



Impact of medications on salivary flow rate in patients with xerostomia: a retrospective study by the Xeromeds Consortium

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Abstract

Objectives This study evaluates the impact of systemic medications and polypharmacy on unstimulated (UWS) and chewing-stimulated whole saliva (SWS) flow rates in patients with xerostomia.

Material and methods This cross-sectional multicenter study is based on data of patients referred to five oral medicine outpatient practices in Europe and USA from January 2000 and April 2014. Relevant demographic, social, medical history and current medications were collected.

Results The study included 1144 patients, 972 (85%) females, with a mean (SD) age of 59 (14.1) years. In unmatched patients, the UWS flow rate was lower in patients taking a medication (vs. not taking a medication) from the following drug categories: opioid analgesics, anticonvulsants, antidepressants, antihypertensives, benzodiazepines, corticosteroids, diuretics, disease-modifying antirheumatic drugs (DMARDs) and hormones. There was a greater negative effect on SWS flow rate in patients taking (vs. not taking) anticonvulsants, antidepressants, benzodiazepines, corticosteroids, and DMARDs. In matched patients, both UWS (0.22 vs. 0.19 ml/min; $p=0.03$) and SWS (0.97 vs. 0.85 ml/min; $p=.017$) flow rates were higher in patients on non-opioid analgesics (vs. not taking). The UWS flow rate was lower in patients taking antidepressants (vs. not taking) (0.16 vs. 0.22 ml/min $p=.002$) and higher (and within normal range) in patients taking sex hormones (vs. not taking) (0.25 vs. 0.16 ml/min; $p=.005$). On the other hand, SWS was lower in patients taking corticosteroid (vs. not taking) (0.76 vs. 1.07 ml/min; $p=.002$), and in patients taking DMARDs (vs. not taking) (0.71 vs. 0.98 ml/min; $p=.021$). Finally, differences in medians of both UWS and SWS were statistically significant in patients taking 1 or more than 1 opioid analgesic (vs. not taking, $p\leq.0001$ and $p=.031$, respectively), 1 or more than 1 anticonvulsants (vs. not taking, $p=.008$ and $p=.007$), 1 or more than 1 antidepressants (vs. not taking, $p<.0001$ for both), 1 or more than 1 DMARDs (vs. not taking, $p=.042$, and $p=.003$).

Conclusions A greater negative impact on UWS and SWS flow rates was seen in patients taking more than one medication from the same drug class. Intake of antidepressants, corticosteroids and DMARDs is associated with lower whole saliva flow rates.

Clinical relevance Salivary flow rate can be modified by some specific medications, mostly by polypharmacy.

Keywords Medication · Saliva · Xerostomia · Hyposalivation · Drug-induced side effects

Introduction

Saliva provides key biologic properties to maintain the integrity of the oral environment. Thus, saliva provides lubrication to the teeth and mucosa and protection of teeth and mucosa from acidic foods/liquids and acid regurgitation.

It also exerts antimicrobial activities and multiple functions in relation to the digestive processes of taste, initial breakdown of foods, chewing, bolus formation and swallowing [1]. Consequently, salivary gland hypofunction can negatively affect oral health and functions.

Salivary gland dysfunction can lead to xerostomia (the subjective feeling of a dry mouth), salivary gland hypofunction (an objective reduction in saliva secretion), hyposalivation (pathologic low saliva secretion) and changes in salivary composition [1]. Although xerostomia is frequently

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a manifestation of reduced salivary flow rate, it can also be a symptom on its own. Previous research has shown that xerostomia may also be related to changes in the biochemical composition of saliva or altered protein structure [2].

A number of systemic diseases have been associated with xerostomia and hyposalivation, including Sjögren's disease, rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, infectious diseases, including those caused by human immunodeficiency virus, cytomegalovirus, herpes virus and hepatitis C virus, as well as cancer therapy, particularly high-dose radiotherapy for head and neck cancer [2, 3].

Xerostomia has been reported as a side effect of numerous medications [4]. Xerostomia does not always correlate with salivary function as some patients with xerostomia may have normal salivary flow rates and vice versa [5]. Xerostomia usually occurs when the unstimulated whole saliva flow rate is reduced with approximately 50% of the baseline value, even if the flow rate is in the normal range [6].

The salivary secretion is regulated by the autonomic nervous system and activation of muscarinic, adrenergic and peptidergic receptors located on the plasma membranes of the salivary gland cells [7]. Consequently, medications with antagonistic effects to the autonomic nerves involved in the salivary secretion system can affect the fluid, electrolyte and protein secretion from the salivary glands leading to reduction in the flow rate and/or changes in the salivary composition. However, some medications without a clear impact on the nervous regulation may still be associated with xerostomia and salivary gland hypofunction, and affect salivary secretion through various other mechanisms [8]. Several investigations have studied the relationship between medications and salivary flow rates, many showing reduction of salivary secretion by various categories of medications [4, 9–14]. A systematic review of the association between medication intake and salivary gland dysfunction demonstrated strong evidence for 56 medications, moderate evidence for 50 medications and weak evidence for 48 medications [8].

Limitations of previous studies on the impact of medications on salivary gland function, xerostomia and additional oral adverse effects include insufficient sample size to assess the impact of polypharmacy and confounding factors on salivary flow rates and xerostomia, and the use of solely subjective measures and not additional objective measures of the actual salivary flow rates [8]. To address these issues, the Xeromeds Consortium was established to more accurately determine the impact of various factors on the salivary flow rates in a large cohort of patients from different international sites.

The overall aim of the present study was to evaluate the impact of medications and polypharmacy on unstimulated (UWS) and chewing-stimulated whole saliva (SWS) flow rates in patients with xerostomia. Additionally, our analysis included the impact of concurrent systemic diseases on UWS and SWS flow rates.

Methods

Study design and setting

This was a retrospective cross-sectional study of patients with a complaint of xerostomia who underwent sialometry with measurement of UWS and SWS flow rates between January 1, 2000 and April 30, 2014. Enrollment sites included Atrium Health Carolinas Medical Center (AH), USA; University of Zagreb (SFZG), Croatia; University of Copenhagen (UCPH), Denmark; University Medical Center Groningen (UMCG), Amsterdam UMC and Academic Center for Dentistry (ACTA), Netherlands; and University of Palermo (UniPa), Italy. Appropriate Ethics Board approval was obtained for patients assessed in the present study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Participants

Patients with a complaint of dry mouth and sialometry completed were assessed in the present study. All enrollment sites routinely measure UWS and SWS flow rates as part of routine clinical practice. No patients were excluded based on gender, race or socio-economic class.

