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Xerogenic medications may contribute to decreased unstimulated salivary flow in patients with oral burning and/or gastro-esophageal reflux disease

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Background: Patients who complain of mucosal burning sensations (i.e., glossodynia and gastro-esophageal reflux disease, GERD) often take multiple medications. However, the relationship between xerogenic medication intake and salivary flow in these patients has not been thoroughly examined.

Methods: A retrospective study of 192 consecutive patients diagnosed with glossodynia (ICD-10-CM) at a regional center over a six-year period was performed. Data from electronic health records were extracted and relationships between medication intake, unstimulated whole salivary flow rate (UWSFR), xerostomia, and GERD were determined by chi-square, *t*-test, and correlation analysis.

Results: Of 134 records that met inclusion criteria, 87.1% of patients reported daily intake of one or more xerogenic medications. Two or more xerogenic medications were taken significantly more often by patients with glossodynia reporting GERD than those with glossodynia without GERD ($p = .02$). UWSFR was negatively correlated with number of medications [$r(103) = -.277, p = .005$] and xerogenic medications [$r(103) = -.195, p = .049$]. The lowest UWSFR was observed with use of trazodone and cyclobenzaprine.

Conclusions: Daily xerogenic medication intake, hyposalivation, and xerostomia were commonly present and potentially interrelated in patients who suffer from glossodynia and/or GERD.

Practical implications: Clinicians should be aware of the consequences of prescribing multiple and certain xerogenic medications in reducing UWSFR, especially in patients physiologically at risk of hyposalivation such as those suffering from GERD and/or glossodynia.

KEYWORDS

adverse effects, burning mouth syndrome, gastroesophageal reflux disease, glossodynia, xerostomia

1. Introduction

Saliva is a complex fluid comprised of major and minor salivary gland secretions important for intraoral hard and soft tissues (1), neutralizing acids in the oral cavity (2), and decreasing the time that acid is in contact with esophageal mucosa (3). A healthy individual produces on average 500 ml–1.5 L of saliva daily, about 0.35 ml/min (4).

Alterations in saliva, quality or quantity, can result from several etiological factors, including systemic conditions (5), such as obesity (6), diabetes (7), autoimmune disease (Sjogren's syndrome) (8), syndromes (Down syndrome) (9), neurodegenerative diseases (Alzheimer's disease) (10), infections [hepatitis (11), HIV-infection (12)]; iatrogenic cause, such as hemodialysis (13), radioactive iodine therapy (14), radio- or chemotherapy (15, 16); environmental factors, like dietary change, tobacco, alcohol or recreational drug use (17); physiological changes (18), including aging (19, 20); or medication intake (21–24). Medications, alone or in combination, are routinely prescribed to treat systemic or local conditions. However, many medications induce dry mouth and low salivary flow (25), which can contribute to mucosal atrophy and fissuring (26), dental caries (27), and fungal infections (28).

Reduced salivary volume may also contribute to glossodynia. Among studies that investigated this association, on average 64% of patients with glossodynia have xerostomia (range 23%–100%) (29–38) and 56% have hyposalivation (range 33%–100%) (29, 31–34, 37–44). Despite the established association between glossodynia and diminished salivary flow, to the best of our knowledge their relationship with xerogenic medications has not been thoroughly examined.

A comorbidity frequently seen among patients with glossodynia is gastro-esophageal reflux disease (GERD), a condition known to produce burning sensation. This can be initiated or maintained from a reduced salivary volume, which may itself contribute to symptoms felt in anatomical structures distal to the mouth (45). In the available literature, eleven studies measured unstimulated salivary flow (UWS) in patients with GERD, and four of these conducted on a total of 351 subjects confirmed a significant reduction in UWS, compared to 297 healthy controls (46–49). Moreover, patients with GERD tend to be managed with further medication intake, that can contribute to decreased salivary volume. Hence, the vicious cycle between xerogenic medications, salivary flow, and GERD may be important. However, few studies have investigated the presence of GERD in patients diagnosed with glossodynia with respect to xerogenic medications (50–55).

Therefore, the objectives of this study were to investigate the patients diagnosed with glossodynia (1) the prevalence of xerogenic medication; (2) the association between salivary flow volume and medication use; (3) which medications were associated with hyposalivation; and (4) the presence and association of xerostomia and hyposalivation with or without GERD. The null hypothesis was that patients with glossodynia are unlikely to take xerogenic medications and have concurrent GERD symptomatology.

