Medication and Dry Mouth: Findings from a Cohort Study of Older People

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Abstract

Objectives: *The aim of this study was to examine the association between medication exposure and (1) unstimulated whole-salivary flow rate and (2) the severity of xerostomia among older people while adjusting for multiple medication use.* ***Methods:*** *Data were obtained from participants remaining at the five-year follow-up phase of a cohort study of community-dwelling older South Australians. Medication exposure information was available at baseline and at five years, enabling examination of the effects on dry mouth of long-term exposure to medications. At the five-year follow-up, unstimulated salivary flow was estimated using the spit method, and xerostomia severity was estimated using the 11-item Xerostomia Inventory. Because of the potential difficulties posed by polypharmacy, a two-stage analytical approach was employed: (1) Classification and Regression Tree (CART) analysis was used as an exploratory device to elucidate the relationships among the dependent and independent variables, and (2) linear regression analysis was used as a complementary procedure.* ***Results:*** *Unstimulated flow rate was lower among individuals who were female or taking antidepressants at both baseline and five years, and higher among smokers or people who were taking hypolipidemic drugs. Xerostomia severity was higher among females, or individuals taking: (1) an anginal at baseline and five years, (2) an anginal without a concomitant betablocker at five years, (3) thyroxine and a diuretic at five years, or (4) antidepressants or antiasthma drugs at both baseline and at five years.* ***Conclusions:*** *These results suggest that polypharmacy can be accounted for to a certain extent by using CART analysis in conjunction with more conventional approaches; and that the relationship between medications and dry mouth is a complex one, and differs according to which aspect of dry mouth is being examined. [J Public Health Dent 2000;60(1):12-20]*

Key Words: medication, xerostomia, hyposalivation, cohort study, polypharmacy.

Our present understanding of the relationship between medications and dry mouth in older people is incomplete. A recent review of the causes of salivary gland dysfunction stressed that, because most investigations of the association of medications and dry mouth have been conducted with convenience samples of healthy younger people or patients who were taking particular medication types, "the relationship of salivary function and individual medications in the unhealthy elderly is largely untested" (1).

Dry mouth has been reported to affect between 10 percent and 44 percent of older people (2-5), and the chronic use of medications has been suggested as an important etiological factor, with one review listing more than 400 different preparations implicated in the relationship (6). Medications most commonly implicated in reviews of the field and in epidemiologic studies include antihypertensives (6,7), anticholinergics (4,6,8,9), antidepressants (6-8,10,11), antipsychotics (6,10), and antihistamines (2,6,8,10). Preparations less consistently implicated include anti-Parkinsonian drugs (6,8), diuretics (2,6,8-10,12,13), anorectics (6), cardiac agents (including anginals) (7,11), psychotherapeutic agents (6,8,10,11,13,14), and analgesics (15). Without exception, current evidence is from cross-sectional studies where drug exposure and outcome (dry mouth) were measured simultaneously. The important issue of duration of exposure has not been addressed, and there is an implicit assumption that the medications implicated in those studies had been taken for a sufficiently long period to have had detectable effects on mouth dryness at the time of measurement.

There are a number of prerequisites for satisfactory study of the relationship between medications and dry mouth. First, a suitable method must be used for capturing and analyzing medication data. Second, xerostomia (the subjective perception of dry mouth and its consequences) and salivary gland hypofunction (as measured by salivary flow rate) should be estimated separately, given the possibility that they may be largely discrete conditions (16). Third, xerostomia should be measured as a continuous variable, so that an estimate of symptom severity can be obtained for each individual, and the possibility of misclassification bias minimized. Fourth, a longitudinal design should be used so that duration of exposure to the various medications can be estimated prospectively. Finally, participants should (ideally) comprise a representative sample so that findings can be generalized to the larger population.

