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REVIEW ARTICLE

Chemosensory dysfunction in primary Sjögren's syndrome: a topical review

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Abstract

Primary Sjögren's syndrome is an autoimmune exocrinopathy related to lymphocytic infiltration of the exocrine glandular epithelia (such as salivary, lacrimal, nasal, and sebaceous glands or vaginal mucosa) with systemic manifestations of an immuno-inflammatory nature, and not associated with any other systemic disease. It is characterized by severe dryness (Sicca syndrome), particularly in mouth and eyes, with potential strong impact on quality of life and could increase the risk of depression in Sjögren's patient. To date, the impairment of taste and olfactory functions related to Sjögren syndrome remains poorly assessed; so is the trigeminal functions which remain sparsely studied in patients with Sjögren disease. However, other factors can also modify chemosensory functions (olfactory or gustatory sensations and trigeminal nerves), in particular the reduction of the masticatory coefficient or halitosis, due to oral saliva flow decrease, and poor dental condition, which are often present in Sjögren patients. Of the 12 articles evaluated after a 22-year literature search of this review, chemosensory disorders (including taste, smell, and trigeminal impairments) are described and evaluated in pSS patients, with mainly poorer performance compared to healthy controls. Diagnostic and therapeutic (including rehabilitation) approaches of chemosensory disorders in pSS are discussed in this review. Clinician should be more attentive to taste as well as olfacto-trigeminal disorders in primary Sjögren's disease, if possible at the earlier stage, in order to take the best care of Sjögren's patients. This review also highlights some lack in knowledge on pSS chemosensory disorders that should provide new research perspectives.

Key Points

- *Chemosensory functions (including taste, smell, and trigeminal functions) are altered in patients with primary Sjögren's syndrome (pSS) due to dryness of the mouth and the nose.*
- *The trigeminal nerve which interacts with olfactory and gustatory nerves contributes to olfactory and taste perception but remains little studied to date.*
- *Chemosensory function should be considered in the daily clinical assessment of patients with pSS.*
- *Chemosensory function treatment is not standardized yet, however symptomatic treatment of Sjögren syndrome-associated dryness transiently would improve taste and smell, and olfactory or gustatory rehabilitation in pSS patients would be useful.*

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Introduction

Olfactory, gustatory, and trigeminal interactions contribute to the essential daily functions (nutrition, attention, social interactions) and quality of life (self-esteem, hedonicity, or enjoyment of life). They are, also, essential to the appreciation of foods flavor, palatability, and early warning against toxins or spoiled food. Smell, taste, and trigeminal impairment (chemosensory dysfuction) would induce significant consequences on social withdrawal, depressive syndrome, impairing food intake, unbalance of associated underlying pathologies (diabetes, hypertension…), and therapeutic observance [1]. Today, chemosensory dysfunction remains rarely investigated during the medical follow-up of patients although the recent COVID-19 pandemic reveal that it could be a strong and clear sign of systemic condition [2, 3]. Chemosensory dysfunction has been seldom reported in primary Sjögren's syndrome (pSS) [4].

pSS is defined as an autoimmune systemic disease with a particular tropism for exocrine glands resulting in inflammatory exocrinopathy and autoimmune epithelitis. It is characterized by lymphocytic infiltration associated or followed by the progressive destruction of the exocrine glands (salivary and lachrymal glands…) [5, 6]. When associated with other systemic autoimmune diseases (as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis…), Sjögren's syndrome is now called "associated" rather than "secondary." The decreased exocrine gland function in pSS lead to the combination of eye dryness (xerophtamia), dry mouth (xerostomia), and possibly dry of the nasal mucous membranes [7]. Other exocrine glands may be involved including those of the skin (cutaneous glands), trachea, vagina, and ears causing dryness of these organs. In addition, to dryness features, most of patients present with chronic fatigue and diffuse pain, resulting in the typical triad of symptoms of pSS patients. Also, in 30 to 50% of patients, systemic autoimmune manifestations might occur, such as articular, cutneanous, pulmonary, renal, hematological, and neurological involvements, Raynaud's syndrome [8], cryoglobulinemic vasculitis [5, 9], and in the more severe cases B cell lymphoma [10].

Although olfactory and taste disorders have been described in pSS [11], they remained poorly investigated. The main goal of this review is to provide researchers and doctors a general up of date overview on chemosensory (olfactory, taste, or trigeminal) dysfunction in pSS patients. Particular attention will be paid to pathogenesis, diagnosis, morbidity, and care of these disorders.

Materials and methods

For this literature review, we selected articles and accepted preprints in English or French indexed in PubMed (MEDLINE) or Web of Science (ISI) databases and supported by other research on *Google Scholar* to avoid missing papers. Search terms used were 'primary Sjögren syndrome (pSS)', 'taste', 'olfactory', 'trigeminal', 'trijumeau', 'disorders', 'dysfunction', 'diagnosis', 'management', 'treatment' and 'care'. All abstracts or articles, if directly available, published over the last 22 years (from January 2000 until December 2021) were assessed and selected original articles were reviewed (inclusion criteria). The articles that only mentioned the above-mentioned themes without going in depth in their analyses, without taste, trigeminal function, nor olfaction being the object of the study, have been excluded, as well as duplicated publications (exclusion criteria).