2. Methods

A retrospective study was conducted on data collected from consecutive patients with a complaint of burning mouth sensation, seen at the Orofacial Pain Center (University of Kentucky, Lexington, United States) between January 2014 and April 2020. Due to the retrospective design of the study, a sample size calculation was not performed. However, a post-hoc power analysis on a sample size of 103 revealed a power of 81%.

Patient's electronic health records were reviewed for eligibility, according to the following inclusion criteria: (1) diagnosis of glossodynia (International Classification of Disease ICD-10-CM, Diagnosis Code-14.6); and (2) oral burning pain rated greater than 0, on a 0–10 numerical rating scale (NRS, 0 = “no pain” and 10 = “worst possible pain”). Patients were categorized as presenting with GERD symptomatology when they had either a physician diagnosis or self-reported GERD on intake forms. Exclusion criteria included patients with complaints of oral burning due to known condition (anemia, oral lesion, diabetes mellitus, Sjogren's syndrome, vitamin deficiency, or use of angiotensin converting enzyme inhibitors). Although GERD has been classified among underlying medical conditions associated with oral burning symptoms, for the current investigation, participants with a complaint of GERD were included in the study population. The study was approved by the Institutional Review Board of the Office of Research Integrity at the University of Kentucky (Lexington KY, United States; IRB #74332).

2.1. Procedure

All patients underwent a clinical evaluation for their oral burning complaint by the same Diplomate of the American Board of Oral Medicine (C.M.). A thorough medical history was collected with specific questions that investigated chief complaint, systemic medical conditions, medications, parafunctional habits, alcohol consumption, smoking status, daily physical activity, and laboratory results.

2.1.1. Oral burning sensation

The chief complaint was investigated by ascertaining the pain location, quality, frequency, and duration, the presence of taste disturbances, and triggering, aggravating, and relieving factors. Pain intensity was collected on a 0–10 NRS, with 10 being the worst possible pain.

2.1.2. Medications

The number and types of prescribed medication were recorded, with a focus on those known to be xerogenic (21, 22, 56).

2.1.3. Xerostomia

Xerostomia, defined as a subjective complaint of dry mouth (57–59), was assessed by self-report or with the Short-Form Xerostomia Inventory questionnaire (SXI) (60). The following statements on the SXI: “My mouth feels dry”; “My mouth feels dry when eating a meal”; “I have difficulties in eating dry food”; “I have difficulties swallowing certain foods”; and “My lips feel dry” were scored as “Never” 1; “Occasionally” 2; and “Often” 3. A cut-off of 10 or higher was used as clinical definition of “xerostomia” (personal communication with WM Thomson) (60).

2.1.4. Hyposalivation

Unstimulated whole salivary flow rate (UWSFR) was measured by instructing the patient to allow saliva to collect in the mouth and spit into a cup every 20 s for 5 min, while sitting upright and undisturbed in a comfortable position. Samples were collected between 1 pm and 4 pm, with participants refraining from eating or drinking one hour

before the procedure (61). Hyposalivation was defined as UWSFR < 0.2 ml/min, which represents the lowest 10th percentile as determined in our clinic (data not shown) and many previous studies (62, 63).

UWSFR of all patients was measured by the same Diplomate of the American Board of Oral Medicine (C.M.) to increase the reproducibility and standardization of the procedure.

2.2. Statistical analysis

Data normality was checked with a Shapiro-Wilk test. Variables were expressed as means and standard deviations. Hyposalivation, GERD symptomatology, and xerostomia were coded as dichotomous variables (1 = yes, 0 = no). Medications and salivary flow rate were coded as continuous variables. Descriptive statistics were completed for patients with data on salivary flow rate and xerostomia. Bivariate correlation analysis was performed to test the association between UWSFR and medication (number of medications, number and types of xerogenic medications), and between UWSFR and GERD. According to GERD symptomatology, the total population was divided in two groups (patients presenting with GERD symptoms = 1; patients not presenting with GERD symptoms = 0). Chi-square and McNemar tests were used when appropriate to compare the two groups in terms of gender, number, and type of medication. Independent *t*-test was used to compare the two groups in terms of age, medical conditions, pain intensity, xerostomia, and UWSFR. Statistical significance was set at $\alpha = 0.05$. Data were analyzed with SPSS (IBM SPSS Statistics Macintosh, Version 27.000, IBM Corp, Armonk, NY).