Polypharmacy presents a formidable methodologic challenge. Most older people take at least one medication, and the majority take more than one. With one exception (2), not one of the reported analyses of medications and dry mouth has attempted to ad-

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dress the issue of multiple medication use. There are at least two possible reasons for this. First, it is analytically complex, and the risk of Type I error increases with the larger number of statistical tests that are required when conventional approaches are used. Second, there are very real sample size limitations. For example, if only the most prevalent 20 medication types are examined in an epidemiologic study of older people, there are still 2^{19} different possible combinations of medications to examine, and the Bonferroni-corrected alpha value for that number of tests would be 0.00000005. For there to be meaningful numbers in each combination subgroup, the number of individuals in the sample would have to be prohibitively large. Moreover, as so much is unknown about the relationship between medication use and dry mouth, conventional a priori approaches carry the very real risk of missing a substantial association. Analyses therefore need to have more of an exploratory approach than is customary in epidemiologic studies. Two other potential problems are: (1) possible intercorrelations among the predictors (for example, someone taking an anginal is more likely to be taking a betablocker than someone who is not); and (2) possible interaction effects, the detection of which may be problematic because of the considerable a priori knowledge required.

Aside from medications, epidemiologic studies have suggested a number of other modifiers of the occurrence of dry mouth among older people. Sex is frequently cited, with the most common finding being that xerostomia is more prevalent among females (10,15,17,18). The association between sex and flow rate is less clear, with some studies reporting lower flow rates among older females (2,7,10,19); however, a recent study of a convenience sample of older people in Rochester reported no significant association (18). Smoking also has been implicated, but the findings to date are equivocal. Xerostomia was reported to be associated with current smoking among males in the Rochester study, but the possible association between salivary flow rate and smoking was not reported (18). No association was found between xerostomia and smoking among a sample of older women who were retiring from the work force (20); however, an increased secretion (by 27%) from the minor salivary glands among smokers was reported recently (21). Although the latter finding pertained to the minor gland secretions only (as major gland output was not measured), it suggests that the local irritant effect of tobacco smoke may actually increase glandular output. Support for this effect can be found in the recent Swedish population-based study of dental status and smoking (22), where male smokers had significantly higher stimulated salivary flow rates than male nonsmokers. Unstimulated flow rate was not estimated in that study, and it is notable that smokers reported more frequent dry mouth. On the basis of the evidence from these studies, tobacco usage should be considered to be at least a potential modifier of the occurrence of dry mouth in older people, if only on the basis of the widespread observations of smoking's detrimental associations with many other biological and health characteristics. Similarly, alcohol use also should be considered a potential modifier: while no epidemiologic association has reported on alcohol use and dry mouth, a report of increased flow rates in laboratory rats chronically exposed to ethanol (23) raises the possibility that a similar phenomenon might be observed among humans. It is appropriate, therefore, to include smoking and alcohol exposure as explanatory variables when modeling the occurrence of dry mouth.

There are no reports from longitudinal studies of the association between dry mouth and particular medications in community-dwelling older people, and none have made allowances for polypharmacy. The purpose of the present study was to examine the association between dry mouth and five-year exposure to medications that commonly are taken by noninstitutionalized older people, while allowing for multiple medication use.

Methods

The South Australian Dental Longitudinal Study (SADLS) began in 1991, and is a cohort study of older people living in Adelaide and Mt. Gambier, South Australia. The SADLS sampling strategy and data collection have been described previously (24), with the baseline and two-year data collections taking place in 1991 and 1993, respectively. Dry mouth was not investigated at baseline or two years. At five years (1996), the participants again were examined and interviewed, with computer-assisted telephone interviews being conducted just prior to the clinical examination.

At the five-year follow-up, the Xerostomia Inventory (25) was sent to all examination participants as one of two postal questionnaires, and participants were instructed to bring the completed questionnaires to the clinical examination or return them by post. The Xerostomia Inventory (or "XI") is an 11-item summed rating scale that requires respondents to choose one of five responses (never=1, hardly ever=2, occasionally=3, fairly often=4, and very often=5) to the following statements: "my mouth feels dry," "my lips feel dry," "I get up at night to drink," "my mouth feels dry when eating a meal," "I sip liquids to aid in swallowing food," "I suck sweets or cough lollies to relieve dry mouth," "my throat feels dry," "the skin of my face feels dry," "my eyes feel dry," "my lips feel dry," and "the inside of my nose feels dry." Each individual's responses are scored and summed to give a single XI score that has a theoretical range from 11 to 55. Initial testing of its content and construct validity has been reported previously (25).