Global research results

Among the retrieved 36 publications, 12 articles relating to olfactory, trigeminal, and taste function in pSS patients were reviewed and discussed. The following publications were selected (Fig. 1 (Supplemental file): selected articles chart flow):

- 'pSS' and 'taste'' search: only 15 publications of which 13 articles after 2000; and only 5 were eligible;
- only 14 articles for 'pSS' and 'olfactory'' search of which 12 articles after 2000, and only 7 were eligible;
- and 4 articles for 'pSS' and 'trigeminal nasal or oral's search were found and there are two articles evaluating trigeminal clinical manifestations such as burning sensations in the tongue (BST). For 'pSS' and 'trigeminal involvement' search, 6 articles met the inclusion criteria.

However, in 4 articles, olfactory and taste disorders in pSS were evaluated concomitantly and 2 articles deal with oral trigeminal manifestations and taste disorders in pSS patients.

Discussion

Sjögren's syndrome

pSS is a systemic auto-immune disease, considered as a rare disease (affecting less than 1/2000 people) in some European countries, with a female predominance (more than 90% of cases), mostly in their fourth and fifth decades of life. pSS's prevalence has been reported to range from 0.03% in most recent studies to 2.7% worldwide in older studies applying

ancient classification criteria and different methodology [12]. It is considered that approximately half of all sufferers are currently undiagnosed [13].

Although not completely understood, pSS pathogenesis is the complex result of both environmental and genetic factors. Interestingly, lymphocytic hyperreactivity could lead to epithelial cells apoptosis as wells as exocrine glands and other organ destruction. The epithelial damage preceding lymphocyte (B and T) demargination and production of antibodies suggests that chemosensory (olfacto-gustatory and trigeminal) damage may occur earliest in pSS. Moreover, specific modifications are also described such as high expression of angiotensin-converting enzyme 2 receptor in nasal epithelium [2, 13], which may contribute to the chronic epithelitis and secondary lead to olfactory neuroepithelium impairment, containing among others olfactory receptors.

The clinical presentations of pSS are multiple, which often makes the diagnosis difficult, despite the updating of the diagnostic criteria for the Sjögren classification by the 2016 American-European Consensus [14]. Indeed, different symptoms should lead to pSS [e.g., persistent eyes or mouth dryness, parotidomgaly, unexplained dental caries, or abnormal results of specific serologic tests (e.g., anti-Ro/SSA antibodies with or without anti-La/SSB antibodies, rheumatoid factor, and hyperglobulinemia…)]. Thus, pSS diagnosis is established in the presence of compatible clinical symptoms, ascertained by laboratory/histological features, after exclusion of other causes of eyes or oral dryness. Nevertheless, although oral dryness is one of the most prominent signs in pSS diagnosis, there is no mention of taste disorders, let alone smell disorders.

Smell alteration in primary Sjögren's syndrome patients

- Definition and assessment of smell alteration in daily practice and for clinical research

  The sense of smell, the ability to notice a substance by using the nose, has two main sensory modalities, the olfactory system and the system trigeminal compounds (which are involved among others, in the perception of nasal inflammation, protection, and activation of the autonomic nervous system) that interfere [15, 16]. The olfactory function has two independent components, one called "peripheral" and the other "central." The "peripheral" component, which is located in the olfactory epithelium, corresponds to olfactory sensitivity (or acuity) and trigeminal (sensorineural) function of the nose; and is evaluated by measuring odor detection thresholds or differential odor thresholds. The "central" component involves more complex cognitive components such as the ability to differentiate quality of different odors (discrimination), to recognize previously smelled target odors (memory) or to name an odor using a word list (identification) [15], and is more likely assessed by olfaction suprathreshold tests [17]

  Olfactory dysfunction can be classified as anosmia, hyposmia, and dysosmia [18] and depending on their long-lasting (temporary or longer-lasting) (Table 1). Overall, olfactory dysfunction (impairment) could also be classified as: (*1*) quantitative (impairment of the strength (anosmia, hyposmia)and/or (*2*) qualitative (= impairment of the quality or degree of distortion (dysosmia)).

  Olfactory tests primarily supply information about quantitative impairment, while history provides crucial information on qualitative impairment (such as distortion) [19].

  Various tests have been described to assess smell capability. Olfactory psychophysical assessment tools include commonly one or a combination of odor threshold tests (e.g., Sniffin' Sticks) or olfaction's suprathreshold tests such as odor discrimination and odor identification tests (e.g., smell identification test) (Table 1, Table 1 (Supplemental file)). Psychophysical testing studying retronasal olfaction is also available. This involves placing "taste powder" in the mouth (20 different taste stimuli (food and spices)) and the subject should identify the taste in a list of 4 choices.