3. Results

Of 192 records identified, 58 were excluded due to missing data or a diagnosis different from glossodynia (ICD-10 14.6). A total of 134

patients diagnosed with glossodynia (mean age of 63.43 ± 11.84 , 80.6% females) were included in the analysis (Table 1). The mean pain intensity was 6.30 ± 2.39 , and 38.1% reported a taste disturbance. On average, patients had 5.17 ± 3.28 systemic medical conditions, with hypertension being the most common (44.8%), followed by GERD (44.0%) and depression (22.4%). Salivary flow was measured in 104 patients (77.6%). Their mean UWSFR was 0.24 ± 0.30 ml/min, and 68 (65.4%) had hyposalivation. Xerostomia was determined by questionnaire to be present in 76 patients out of 98 (77.6%), and the SXI yielded a mean score of 12.84 ± 5.90 . Seventy-eight percent of xerogenic patients had hyposalivation [$\chi^2(104) = 15.11, p = .001$]. Of those, 38 (50.7%) reported GERD symptoms.

3.1. Medication and salivary flow rate

The mean number of daily prescribed medications for the 134 patients diagnosed with glossodynia was 5.5 ± 3.49 . A significant negative correlation was found between the number of medications and UWSFR [$r(103) = -.277, p = .005$, Figure 1A]. The mean number of daily xerogenic medications of the total sample size was 3.11 ± 2.22 . Overall, 72.7% reported taking 2 or more xerogenic medications; 14.4% reported taking 1 xerogenic medication, and 12.9% of the total participants did not report any daily xerogenic medication intake. A negative correlation was found between the number of xerogenic medications and UWSFR [$r(103) = -.195, p = .049$, Figure 1B]. The most common xerogenic medications were selective serotonin reuptake inhibitors (SSRIs, 31.3%) and non steroid anti-inflammatory drugs (NSAIDs, 13.4%) (Table 2). Daily use of omeprazole was ascertained in 27.6% of the patients. Daily cyclobenzaprine [$r(104) = -.201, p = .041$] and ibuprofen use [$r(104) = -.206, p = .036$] were negatively associated with UWSFR. The medication profiles between patients reporting GERD and those not reporting GERD were similar (all p 's > 0.05, Table 2). Not

TABLE 1 Characteristics of the study population and differences between participants with and without GERD symptomatology.

	Total (N = 134)	GERD symptomatology (N = 59)	No GERD symptomatology (N = 75)	p value*
Gender (%)				
Male	26 (19.40)	13 (22.03)	13 (17.33)	.517
Female	108 (80.60)	46 (77.97)	62 (82.67)	
Age (years), mean \pm SD	63.43 \pm 11.84	62.79 \pm 12.11	63.94 \pm 11.68	.579
N medical conditions, mean \pm SD	5.17 \pm 3.28	6.64 \pm 3.83	4.03 \pm 2.21	.000
Taste disturbance (%)	51 (38.06) [¥]	20 (33.90)	31 (41.33)	.381
Pain intensity, mean \pm SD	6.30 \pm 2.39 [§]	6.09 \pm 2.56	6.46 \pm 2.25	.411
Reported dry mouth (%)	76 (77.55) [£]	38 (82.61)	38 (73.08)	.192
UWSFR, mean \pm SD	0.24 \pm 0.30 [†]	0.23 \pm 0.27	0.24 \pm 0.32	.980

GERD: gastro-esophageal reflux disease; UWSFR: Unstimulated Whole Salivary Flow Rate.

¥Value calculated on a total of 124 subjects.

§Value calculated on a total of 121 subjects.

£Value calculated on a total of 98 subjects.

†Value calculated on a total of 104 subjects.

*p-values obtained from a chi-square test for categorical variables, and from an independent sample *t*-test for continuous variables.