Unstimulated whole saliva was collected at the five-year clinical examination appointment using the "spit" method (26). Each participant had been instructed to refrain from eating, drinking, and smoking for the 60 minutes prior to collection. Some five minutes before collection, participants were instructed to rinse out the mouth with plain water and then to sit quietly while administrative procedures were attended to. Immediately prior to saliva collection, each participant was asked to clean the mouth by swallowing, and then to actively spit saliva into a preweighed plastic collection tube over the next four minutes. At the end of that time, a beeper sounded and the participant was asked to spit any remaining saliva into the tube, which was then sealed and placed in a cool storage bin. The collection time was recorded. The tubes were weighed later at the University of Adelaide. Unstimulated saliva flow (in ml/min) was computed as the weight of saliva collected (assuming 1 g=1 ml) divided

by the collection time in minutes.

At five years, participants were asked about their use of cigarettes and alcohol over the previous month. Individuals were categorized as smokers (one or more cigarettes in the previous month) or nonsmokers. Alcohol use was dichotomized: those who had used alcohol on one or more occasions during the previous month, and those who had not.

Medication data were collected at the time of the dental examination at both baseline and five years: participants were asked to bring the containers for all medications they had taken in the previous two weeks; to enable ready analysis, each medication was subsequently assigned a five-digit numeric code using the MedCap system (27). This system was used because of the ease of analysis afforded by its five-digit numeric, hierarchical coding structure. For each of the 20 most prevalent medication categories, two alternative exposure classifications were used: medication X was taken (coded 1) or not taken (coded 0) at five years; and medication X was taken at both baseline and five-year follow-up (coded 1), or other (coded 0). For convenience, those taking a medication at both data collections are referred to as continuous users in this paper.

The CART (Classification and Regression Tree) technique (28) was used to explore the medication and dry mouth data (Answer Tree Version 1.0, SPSS Inc., 1998) using unstimulated flow rate and then the XI score as the dependent variable. The 20 most prevalent medication categories were used as the independent variables in each analysis. This type of approach is said to be useful where the challenge lies in determining which of many possible predictors in a large data set are actually associated with the dependent variable, and in what way they are associated with each other (29).

Following the identification of putative predictors in the CART analysis, appropriate interaction terms were computed, and linear regression analysis was used to examine the observed associations for flow rate and XI scores, using SPSS Version 6.0 (SPSS Inc., 444 N. Michigan Ave, Chicago). Age group (65–69, 70+), sex, smoking status (current smoker vs nonsmoker) and alcohol use (alcohol drunk in previous month vs nondrinker) also were used as independent variables in the multivariate analyses. Two models were produced for each dependent variable—one using the medications taken at five years, the other using only the medications taken at baseline and five years.

Results

Description of Sample. Of the 913 people (55.3% of the 1,651 people interviewed at baseline) who participated in the study at five years, 462 (50.6%) were male and 451 (49.4%) were female. The ages of study members ranged from 65 to 100, with a mean age of 75 years (SD=7 years). Xerostomia questionnaires were mailed to the 708 (77.5%) who had a dental examination appointment. The XI questionnaires were completed and returned by 649 (91.7%) of those individuals, and XI scores were able to be computed for 619 of those (the remaining 30 had not completed all of the items). Of these, 201 (31.0%) were from Mt. Gambier and 448 (69.0%) were Adelaide residents. Where there were difficulties in getting cooperation from participants, priority was given to the dental examination rather than the saliva collection; consequently, saliva samples were collected from 700 (98.9%) of those examined at five years. Some 623 dentally examined individuals provided XI, flow rate, medication, and interview data.

Comparison of the baseline characteristics of participants who remained in the study at five years with those who were lost to follow-up (Table 1) showed that the group which remained comprised proportionately more females and regular users of dental services and more whose dental self-care was favorable. The number of medications taken was also lower.

Occurrence of Dry Mouth. The mean XI score was 19.95 (SD=7.03), and scores ranged from 11 to 49. The median score was 19. Unstimulated whole salivary flow rates ranged from 0.00 ml/min to 1.84 ml/min, with a mean flow rate of 0.27 ml/min (SD=0.22). The median flow rate was 0.21 ml/min. The correlation between unstimulated salivary flow rate and the XI scale scores was low and negative (Pearson's correlation coefficient=–0.05; P=.25).