  The ability to localize trigeminal stimuli was assessed using a test based on trigeminal lateralization, which consists in measuring trigeminal sensitivity by identifying the nostril stimulated by a stimulus (odorous substance) during a two-alternative forced-choice procedure [20]. Finally, electrophysiological tests, such as olfactory event-related potentials (OERPs), are also use to assess intranasal olfactory and trigeminal chemosensory function. A positive OERP is in favor of the existence of an ability to perceive odors (Table 1, Table 1 (Supplemental file)). It is recommended to use, if possible, electrophysiological tests which are more reliable than a subjective assessments (e.g., visual analog scales, ordinal scales, patient-reported outcome measures) alone. One should be cautious when assessing chemosensory disorders. A focus on history and a physical examination of the nose, as well as the mouth, should be done to screen out others underlying pathology such as sinus disease, upper respiratory infections, oral infections, dental procedures, oral appliances (e.g., dentures), head trauma, Bell's palsy, or medications [21].

  Ultrasonography is a sensitive tool for morphological diagnosis of major salivary gland abnormalities in pSS, contributing therefore to Sjögren's syndrome diagnosis [22].

  Others iconographic examinations (computed tomographic scanning, magnetic resonance imaging, or functional magnetic resonance imaging) could also be carried

Table 1 Some Clinical signs and symptoms suggestive of chemosensory (olfacto-trigeminal and taste) dysfunction in Sjögren's disease (SS) and factors influencing them

	Items	Clinical signs	**Some complementary examinations**
Symptoms suggestive of chemosensory (olfacto-trigeminal and taste) dysfunction in Primary Sjögren's disease (pSS)	*Olfactory dysfunction*	Longer-lasting olfactory dysfunction include anosmia, hyposmia or dysosmia	• Olfactory psychophysical assessment tools: -Odor detection thresholds, or differential odor thresholds (or "just noticeable" difference) (e.g., Sniffin' Sticks…) (→olfactory sensitivity) -Suprathreshold tests of olfaction: odors discrimination tests, odors memory tests or odors identification tests (e.g., smell identification test…); retronasal olfaction testing (→central component of olfaction) • Electrophysiological testing: olfactory event-related potentials (OERPs) (have medicolegal importance); electro-olfactograms) • Subjective assessment (e.g., visual analog scales, ordinal scales, patient-reported outcome measures) (less reliable)
	Taste dysfunction	Chronic impaired gustation (basic tastes impairment: sweet, sour, salty, bitter, savory, or fat) include hypogueusia (decrease of taste sensitivity), agueusia (complete loss of taste; *less frequent*), or dysgeusia (distorted sense of taste)	• Chemogustometry: Taste and flavor psychophysical assessment tools: basic whole-mouth test (WMT) using taste sprays; taste strips method; detection thresholds and recognition tests the basic tastes (paper discs), least noticeable difference's taste threshold … • Electrogustometry using electric stimuli for taste threshold • Iconographies (e.g., salivary gland ultrasound) • Subjective assessments (e.g., gustatory scores using self-reported perception of taste)
	Trigeminal impairment	Trigeminal (somatosensory) sensations include stinging, burning, cooling, and sharpness) in nose or mouth (leading for instance to stomatodynia, burning mouth sensation/numbness)	• Olfactory psychophysical assessment tools: trigeminal lateralization test • Electrophysiological testings: olfactory event-related potentials (OERPs); electro-olfactograms
Co-factors influencing taste and smell	*Halitosis* (oral malodour), *cacogeusia* (an unpleasant taste in the mouth), *masticatory disorders*, *hyposialy*, *poor oral condition* (caries, periodontal disease)		

out to assess the absence of any obstructing polyps and others masses or inflammation.

- **Smell disorders in pSS patients**

  Temporary or longer-lasting olfactory dysfunction has been described on pSS patients in some studies [11, 23] (Table 2) and could be classified as anosmia, hyposmia, and dysosmia [18]. In a study assessing chemosensory function in 58 pSS patients, 22 non-Sjögren's syndrome sicca patients, and 57 age-matched healthy controls, it has been highlighted significantly lower olfactory scores in pSS patients (Table 2) [23]. Kamel et al. using standardized smell thresholds tests also found a significant impairment of olfactory sensitivities in pSS patients compared to matched (age and gender) controls, without dry syndrome (Table 2) [12]. In an another trial, using self-reported visual analogue scale (VAS) smell score and smell Sniffin' Sticks tests, Šijan Gobeljić et al. found more significantly lower score in pSS patients than gender-matched healthy controls on VAS, as well as using Sniffin Sticks test there were also more anosmic and hyposmic and significantly fewer normosmic pSS patients compared to healthy controls (Table 2) [24]. Furthermore, Xu et al. recently shown in a study including 52 pSS patients versus matched healthy control subjects, impaired olfactory functions (assessed by odors threshold, identification, and memory tests) in pSS patients (all $p \leq 0.01$); they found more anosmia and hyposmia in pSS patients. They also highlight a close correlation between olfactory dysfunction and pSS severity or activity (evaluated by ESSDAI and ESSPRI scores) and immunological abnormalities (Table 2) [4]. However, we have not identified any specific longitudinal studies on olfactory disorders in SS patients, to further strengthen these results. In addition, olfactory receptor gene clusters are located in proximity to key locus of susceptibility for autoimmune diseases, including Sjögren disease, such as the major histocompatibility complex, suggesting not only a physic linkage, but also a functional association.

