Factors Associated with Xerostomia in Non-Radiated Patients

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ABSTRACT

Objective: To identify factors significantly associated with xerostomia in non-radiated patients.

Methods: Patients who attended the outpatient otolaryngology clinic at Siriraj Hospital (Bangkok, Thailand) with complaints of dry mouth were invited to join this study. Collected data included age, gender, body mass index, smoking status, alcohol use, underlying disease, and previous medication and/or therapy. Irradiated patients were excluded. Participants were classified into either the diseased or xerostomia group by abnormal oral cavity examination and symptoms, or the no xerostomia group, which was defined as dry mouth symptoms with no presence of abnormal physical findings.

Results: Two hundred and two participants with a history of dry mouth were consecutively enrolled. There were 86 patients with physical findings compatible with xerostomia, and 116 symptomatic patients without xerostomia. Multivariate analysis revealed age over 50 years (adjusted odds ratio [aOR]: 3.1, 95% confidence interval [CI]: 1.3-7.9; p=0.012), analgesic and muscle relaxant intake (aOR: 3.6, 95% CI: 1.3-9.7; p=0.012), psychotherapeutic medication (aOR: 7.8, 95% CI: 2.6-23.7; p<0.001), and radioactive iodine therapy (aOR: 3.7, 95% CI: 1.2-11.8; p=0.015) to be independent predictors of xerostomia.

Conclusion: Xerostomia is a condition that can adversely affect quality of life. The results of this study revealed older age (≥50 years), analgesics and muscle relaxants, psychotherapeutic medications, and radioactive iodine therapy to be significantly associated with xerostomia. A thorough understanding of the symptoms, diagnosis, relevant risk factors, and effective management is essential for improving outcomes among patients with xerostomia.

Keywords: Xerostomia; underlying disease; medication; non-radiation patients (Siriraj Med J 2019; 71: 377-384)

INTRODUCTION

Saliva plays an important role in oral health by helping to prevent infection, and by facilitating chewing, swallowing, and speaking. Xerostomia and salivary gland hypofunction are two terms that highlight the important relationship between saliva and oral health. However, no significant association between these two conditions has been reported. Some patients have salivary gland hypofunction without having xerostomia. However, it was reported that individuals with xerostomia may have abnormal or low flow of saliva.[1,2] Stimulated and non-stimulated saliva flow rates of <0.1 ml/min and <0.7 ml/min, respectively, are diagnosed as salivary gland hypofunction.[3] Xerostomia is a common subjective complaint of dryness in the mouth.[4] Defining xerostomia can be problematic and potentially confusing, because there are different questionnaires that use different criteria to identify xerostomia. Among the available questionnaire-based tools for diagnosing xerostomia, the Xerostomia Inventory is the most frequently used tool in a research setting. The Xerostomia Inventory is an 11-item tool that quantifies the severity of xerostomia.[5,6]

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Saliva has various roles and functions. First, it provides a defense against bacterial pathogens via enzymes, such as immunoglobulin A and lysozyme.[7,8] Second, it is an emulgent that aids enzymes that assist in the digestion of food. Third, saliva provides a physical glycoprotein and mucoid coating to prevent unfavorable substances from attaching to the teeth. This coating also aids in oral lubrication and swallowing.[9] Fourth, the bicarbonate and phosphate buffers in saliva help to maintain a neutral oral pH.[7] Therefore, patients that have xerostomia with either low or abnormal salivary flow are at high risk for developing oral health-related problems, such as dental caries, mucosal ulceration, oral candidiasis, and dysphagia – all of which can adversely impact quality of life.[10] It is, therefore, necessary for clinicians to understand the multidimensional aspects of this condition so that proper diagnosis can be made and proper treatment can be given in order to reduce complications and improve patient outcomes.

Xerostomia affects millions of people around the world. It is difficult to determine the exact prevalence of this condition; however, the prevalence was reported to range from 12% to 30%.[7] The most commonly reported cause of xerostomia is radiation to the head and neck region. Other possible causes that have been reported include medications and some specific diseases.[11-13]

Improved understanding of the factors that significantly associate with xerostomia will improve our understanding of this condition, and improve diagnosis, treatment, and outcomes. Accordingly, the aim of this study was to identify factors significantly associated with xerostomia in non-radiated patients that presented with dry mouth symptoms at Siriraj Hospital – Thailand's largest national tertiary referral hospital.