The mean flow rates of males and females differed significantly, but their XI scores did not (Table 2). There were no statistically significant differences across the three age groups. The mean number of medications taken was 3.2 (SD=2.6), made up of a mean 2.9 (SD=2.5) doctor-prescribed medications and a mean 0.3 (SD=0.7) self-prescribed preparations. Doctor-prescribed medications were taken by 580 individuals (81.9% of those examined at five years), with a range from 1 to 17. Self-prescribed medications were taken by 124 individuals (17.5% of those examined at five years). Both smoking and alcohol consumption were associated with mean flow rates, but not with xerostomia (Table 2).

Medication Prevalence. Antihypertensives and analgesics were predominant. At least one antihypertensive preparation was taken by 370 individuals (52.4%) at five years, and by 237 (33.6%) at both baseline and five years. One or more analgesics were

TABLE 1
Comparison of Baseline Characteristics of Those Who Remained in the Study at Five Years and Those Who Did Not

	Lost to Follow-up (SD)	Retained (SD)
Number	738	913
Percent female	44.7 (2.0)	49.3 (2.8)
Percent living in Adelaide	71.7 (2.0)	69.2 (1.8)
Mean age*	74.0 (0.3)	69.9 (0.2)
Percent regular dental visitors†	13.0 (3.5)	30.2 (2.8)
Percent flossing teeth at least once/week†	17.5 (3.4)	33.4 (2.7)
Mean number of medications taken*	2.0 (0.1)	1.6 (0.1)

*P<.05.
†P<.01.

TABLE 2
Bivariate Associations with Unstimulated Flow Rate, XI score, and Number of Medications Taken at Five Years

	Mean Flow Rate (SD)	Number with Flow-rate Data (*n*=700)	Mean XI Score (SD)	Number with XI Data (*n*=619)	Mean Number of Medications Taken (SD)	Number with Medication Data (*n*=706)
Sex						
Male	0.30 (0.24)*	378	19.47 (6.83)	333	3.1 (2.6)	381
Female	0.24 (0.24)	322	20.50 (7.23)	286	3.3 (2.7)	325
Age group (years)						
65–69	0.29 (0.25)	186	19.56 (6.44)	173	2.5 (2.4)†	187
70+	0.26 (0.21)	514	20.10 (7.25)	446	3.4 (2.7)	519
Medications taken						
None	0.30 (0.28)	95	17.85 (5.01)†	95	—	101
One or more	0.27 (0.21)	603	20.33 (7.28)	524	3.7 (2.5)	605
Smoking status						
Nonsmoker	0.26 (0.21)*	658	19.91 (7.10)	581	3.2 (2.7)*	664
Current smoker	0.38 (0.33)	42	20.50 (5.88)	38	2.3 (1.9)	42
Drinking status						
Nondrinker	0.25 (0.19)*	296	20.30 (7.29)	254	3.5 (2.8)*	301
Current drinker	0.28 (0.24)	404	19.70 (6.84)	365	2.9 (2.4)	405

*$P<.01$.
†$P<.05$.

taken by 210 (29.7%), and by 86 (12.2%) at both baseline and five years. The prophylactic use of daily aspirin was also high, at 30.7 percent at five years. The 20 most prevalent medications at the five-year follow-up and over the study period are presented in Table 3. Most (87.4%) of those taking betablocker drugs were also taking that class of medication at baseline. In contrast, there appeared to have been a large increase in the prevalence of ACE inhibitors since the first data collection.

Medications and Dry Mouth. The correlation between the total number of drugs taken and the XI score was significant (r=0.27; $P<.01$), but that with flow rate was not (r=–0.06; $P>.05$). Bivariate associations between overall medication use characteristics and dry mouth are presented in Table 2, which confirms that the total number of medications was significantly associated with xerostomia severity, but not mean flow rates.

