, especially type 1, is another disease that has been frequently reported to be associated with

complaints of dry mouth[64]. However, the exact rate of this association remains controversial[65]. Other diseases or health conditions that may cause dry mouth/xerostomia include: dehydration due to impaired fluid intake, emesis, diarrhea or polyuria[4]; psychogenic causes, such as depression, anxiety, stress or fear may lead to xerostomia; systemic conditions that cause salivary gland dysfunction. This is the case in Parkinson's disease[66,67], Alzheimer's disease (patients may complain of dry mouth despite normal salivary flow due to altered perceptions), Biermer's anemia and hyperthyroidism[42]. Dry mouth has been mentioned to be associated with asthma, renal impairment, especially in dialysis patients and COVID. In a review on Parkinson's disease[67], the prevalence of self-reported xerostomia ranged from 49% to 77% and that of self-reported drooling from 5% to 80%. In total, 10 articles reported significantly lower mean salivary flow in patients with Parkinson's disease than in controls. Patients with Parkinson's disease were shown to have lower salivary flow rate and higher prevalence of both xerostomia and drooling than controls. A recent study conducted in the United States (cross-sectional analyses of 12-month follow-up data [N=976; collected in 2020-2021] from a cohort of adolescents recruited from public high schools in Northern California) compared self-reported past 30-day e-cigarette, cannabis and other tobacco use with dry mouth occurrence (overall dry mouth experience; shortened Xerostomia Inventory)[68]. After adjustment, frequent e-cigarette use was not significantly associated with dry mouth (OR: 1.40; 95%CI: 0.69-2.84), whereas frequent cannabis use (OR: 3.17; 95%CI: 1.47-6.82) and combustible tobacco use (OR: 1.92; 95%CI: 1.38-2.68) were associated with more frequent dry mouth.

5.4. Local factors

Many local factors may be responsible for dry mouth, including sialadenitis, sialolithiasis, acute oropharyngeal infections, mouth neoplasms and, as previously mentioned above, damage to the secretory tissues of the salivary glands due to radiation therapy for head and neck cancers, depending on modalities and doses.

6. Management and Therapies of Dry Mouth

The first point in the dry mouth/xerostomia management should be to identify its potential etiology so as to try to treat the cause[4,16,69]. The treatment is directed at local and systemic salivary gland stimulation, symptomatic improvement, prevention and treatment of oral and general complications associated with hyposalivation, as well as modification of medication use, especially in the elderly.

Patients with xerostomia should undergo frequent dental examinations for early diagnosis of oral complications. Patients should be encouraged to perform daily oral self-examinations for mucosal lesions, ulcers or dental carries and to report any unusual findings. The mainstay of caries prevention is meticulous plaque control through excellent oral hygiene. Patients should be invited to brush their teeth twice daily. They should be discouraged from using alcohol and tobacco and advised to follow a low-sugar diet to control dental caries. Salivary stimulation is the preferred treatment in patients with residual salivary gland capacity. Salivary secretion is increased by non-specific mechanical and gustatory stimulants. The combination of chewing and taste, as provided by gums and mints, may relieve symptoms. Citric acid can stimulate salivation, but must be monitored as it can lead to mucosal irritation.

Pharmacologic agents stimulate salivation and produce a sustained effect throughout the day. Pilocarpine and cevimeline are approved in the United States for use in xerostomic patients[70-72]. Pilocarpine is a non-specific muscarinic agonist with broad pharmacologic effects on the body. When taken as tablets of 5-10mg, three times daily, adverse effects such as sweating, chills, nausea, dizziness, rhinitis and asthenia have been observed in patients with radiation-induced xerostomia. The recommended initial dose is one 5mg tablet 3 to 4 times per day; the usual dose range is 3-6 tablets (15-30mg) per day, not to exceed two tablets (10mg) per dosing. Slow-release preparations of pilocarpine are available to reduce side effects and prolong its duration of action. Pilocarpine-loaded nanoparticles are being investigated as a new mode of drug delivery[73]. Cevimeline is a cholinergic agonist with high affinity for M3 muscarinic receptor subtypes located on salivary and sweat glands. Therefore, it stimulates salivation and minimizes adverse effects on cardiac and pulmonary function. This agent is contraindicated in patients with asthma and narrow-angle glaucoma. It may be used during pregnancy if the benefit/risk is deemed acceptable, although animal studies have shown adverse effects on the fetus. The recommended dose is 30mg three times daily. Bethanechol, another cholinergic-muscarinic sialagogue, has been shown to increase salivary secretion in irradiated patients when taken at 25mg three times daily. Anethole trithione is used to treat xerostomia in patients with SS. Unlike other sialagogues, this agent increases receptor sites on salivary acinar cells. Some beneficial effects have been reported in SS patients at a dose of 25mg three times daily[74]. A combination of pilocarpine and anethole trithione has shown a synergistic effect on salivary secretion[75]. Human interferon-alpha, used as low-dose lozenges, has been shown to significantly increase salivary secretion in SS patients[76-78]. If salivation cannot be stimulated, use of saliva substitutes is recommended for symptomatic treatment (Table 3). Patients should be encouraged to drink water frequently throughout the day. Using water with meals can help with swallowing and improve taste perception.

Commercially available saliva substitutes containing thickeners such as carboxymethylcellulose or mucin are the most common. More recently, saliva substitutes based on polyacrylic acid and xanthan gum have been developed and are recommended for patients with extremely low salivary production rates. Despite the high frequency of hyposalivation in the elderly, this condition is still poorly evaluated and managed.