Taste alteration in pSS patients

- **Definitions of the taste disorders**

  The taste is one of the basic sense that is partially responsible for the perception of a flavor, responding to chemical stimuli [25]. Five basic tastes are now universally recognized: sweet, salty, sour, bitter, and umami (savor). Taste dysfunctions could be quantitative or qualitative:

  - Quantitative taste dysfunction could be related to *hypogeusia* (a decreased sensitivity to all tastants), *ageusia* (a complete loss of taste function of the tongue), or on the opposite side *hypergeusia* (an enhanced gustatory sensitivity). *Normogeusia* is a normal gustatovy sensitivity and *presbygeusia* (little diminution of taste sensitivity for stimuli with age) is also noted in elderly [25]. Quantitative taste dysfunction is classically assessed using quantitative measures of taste (Table 1) which include chemogustometry and electrogustometry [25]. Among taste chemogustometry, the are *basic whole-mouth test* (WMT) using taste sprays, and *psychophysical chemical taste* test like "taste strips" which assess detection taste threshold and recognition of some of the basic tastes (sweet, salty, sour, bitter, and umami, or more) at different concentrations, randomly starting with the weakest concentration [26].Taste strips allow the detection of local taste loss (regional test) [27]. Electrogustometry contributes to the measurement of taste threshold using electrical stimuli, by passing a controlled anodal current through the tongue [28].

  - Qualitative taste impairment corresponds to *dysgeusia or parageusia*, corresponding to a distortion in taste perception (metallic, foul, salty, or rancid) or *phantogeusia*, i.e., a perception of taste although the absence of a stimulus. *Total dysgeusia* is defined as the inability to interpret all basic tastes. Qualitative taste dysfunctions are assessed through patients' own reports [27].

- **Taste disorders assessment in pSS patients**

  Saliva plays an important role in taste function [29]; its reduction as in Sjögren patients induces therefore changes in taste perception. Quantitative taste alterations (ageusia and hypogeusia) are the main taste modifications studied in Sjögren's patients (Table 1). Significantly lower gustatory scores have been found in pSS patients and in non-Sjögren's sicca patients, compared to age-matched healthy controls using self-reported perception of taste test (on a visual analogue scale) (Table 3) [23, 30].

  Using taste strips, a more reliable taste perception test, a mean gustatory score decrease was found in Sjögren patients compared to healthy controls (Table 3) [12]. Moreover, the prevalence of ageusia and hypogeusia was higher in Sjögren patients compared to healthy controls (Table 3) [12, 30]. Yet, in a study conducted by Singh et al., there were oral complaints both in pSS patients than non-Sjögren's syndrome sicca patients (Table 3) [23], and there were no statistical difference for the hypogeusia results nor for dysgeusia (metallic, bitter, and sour tastes) [23]. Finally, Gomez et al. however found that pSS patients and age- and gender-matched healthy controls exhibited different degrees of dysgeusia; they were mildly dysgeusic for sweet and salty tastes and clearly dysgeusic for sour and bitter tastes (Table 3) [31].

  Concerning the qualitative assessment of the state in SS patients, a study compared, in 2004, pSS or sec-