The outcome of the CART analysis of flow rate and medication use at five years only is presented in Figure 1. Mean flow rates were lower among those who were taking antidepressants. Among the remainder, they were lower among individuals taking diuretics, but not among those who

TABLE 3
Prevalence of 20 Most Frequent Medication Categories in Sample Examined at Five Years: at Five Years Only, and Use at Baseline and Five Years

Medication Category	5 Years Only (%)	Baseline *and* 5 Years (%)
Antihypertensives and cardiac preparations		
Betablockers	98 (14.0)	27 (3.9)
Diuretics	166 (23.7)	85 (12.1)
ACE inhibitors	126 (18.0)	4 (0.6)
Calcium antagonists	141 (20.1)	58 (8.3)
Sympatholytics	29 (4.1)	11 (1.6)
Anginals	53 (7.6)	22 (3.1)
Cardiac inotropic preparations	50 (7.1)	8 (1.1)
Analgesics		
Simple analgesics	22 (3.1)	1 (0.1)
NSAIDs	100 (14.3)	46 (6.6)
Antigout drugs	42 (6.0)	22 (3.3)
Narcotic analgesics	78 (11.1)	10 (1.4)
Others		
Daily aspirin	214 (30.6)	52 (7.4)
Psychotherapeutics	52 (7.4)	21 (3.0)
Antidepressants	36 (5.1)	12 (1.7)
Hypoglycemics	46 (6.6)	24 (3.4)
Hormone replacement therapy	34 (4.9)	12 (1.7)
Antiulcer drugs	107 (15.3)	21 (3.0)
Hypolipidemic agents	58 (8.3)	23 (3.3)
Bronchodilators	56 (8.0)	20 (2.9)
Thyroxine	30 (4.3)	18 (2.6)

were taking a diuretic and an ACE inhibitor concurrently. Individuals who were taking hypolipidemic drugs (without a concurrent antidepressant or diuretic) had higher mean flow rates.

The outcome of the CART analysis of flow rate and "continuous" medication use is presented in Figure 2. A lower unstimulated flow rate was associated with taking antidepressants at baseline and five years. Flow rates also were lower among those who were taking antidepressants; among people who were taking antiulcer drugs at both stages; and among those who were not taking antiulcer drugs, but were taking a cardiac inotropic at baseline and five years.

The outcome of the CART analysis of XI scores and medication use at five years only is presented in Figure 3. Individuals who were taking anginals had more severe dry mouth symptoms, but those who were taking a concurrent betablocker did not. Among those not taking anginals, people who were taking thyroxine had more severe dry mouth, and this was more severe if they were taking a concurrent diuretic. Taking HRT (hormone replacement therapy) was associated with more severe xerostomia among those taking neither thyroxine nor anginals.

The outcome of the CART analysis of XI scores and "continuous" medication use is presented in Figure 4. The use of anginals was associated with more severe xerostomia. Among those who were not taking anginals at baseline and five years, those taking antidepressants had higher XI scores. The "continuous" use of antiasthma drugs also was associated with higher XI scores among those who were not taking an anginal or an antidepressant at both stages.

Flow rate and XI scores were each used as the dependent variable in linear regression analyses (Tables 4 and 5) that used the significant five-year-only and "continuous use" variables from each of the CART analyses (as well as age group, sex, cigarette use, and alcohol use) as independent variables. In the models for flow rate, being female predicted a lower flow, as did using antidepressants at both baseline and five years. By contrast, the recent use of hypolipidemics predicted a higher mean flow, as did cigarette smoking. The models explained

FIGURE 1
CART Tree Pattern for Resting Flow Rate Using Medication Exposure at Five Years Only