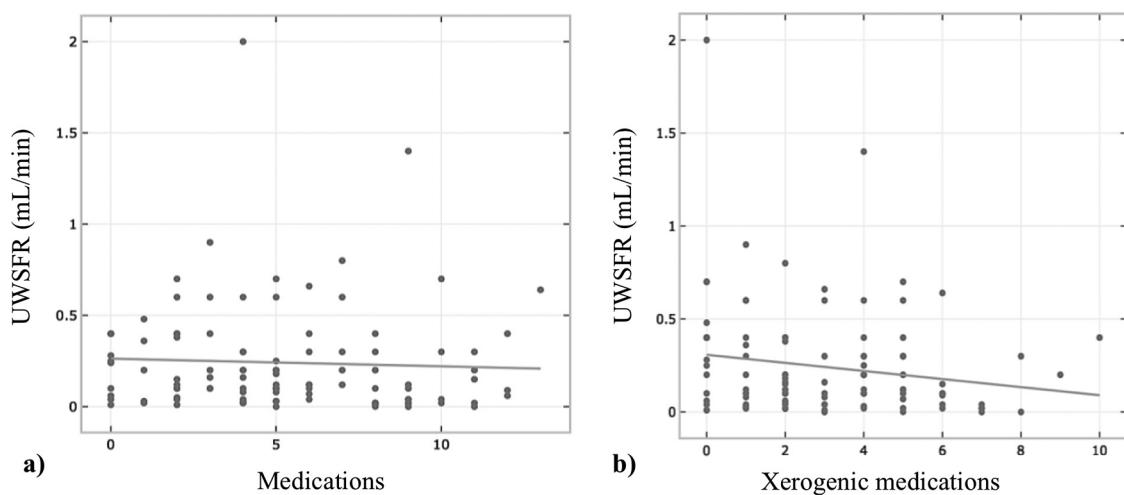


FIGURE 1
Relationship between number of medications (A) and xerogenic medications (B) and unstimulated whole salivary flow rate (UWSFR) ($N = 104$).

surprisingly, daily intake of omeprazole was significantly higher in those with GERD symptoms (39.0% vs. 18.7%, $p = .009$). Also, two or more xerogenic medications were used significantly more often by patients with glossodynia reporting GERD than those who took fewer than two xerogenic meds [$\chi^2(132) = 7.85$, $p = .020$].

Figure 2 displays the overall mean UWSFR of patients who used xerogenic medications daily. Those with daily intake of trazodone and cyclobenzaprine alone or in combination with another drug had the lowest UWSFR (0.03 ± 0.02 ml/min); those using omeprazole did not present with hyposalivation (0.29 ± 0.19 ml/min).

3.2. UWSFR, xerostomia, and GERD

Fifty-nine of those with glossodynia (44.0%) reported GERD. Of those, 61.4% had hyposalivation. A significant difference was not found in UWSFR between patients who reported GERD symptoms and those who did not (Table 2). A difference in xerostomia was not found between participants with and without GERD [$\chi^2(134) = 2.540$, $p = .194$].

4. Discussion

This study is one of the first to explore the interaction between medication intake and salivary flow in patients with glossodynia, with or without GERD symptomatology. The findings indicate that the majority of patients complaining of intraoral burning took xerogenic medications. A positive association was found between the number of xerogenic medications and low UWSFR in those with glossodynia. A high prevalence of GERD symptomatology (44%) was observed in patients with oral burning sensations and daily xerogenic medication intake. Despite this frequency, the presence of GERD and omeprazole use by themselves were not related to salivary flow rate.

Xerostomia was identified in 78% of patients diagnosed with glossodynia in this study, which is higher than the prevalence of xerostomia found in population-based studies (ranges from 0.9% to 64.8%) (64–67). Several factors may explain the greater prevalence of xerostomia in our patient population. In our clinic, the intake forms ask specifically about xerostomia whereas other studies may not. Also, xerostomia is common with aging and with use of xerogenic medications. Many of our patients took xerogenic medications, and many other studies did not explore the relationship with xerogenic medications (29, 31, 35, 40, 68). Finally, xerostomia is a subjective complaint based on self-reported data that may not be reliable; however, our study attempted to make the condition more objective by the administration of, and use of data from, the SXI form.

Our study demonstrated that 78% of those reporting xerostomia had hyposalivation. The present study utilized a cut-off of 0.2 ml/min to define hyposalivation, because patients below this threshold are in the lowest 10th percentile and often have symptoms or clinical findings consistent with the presence of hyposalivation-associated disorders. This is in contrast to the literature, where a cut-off of 0.1 ml/min is a commonly used definition for hyposalivation, as originally indicated by Ericsson and Hardwick (69). In the current study, hyposalivation was observed in 65% of patients diagnosed with glossodynia, which may be attributed to the age of our patient population and the extensive list of xerogenic medications used in this cohort. Alternatively, this finding may point to the potentially intrinsic common root between hyposalivation and glossodynia. In this regard, the results of the present study corroborate the negative association between number of medications and UWSFR (39, 70–77). Specifically, the lowest UWSFRs were observed in patients with glossodynia who took a daily combination of xerogenic medications, as shown in Figure 2. These observations are consistent with studies that reported difference between monotherapy and polytherapy (75, 78). However, these findings highlight a difficulty with the management of glossodynia; that

TABLE 2 Number and type of medication intake in the study population and differences between participants with and without GERD symptomatology.