Table 2 Results of study on olfactory assessment in Sjögren's patients

Study	Site	Methods	Participants	Olfactory assessment	Results
Kamel et al. 2009	England	Cross-sectional cohort-matched	Gpe 1. 28 primary Sjögren patients (according to the American European Consensus classification)—(25 females; 2 smokers)—58 ± 10.7 years old Gpe 2. 37 healthy controls age- and sex-matched—(35 females; 6 smokers)—56 ± 11.7 years old	Smell thresholds	There was the reduction of Smell threshold by 1 point ($P = 0.002$; 95% CI 0.35, 1.54) ($P < 0.001$; 95% CI 1.80, 5.22) in the SS group compared with controls
Xu et al. 2021	China	Cross-sectional cohort-matched	52 pSS patients (49 women (47.67 ± 12.81 [21; 70] years) and 3 men (42.33 ± 6.51 [36; 49] years)) and 52 matched healthy control subjects	testings who were computerized included the three stages of smell: threshold, identification, and memory of odors	All the olfactory scores (olfactory threshold, identification, and memory) in pSS patients were significantly decreased than the control group (all $P < 0.01$) pSS patients had higher proportion of anosmia (13.5% vs 0%) and hyposmia (19.2% vs 11.5%) than controls ($\chi 2 = 10.526$, $P < 0.01$) ESSDAI and the symptoms of dryness, fatigue multivariable, and limb pain had negative influence on olfactory function (adjusted $R^2 = 0.381$, 0.387, 0.513, and 0.614, respectively), using regression analysis ESSPRI showed significantly negative association with olfactory tests (thresholds, identification, memory, and total scores)
Rusthen et al. 2017	Norway	Cross-sectional cohort-matched	Gpe 1. 31 primary Sjögren patients (according to the American European Consensus classification)—(31 females; 3 smokers)—52.0 ± 12.4 years old; duration of the disease = 8.6 ± 6.6 years Gpe 2. 33 healthy patients (33 females; 1 smoker)—50.1 ± 12.7 years old	Visual Analog Scale' smell perception (twelve-stick) identification test	Patients had significantly lower olfactory performances (8.8 ± 3.5 vs. 10.7 ± 1.2) than controls A significantly higher proportion of pSS patients had anosmia (13% vs. 0%), or hyposmia (29% vs. 9%)
Singh et al. 2019	Norway	Cross-sectional	Gpe 1. 58 primary Sjögren patients (according to the American European Consensus classification)—(56 females)—52.9 ± 13.4 years-old Gpe 2. 22 non Sjögren's patients with dryness (22 females)—52.0 ± 10.4 years old Gpe 3. 57 healthy patients (42 females)—49.7 ± 16.5 years-old	Visual Analog Scale' smell perception (twelve-stick) identification test	pSS patients had significantly lower olfactory compared to controls

Table 2 (continued)

Study	Site	Methods	Participants	Olfactory assessment	Results
Eren et al. 2021	Turkey	Cross-sectional	34 consecutive pSS versus control group consisted of 21 (age- and sex)-healthy matched volunteers	Connecticut Chemosensory Clinical Research Center test	Significant differences (compared to controls) smell (a decrease) ($P = .005$) were highlighted (chi-squared test). Neither olfactory function nor mucociliary clearance differed between the groups
Šijan Gobeljić et al. 2020	Serbia	Cross-sectional age-matched	58 pSS patients [54.91 ± 13.68 years old] and 55 (age- and gender)-matched healthy controls [51.42 ± 13.82]	Visual analogue scale (VAS) smell Sniffin Sticks test	pSS patients had significantly lower self-reported VAS smell score (8.6 016) than healthy controls. ± 2.2 vs. 9.6 ± 0.7, p = 0. A greater proportion of pSS patients had anosmia (3.8% vs. 0.0%) or hyposmia (36.5% vs. 13.2%), using Sniffin Sticks test
Topan et al. 2021	Turkey	Cross-sectional	38 pSS patients (49.47 ± 10.06 years) and 20 healthy volunteers (47.40 ± 8.92 years) were enrolled in this study	Chemosensory Clinical Research Center (CCCRC) test	There were significant decrease scores in mean odour threshold, odour identification, CCCRC and VAS in the pSS group ($p < 0.001$) compared to controls

ondary Sjögren patients to a group of non Sjögren syndrome patients complaining of dry mouth. Although more Sjögren patients complained of taste disorders (self-report), there was no difference in taste perception using electrogustometer analysis between the groups [32]. However, some authors argue that psychophysical tests have quite often more sensitive and reliable results in detecting and quantifying chemosensory disturbances than extant electrophysiological tests [28].

Finally, pSS patients often experience stomatodynia, burning mouth sensation (trigeminal function), and other chemosensory function, halitosis, cacogeusia, and masticatory disorders which may also impact the gustatory sense. Indeed, halitosis which is an unpleasant odor from the mouth, commonly referred to as bad breath, can disrupt taste perception. It is evaluated in daily clinical practice by organoleptic test. Basically, a trained healthcare professional sniffs the air exhaled through the mouth and subjectively defines the presence or absence of oral malodor. A degree of severity is assigned according to the intensity of the odor. The most common classification is between 0 and 5, where 0 indicates undetectable odor and 5 indicates strong halitosis [33]. But cacogeusia which is a sensation of bad taste not related to the ingestion of specific substances or in in absence of gustatory stimuli, and is often related to side effects of some drugs (tranquilizer), to uncinate epilepsy, hallucinations, or delusional states does not yet have a validated test to evaluate it, although tests can be performed to rule out a cause of cacoguesia (part of dysguesia), among them neurological disorders. Also, at present, there is no gold standard to evaluate the masticatory performance [34]. However, chewing capacity is often evaluated by recording the number of opposing natural and prosthetic pairs of premolars and molars, called the functional tooth units.

Burning mouth syndrome (or stomatodynia) which is a component of trigeminal sensitivity is often misdiagnose by clinicians. In the case of probable Burning mouth syndrome, a variety of tests can be used mainly to diagnose the type of neuropathy (central or peripheral) underlying or involved rather than to assess the severity of the stomatodynia. However, some studies evaluating treatment's efficacy of stomatodynia, the visual analog scale (VAS) has been used [35].