Inclusion criteria

1. Patients with a complaint of a dry mouth (i.e. xerostomia).
2. 18 years of age or older.
3. All data necessary for this study present in the patients' medical chart.

Exclusion criteria

1. Classification of Sjögren's disease.
2. Previous or concurrent chemotherapy and/or radiotherapy for head and neck cancer.
3. Current use of parasympathomimetics, e.g. pilocarpine or cevimeline.

Variables

Selected variables were collected from the electronic health record the same day the sialometry was performed. Demographic information collected for all patients included age and sex. Current smoking and drinking were documented. Systemic diseases and all medications listed in the electronic

health record were documented and categorized by main treatment categories.

Case report forms (CRFs) were designed to collect data in a standardized manner. One data abstractor per site, with specialized knowledge of the research question, performed data abstraction from the medical charts to the case report forms. To verify correct transfer of data from the medical record to the CRF, random checks were performed prior to data entry. This was done according to the 100–20 rule in which 100% of the data is checked in 20% of the CRFs and 20% of the most important data was checked in 100% of the CRFs to prevent mistakes in data retrieval [15].

Unmatched comparison group

As has been completed in prior studies assessing the impact of medications on salivary flow rates, we first completed a raw comparison of the salivary flow rates of patients taking a medication category vs. all other patients in the cohort not taking a medication in that same category, but not controlling for other potential confounding factors.

Matched comparison group

In order to control for identified confounding factors, a matched comparison group was established for each medication category. The matched group were individuals not taking a particular medication category, but equally matched on relevant confounding factors. As an example, patients taking hypoglycemics were compared to a matched group not taking hypoglycemics but were equally matched to the hypoglycemic group on number of concurrent medications, number of systemic diseases, age and sex.

Salivary flow rate measurement

UWS and SWS flow rates were measured in a standardized manner [16]. Patients were instructed to refrain from eating, drinking, chewing gum, brushing teeth, using mouthwash and smoking for 90 min prior to sialometry. The preference for salivary flow measures was in the morning hours to minimize diurnal variations.

Patients were instructed to begin collecting saliva immediately after an initial swallow and to expectorate in the tube as soon as they collect saliva, and not to swallow. Saliva was collected for different length of times at enrollment sites with a minimum of 5 min for both UWS and SWS. Assessment of the UWS flow rate was followed by assessment of the SWS flow rate, where the patient was asked to chew a standard piece of paraffin wax or flavorless gum base and repeat the test in the same way.

Calculation of the UWS and SWS flow rates was made by pre-weighing both tubes before saliva collection and

subtracting the weight of tube after the test. Values were expressed in g/min which are considered equivalent to ml/min [16].

Statistical analyses

Descriptive statistics included means and standard deviation (SD), medians and interquartile ranges, which were considered appropriate based on the distribution of the data. Kolmogorov–Smirnov test was used to determine normality distribution of the study population. The impact of medication on UWS and SWS flow rates was analyzed by means of non-parametric tests except for age. Analysis of variance (ANOVA) test was used for determination of age differences, and the chi-square test of independence for determination of differences in sex, smoking (current vs. former/never) and alcohol (current vs. former/never). The Kruskal–Wallis test was used to evaluate the difference of medians with regard to number of medications, number of systemic diseases, UWS and SWS flow rates (ml/min) among all sites, as well as between systemic diseases and UWS and SWS flow rates. The same test was also used to calculate the median differences in UWS and SWS flow rates among patients taking no medication, one medication or more than one medication in the same medication category. The latter test was applied only for medications taken by a sample size that turned out to represent at least 5% of the patient cohort. The goal of the sample size was to gather at least 50 patients who were taking a medication category or individual medication to be evaluated.

In order to evaluate the effect of medications only on UWS and SWS flow rates, unmatched and matched analyses were completed for each medication category. Significant confounding factors were identified by unadjusted linear regression analysis of the entire cohort of patients. For the unmatched analysis, the entire sample was divided into two subgroups: one characterized by the variant to be analyzed and the other comprising of all the rest. A matching analysis for each medication category was planned with a control group (patients not taking a specific medication category) matched for the number of concurrent medications, number of systemic diseases, sex and age. Results are described for both unmatched and matched groups to better highlight the differences. All other comparisons of UWS and SWS flow rates (e.g. systemic disease) included only unmatched analyses.

The goal of matching by each individual medication category was to produce covariate balance, i.e. the distributions of covariates in the two groups (patients taking or not taking medication from a specific medication category) is approximately equal to each other, as they would be in a successful randomized experiment. The matching analysis contains the balance improvement, i.e. the percentage improvement by using the matched data relative

to all the data. It shows how much balance increased or decreased between patients taking and not taking medication (control group). Values between 0 and 100 indicate that balance improved after matching as measured by the statistic. This new analysis allowed to determine the improvement of similarity between two groups (patients taking and not taking medications) in relation to confounding factors.

Only for the matching analysis, means and not medians were used, because all matching analysis are based on a parametric approach, since this test is performed on distances (that are hypothesized to be continuous) and not on single variables.

Lastly, heat map plots were used to explain the association between medication variables (single medication and medication category) with systemic diseases and site of enrollment. The intensity of red color explains the co-occurrence frequency between the variables. Increased intensity of the red color indicates increased association.

Analyses were carried out using the SPSS version 25.0 (IBM Corp. 2017, Armonk, NY, USA) and R language (R Core Team 2020, Vienna, Austria).

Results

Cohort characteristics

The study included a total of 1144 patients, of whom 972 (85%) were women. The mean age was 59 (SD 14.1) years. Enrollment ranged from 62 to 474 patients for five different sites. The patients enrolled from Amsterdam UMC and ACTA were excluded from this analysis due a Sjögren's disease diagnosis. A total of 129 (11.6%) were current smokers,

and 396 (35.4%) were current alcohol consumers. The median (Q1–Q3) number of medications was 3 (1–5), and the median number of systemic diseases was 1 (0–3). Apart from sex, these variables differed between sites (Table 1).

Whole saliva flow rates

The median (interquartile range) UWS and SWS flow rates for the entire cohort were 0.16 (0.05–0.30) ml/min and 0.78 (0.41–1.32) ml/min, respectively (Table 1). The salivary flow rates differed significantly between sites.