MATERIALS AND METHODS

Study design and population

The protocol for this prospective cross-sectional study was approved by the Siriraj Institution Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 512/2016). We consecutively recruited two hundred and two participants aged >18 years with symptomatic dry mouth from the outpatient clinic of the Department of Otorhinolaryngology during the September 2016 to December 2017 study period. Patients satisfying one or more of the following criteria were excluded: 1) declined to participate in the study; 2) unable to answer the questionnaire; 3) unable to undergo the physical examination; and/or, 4) had history of radiation therapy or chemotherapy at the head and/or neck.

Data collection

Patients that complained of dry mouth were asked to take the five-question Xerostomia Inventory – Dutch Version.[5,6] If the patient reported having one or more of the five listed symptoms, the patient was invited to join the study. Written informed consent was obtained from all participating patients. Clinical history to taken and physical examination was performed. Information that was collected included age, gender, body mass index, smoking status, alcohol use, medications, and current medical status. Using this information and the results of the physical examination, participants were allocated to either the diseased or xerostomia group[12,14] (defined as patients who had history of dry mouth with physical examination that revealed abnormal oral cavity) or the no xerostomia group (defined as having symptoms of dry mouth, but with no presence of abnormal physical findings) (Fig 1).

Statistical analysis

SPSS statistics version 18 (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses. Descriptive statistics were used to summarize patient demographic and clinical data. Data are presented as frequency and proportion. Univariate analysis using chi-square test of independence was performed to evaluate association between investigated variables and xerostomia. Variables with a p-value <0.2 in univariate analysis were included in multivariate analysis using logistic regression model. The results of multivariate analysis are presented as odds ratio (OR) with 95% confidence interval (CI) and adjusted OR (aOR) with 95% CI. A p-value <0.05 indicates statistical significance.

RESULTS

The study population comprised 202 participants with complaint of dry mouth, and the age range of patients was 19-81 years. Eighty-six participants were allocated to the xerostomia group, and 116 participants were assigned to the no xerostomia group. The mean age of patients was 63.30±11.26 years in the xerostomia group, and 57.44±14.7 years in the no xerostomia group. Among the entire study cohort, 57 (28.2%) participants were male and 145 (71.8%) were female.

As shown in Table 1, significantly more patients in the xerostomia group acknowledged having the symptoms listed on the self-report questionnaire than patients in the no xerostomia group for all 5 of the listed symptoms (all p<0.001). "My mouth feels dry" (87%) and "My lips feel dry" (77%) were the two most commonly reported symptoms.