The trigeminal and the smell and taste senses: an under-investigated field

In pSS patients, clinical investigations of trigeminal functions should be of interest as they contribute majorly to

Table 3 Results of study on taste assessment in Sjögren's patients

Study	Site	Methods	Participants	Taste assessment	Salivation assessment	Xerostomia assessment	Results
Kamel et al. 2009	England	Cross-sectional cohort-matched	Gpe 1. 28 pSS patients (25 females; 2 smokers)—58 ± 10.7 years old Gpe 2. 37 healthy controls age- and sex-matched (35 females; 6 smokers)—56 ± 11.7 years old	Taste strips (sweet, sour, salty, bitter)	N/A	N/A	The was reduction of taste threshold by 3.5 points ($P < 0{,}001$; 95% CI 1.80, 5.22) in the SS group compared to the controls
Rusthen et al. 2017	Norway	Cross-sectional cohort-matched	Gpe 1. 31 pSS patients (31 females; 3 smokers)—52.0 ± 12.4 years old; duration of the disease = 8.6 ± 6.6 years Gpe 2. 33 healthy patients (33 females; 1 smoker)—50.1 ± 12.7 years old	Questionnaire Taste strips	Unstimulated and stimulated salivary flow measurement	N/A	Patients has significantly lower taste (18.9 ± 7.1 vs. 25.4 ± 4.3) scores than controls, and significantly complained of dysgueusia (58.1% vs. 0%). A significantly higher proportion of pSS patients had ageusia (19% vs. 0%) and hypogeusia (32% vs. 12%)
Singh et al. 2019	Norway	Cross-sectional	Gpe 1. 58 pSS patients (56 females)—52.9 ± 13.4 years old Gpe 2. 22 non Sjögren's patients with dryness (22 females)—52.0 ± 10.4 years old Gpe 3. 57 healthy patients (42 females)—49.7 ± 16.5 years old	Visual Analog Scale Taste strips Questionnaire	Unstimulated and stimulated salivary flow measurement	Summated Xerostomia Inventory Dutch	A significantly higher proportion pSS and non-SS patients had ageusia, dysgeusia compared to controls. pSS patients had significantly lower gustatory scores compared to controls
Gomez et al. 2004	Mexico	Cross-sectional age-matched	Gpe 1. 21 pSS patients (21 females; 0 smoker)—53.1 ± 9.8 years old; duration of the disease = 8.6 ± 6.6 years Gpe 2. 20 healthy patients (33 females; 0 smoker)—50.3 ± 11.9 years old	Taste threshold (method of least noticeable difference)	Salivary flow measurement using the Saxon's test	N/A	All subjects recognized the 4 basic tastes when these were tested at suprathreshold concentrations The detection thresholds for the sweet, sour and bitter tastes were higher in pSS patients, as well as the recognition thresholds for the salty, sour, and bitter tastes

Table 3 (continued)

Study	Site	Methods	Participants	Taste assessment	Salivation assessment	Xerostomia assessment	Results
Šijan Gobeljić et al. 2020	Serbia	Cross-sectional age-matched	58 pSS patients [54.91 ± 13.68 years old] and 55 age- and gender-matched healthy controls [51.42 ± 13.82]	visual analogue scale (VAS) taste taste strips	N/A	N/A	The pSS patients had impaired chemosensory function and indicators of oral health in comparison with the age- and gender-matched healthy controls Indeed, pSS patients had significantly lower self-reported VAS taste score (8.5 ± 2.1 vs. 9.5 ± 0.7, $p = 0.014$) than healthy controls Using taste strips, higher proportion of pSS patients had ageusia for basic tastes: sweetness (34.0% vs. 7.5%), sourness (10.6% vs. 0.0), saltiness (10.0% vs. 5.7%) or bitterness (19.1% vs. 1.9%)

Table 4 Results of study on trigeminal assessment in Sjögren's patients

Study	Site	Methods	Participants	Trigeminal assessment	Results
Rusthen et al. 2017	Norway	Cross-sectional cohort-matched	Gpe 1. 31 primary Sjögren patients (according to the American European Consensus classification)—(31 females; 3 smokers)—52.0 ± 12.4 years old; duration of the disease = 8.6 ± 6.6 years Gpe 2. 33 healthy patients (33 females; 1 smoker)—50.1 ± 12.7 years old	Burning sensation in the tongue (BST) questionnaire	More patients complained significantly complained of, BST (54.8% vs. 6.1%)
Šijan Gobeljić et al. 2020	Serbia	Cross-sectional age-matched	58 pSS patients [54.91 ± 13.68 years old] and 55 matched (age and gender) healthy controls [51.42 ± 13.82]	BST questionnaire	A higher proportion of pSS patients complained of BST (45.6% vs. 0.0%, $p < 0.0001$)
Cojocaru et al. 2011	Romania	Case Reports	A 50-year-old woman	N/A	After 2 years from the onset, it was highlighted a bilateral trigeminal neuropathy, and after 9 months the anti-SS-A and anti SS-B antibodies were positive. The sialography and the minor salivary ducts biopsy (in the absence of xerostomia and xerophthalmia) have established the diagnosis of pSS
Ozasa et al. 2021	Japan	Case reports	A 76-year-old woman	N/A	She presented a numbness of her left face and was subsequently diagnosed with Sjögren's syndrome and primary biliary cirrhosis. Her somatosensory disturbance severity was higher in the trigeminal area than in the forearm, suggesting that the trigeminal nerve, is more susceptible to be impaired than other parts of the nervous system in patients with Sjögren's syndrome and primary biliary cirrhosis
Yuan et al. 2018	China	Case report and literature review	A 30-year-old woman	N/A	She was diagnosed with trigeminal damage secondary to pSS and presented atypical trigeminal neuralgia of numbness of the right head and face. pSS combined with trigeminal lesion is assume to be common, but cases of pSS with trigeminal involvement as initial symptom have rarely been reported
Papadimitraki et al. 2004	Greece	Review	N/A	N/A	Trigeminal nerve dysfunction may occur in pSS patients

