Original Article

Anticholinergic medication and dental caries status in middle-aged xerostomia patients-a retrospective study

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Abstract *Background/purpose:* Xerostomia is the most frequent side effect of anticholinergic (AC) medications, which block the cholinergic neurotransmission of saliva secretion. As the most significant increase in AC medications' usage reported in middle-aged adults, we aimed to explore whether the level of exposure to AC medication show association with the severity of caries status of middle-aged individuals who complained about medication-induced xerostomia.
Materials and methods: Our retrospective study included 414 individuals (between 45 and 64 years) with self-reported xerostomia. We determined caries status by the Decayed, Missing, or Filled Teeth (DMFT) index and quantified the level of AC drug exposure by the AC Drug Scale (ADS), verified through electronic medication records. Statistical analyses were performed using chi-square and ANOVA tests. Covariates were age, gender, smoking, edentulism, comorbidities, polypharmacy, number, and the type of AC medications.
Results: In total, 54% of patients were taking five or more AC drugs. The mean number of anticholinergics was 5.41 ($\pm$3.44), most frequently antidepressants and antipsychotics, among all medications 10.63 ($\pm$5.79). Higher ADS scores were associated ($p = 0.006$) with a higher number of missing teeth. Multiple linear regression model showed that the number of AC medications, age, and smoking status are associated with DMFT (mean of 18.7 ± 8.96) scores.
Conclusion: Caries status of middle-aged xerostomia patients was found to be reflective of the level of AC exposure from medications. Our finding emphasizes the importance of assessing AC medication burden in affected dental patients to improve clinical prevention strategies and guide interdisciplinary treatment plans.
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Introduction

A large group of medications possesses anticholinergic (AC) activity by blocking the binding of the neurotransmitter acetylcholine to muscarinic receptors in various organs and tissues. These medications often cause peripheral (dry mouth, constipation, blurred vision, increased heart rate, urinary retention) and central side effects (sedation, confusion, dizziness, and cognitive impairment). Commonly used AC medications such as antispasmodics, antimuscarinics, antiparkinson drugs, tricyclic antidepressants, antipsychotics, and antiallergics[1] contribute to higher AC exposure of patients. Literature reported that increasing AC exposure contributed to a significant increase in AC burden since 1995. [2] Moreover, the combination of multiple AC medications could potentiate AC burden[3] and increase the risk of severe side effects and higher morbidity rates. [4]

AC medication-induced[5] xerostomia (oral dryness) has a detrimental impact on oral and general health. [6] Clinically, xerostomia is often associated with decreased saliva flow (dry mouth), leading to rampant caries, damage to soft tissues, and reduced quality of life. The Executive Summary of Evidence-based Clinical Recommendations of the American Dental Association[7] identified medication-induced dry mouth as a major risk factor for dental caries. Although the highest increase in prescription drug intake was reported among the middle-aged population,[8] our knowledge is minimal about the prevalence of AC burden and its potential association with caries status in medication-induced xerostomia patients under 65 years. This study aimed to explore whether DMFT in xerostomia patients reflects the frequency and severity of AC medication usage. We hypothesized that a measurable difference in caries experience is related to higher AC exposure. Our hypothesis is supported by a 2019 Swedish longitudinal study of 34,037 older adults[9] showing a dose—response relationship between tooth loss and a total number of xerogenic medications. We hypothesized that a higher DMFT index (decayed, D; missing, M; or filled, F tooth) is associated with a higher AC drug burden in medication-induced xerostomia patients. AC medications that interfere with the cholinergic saliva stimulation[10] can be ranked by their AC activity and estimated dry mouth risks. Accordingly, we quantified the cumulative AC burden[11] from medications by calculating AC Drug Scale (ADS) scores,[12] associated with caries experience in middle-aged patients. [13]

Materials and methods

The URMC institutional review board (IRB) approved the research protocol and details of the clinical investigation (RSRB No.00003301, approved on February 19, 2019) in accordance with the Declaration of Helsinki and US Federal Policy for the Protection of Human Subjects. Our convenient sample included adult patients between 45 and 64 years who received dental care at Eastman Institute for Oral Health (EIOH). Two investigators reviewed the electronic medical and dental records based on written agreements of the eligibility criteria, collection method of study variables, and data interpretation.

Inclusion criteria were: (1) xerostomia (the subjective feeling of oral dryness) reported by the adult participants answering "yes" to the question "Does your mouth feel dry?", (2) dental examination at the Department of Dentistry, EIOH between April 2010 and January 2019, (3) age from 45 to 64 years, and (4) verified and up-to-date medication list (by medical records or prescriber note). We compiled medication lists using the Anatomical Therapeutic Chemical (ATC) classification to avoid underestimating drug use due to self-report. We verified it from electronic medical records or written confirmation from the prescribing providers.