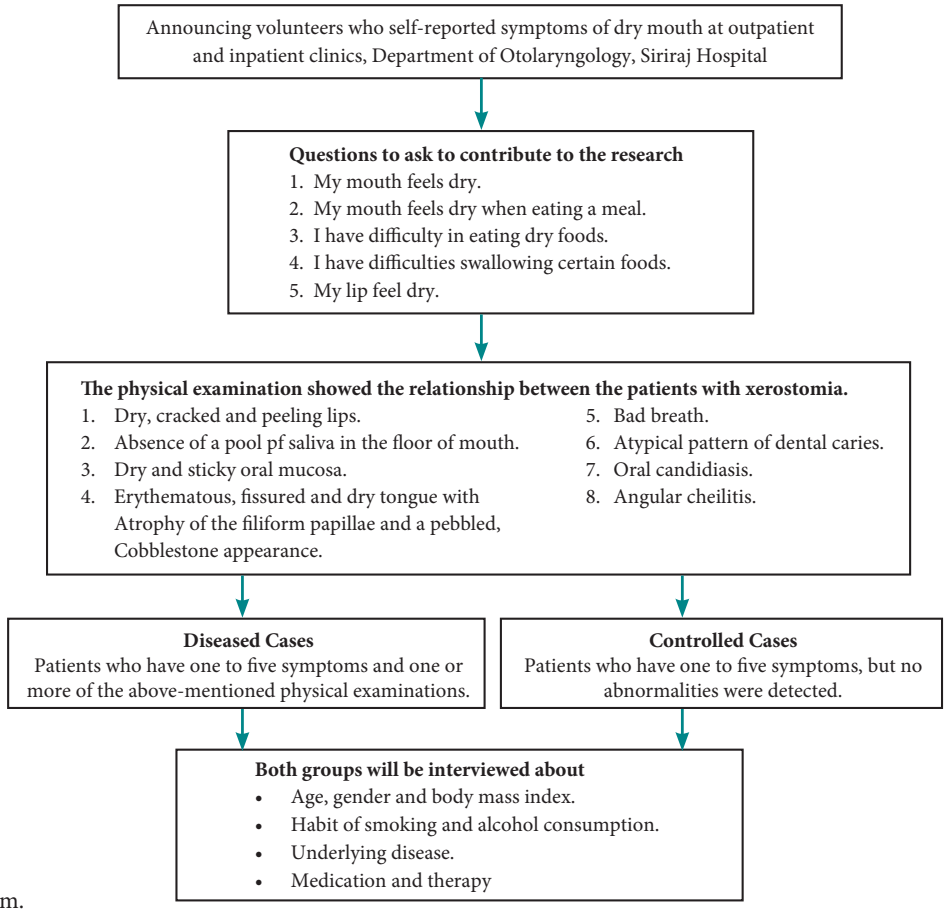

Fig 1. Flow diagram.

TABLE 1. Patient-reported symptoms.

Variable	Number (%)		Odds Ratio	*P*-value
	Xerostomia (N=86)	No-Xerostomia (N=116)	(95%CI)	
My mouth feels dry	75 (87.2)	75 (64.7)	3.7 (1.8-7.8)	< 0.001**
My mouth feels dry when eating a meal	15 (17.4)	2 (1.7)	12.0 (2.7-54.2)	< 0.001**
I have difficulty in eating dry foods	21 (24.4)	3 (2.6)	12.2 (3.5-42.4)	< 0.001**
I have difficulties swallowing certain foods	26 (30.2)	7 (6.0)	6.7 (2.8-16.5)	< 0.001**
My lips feel dry	66 (76.7)	39 (33.6)	6.5 (3.5-12.3)	< 0.001**

**P<0.05: statistical significant

Fig 2 illustrates the results of various physical examinations in the xerostomia group. The most common findings from physical examination in the xerostomia group were lack of a saliva pool in the floor of the mouth (61.6%); presence of erythematous, fissured, and dry tongue with atrophy of the filiform papillae, and a pebbled cobblestone appearance (58.1%); dry, cracked, and peeling lips (50.0%); and, dry and sticky oral mucosa (48.8%).

Univariate analysis revealed the prevalence of xerostomia to be significantly increased in the ≥50 age group compared to the 0-49 age group (odds ratio [OR]: 2.9, 95% confidence interval [CI]: 1.3-6.7; p=0.006). There were no significant differences between the xerostomia and no xerostomia groups for gender, body mass index, smoking status, or alcohol consumption. Univariate analysis for association between xerostomia with underlying

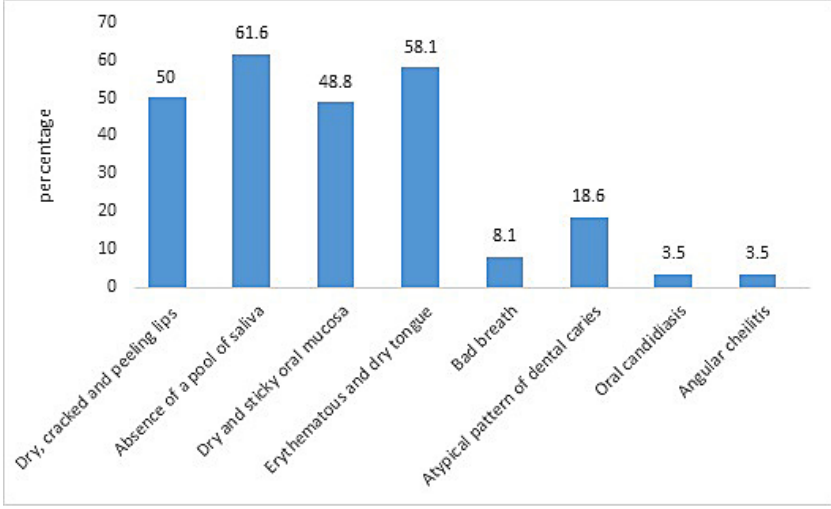

Fig 2. Prevalence of physical examination in xerostomia group.

disease, medications and therapies is presented in Table 3. Factors with a *p*-value <0.2 in univariate analysis and factors of interest were included in multivariate analysis.