In a systematic review on available treatments for xerostomia and hyposalivation, Gil-Montoya et al. identified a total of 26 well-designed clinical trials with a JADAD score of 4 or 5[79]. Of these, 14 trials tested a drug, mostly cholinergic agents (muscarinic agonists) such as pilocarpine[80-84], cevimeline[85,86] and bethanechol[87]. Four trials tested the efficacy of agents such as malic acid[88-90] or physostigmine[91]. Finally, two studies analyzed the improvement of dry mouth symptoms in patients with pathologies such as SS by directly targeting the pathophysiology of the disease using a specific monoclonal antibody such as rituximab[92] or rebamipide[93]. A summary of the results shows that pilocarpine at 5mg improves dry mouth symptoms in SS and is helpful for patients. Other products did not show clear significant dry mouth changes in SS patients. Patients with drug-induced xerostomia did not show significant symptom improvement with

any of the drugs tested, except for a 1% malic acid spray, which appeared to reduce dryness symptoms and increase salivary flow.

For non-pharmacologic/local treatments, eight successfully designed studies were identified that used artificial saliva or saliva substitutes in patients with xerostomia and two tested the efficacy of oral supplements in improving the dry mouth signs and symptoms[79,94-103]. Most oral lubricants, mouthwash, saliva supplements or saliva complements slightly improved symptoms. In most cases, however, the salivary flow was not significantly increased.

Finally, two trials investigated alternative treatments: intraoral electrostimulation on the symptoms and signs of xerostomia in patients with this condition, resulting in a short-term improvement of symptoms such as dryness and difficulty swallowing at 3 months and an improvement in the frequency and severity of dryness oral discomfort, difficulty sleeping and talking and the rate of unstimulated salivary secretion at 5 months[104]. Simcock, et al. investigated the efficacy of acupuncture compared with two sessions of oral education (advice on dietary products to alleviate xerostomia and oral hygiene) in patients treated with radiotherapy.[105] After 8 weeks, acupuncture-treated patients had significant improvements in dry mouth, sticky saliva, less need to drink to swallow food and less waking at night to drink. There were no differences in the rates of stimulated or unstimulated salivary secretion.

In conclusion, in addition to diet, hydration and hygiene recommendations for maintaining good oral-dental health, local non-systemic treatments such as saliva supplements (artificial or substitutes) seem to be very helpful with a very good safety profile, which is a major concern, especially in the elderly.

In this regard and in addition to the above-mentioned trials in the Gil-Montoya review[79], another preparation has been tested in two published 2-week randomized controlled clinical trials: oxygenated glycerol triester (OGT, Epaline®) spray, a lubricant that forms a lipid film on the mucosa. Mouly compared OGT with Saliveze®, an aqueous electrolyte solution, also supplied as a spray, administered at least five times daily in elderly patients in long-term hospital care (41 institutionalized patients) and the same investigators compared the same products in a younger population (74 patients) taking antipsychotic medications that cause dry mouth as a side-effect[106,107]. Both trials had an unclear risk of bias. However, the outcome favored the OGT spray at Day 14 in both studies, with a combined standardized mean difference (SMD) for oral dryness of 0.77 (95%CI: 0.38–1.15; Chi^2=5.44 [df = 1]; P=0.02; I^2=82%), which represents a mean difference of approximately two points on a 10-point visual analog scale (VAS) assessing patient-reported dry mouth.

The Cochrane review of interventions for managing dry mouth included topical therapies[69], thereby recognizing the importance of local treatments, analyzed many artificial saliva preparations or substitutes and performed an extensive review of available trials, concluding that: “There is no strong evidence from this review that any topical therapy is effective in relieving dry mouth symptoms.” However, the reviewers did acknowledge the efficacy of the OGT spay: “OGT spray is more effective than an aqueous electrolyte spray (SMD 0.77, 95%CI: 0.38-1.15), which is approximately equivalent to a mean difference of two points on a 10-point VAS scale for mouth dryness. Chewing gum appears to increase saliva production in those with residual secretory capacity and may be preferred by patients, but there is no evidence that gum is better or worse than saliva substitutes. Integrated oral care systems and oral reservoir devices may be helpful, but more research is needed to confirm this. Well designed, adequately powered randomized controlled trials of topical interventions for dry mouth and reported according to CONSORT guidelines are needed to provide further evidence to guide clinical care. For many people, dry mouth symptoms are a chronic problem and trials should evaluate whether potential treatments are palatable, effective in reducing xerostomia and have a long-term impact on patients’ quality of life.” Patient preference is an important concern, along with consideration of the potential treatment-related adverse effects, which appear to be much less frequent and severe with local treatments such as artificial saliva, saliva supplements, OGT spray, chewing gums and hydration.

A major concern regarding the current literature on studies and therapeutic trials evaluating the efficacy of systemic/local drugs or local non-pharmacological treatments is the lack of long-term evaluation, which is critical since dry mouth is a chronic pathology. Another concern, as mentioned above, is the lack of attention to hyposalivation and dry mouth in the elderly, who make up the vast majority of the affected population, with drug-induced xerostomia/dry mouth in second rank.

These two issues need to be addressed and longer randomized clinical trials are needed, especially in these populations. Dry mouth is indeed an important public health issue and should be given more attention.

7. Declarations

7.1. Ethics approval and consent to participate

Not applicable.

7.2. Consent for publication

Not applicable.

7.3. Availability of data and materials

The data presented in this review article all come from published literature.

7.4. Conflicts of interest

Emmanuel Maheu has consulted for Carilène, Expanscience, Fidia, IBSA, and TRB Chemedica. Odile Reynaud-Lévy has consulted for Sanofi, Novartis, GSK, and Lilly

7.5. Funding

None.

7.6. Authors’ contributions

The two authors of this article contributed to the literature search and drafting of the manuscript.

7.7. Acknowledgements

None.

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