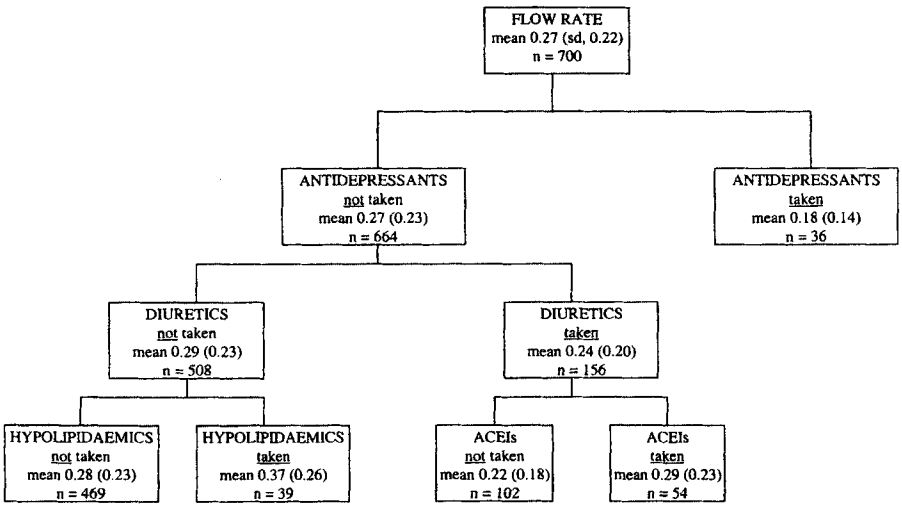

FIGURE 2
CART Tree Pattern for Resting Flow Rate Using Medication Exposure at Baseline and Five Years (Continuous Users)

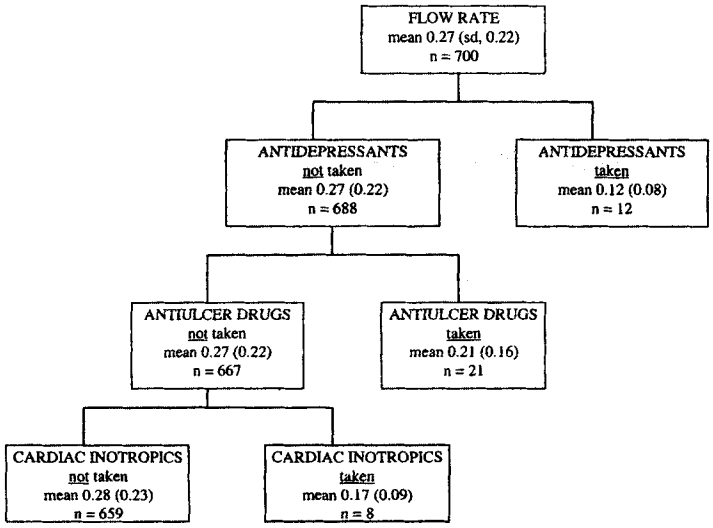

FIGURE 3
CART Tree Pattern for Xerostomia Inventory Using Medication Exposure at Five Years Only

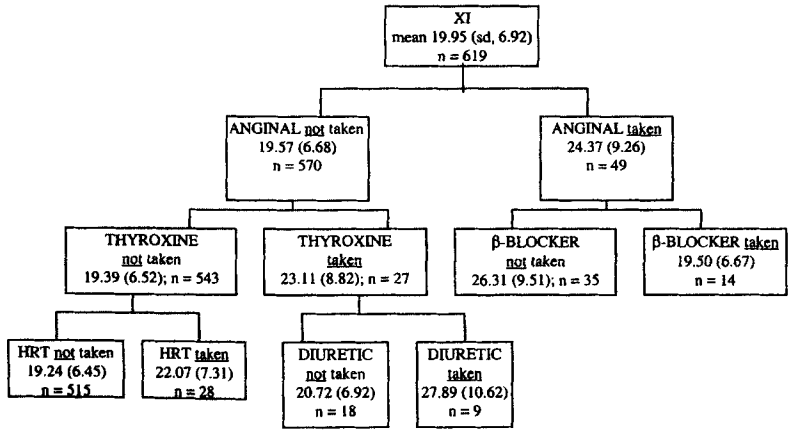

FIGURE 4
CART Tree Pattern for Xerostomia Inventory Using Medication Exposure at Baseline and Five Years (Continuous Users)