Multivariate analysis revealed age ≥50 years (adjusted OR [aOR]: 3.1, 95% CI: 1.3-7.9; *p*=0.012), analgesic and muscle relaxant medication (NSAIDs, gabapentin) (aOR: 3.6, 95% CI: 1.3-9.7; *p*=0.012), psychotherapeutic medication (antidepressant, anxiolytic, antipsychotic) (aOR: 7.8, 95% CI: 2.6-23.7; *p*<0.001), and radioactive iodine therapy (131I) (aOR: 3.7, 95% CI: 1.2-11.8; *p*=0.015) to be independent predictors of xerostomia (Table 4).

TABLE 2. Univariable analysis of associations with xerostomia (Age group, Gender, BMI, Smoking and Alcohol consumption).

Variable	Number (%)		Odds Ratio	*P*-value
	Xerostomia (N=86)	No-Xerostomia (N=116)	(95%CI)	
Age category				
0-49	9 (10.5)	30 (25.9)	1.0	0.006*
≥50	77 (89.5)	86 (74.1)	2.9 (1.3-6.7)	
Gender				
Male	18 (20.9)	39 (33.6)	1.0	0.058*
Female	68 (79.1)	77 (66.4)	1.9 (1.0-3.6)	
BMI				
0-22.99	41 (47.7)	53 (45.7)	1.0	0.887
≥23	45 (52.3)	63 (54.3)	0.9 (0.5-1.6)	
Smoking				
Never/former	85 (98.8)	114 (98.3)	1.0	1.000
Current	1 (1.2)	2 (1.7)	0.7 (0.1-7.5)	
Alcohol consumption				
Never/former	85 (98.8)	110 (94.8)	1.0	0.242
Current	1 (1.2)	6 (5.2)	0.2 (0.0-1.8)	

*P-value less than 0.2 will be selected for multivariable analysis
Abbreviation: BMI= Body mass index

TABLE 3. Univariable analysis of associations with xerostomia (underlying disease, medication and therapy).

Variable	Number (%)		Odds Ratio	*P*-value
	Xerostomia (N=86)	No-Xerostomia (N=116)	(95%CI)	
Diabetes mellitus	20 (23.3)	19 (16.4)	1.5 (0.8-3.1)	0.279
Hypertension	41 (47.7)	45 (38.8)	1.4 (0.8-2.5)	0.250
Cardiovascular disorders	6 (7.0)	3 (2.6)	2.8 (0.7-11.6)	0.174
Thyroid disorders	19 (22.1)	35 (30.2)	0.7 (0.3-1.3)	0.260
Psychological disorders	13 (15.1)	1 (0.9)	20.5 (2.6-159.9)	< 0.001**
Neurological disorders	6 (7.0)	8 (6.9)	1.0 (0.3-3.0)	1.000
Rhinitis	13 (15.1)	25 (21.6)	0.6 (0.3-1.3)	0.278
Autoimmune disorders	4 (4.7)	2 (1.7)	2.8 (4.5-15.5)	0.405
Respiratory disorders	3 (3.5)	7 (6.0)	0.6 (0.1-2.2)	0.522
Dyslipidemia	33 (38.4)	41 (35.3)	1.1 (0.6-2.2)	0.768
Skeletal disorders	12 (14.0)	7 (6.0)	2.5 (0.9-6.7)	0.086
Hematologic disorders	0 (0.0)	2 (1.7)	0.6 (0.5-0.6)	0.509
Extraesophageal symptoms	5 (5.8)	4 (3.4)	1.7 (0.5-6.6)	0.500
Renal disorders	1 (1.2)	3 (2.6)	0.4 (0.0-4.3)	0.638
Gastrointestinal disorders	5 (5.8)	4 (3.4)	1.7 (0.4-6.6)	0.500
Antihypertensive medication	41 (47.7)	49 (42.2)	1.2 (0.7-2.1)	0.476
Endocrinologic medication	38 (44.2)	42 (36.2)	1.4 (0.8-2.5)	0.309
Analgesic and muscle relaxant medication (NSAIDs, gabapentin)	16 (18.6)	7 (6.0)	3.6 (1.4-9.1)	0.007*
Antihistamine	14 (16.3)	24 (20.7)	0.7 (0.4-0.5)	0.471
Psychotherapeutic medication (antidepressant, anxiolytic, antipsychotic)	18 (20.9)	5 (4.3)	5.9 (2.1-16.1)	< 0.001*
Antiplatelet (aspirin, clopidogrel)	16 (18.6)	8 (6.9)	3.1 (1.3-7.6)	0.015*
Anticoagulation	1 (1.2)	3 (2.6)	0.4 (0.0-4.3)	0.638
Respiratory medication	4 (4.7)	3 (2.6)	1.8 (0.4-8.4)	0.462
Antidyslipidemia	34 (39.5)	37 (31.9)	1.4 (2.8-2.5)	0.298
Gastrointestinal medication (prokinetic, laxative)	5 (5.8)	2 (1.7)	3.5 (0.7-18.6)	0.138*
Proton pump inhibitor	13 (15.1)	6 (5.2)	2.8 (1.1-7.3)	0.041*
Nutritional medication	21 (24.4)	23 (19.8)	1.3 (0.7-2.6)	0.492
Neurological medication	2 (2.3)	2 (1.7)	1.4 (0.2-9.8)	1.000
Cardiovascular medication	2 (2.3)	1 (0.9)	2.7 (0.2-30.7)	0.576
Immunosuppressant medication	1 (1.2)	1 (0.9)	1.3 (0.1-21.9)	1.000
Radioactive Iodine therapy (^{131}I)	9 (10.5)	6 (5.2)	2.1 (0.7-6.3)	0.181*