Systemic diseases and whole saliva flow rates

Analysis of the whole saliva flow rates in relation to the presence or absence of individual systemic diseases revealed that patients with depression had lower median UWS (0.10 vs. 0.18 ml/min) ($p < 0.001$) and SWS flow rates (0.60 vs. 0.82 ml/min) ($p < 0.001$), whereas patients with hypertension had lower SWS flow rates (0.61 vs. 0.84 ml/min) ($p = 0.004$) (Table 2). To determine if lower salivary flow rates were the result of the systemic disease or to medication side effects, the following salivary flow rate comparisons were completed: patients with depression ($n = 174$) taking antidepressants ($n = 127$) vs. not taking antidepressants ($n = 47$); and patients with hypertension ($n = 211$) taking antihypertensive ($n = 169$) vs. not taking antihypertensives ($n = 42$). The UWS and SWS flow rates were significantly lower in patient with depression taking antidepressants vs. not taking antidepressants—UWS: 0.09 vs. 0.18 ml/min ($p = 0.01$) and SWS: 0.57 vs. 0.75 ml/min ($p = 0.02$). On the other hand, there were no significant differences in salivary flow rates in patients with hypertension taking vs. not taking

Table 1 Characteristics of the study population and differences between the enrollment sites. Data is provided as number of patients (%) and as median values (interquartile range)

	All sites ($n = 1144$)	AH, USA ($n = 474$)	SFZG, Croatia ($n = 428$)	UCPH, Denmark ($n = 116$)	UMCG, The Netherlands ($n = 64$)	UniPa, Italy ($n = 62$)	<i>p</i> value
Age, yr, mean (SD)	59.0 (14.1)	57.7 (14.4)	62.2 (13.1)	59.4 (14.2)	52.7 (14.7)	52.8 (12.8)	<0.001
Female (%)	972 (84.9)	403 (85)	359 (83.8)	93 (80.2)	58 (90.6)	59 (95.1)	0.06
Current smokers (%)	129 (11.3)	37 (5.7)	46 (10.7)	29 (25)	6 (9.3)	11 (17.7)	<0.001
Current alcohol intake (%)	396 (34.6)	278 (58.6)	8 (1.9)	86 (74.1)	24 (37.5)	0 (0)	<0.001
No. of medications	3 (1–5)	4 (2–6)	3 (1–4)	2 (1–4)	2 (1–4)	0.5 (0–2)	<0.001
No. of systemic diseases	1 (0–3)	3 (2–5)	0 (0–1)	2 (1–3)	1 (0–2)	0 (0–1)	<0.001
UWS (ml/min)	0.16 (0.05–0.3)	0.19 (0.08–0.38)	0.16 (0–3.6)	0.06 (0.01–0.15)	0.14 (0.06–0.35)	0.2 (0.09–0.39)	<0.001
SWS (ml/min)	0.78 (0.41–1.32)	0.89 (0.47–1.42)	0.84 (0.48–1.32)	0.61 (0.24–1.32)	0.37 (0.26–0.71)	0.51 (0.22–1)	<0.001

AH Atrium Health Carolinas Medical Center, SFZG University of Zagreb, UCPH University of Copenhagen, UMCG University Medical Center Groningen, UniPa University of Palermo, UWS unstimulated whole salivary flow rate, SWS chewing-stimulated whole salivary flow rate

Table 2 Association of unstimulated (UWS) and chewing-stimulated (SWS) whole salivary flow rates and systemic diseases

Systemic diseases	Presence	No. of patients	Unstimulated whole salivary flow rate (UWS, ml/min)				Chewing-stimulated whole salivary flow rate (SWS, ml/min)			
			Median	Q1	Q3	<i>p</i> value	Median	Q1	Q3	<i>p</i> value
Anxiety	N	1042	0.16	0.05	0.30	0.422	0.80	0.41	1.33	0.251
	Y	102	0.16	0.06	0.30		0.72	0.42	1.21	
Asthma	N	1079	0.16	0.05	0.29	0.904	0.79	0.42	1.32	0.198
	Y	65	0.15	0.05	0.33		0.72	0.34	1.27	
Depression	N	970	0.18	0.06	0.30	<0.001	0.82	0.42	1.38	<0.001
	Y	174	0.10	0.00	0.24		0.60	0.36	1.04	
Diabetes	N	1058	0.16	0.06	0.30	0.134	0.80	0.40	1.32	0.504
	Y	86	0.13	0.02	0.03		0.72	0.50	1.20	
GERD	N	978	0.15	0.05	0.28	0.128	0.78	0.42	1.32	0.621
	Y	166	0.17	0.06	0.34		0.82	0.40	1.30	
Headache	N	1076	0.16	0.05	0.30	0.557	0.78	0.78	1.31	0.388
	Y	68	0.10	0.05	0.29		0.80	0.37	1.25	
Hyperlipidemia	N	1078	0.16	0.05	0.29	0.599	0.78	0.42	1.32	0.544
	Y	66	0.16	0.02	0.37		0.97	0.40	1.45	
Hypertension	N	933	0.18	0.06	0.30	0.124	0.84	0.46	1.33	0.004
	Y	211	0.12	0.04	0.27		0.61	0.30	1.20	
Hypothyroidism	N	1046	0.16	0.05	0.30	0.606	0.80	0.42	1.33	0.060
	Y	98	0.14	0.06	0.31		0.69	0.31	1.16	
Osteoarthritis	N	1044	0.16	0.05	0.30	0.271	0.79	0.42	1.32	0.326
	Y	100	0.14	0.03	0.24		0.76	0.37	1.23	
RA	N	1075	0.16	0.05	0.30	0.196	0.80	0.42	1.32	0.272
	Y	69	0.12	0.04	0.28		0.60	0.32	1.44	
Autoimmune diseases	N	1068	0.16	0.05	0.30	0.488	0.78	0.39	1.32	0.161
	Y	76	0.13	0.04	0.26		0.87	0.56	1.28	

GERD gastroesophageal reflux disorder, RA rheumatoid arthritis, Y yes, N no

antihypertensives—UWS: 0.12 vs. 0.14 ml/min (*p* = 0.81) and SWS: 0.60 vs. 0.83 ml/min (*p* = 0.31).