	Total (N = 134)	GERD symptomatology (N = 59)	No GERD symptomatology (N = 75)	p value*
Mean number of medications ± SD	5.5 ± 3.49	6.12 ± 3.46	5.02 ± 3.46	.074
Mean number of xerogenic medications ± SD	3.11 ± 2.22	2.02 ± 2.03	2.35 ± 0.27	.157
SSRIs (%) ^a	42 (31.34)	18 (30.51)	24 (32.00)	.853
Paroxetine	2 (1.49)	1 (1.69)	1 (1.33)	1.000
Escitalopram	14 (10.45)	7 (11.86)	7 (9.33)	.634
Alprazolam	11 (8.21)	2 (3.39)	9 (12.00)	.111
Trazodone	7 (5.22)	1 (1.69)	6 (8.00)	.134
Sertraline	4 (2.99)	2 (3.39)	2 (2.67)	1.000
Fluoxetine	3 (2.24)	1 (1.69)	2 (2.67)	1.000
Bupropion	12 (8.96)	7 (11.86)	5 (6.67)	.296
PPI				
Omeprazole	37 (27.61)	23 (38.98)	14 (18.67)	.009*
Muscle relaxant				
Cyclobenzaprine	6 (4.48)	2 (3.39)	4 (5.33)	.694
NSAIDS	18 (13.43)	9 (15.25)	8 (10.67)	
Ibuprofen	7 (5.22)	5 (8.47)	2 (2.67)	.240
Meloxicam	6 (4.48)	2 (3.39)	4 (5.33)	.694
Naproxen	5 (3.73)	3 (5.08)	2 (2.67)	.654
ACE				
Lisinopril	17 (12.69)	7 (11.86)	10 (13.33)	.506
Calcium Channel Blocker				
Amlodipine	15 (11.19)	5 (8.47)	10 (13.33)	.376
Sedative-hypnotics				
Zolpidem	14 (10.45)	7 (11.86)	7 (9.33)	.634
SNRIs	11 (8.21)	5 (8.47)	6 (8.00)	.921
Duloxetine	8 (5.97)	4 (6.78)	4 (5.33)	.731
Venlafaxine	3 (2.24)	1 (1.69)	2 (2.67)	.717

ACE, Angiotensin-Converting Enzyme; N, number; NSAIDS, nonsteroidal anti-inflammatory drugs; PPI, Proton Pump Inhibitors; SD, standard deviation; SNRIs, Serotonin Norepinephrine Reuptake Inhibitors; SSRIs, Selective Serotonin Reuptake Inhibitors.

^aSome patients took more than one SSRI.

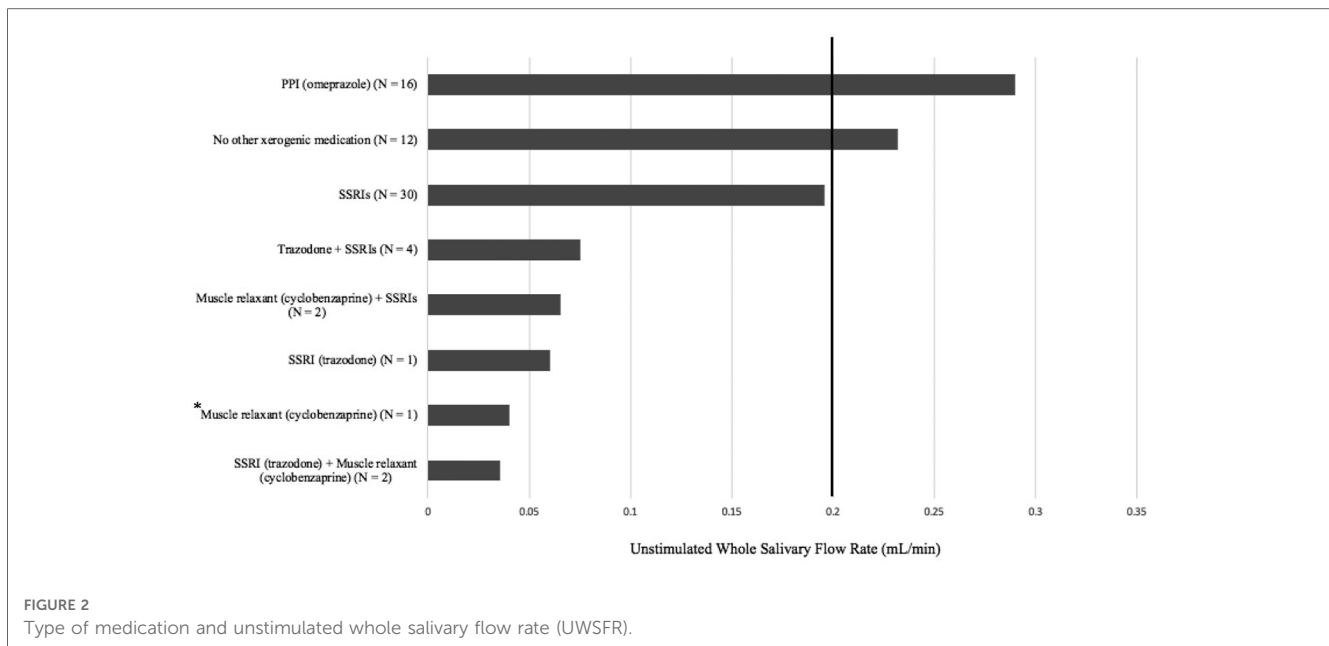
*p-values were obtained from a chi-square test or McNemar test for categorical variables as appropriate, and from an independent sample t-test for continuous variables.