Table 5 Taste and olfactory offending agents and selected etiologies

Offending agents	*Examples*
Selected drugs that could may impair smell and taste	
Antibiotics	Ampicillin, macrolides, fluoroquinolones (ciprofloxacin, ofloxacin), griseofulvin, metronidazole, tetracycline
Anti-viral (chronic hepatitis C)	Pegylated interferon alfa and ribavirin
Anti-epileptics	Carbamazepine, phenytoin
Antidepressants	Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline
Antihistamines and decongestants	Chlorpheniramine, loratadine, pseudoephedrine
Antihypertensives and cardiac medications	Amiloride, betaxolol, captopril, diltiazem, enalapril, hydrochlorothiazide and combinations, nifedipine, nitroglycerin, propranolol, spironolactone
Anti-inflammatory agents	Auranofin, colchicine, dexamethasone, hydrocortisone, penicillamine
Antimanic drug	Lithium
Antineoplastics	Cisplatin, doxorubicin, methotrexate, protein kinase inhibitors, vincristine
Antiparkinsonian agents	Levodopa
Antipsychotics	Clozapine, trifluoperazine
Antithyroid agents	Methimazole, propylthiouracil
Muscle relaxants	Baclofen, dantrolene
Lipid-lowering agents	Fluvastatin, Lovastatin, Pravastatin
Antimycotics drugs	terbinafine
Others eventual aetiologies of smell disturbance	
Illicit drug	Cocaine abuse (intranasal)
Toxic chemical exposure	e.g., benzene, butyl acetate, carbon disulfide, chlorine, ethyl acetate, formaldehyde, paint solvents, sulfuric acid, thrichloroethylene
Industrial agent exposure	e.g., ashes, cadmium, chalk, chromium, iron carboxyl, lead, nickel, silicone dioxide
Nutritional factors	e.g., vitamin deficiency [A, B6, B12], zinc or copper deficiency, malnutrition
Radiotherapy	Radiation treatment of head and neck
Congenital conditions	e.g., congenital anosmia, Kallmann's syndrome
Common causes	- Nasal and sinus disease (e.g., allergic or vasomotor rhinitis, chronic sinusitis, nasal polyps, adenoid hypertrophy) - Upper respiratory infection - Head trauma (e.g., frontal skull fracture, occipital or nasal fractures) - Cigarette smoking - Neurodegenerative disease (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis) - Parkinson disease -Lewy body dementia - Old age
Uncommon causes	- Some neoplasms or brain tumors - Psychiatric conditions (e.g., malingering, schizophrenia, depression, olfactory reference syndrome) - Chronic diseases: chronic renal failure, liver disease [including cirrhosis], acquired immunodeficiency syndrome - Endocrine disorders (e.g., adrenocortical insufficiency, Cushing's syndrome, diabetes mellitus, hypothyroidism, primary amenorrhea, pseudohypoparathyroidism) - Pregnancy - Epilepsy (olfactory aura) - Alzheimer disease - Migraine headache (olfactory aura) - Cerebrovascular accident - Sjögren's syndrome - Systemic lupus erythematosus

Adapted from (1) Bromley SM.2000 [21], (2) Foguem C.2017 [5], and (3) Tuccori M, et al. 2011 [50]

nasal and taste chemoreception. Indeed, many foods induced somatosensory (trigeminal) sensations through trigeminal nerve (cranial nerve V or CNV) fibers pathways in the tongue and oral mouth, often with co-stimulation taste buds.

Similarly, in the nose, most odorous substances activate both olfactory and trigeminal (including first and second branches of CNV and their ramifications) systems concomitantly or differentially [16, 36, 37]. The complex interactions between these above two systems, taking place at the peripheral (perceptual) [1, 38] and central levels [39], contribute to good odor perception [1]. Few articles have been published on trigeminal impairment in Sjögren's syndrome patients, often as clinical cases or case series [40–43] (Table 4). Interestingly, trigeminal lesion in pSS patients seem more common than expected [41], probably related to undervaluation or less complains of patients about it. However, the link between trigeminal impairment in pSS and gustatory or olfactory disorders is not emphasized in these articles, the majority of which were published before 2000.