Medication categories and whole saliva flow rates in unmatched patients

There was a greater negative effect on the UWS flow rate in patients taking medications (vs. not taking medications) in the following individual categories of medications: opioid analgesics (0.16 vs. 0.22 ml/min; *p* < 0.0001), anticonvulsants (0.15 vs. 0.21 ml/min; *p* = 0.002), antidepressants (0.16 vs. 0.22 ml/min; *p* < 0.001), antihypertensives (0.18 vs. 0.23 ml/min; *p* < 0.001), benzodiazepines (0.18 vs. 0.22 ml/min; *p* = 0.004), corticosteroids (0.17 vs. 0.21 ml/min; *p* = 0.017), diuretics (0.18 vs. 0.21 ml/min; *p* = 0.028), disease-modifying antirheumatic drugs (DMARDs) (0.15 vs. 0.21 ml/min; *p* = 0.002) and hormones (0.18 vs. 0.21 ml/min; *p* = 0.034) (Table 3).

There was a greater negative effect on SWS flow rate in patients taking (vs. not taking) anticonvulsants (0.75 vs. 0.95 ml/min; *p* = 0.002), antidepressants (0.81 vs. 0.97 ml/

min; *p* = 0.001), benzodiazepines (0.87 vs. 0.96 ml/min; *p* = 0.05), corticosteroids (0.76 vs. 0.96 ml/min; *p* = 0.003) and DMARDs (0.71 vs. 0.95 ml/min; *p* = 0.002) (Table 3). None of the medications were associated with a higher salivary flow rate.

Medication categories and whole saliva flow rates in matched patients

The univariate analyses identified several confounding factors including the number of concurrent medications, systemic diseases, age and sex, which could have an impact on salivary secretion and therefore needed to be adjusted for in the matched analyses. Enrollment site was also identified as a confounding factor, but due to enrollment of small numbers (*n* = 62–116) of participants at three of the five sites, this factor could not be controlled for appropriately in the matched analyses.

The matched control group comparison (i.e. patients not taking a specific medication category, but equally matched for the number of concurrent medications,

Table 3 Association of unstimulated (UWS) and stimulated (SWS) whole salivary flow rate with medications in unmatched and matched patients*

Medication category	Unmatched patients				Matched patients				Balance improvement (%)		
	No. patients	UWS (mean)	<i>p</i> value	SWS (mean)	<i>p</i> value	No. of patients	UWS (mean)	<i>p</i> value		SWS (mean)	<i>p</i> value
Opioid analgesics											
Not taking	983	0.22	<0.001	0.95	0.09	160	0.20	0.11	0.89	0.58	95.46
Taking	161	0.16		0.85		160	0.16		0.85		
Non-opioid analgesics											
Not taking	753	0.20	0.20	0.92	0.23	390	0.18	0.03	0.85	0.017	77.45
Taking	307	0.22		0.97		390	0.22		0.97		
Anticonvulsants											
Not taking	1045	0.21	0.002	0.95	0.002	98	0.20	0.09	0.82	0.44	96.23
Taking	99	0.15		0.75		98	0.15		0.75		
Antidepressants											
Not taking	908	0.22	<0.001	0.97	0.001	235	0.22	0.002	0.92	0.06	77.44
Taking	236	0.16		0.81		235	0.16		0.81		
Antihistamines											
Not taking	997	0.21	0.10	0.95	0.65	147	0.20	0.563	0.89	0.814	94.79
Taking	147	0.18		0.91		147	0.18		0.91		
Antihypertensives											
Not taking	694	0.23	<0.001	0.96	0.24	450	0.20	0.058	0.93	0.651	53.95
Taking	450	0.18		0.91		450	0.18		0.91		
Lipid-lowering agents											
Not taking	921	0.21	0.22	0.95	0.25	223	0.17	0.317	0.85	0.537	85.46
Taking	223	0.19		0.89		223	0.19		0.89		
Benzodiazepines											
Not taking	887	0.22	0.004	0.96	0.050	257	0.18	0.80	0.91	0.545	97.66
Taking	257	0.18		0.87		257	0.18		0.87		
Bone remodeling agents											
Not taking	1079	0.21	0.43	0.95	0.25	65	0.16	0.377	0.88	0.74	99.95
Taking	65	0.19		0.84		65	0.19		0.84		
Corticosteroids											
Not taking	1045	0.21	0.017	0.96	0.003	99	0.21	0.11	1.07	0.002	99.03
Taking	99	0.17		0.76		99	0.17		0.76		
Diuretics											
Not taking	958	0.21	0.028	0.95	0.12	186	0.16	0.407	0.81	0.365	95.52
Taking	186	0.18		0.87		186	0.18		0.87		

Table 3 (continued)

Medication category	Unmatched patients			Matched patients					Balance improvement (%)	
	No. patients	UWS (mean)	p value	SWS (mean)	p value	No. of patients	UWS (mean)	p value		SWS (mean)
DMARDs**										
Not taking	1073	0.21	0.002	0.95	0.002	70	0.17	0.21	0.98	0.021
Taking	71	0.15		0.71		70	0.14		0.71	
Hormones***										
Not taking	936	0.21	0.034	0.95	0.17	208	0.20	0.363	0.94	0.426
Taking	208	0.18		0.88		208	0.18		0.88	
Hypoglycemics										
Not taking	1058	0.21	0.076	0.95	0.10	86	0.19	0.546	0.80	0.602
Taking	86	0.17		0.84		86	0.17		0.84	
Hypnotics****										
Not taking	1060	0.21	0.80	0.95	0.386	84	0.18	0.432	0.90	0.81
Taking	84	0.20		0.88		84	0.20		0.88	
Proton pump inhibitors										
Not taking	840	0.21	0.45	0.95	0.20	304	0.19	0.624	0.94	0.501
Taking	304	0.20		0.90		304	0.20		0.90	
Sex hormones										
Not taking	1065	0.21	0.11	0.93	0.33	79	0.16	0.005	0.92	0.393
Taking	79	0.25		1.03		79	0.25		1.03	

*Category medications and single medications were included in the analyses only for a sample size equal to or greater than 50

**Disease-modifying antirheumatic drugs

***Included 18 different types of estrogens, progesterones and testosterone

****Non-benzodiazepines hypnotics

number of systemic diseases, sex and age) showed a greater negative effect on the UWS flow rate (0.16 vs. 0.22 ml/min; $p = 0.002$) in patients taking (vs. not taking) antidepressants and the SWS flow rate in patients taking (vs. not taking) corticosteroids (0.76 vs. 1.07 ml/min; $p = 0.002$) and DMARDs (0.71 vs. 0.98 ml/min; $p = 0.021$) (Table 3).