is, how do clinicians who treat these patients eliminate hyposalivation when xerogenic medications are needed for management of their comorbidities? Novel study designs may be needed to address this concern to better understand confounders vs. root causes of glossodynia.

The findings from this study help support the concept that polypharmacy and hyposalivation underlie burning sensations that occur in the mouth and upper gastro-intestinal tract (53, 79–82). In this regard, 40% of those with hyposalivation also reported GERD symptomatology, although the difference was not statistically significant. Contradictory results are found in the literature, with studies supporting a relationship between hyposalivation and GERD (83–87) and studies that fail to

demonstrate a correlation (53, 80, 81, 84). This may be due to the different (1) criteria used to diagnose GERD [endoscopy (53, 81, 84) vs. questionnaires and self-reported reflux symptoms (83, 47)]; and (2) assessment methods of salivary flow [different duration (80, 81, 83), frequency (53, 80, 81), and time (53, 81, 83) of spitting method (53, 80, 81, 83, 84, 85), vs. Saxon method (48, 49), salivary scintigraphy (46), or modified cotton roll method (47)].

This study has limitations. First, the retrospective design did not permit control of confounding factors, such as medical condition, dosage of the medication taken, or allow retrieval of all the data. Hence, missing items were imputed using multiple imputation as appropriate. Future studies with more rigorous



methodology, which include the comparison with a healthy control group, are needed to control for factors that may influence the results. Similarly, the association observed between UWSFR and medication intake does not prove causation. Second, medication intake was self-reported and not investigated in terms of daily frequency, dosage, duration, and compliance. These factors have been shown to influence salivary flow rate (71, 86, 87). The sample included mostly elderly females, due to age and gender predilection of glossodynia. Therefore, these findings might not be generalizable to males or larger populations. Moreover, hormonal disturbances may influence the high prevalence of hyposalivation and xerostomia, which was not taken into consideration in the present investigation. As 18.7% of patient without GERD reported to take omeprazole, it is possible that they may have been misclassified. Therefore, we reanalyzed the data by classifying these patients within the GERD group, and these analyses did not alter the results (data not shown). Similarly, the presence of other comorbid systemic conditions was not included in the analysis as a confounding factor. Last, although an interesting trend was seen between UWSFR and type of medication, some of the findings are based on small sample size (e.g., medication use) and should be interpreted with caution until larger studies are performed.

5. Conclusions

These findings suggest that polypharmacy medication intake, hyposalivation, and xerostomia are commonly seen among patients with glossodynia and/or suffering from GERD. Because of these associations and the possible effect of burning sensation secondary to medication-induced hyposalivation, clinicians should be cautious in prescribing xerogenic medications and consider ways to deprescribe xerogenic medications in patients

who display concurrent hyposalivation and mucosal burning sensations to help evaluate alleviation of symptoms.

Data availability statement

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by by the Institutional Review Board (IRB, #74332) of the Office of Research Integrity at the University of Kentucky. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: CM; data curation: LS, WE; formal analysis: LS; methodology: CM; supervision: CM; roles/writing: LS, CM; writing – review and editing: LS, CM. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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