Exclusion criteria were: (1) Sjögren's syndrome or other known diseases affecting the salivary glands, (2) past or current head and neck radiation therapy or radioiodine treatment, and (3) and current therapy with a cholinergic agonist.

We calculated caries experience as our primary outcome, extracted from electronic dental records, by using the DMFT - decayed (D), missing (M), or filled (F) - tooth index (WHO Oral Health Surveys - Basic Methods, 4th edition, 1997). We determined AC exposure[11] of each patient, which quantifies the cumulative effect of AC drugs, by using the AC Drug Scale (ADS). [12] ADS is an expert opinion-derived risk scale based on a radioligand assay to measure in vitro antimuscarinic activity of AC drugs. We utilized the modified (updated and dose-weighted) ADS method,[14,15] including 536 medications. Among those, 419 have low potency with rank 0, and 117 medications have numerical ranking between 1 (potentially anticholinergic) and 3 (markedly anticholinergic). We determined whether a higher DMFT index corresponds with a higher ADS in middle-aged adults and indicates a higher level of AC exposure.

Analyses and descriptive statistics were performed to calculate demographic data using SPSS software (26.0.0.1, IBM, Armonk, NY, USA). Statistical analyses were performed using chi-square and ANOVA tests. Multiple Linear Regression analysis was performed to identify factors associated with the DMFT index based on the smoking (Y/N), gender, medical conditions, age, the total number of medications, total number of AC medications, and AC burden (ADS). An α level of <0.05 was used to declare significance.

Results

Study group characteristics

Our search for the phrase "xerostomia" in the digital dental database (Axium 7.01.04.56, 1996-2018) identified 946 potentially eligible adult patients. Study eligibility, based on inclusion and exclusion criteria, resulted in the exclusion of 408 patients at the completion of the chart review. Further, 124 patients with non-confirmed medication history or verifiable medication lists were excluded. In total, 414 adults were included in the retrospective chart review. The demographics and other variables of the study participants are summarized in Table 1. The comorbid characteristics of the patients are presented in Table 2.

AC burden in middle-aged patients complaining of xerostomia

Our study patients, except nine individuals, were taking at least one prescription medication (Fig. 1a), and 359

Table 1 Demographic characteristics, smoking status, and dental variables among middle-aged xerostomia patients (n = 414).

	Number	Percent (%)
Gender		
Male	108	26.1
Female	302	72.9
Missing	4	1.0
Age (years)		
45—54	176	42.5
55—64	238	57.5
Race & Ethnicity		
White	229	55.3
African American	60	14.5
Hispanic	2	0.5
Non-Hispanic	120	29.0
Other	3	0.7
Smoking status		
Yes	163	41.6
No	242	58.4
Edentulism		
Complete	49	11.8
Partial	256	61.8
Not edentulous	109	26.4
Removable denture		
Complete	42	10.1
Partial	210	50.7
No dentures	162	39.2
Dry mouth treatment		
Yes[a]	26	6.3
No	388	93.7

[a] Dry mouth management such as 1.1% fluoride toothpaste, artificial saliva, and commercially available products for oral dryness relief.

patients had polypharmacy, taking 5—14 medications daily. The most commonly prescribed medications were prescribed for neurologic and psychiatric indications (77.1%), followed by cardiovascular medications (49.0%), obstructive airway medications (44.7%), systemic antihistamines (33.3%), and opioids or narcotics (22.9%).

The majority of study patients, n = 336, used at least one AC medication with an ADS score. The utilization frequencies of AC medications with ranked ADS score (ADS 0-3) are summarized in Fig. 2. Overall, the most frequently used AC drugs were antidepressants and antipsychotics (Tables 3 and 4). The most frequent comorbid condition associated with AC drug exposure was a diagnosed psychiatric condition. Cumulative ADS score for most patients (n = 282) was between one and seven, and 55% of participants used at least one markedly anticholinergic medication (ADS = 3).

The number of missing teeth associated with current usage of anticholinergic medications.