The UWS (0.22 vs. 0.19 ml/min; $p = 0.03$) and SWS flow rates (0.97 vs. 0.85 ml/min; $p = 0.017$) were higher (but still within the range of normal) in patients taking (vs. not taking) non-opioid analgesics. Additionally, the UWS flow rate was higher (but still within the range of normal) (0.25 vs. 0.16 ml/min; $p = 0.005$) in patients taking (vs. not taking) sex hormones.

Lastly, the matching analysis demonstrated an overall improvement in similarity between the groups of patients taking vs. not taking a specific class of medication. Such improvement ranged from 54% (in the group of patients taking antihypertensives) to 99.95% (in the group of patients taking bone remodeling agents) (Table 3).

Impact of polypharmacy from same medication class on whole saliva flow rates

To determine the impact of taking more than one medication from the same category of medication, a comparison of patients taking no medications, one medication and more than one medication of a medication category was completed. There was a greater negative effect on UWS and SWS flow rates based on increased number of drugs in the same individual category, i.e. in patients taking 1 or more than 1 opioid analgesic (vs. not taking, $p \leq 0.0001$ and $p = 0.031$, respectively), 1 or more than 1 anticonvulsants (vs. not taking, $p = 0.008$ and $p = 0.007$), 1 or more than 1 antidepressants (vs. not taking, $p < 0.0001$ for both), 1 or more than 1 DMARDs (vs. not taking, $p = 0.042$ and $p = 0.003$). Furthermore, there was a greater negative effect on UWS flow rates in patients taking 1 or more than 1 antihypertensives (vs. not taking, $p < 0.001$) and SWS flow rates in patients taking 1 or more than 1 corticosteroids (vs. not-taking, $p = 0.01$) (Table 4).

Co-occurrence frequency of medications with systemic diseases and site of enrollment

Depression, gastroesophageal reflux disease (GERD) and hypertension displayed the strongest association with a single medication (Fig. 1) and medication category (Fig. 2). These associations were stronger between diseases and single/category medications that were therapeutically linked, e.g. diabetes with metformin or GERD with pantoprazole.

AH was the site with the highest number of strong associations with medication categories, mainly non-benzodiazepine hypnotic drugs, sex hormones, lipid lowering agents, antihistamines, antidepressants and anticonvulsants (Fig. 3), whereas SFZG was the site with the highest number of strong associations with single medication, mainly ramipril, pantoprazole, diazepam and bisoprolol (Fig. 4).

Discussion

The current study found that patients affected by depression and taking antidepressants (vs. not taking antidepressants) and hypertension (vs. no hypertension) had lower salivary flow rates, and patients taking antidepressants, corticosteroids and DMARDs had lower whole saliva flow rates than patients not taking these medications. Previous studies have shown that numerous categories of medication interfere with salivary gland function and that polypharmacy and intake of certain medication are associated with reduction in UWS and SWS flow rates [4, 9, 10], particularly in older people [11–14, 17, 18]. The most prevalent medication categories noted to impact salivary function include cardiovascular medication, antidepressants/anxiolytics, gastrointestinal medications, antihistamines, analgesics and antipyretics [12]. A systematic review by Wolff et al. identified 56 medications with stronger evidence of affecting salivary gland function and included medications from the alimentary tract and metabolism, cardiovascular system, genitourinary system and sex hormones, antineoplastic and immunomodulating agents, musculoskeletal system, nervous system, respiratory system and sensory organs [8]. The current multi-center study includes a large cohort of dry mouth patients assessed for salivary flow rate, which allowed for control of confounding factors and thus provide a more accurate impact of medication categories on salivary flow rates than has been previously published.

The negative impact of certain systemic diseases on salivary secretion is likely aggravated by concomitant intake of medication. For example, depression and anxiety can cause xerostomia and salivary gland hypofunction, and the antidepressants and anxiolytics can add to these conditions. Patients reporting depression and taking an antidepressant had lower USW and SWS flow rates than patients with depression not taking antidepressants, pointing to the key role of medications in salivary secretions in patients with depression. On the other hand, patients with hypertension and taking antihypertensives did not have significantly lower salivary flow rates than patients with hypertension not taking antihypertensives. This may be related to a type II error from insufficient sample size; patients with hypertension are treated with other medication categories which cause lower salivary flow rates or hypertension physiologically decreases salivary flow rates.

Table 4 Association of stimulated and unstimulated whole salivary flow rate and patients who did not take any drug, 1 medication per group and more than one in the same group of medications

Medication	No. of patients	Unstimulated whole salivary flow rate (UWS) (ml/min)			<i>p</i> value	Stimulated whole salivary flow rate (SWS) (ml/min)			<i>p</i> value
		Median	Q1	Q3		Median	Q1	Q3	
No narcotic analgesic	983	0.17	0.06	0.30	<.0001	0.82	0.42	1.34	.031
1 narcotic analgesic	144	0.11	0.02	0.26		0.70	0.36	1.20	
More than 1 narcotic analgesic	17	0.02	0.00	0.14		0.56	0.08	0.87	
No anticonvulsants	1045	0.16	0.06	0.30	.008	0.81	0.43	1.34	.007
1 anticonvulsant	93	0.10	0.02	0.25		0.57	0.27	1.04	
More than 1 anticonvulsant	6	0.09	0.00	0.11		0.91	0.30	1.47	
No antidepressants	908	0.18	0.06	0.30	<.0001	0.84	0.46	1.39	<.0001
1 antidepressant	191	0.11	0.03	0.24		0.72	0.38	1.13	
More than 1 antidepressant	45	0.05	0.01	0.14		0.44	0.24	0.80	
No antihypertensives	694	0.18	0.06	0.30	.001	0.84	0.42	1.38	.566
1 antihypertensive	280	0.14	0.03	0.26		0.72	0.38	1.26	
More than 1 antihypertensive	170	0.12	0.02	0.24		0.72	0.42	1.26	
No benzodiazepines	887	0.16	0.06	0.30	.054	0.82	0.40	1.38	.268
1 benzodiazepine	236	0.12	0.02	0.26		0.72	0.41	1.20	
More than 1 benzodiazepine	21	0.14	0.05	0.26		0.72	0.39	1.29	
No corticosteroids	1045	0.16	0.05	0.30	.164	0.81	0.44	1.33	.010
1 corticosteroid	93	0.11	0.03	0.25		0.54	0.28	1.20	
More than 1 corticosteroid	6	0.07	0.03	0.24		0.71	0.16	0.98	
No diuretics	958	0.16	0.06	0.30	.092	0.81	0.42	1.37	.373
1 diuretic	160	0.14	0.02	0.26		0.72	0.37	1.20	
More than 1 diuretic	26	0.12	0.00	0.25		0.75	0.40	1.18	
No DMARDs	1073	0.16	0.05	0.30	.042	0.82	0.43	1.34	.003
1 DMARD	58	0.10	0.03	0.23		0.53	0.30	1.21	
More than 1 DMARD	13	0.08	0.06	0.15		0.34	0.23	0.87	
No hormones	936	0.16	0.05	0.30	.074	0.80	0.42	1.33	.066
1 hormone	205	0.12	0.04	0.24		0.75	0.36	1.31	
More than 1 hormone	3	0.05	0.00	0.11		0.25	0.05	0.36	