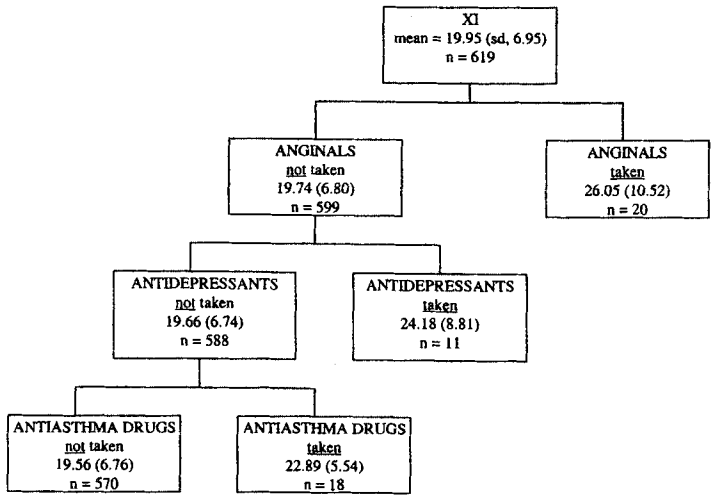

TABLE 4
Multivariate Models for Unstimulated Flow Rate

Model	B	Standard Error of B	Significance of T
Model 1: medications taken at 5 years (R^2=0.069)			
Antidepressant	–0.114	0.044	.01
Hypolipidemic*	0.100	0.035	.004
Diuretic	0.067	0.081	.41
Diuretic without antidepressant	–0.113	0.085	.18
Diuretic without ACEI	0.068	0.037	.06
ACEI at 5 years without diuretic	0.004	0.028	.89
Female	–0.065	0.017	<.001
Age 70+	–0.021	0.019	.27
Cigarette smoker	0.110	0.035	.002
Current drinker	0.016	0.017	.36
Constant	0.303	0.023	<.001
Model 2: medications taken at baseline *and* 5 years (R^2=0.054)			
Antidepressant	–0.145	0.064	.02
Antiulcer drug without antidepressant	–0.070	0.048	.15
Cardiac inotropic without antidepressant	–0.117	0.078	.13
Female	–0.066	0.017	<.001
Age 70+	–0.021	0.019	.26
Cigarette smoker	0.112	0.035	.001
Current drinker	0.015	0.017	.39
Constant	0.307	0.022	<.001

*Exposure to hypolipidemics at 5 years in the absence of antidepressants and diuretics.

6.9 and 5.4 percent of the variance in flow rate, respectively.

In the XI models, scores were higher for people taking anginals at five years without a concurrent betablocker; for those who were taking thyroxine and a diuretic at five years; or for those who were using antidepressants, anginals, or antiasthma drugs at both data collections. Being female was a significant predictor in the second model, but not in the first. The models explained 9.1 and 4.9 percent of the variance in XI scores, respectively. The lack of a significant association between XI scores and betablockers, thyroxine, or diuretics indicated that the anginal-betablocker and thyroxine-diuretic interactions were independent.

Discussion

The current study has used a number of approaches new to this field. First, the method of capturing and analyzing medication data uses a hierarchical system of five-digit numeric codes, enabling more flexible analysis of medication exposure than alternative systems such as the WHO Anatomic Therapeutic Classification (30), which may be more comprehensive, but is analytically far more cumbersome because it employs alphanumeric codes. A more detailed comparison has been published elsewhere (27).

Second, xerostomia has been measured as a continuous variable that purports to represent the condition's severity. This approach has allowed the exploration of subtle associations between xerostomia severity and medication exposure while avoiding the risk of misclassification bias, a very real issue in previous studies that have usually examined xerostomia prevalence using a single-item dichotomous classification (say, xerostomic or nonxerostomic). However, one of the limitations of this study is concern about the validity and reliability of the Xerostomia Inventory, and further research is needed before it can be accepted as a truly viable alternative method of measuring xerostomia. Was the almost complete absence of overlap in the predictor medications for xerostomia and salivary gland function (SGH) due to real differences between the two conditions, or did it result from unresolved problems with the XI? Antidepressants were the only medication category to emerge as a predictor for both xerostomia and SGH: for xerostomia, their effect was apparent only for individuals who were using them at both data collections, and that particular group had the very low mean flow rate of 0.12 ml/min (SD=0.08), indicating that the two conditions do tend to concur when flow rate is very low.