We identified statistically significant associations between the number of AC medications DMFT (p < 0.001) and the number of missing teeth -M (p = 0.006). Moreover, M was significantly associated with ADS (p = 0.006). Gender, psychiatric/behavioral conditions, the total number of medications did not explain significant variance in the DMFT. The number of AC medications, age, and smoking status were significant predictors of DMFT score using a multiple linear regression; $F_{(3,357)}$ = 22.94, p < 0.001. Each extra ADS from AC medication increases mean DMFT by 29.8% (95% CI: 5.1%—54.4%, p = 0.018). Similarly, an increase of age by one year increases mean DMFT by 60.7% (95% CI: 45.0%—76.5%, p < 0.001). Moreover, smokers compared to nonsmokers have 2.32 times increased mean DMFT (95% CI: 0.57—4.07, p = 0.009).

Discussion

Our report is the first dental study in middle-aged patients, and it confirms the results of a recent retrospective study[16] conducted by the Department of Veterans Affairs. They investigated 95,850 dentate patients and found an 8% increase in the rate of dental caries-related treatment in individuals taking at least one potentially AC (ADS > 1) medication. We assessed the dental caries status of our

Table 2 Most frequent medical conditions in younger (45-54) and older (55-64) middle-aged xerostomia patients.

Comorbidities	45-54 (n = 176)	(%)	55-64 (n = 238)	(%)	Total (n = 414)	(%)
Anemia	16	(9.1)	44	(18.5)	60	(14.5)
Cardiac	20	(11.4)	63	(26.5)	83	(20.0)
Malignancy, cancer	14	(8.0)	45	(18.9)	59	(14.2)
Developmental/childhood onset	7	(4.0)	10	(4.2)	17	(4.1)
Diabetes	32	(18.2)	71	(29.8)	103	(24.9)
Gastrointestinal	87	(49.4)	124	(52.1)	211	(51.0)
Endocrine	68	(38.6)	55	(23.1)	123	(29.7)
Infectious	16	(9.1)	22	(9.2)	38	(9.2)
Musculo-skeletal	70	(39.8)	153	(64.3)	223	(53.9)
Neurological	88	(50.0)	75	(31.5)	163	(39.4)
Psychiatric/behavioral	106	(60.2)	150	(6.3)	256	(61.8)
Respiratory	28	(15.9)	97	(40.8)	125	(30.2)
Urinary	45	(25.6)	38	(16.0)	83	(20.0)
Sleep apnea	17	(9.7)	26	(10.9)	43	(10.4)
Skin	41	(23.3)	57	(23.9)	98	(23.7)
Circulatory	76	(43.2)	135	(56.7)	211	(51.0)

Frequency expressed in percentage are mentioned in italics.
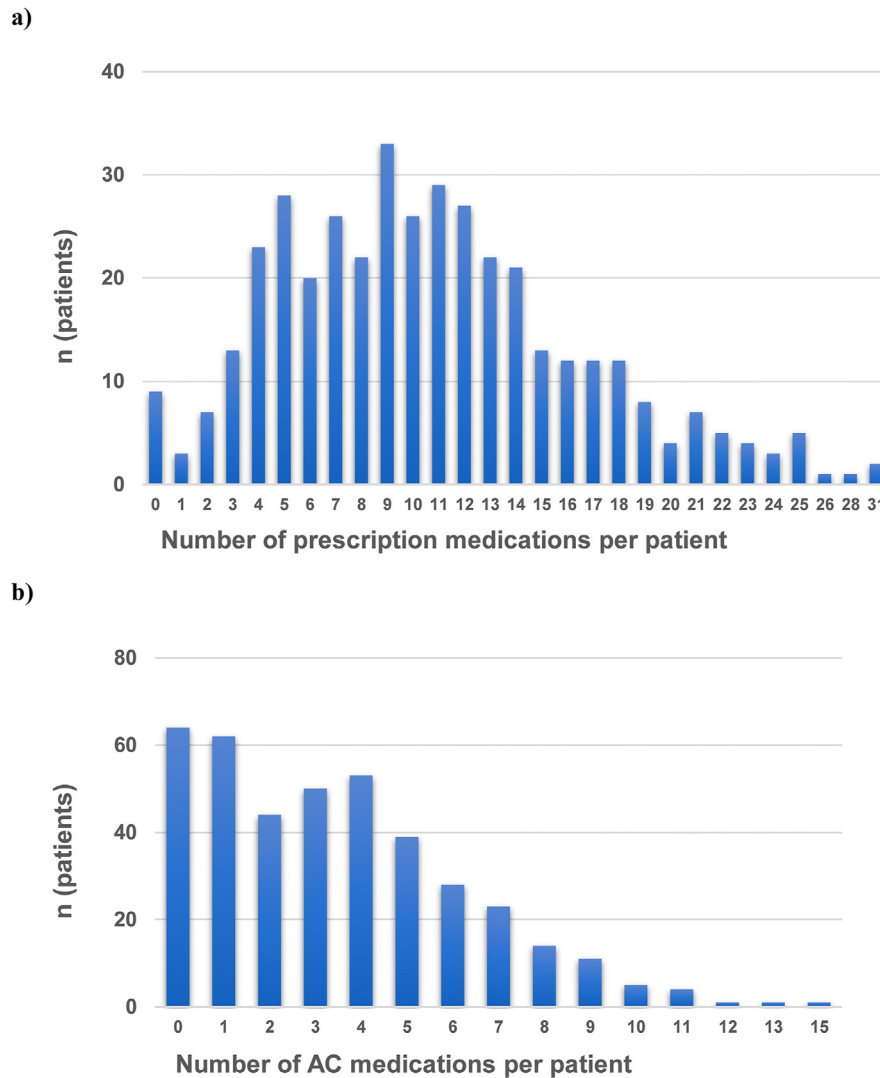
a)