*P-value less than 0.2 will be selected for multivariable analysis, **P<0.05: statistical significant

TABLE 4. Factors associated with xerostomia, using multivariate analysis.

Factors	Crude Odds Ratio (95%CI)	Adjusted Odds ratio (95%CI)	*P*-value
Age (years)			
0-49	1.0	1.0	0.012**
≥50	2.9 (1.3-6.7)	3.1 (1.3-7.9)	
Gender			
Male	1.0	1.0	0.075
Female	1.9 (1.0-3.6)	1.9 (0.9-4.0)	
Analgesic and muscle relaxant medication (NSAIDs, gabapentin)	3.6 (1.4-9.1)	3.6 (1.3-9.7)	0.012**
Psychotherapeutic medication (antidepressant, anxiolytic, antipsychotic)	5.9 (2.1-16.1)	7.8 (2.6-23.7)	< 0.001**
Antiplatelet (aspirin, clopidogrel)	3.1 (1.3- 7.6)	2.6 (0.9-7.2)	0.064
Gastrointestinal medication (prokinetic, laxatives)	3.5 (0.7-18.6)	2.8 (0.4-18.2)	0.283
Proton pump inhibitor	2.8 (1.1-7.3)	2.5 (0.7-8.3)	0.117
Radioactive Iodine therapy (^{131}I)	2.1 (0.7-6.3)	3.7 (1.2-11.8)	0.015**

**P<0.05: statistical significant

DISCUSSION

This study investigated the risk factors associated with xerostomia in non-radiated patients. A systemic review conducted by Tanasiewicz M, *et al.*[7] revealed a prevalence of xerostomia in population-based studies that ranged from 12% to 30%, with the wide range explained by differences in the assessment methods used among studies. There was no universal assessment available to compare xerostomia among those studies. Several different questionnaires for diagnosing xerostomia have been developed. A frequently used questionnaire in research is the 11-item Xerostomia Inventory.[1,2,15,16] The Xerostomia Inventory-Dutch Version is an abbreviated version of the original version that includes only the following 5 items: "My mouth feels dry", "My mouth feels dry when eating a meal", "I have difficulty in eating dry foods", "I have difficulties swallowing certain foods", and "My lips feel dry". The fact that the modified version has targeted statements/questions improved the validity of this version compared to the original version.[5,6] In the present study, we used this 5-item version and clinical examination to diagnose xerostomia. The positive oral findings include abnormal lips (dry, cracked, and peeling), absence of a saliva pool in the floor of mouth, dry and sticky oral mucosa, abnormal tongue (erythematous, fissured, and dry with atrophy of the filiform papillae, and a pebbled, cobblestone appearance), bad breath, atypical pattern of dental caries, oral candidiasis, and angular cheilitis. We found that significantly more patients in the xerostomia group reported each of the five items when compared to the no xerostomia group (all $p<0.001$). In addition, the following two items were reported by more 80% of patients: "My mouth feels dry when eating a meal" and "I have difficulty in eating dry foods".