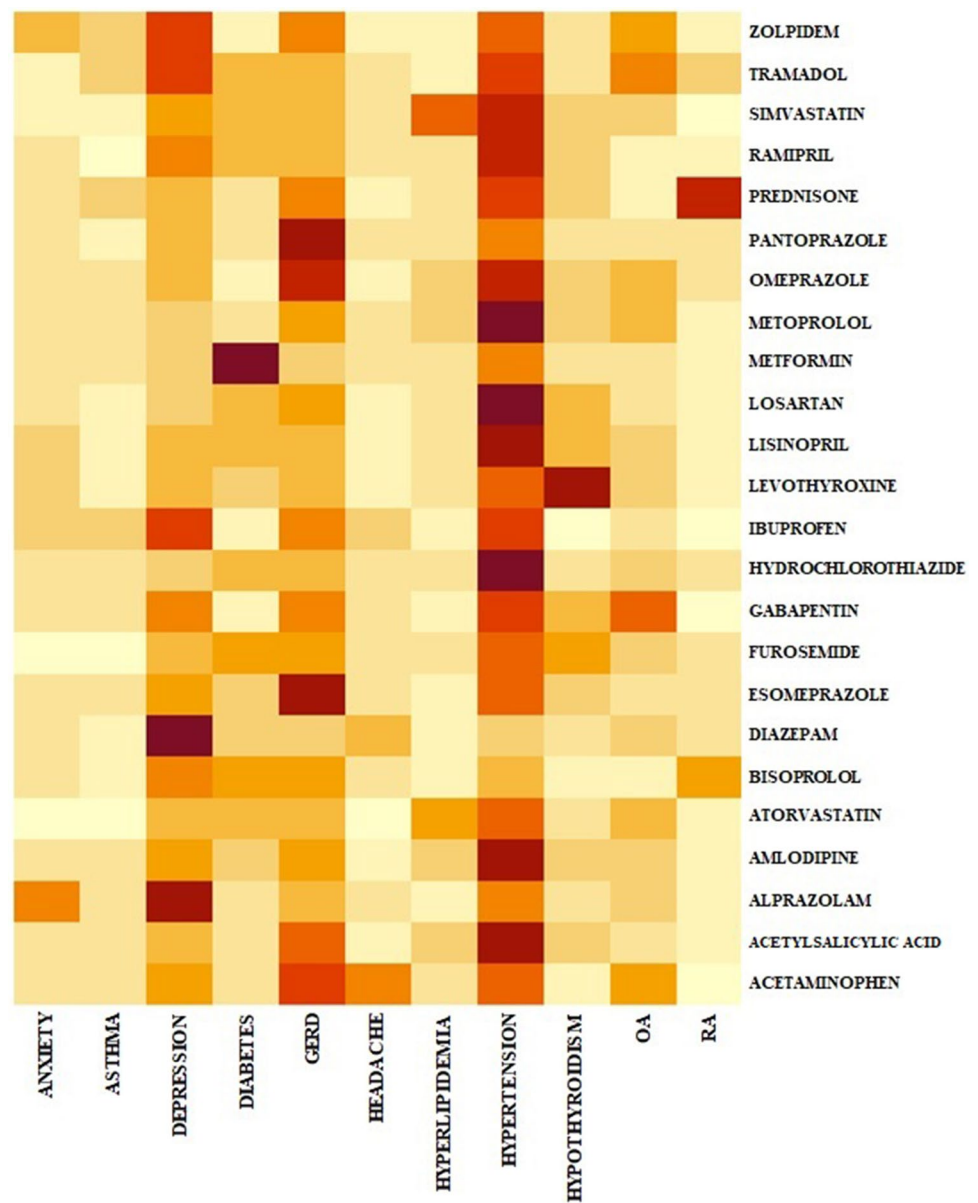
Q1 first Quartile, *Q3* third Quartile

Limitations of previous studies include inconsistency of the methods used for collecting and measuring salivary flow rates or the findings are based on xerostomia with no objective measurements of salivary gland function [8]. There is no consensus on a standard method of collecting saliva. Indeed, over the past decades, many different techniques to collect saliva (unstimulated and stimulated) are utilized from passive drooling of saliva into a tube (as used in the present study) to individual gland collection with a modified Carlson–Crittenden device for parotid saliva collection, and the Wolff apparatus for submandibular/sublingual saliva collection [19]. Different approaches for salivary collection in different studies can make comparisons of studies more challenging. The Xeromeds Consortium included clinical sites with similar whole saliva flow rate measurement techniques completed as part of standard clinical practice. Thus, a database of all sites could be combined to establish a sample size

large enough to control for key factors with the potential to impact salivary flow rate: specifically, number of concurrent medications, systemic diseases, age and sex.

The findings of the present study demonstrate the importance of controlling for key factors when assessing the impact of medications on salivary flow rate. A total of 9 medication categories were associated with lower salivary flow rates compared to all patients in the Xeromeds cohort not on these medications. These medication categories were similar to those identified in prior studies assessing xerostomia and salivary measures [8]. Establishing a matched group for comparison allowed for a more focused assessment of the medication category while controlling for other key factors, which can affect whole saliva flow rates and thus establish a clearer understanding of how medication categories affect salivary flow rates.