b)

Figure 1 Prescription frequencies among middle aged xerostomia patients; a) all medications taken, b) AC (anticholinergic) drugs.

patients by using the DMFT index, which has been previously used and associated with severity of dry mouth.[9,17–19] Thus, medication-induced hyposalivation indicates an increased risk for dental caries and developing oral diseases.[18,20]

The frequencies of various AC scores in our study were comparable with those reported by Tiisanoja et al.[13] Quantifying AC burden of drugs, categorized by the Beers criteria[21] or the Rudolph AC risk scale,[22] is accepted[4,23] for assessing central nervous system toxicity and related adverse events[24] in the elderly. Only two studies investigated the relationship between salivary function and AC burden.[13,14] Both studies expressed AC burden in terms of total ADS in each patient from medications. When saliva secretion rates were measured in 152 female patients (mean age = 80.3), ADS > 3 posed a relative risk of 2.31 for hyposalivation (<0.1 ml/min). When mouth dryness was assessed in individuals above 73 years,[14] ADS > 6 resulted in 0.7-fold lower saliva production than ADS = 3.

Over 80% of the patients in our study had polypharmacy, with an average of nine medications taken daily, and 50% of the participants were taking more than ten medications regularly. These findings confirmed the current tendencies in polypharmacy, which increased by 70%, according to the Centers for Disease Control and Prevention.[25] AC exposure from medications has grown significantly since 1995.[2] Accordingly, 69% of the individuals in the 45-64 years old age group used at least one prescription drug, and 18.3% used five or more drugs.[8] The medication usage in middle-aged (45-64 years) adults mirrors that of older adults, with equal numbers (∼50%) of middle-aged and older adults taking 1 to 4 prescription drugs daily (Health, US, 2013). Medication usage in middle-age individuals predicts risk for xerostomia (the subjective feeling of oral dryness).[5]

The limitations of this study were that our study cohort was relatively small. Dental epidemiologic evidence such as medications and caries indices were collected retrospectively from medical and dental charts. DMFT reflects a cumulative score of disease progression of lifetime dental caries experiences;[26] it includes the results of other pathological processes, such as periodontitis or developmental diseases. DMFT might be insufficiently sensitive because
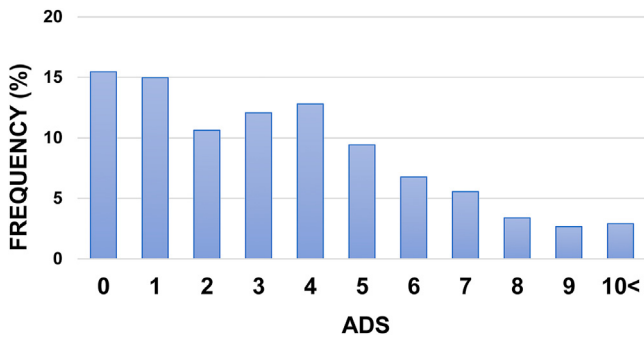
Figure 2 Frequencies (percentage) of AC (anticholinergic) drug scores among middle-aged xerostomia patients. The AC burden is expressed as the cumulative ADS (anticholinergic drug score). Frequencies of ADS were calculated among the study participants (n = 414).

the units of measure are teeth rather than surfaces.[27] Although ADS has prognostic value to assess the impact of AC medications on saliva flow rates,[13] it is an estimate since potentiation effects, active metabolites, or pharmacogenetic variations are not considered in it,[28] which presents a limitation of our study. We must emphasize that ADS do not account for dosage, whereas dose effect is elemental to the degree of xerostomia[4] as the quality of anticholinergic burden scales was recently reviewed.[29] There are a number of drugs that may affect salivary secretion through other mechanisms than by blocking muscarinic receptors of salivary glands. Explanatory variables such as dose-effect,

Table 3 Medications with AC properties ranked by the ADS in middle-aged xerostomia patients (n represents the number of patients using the medication).