In contrast to salivary gland hypofunction, which can be objectively evaluated using sialometry, the measurement of xerostomia remains problematic. Despite no distinctive relationship with hyposalivation, xerostomia is a critical symptom in oral health among clinicians, because it affects both oral health, general health, and quality of life.[8] Our opinion that xerostomia can significantly adversely affect patient quality of life was our motivation to investigate the factors that significantly associate with this important condition.

Oral mucosal lesions that were commonly found in this study were dry, cracked, and peeling lips. We also observed no presence of a saliva pool in the floor of mouth, dry and sticky oral mucosa, erythematous, and fissured

and dry tongue with atrophy of the filiform papillae and a pebbled, cobblestone appearance. Changes of the tongue surface may have both local (salivary gland hypofunction, inflammation, and changes in microcirculation) and systemic (disease and medication intake) pathogenic factors in common.[3,12]

In this study, we found significant association between age ≥50 years and xerostomia in multivariate analysis. This same finding was reported from several previous studies.[7-9,14,17] These results may also be caused by higher medication intake among older adults, with acini atrophy often found in patients with decreased output function.[15,18] The average age that menopause begins among females in Thailand was reported to be 49.5±3.6 years.[19]

A higher prevalence of xerostomia was observed in females than in males in the present study, but there was no statistically significant difference between genders, which is similar to the results reported from other studies.[20,21] However, significant association between gender and xerostomia was observed in most studies. Menopause in women could also affect the amount and characteristics of saliva.[9,22,23] It is also likely that females have to endure a higher level of pain intensity, and they may have more illness conditions that could lead to the development of xerostomia.[24] Other factors, including body mass index, tobacco use, and alcohol consumption, were found not to be associated with xerostomia.

Of note, xerostomia tends to markedly increase in patients with psychological disorders. Unstable emotions and changes in personality may play a role in xerostomia, with changes that can influence the nervous, immune, and endocrine systems. Moreover, anti-sialogic effects were observed in those taking drugs.[17,25]

In this study, multivariate analysis revealed significant associations between xerostomia and medications or therapy, including analgesic NSAIDs, gabapentin, muscle relaxants, psychotherapeutic drugs, and radioactive iodine therapy. Despite the fact that some of the mechanisms remain unknown, medication-induced xerostomia is commonly caused by the altering of neural pathways that stimulate the secretion of saliva.[10] Villa A, *et al.*[10] showed that patients taking analgesic medication (NSAIDs), and Scully C, *et al.*[26] reported that muscle relaxant medication, which blocks sodium and calcium channels, could be associated with significant xerostomia.

Psychotherapeutic medications in our study included antidepressants (tricyclic antidepressant and selective serotonin-reuptake inhibitor), anxiolytics, and antipsychotics. Tricyclic antidepressant (TCA) acts as a noradrenaline and serotonin stimulator by blocking their reuptake at the neuronal membrane. The block is also to histaminic, a1-adrenergic, and muscarinic cholinergic receptors, which can cause unfavorable drug reactions like xerostomia. Even though xerostomia can result from selective serotonin-reuptake inhibitor (SSRIs), they are less likely to cause anticholinergic side effects than TCA.[22,27] Anxiolytics and antipsychotics are also prone to cause xerostomia.[11]

We also found radioactive iodine therapy to be a factor significantly associated with xerostomia. Accumulation of radioactive iodine (131I) inflicts damage to the salivary gland, which can cause long-term complications. Qualitative and quantitative scintigraphy of salivary gland can be helpful for assessment and follow-up of salivary gland dysfunction after radioactive iodine therapy.[28-30]

Future studies should investigate whether drug dosage plays a role in the development of xerostomia, and comparative studies with a larger sample size would be required to make a clear distinction. Study in animals may also help us to elucidate the pathophysiology of some common medications and their association with xerostomia (e.g., NSAIDs).

CONCLUSION

Xerostomia is a condition that can adversely affect quality of life. The results of this study revealed older age, analgesics and muscle relaxants, psychotherapeutic medications, and radioactive iodine therapy to be significantly associated with xerostomia. A thorough understanding of the symptoms, diagnosis, relevant risk factors, and effective management is essential for improving outcomes among patients with this condition.

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