Underlying pathophysiology of trigeminal neuropathy associated with Sjögren syndrome is not yet fully understood; nevertheless, it is mainly suggested to be dorsal root ganglionitis with the T lymphocyte cells infiltration [40]. Trigeminal impairments related to pSS are often feature as chronic progressive sensory neuropathy in a pSS already known (Table 4) [40, 41]; but in some published cases, these symptoms were warning of the disease, and contribute to diagnosis of Sjögren's syndrome (Table 4) [41, 44–46]. Some authors suggested that in neuropathies of unknown cause, particularly if involving trigeminal nerve, in a context of chronic asthenia for instance, Sjögren's syndrome should be considered or investigated [47], before being considered idiopathic [47].

Globally, very few studies have been done on nasal and oral trigeminal functions and their dysfunctions in humans [16, 38, 39]. Considering their proven interactions and their importance for the perception of taste and smell, more studies should be done in this field for a better understanding of trigeminal dysfunction in particular and chemosensory disorders in general in healthy and sick subjects.

Complications and management of olfactory and taste dysfunction in pSS patients

In addition to the physical discomfort (dryness, burning mouth, or nasal somatosensory (trigeminal) sensations (e.g., stinging, burning, cooling…) and pain they cause [12, 36], chemosensory disorders also have a significant impact on quality of life. Moreover, they can adversely affect food intake leading to malnutrition and its effects [23] or worsening of others medical illness. However, paradoxically, compensating impaired senses of taste or smell in pSS patients could increase use of sugar, salt, or other ingredients inducing metabolic disorders (obesity, hypercholesterolemia, diabetes mellitus…), cardiovascular disease (hypertension…), or dental health. Indeed, mouth dryness in pSS patients contribute to more dental caries compared to non-Sjögren's control [23]. Extent and severity of carious disease is often considered as one of several potential markers of autoimmune-mediated salivary gland dysfunction, as in pSS [48]. To prevent tooth decay, the application of topical fluoride is suggested as well as careful regular dental checkups, and avoidance of sucrose and other metabolizable carbohydrates between meals [49].

Taking some hygienic and dietetic measures could also be of some help for taste disorders.

Efficient management of chemosensory disorders related to pSS should start with an accurate diagnosis of pSS. A drug investigation should be carried out to unmask drugs that could lead to these disorders; in these cases, symptoms can be reversed by stopping the offending agent (Table 5) [11, 50]. Proper oral and nasal moisture balance is a useful tool in the management of oral or nasal dryness in pSS [51]. The physiologic sialogogues (pilocarpine) stimulating salivary secretion or artificial saliva may be of some use in pSS patients with xerostomia [49] or spray nasal (e.g., sodium hyaluronate spray), in case of dry nose. In parallel, differential nasal inflammation, contributing to olfactory dysfunction, should be ruled out by applying specific treatments (local nasal steroids) [52], often with non-permanent effects [53] or systemic steroid therapy.

Improving the taste and appearance (texture or color) of food and temperature can improve overall food experience and quality of life in patients with pSS and chemosensory dysfunction, as well as dietary intake monitoring and counseling.

If these symptomatic approach or treatments remain ineffective, olfactory or taste re-educations in SS patients could be carried out.

pSS systemic therapy including hydroxychloroquine (for the milder systemic symptoms), steroids [53], disease-modifying antirheumatic drugs (DMARDS), and biologicals have not been yet evaluated for pSS chemosensory dysfunction. The use of these drugs is not without side effects and the benefit/risk ratio of the use of these therapies for pSS chemosensory disorders should be carefully considered. Indeed, DMARDS and biologicals, including Ritixumab® (anti-CD20 antibodies), are reserved for more severe extraglandular manifestations of pSS [6, 54]. Some articles have highlighted the improvement of pSS clinical signs, including salivary flow rates and oral dryness, using Biologicals (Rituximab®…) [54].

Conclusion

To sum up, even if olfactory, taste and chemosensory trigeminal impairment among Sjögren's patients might be altered, these disorders are often unnoticed or undervalued. Consequently, this lead to underestimation of their prevalence and incidence in pSS. This article highlights the need to better appreciate and characterized pSS chemosensory disorders in current practice. We could further investigate (1) the assessment of existing and in development Sjögren medication on them and consequently pSS patient'quality of life; (2) the implementation of taste, smell and trigeminal assessment in pSS is warranted to better appraise their true prevalence, their consequences and (3) to assess or evaluate possible treatments or management, including rehabilitation on these neglected symptoms. This review also highlights, because of the few studies found on the subject, the existence of whole areas of research on pSS chemosensory disorders that are not yet well elucidated; these should provide new research perspectives.

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Declarations

Conflict of interest None.

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