ADS = 1	n	%	ADS = 2	n	%
Fluticasone	114	27.5	Cyclobenzaprine	72	17.4
Oxycodone	39	9.4	Quetiapine	26	6.3
Citalopram	37	8.9	Paroxetine	14	3.4
Clonazepam	36	8.7	Carbamazepine	6	1.4
Sertraline	33	8.0			
Ranitidine	31	7.5	ADS = 3	n	%
Triamcinolone	31	7.5	Hydroxyzine	38	9.2
Furosemide	28	6.8	Amitriptyline	23	5.6
Cortisone	29	7.0	Meclizine	19	4.6
Tramadol	27	6.5	Diphenhydramine	16	3.9
Lorazepam	25	6.0	Nortriptyline	14	3.4
Clindamycin	24	5.8	Promethazine	14	3.4
Fluoxetine	24	5.8	Dicyclomine	14	3.4
Diazepam	23	5.6	Clozapine	9	2.2
Escitalopram	22	5.3	Oxybutynin	9	2.2
Prednisone	21	5.1	Olanzapine	8	1.9
Mirtazapine	17	4.1	Doxepin	3	0.7
Alprazolam	17	4.1	Chlorpromazine	2	0.5
Chlorthalidone	11	2.7	Solifenacin	1	0.2
Lithium	11	2.7			
Loperamide	11	2.7			
Fentanyl	8	1.9			
Codeine	7	1.7			

AC, anticholinergic; ADS, anticholinergic drug score.

Table 4 AC medication usage among middle-aged xerostomia patients with self-reported xerostomia (oral dryness).

Age 45-65 years, n = 414	
Number of medications taken, mean ± SD	10.6 ± 5.8
Patients with polypharmacy (drugs taken ≥ 5)	86.7%
Number of AC medications taken, mean ± SD	5.4 ± 3.4
Patients with AC polypharmacy (drugs taken ≥ 5)	65.9%
ADS score, mean ± SD	3.4 ± 2.8
Low ADS < 3	41.1%
Medium 3 < ADS > 6	42%
High ADS < 6	16.9%
DMFT	18.7 ± 8.9
D	1.6 ± 3.1
M	9.8 ± 9.2
F	7.5 ± 5.5
Most frequent comorbidities with AC prescriptions	
Neuro-psychiatric disease	83.7%
Cardio-vascular disease	76%
Obstructive airway disease	49.5%

AC, anticholinergic; ADS, anticholinergic drug score; D, decayed; M, missing; F, filled; SD, standard deviation.

local and periodontal factors, sugar intake, oral habits, the synergy effect of polypharmacy were not considered due to the retrospective design of our study.

Existing evidence on the link between decreased salivary function and the total number of drugs[30−32] is established in the older adult population. In a veteran-based study,[33] dry mouth was more prevalent (57.6%) among patients using AC drugs. A long-term geriatric ward study found that the intake of AC drugs poses an elevated risk for xerostomia (OR = 1.35). Investigations among middle-aged adults regarding AC burden are rare; the only study available is a French survey,[34] which reported that 52.4% of the 34,267 participants aged 45-70 (mean = 57.8) had exposure to two or more different AC drugs. The authors, however, only investigated cognitive impairment and did not address peripheral side effects such as xerostomia. Our study addressed this gap and provided data on AC burden, with an average of ADS = 5 scores in middle-aged xerostomia patients. Our findings that higher ADS sores were associated with a higher number of missing teeth could partly be explained by the higher ADS scores among edentulous and denture-wearing patients. However, as missing teeth are influenced by many oral factors, periodontal scores, and oral habits, other preexisting factors contributed to the current number of missing teeth. Missing tooth number in therefore is unlikely to be sensitive enough as a single outcome measure. Thus, future investigations require including putative risk factors for dental caries and accounting for the incremental nature of tooth loss. Our finding also implies the necessity of a case−control study to identify patients at higher risk of oral complications due to perturbed metabolism of AC drugs. Further exploration of AC medication exposure and related

saliva flow measurements in a prospective study among middle-aged and younger dental patients is required to establish risk ratios for dry mouth.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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