Fig. 1 Heatmap analysis of systemic diseases versus single medication with increased intensity of the red color indicates increased association. Abbreviations: **GERD** gastroesophageal reflux diseases, **OA** osteoarthritis, **RA** rheumatoid arthritis



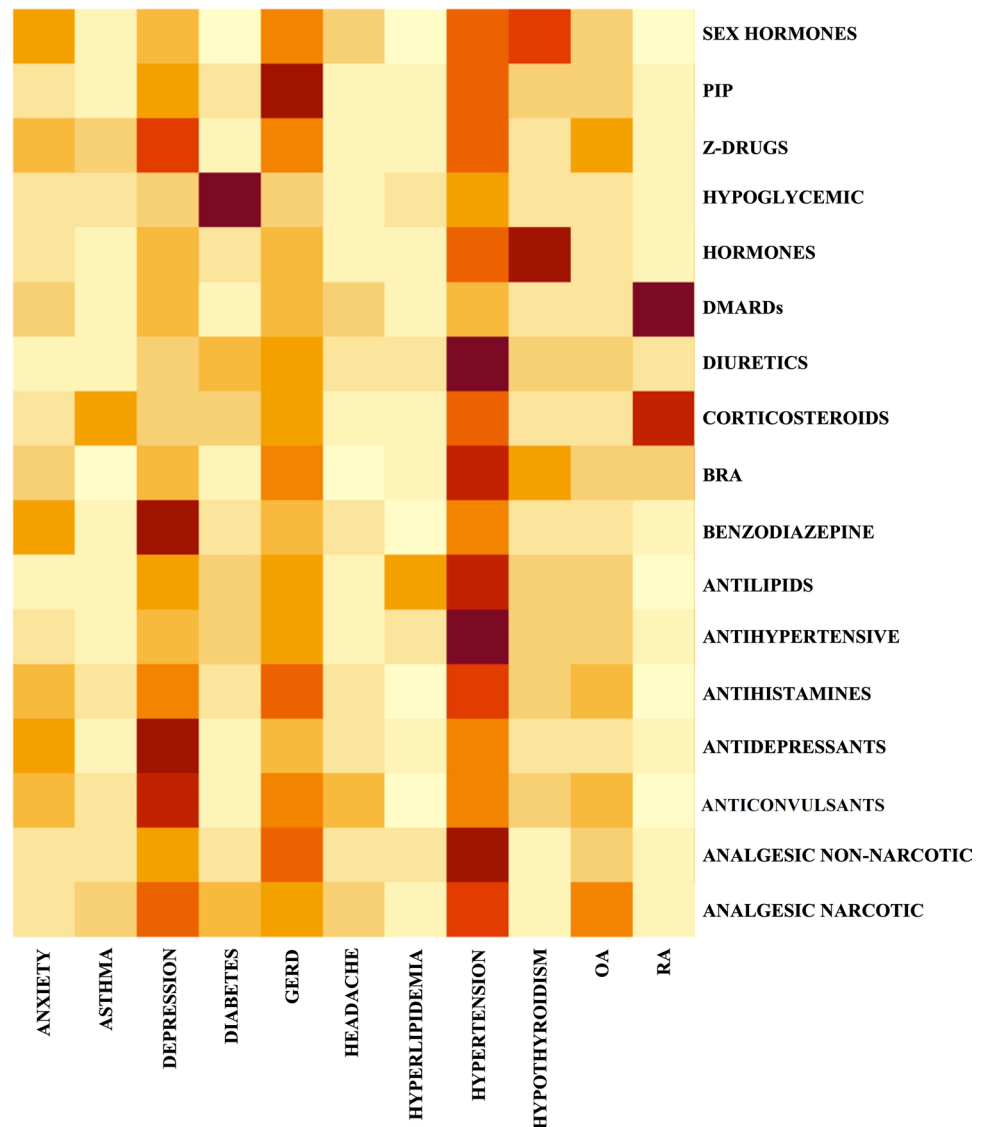
The findings of decreased salivary flow rate with increasing number of medications within the same category does demonstrate an enhanced negative impact on salivary flow rates of patients who take multiple opioids, anticonvulsants, antidepressants and antihypertensives. This underlines the importance of medication review and consideration of using fewer medications from the same category, although using multiple medications from the same category may be necessary and unavoidable to appropriately manage certain medical conditions.

Recognition of medication-induced salivary gland hypofunction should initiate a discussion with the prescriber and/or the pharmacist to determine if medications could be the etiology and if medication(s) can be stopped or replaced by another medication that does not have this side

effect, although a drug from the same category may lead to similar salivary hypofunction. It can also be discussed whether the time of taking the medication can be changed or the dosage can be reduced to manage salivary gland hypofunction and xerostomia.

This study represents the largest cohort of patients with xerostomia evaluated for the impact of medications on whole saliva flow rates compared to previous studies, but there were also a number of limitations. There were site differences noted in a number of outcomes, which may be related to referral bias, differences in medical care approaches in different countries and documentation differences in the electronic health record. Referral to a specialized center treating more severe cases of xerostomia and salivary gland hypofunction could result in their

Fig. 2 Heatmap analysis of systemic diseases versus category medication with increased intensity of the red color indicates increased association. Abbreviations: **GERD** gastroesophageal reflux diseases, **OA** osteoarthritis, **RA** rheumatoid arthritis, **PIP** proton pump inhibitor, **Z-drugs** non-benzodiazepine hypnotic drugs, **BRA** bone remodeling agents



patients having lower flow rates due to the nature of the patient population. There was also a limitation and a possible bias in the control group. Matching analysis could not include the site of enrollment due to small sample size of some participating centers; thus, a larger sample size would have allowed for control of site differences, which was present in the current study.

The Xeromeds Consortium represents a multicenter, multinational study with control of key confounding factors to provide a more accurate reflection of the impact of medications on whole saliva flow rates. Larger future prospective studies can provide an improved methodologic approach of larger sample sizes to control for potential differences between enrollment sites. The matched comparison of the present study provides an approach to control for confounding factors and provides

a more accurate assessment of this common side effect of medications.

From our study, we can conclude that patients affected by depression and taking antidepressants and hypertension may be more prone to develop xerostomia or salivary gland hypofunction compared to other medical conditions. Intake of more than one medication from the same category was associated with lower whole saliva flow rates. Furthermore, the use of antidepressants, DMARDs and corticosteroids had a greater negative impact on saliva secretion compared to a matched control group not taking a medication in this medication category. A larger prospective multi-center study could provide an improved methodologic approach of larger sample sizes to control for potential differences between enrollment sites.

Fig. 3 Heatmap analysis of site versus single medication with increased intensity of the red color indicates increased association. Abbreviations: **PIP** proton pump inhibitor, **Z-drugs** non-benzodiazepine hypnotic drugs, **BRA** bone remodeling agents

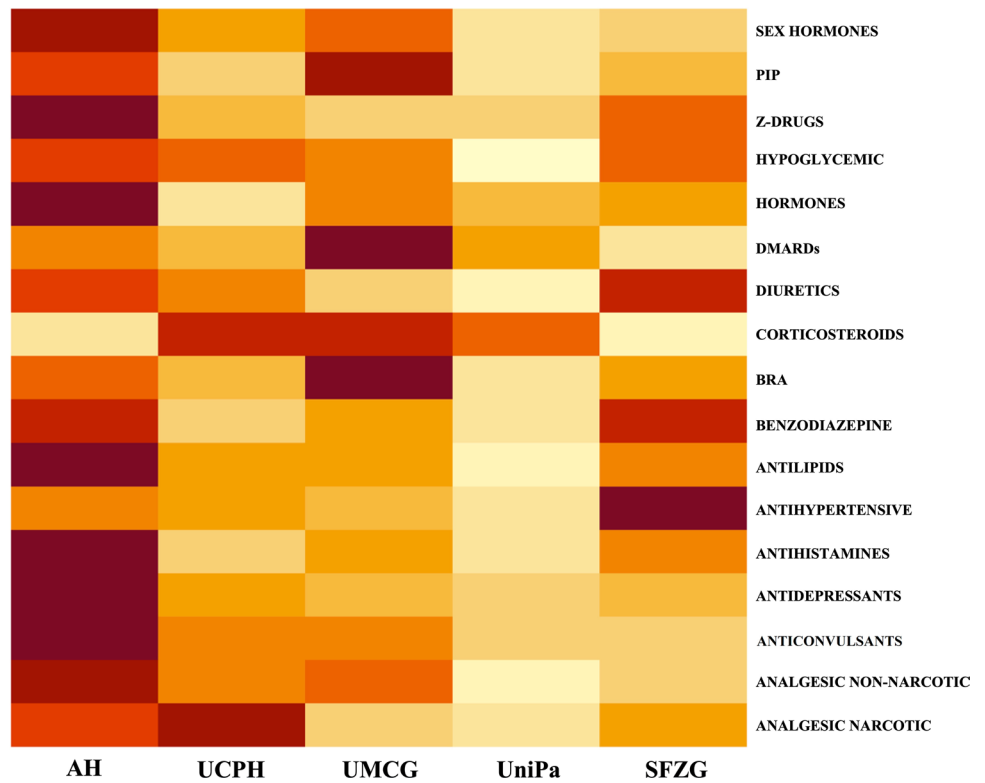
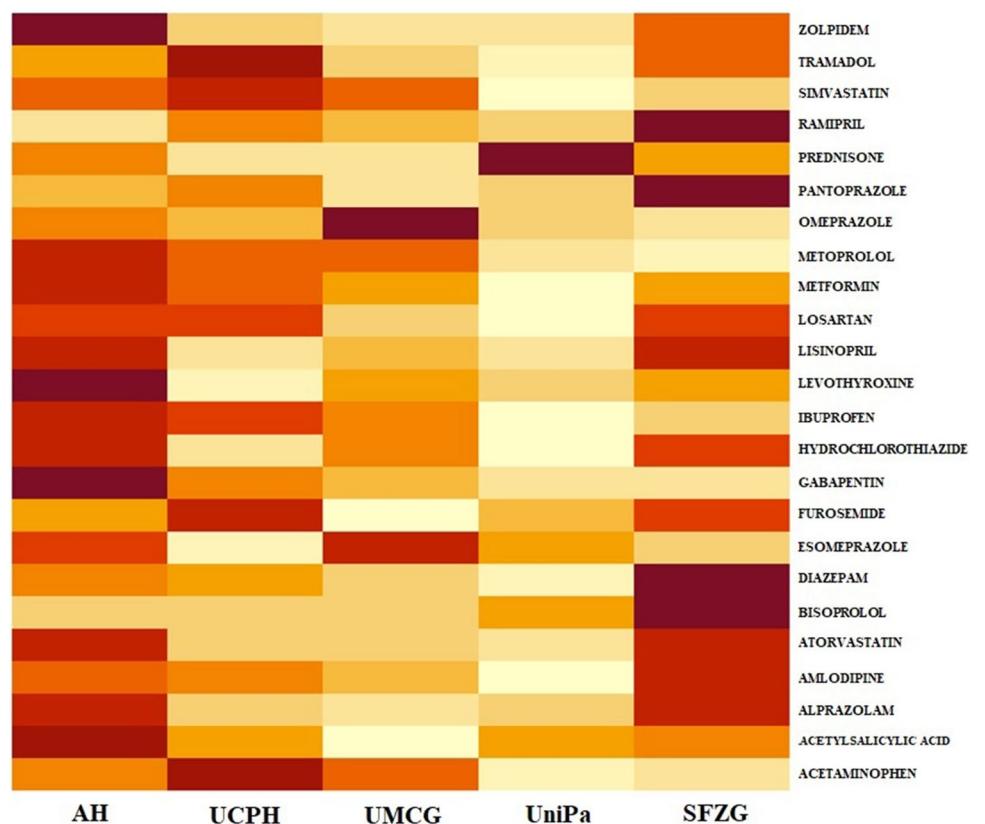


Fig. 4 Heatmap analysis of site versus category medication with increased intensity of the red color indicates increased association



Author contribution All authors made substantial contributions to the study conception or design, or the acquisition, analysis or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content. Details regarding author contributions are as follows:

study conception or design: GF, SW, KS, IA, AAR, AMLP, AV, OF, MA, DJJ, JN, SBJ, AW, MTB; acquisition of data: GF, SW, IA, AAR, AMLP, AV, OF, DJJ, JN, SBJ, AW, MTB; analysis or interpretation of data: GF, KS, IA, AAR, AMLP, AV, OF, MA, DJJ, SBJ, AW, MTB; drafting the work: GF, KS, MA, AW, MTB; editing/revising the work: GF, SW, KS, IA, AAR, AMLP, AV, OF, MA, DJJ, JN, SBJ, AW, MTB. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Declarations

Ethics approval and consent to participate Appropriate Ethics Board approval was obtained for patients assessed in the present study. The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Conflict of interest All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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