Third, a longitudinal approach to medication exposure has been taken, and appears to have been useful. The validity of that particular approach rests heavily on the assumption that a medication taken at baseline and at

TABLE 5
Multivariate Models for Xerostomia Inventory Score

Model	B	Standard Error of B	Significance of T
Model 1: medications taken at 5 years (R^2=0.091)			
Anginal	1.372	1.100	.21
Betablocker	–1.491	0.833	.07
Anginal without betablocker	5.054	1.923	.01
Diuretic	0.754	0.693	.28
Thyroxine and diuretic	6.523	2.876	.02
Thyroxine without anginal	1.045	1.651	.53
Thyroxine	–11.937	7.126	.07
Hormone replacement therapy (female only)	0.949	3.567	.79
Female	0.698	0.603	.25
Age 70+	0.379	0.622	.54
Cigarette smoker	1.004	1.142	.38
Current drinker	–0.031	0.576	.96
Constant	18.666	0.757	<.001
Model 2: medications taken at baseline *and* 5 years (R^2=0.049)			
Anginal	6.676	1.576	<.001
Antidepressant	4.648	2.110	.03
Antiasthma drug	3.754	1.661	.02
Female	1.184	0.577	.04
Age 70+	0.441	0.627	.48
Cigarette smoker	1.070	1.162	.36
Current drinker	–0.397	0.585	.50
Constant	18.843	0.762	<.001

follow-up was, in fact, taken throughout the intervening period. Such an assumption has been used previously (31), although only in describing temporal changes in medication prevalence, and not in modeling the occurrence of side effects such as dry mouth. While it is not possible to state categorically that the assumption is valid, the current study's findings—for example, the strong association between a low flow rate and antidepressant use at baseline and five years—bear it out, and it appears to be intuitively satisfactory. In a dental longitudinal study, the continuous monitoring of medication exposure over the course of the investigation usually is not feasible; thus, such an assumption is necessary.

Fourth, this study has attempted to allow for polypharmacy in the investigation of medications and dry mouth by using an analytical strategy that has been previously reported only once in this field (2). Whether it has been successful or not is difficult to say, as the approach is new and there are no comparable data. However, some intriguing associations and interactions were uncovered that were not found in preliminary analyses using conventional a priori methods. The hierarchical approach and systematic, exploratory nature of CART analysis appear to have potential in the investigation of medications and dry mouth, where its main utility may be in preliminary analysis to identify potential predictors. It could be argued that potential "nonmedication" predictors—such as age group, sex, smoking, and drinking status—should also have been included in this study's CART analysis; however, the aim was to examine the medication-dry-mouth associations free of any other potential confounding variables, and also at two different medication exposure levels (at five years, and baseline and five years). The strong possibility exists that an early split on a variable such as sex would have greatly reduced the numbers in subsequent splits, with the consequence that important predictor medications might have been missed. Thus, the decision was made not to introduce the other potential predictors until the regression analysis stage.

The general approach we used has recently been advocated by Stewart and Stamm (20), who used it with a caries data set, and suggested it as a good exploratory complement to classical multivariate procedures, particularly for data sets that may be large, complicated systems of numerous interrelated variables. There is no question that any data set containing information on medication exposure and dry mouth among older people meets this criterion. This type of exploratory analysis actually has been used previously in this field, in a study of the association between salivary flow rate and medication use among institutionalized older Swedes (2). That study found that individuals taking antidepressants (and antihistamines) and diuretics had lowered flow rates; however, because the drugs in the analysis already had been categorized according to their hypothesized effect on saliva secretion, this a priori approach possibly may have missed some important associations. Moreover, the number of participants was relatively low, at 154, and the association between medication use and the symptoms of dry mouth was not explored.

It is remarkable that no published epidemiologic studies of the association between medications and dry mouth have been reported using multivariate analysis to test the observed associations. It can be argued that there is little merit in examining bivariate findings, as it is only through multivariate analysis that possible confounding by age, sex, or the effects of other medications can be ruled out. The linear regression analyses in this study were used as a complementary method of examining the associations revealed by the CART analysis to evaluate their robustness. The resultant models were not primarily intended to explain completely the occurrence of either flow rate or xerostomia severity (and that was borne out by neither explaining much of the variance in the respective dependent variables), but to control effect confounding by different medications (and characteristics such as age group, sex, smoking status, and alcohol use) and to see which of the associations uncovered in the CART analyses also emerged from the regression analyses.

Most did so, although for flow rate, the diuretics, cardiac, and antiulcer medications did not. For the severity of dry-mouth symptoms (XI score), the taking of HRT at five years did not reach significance in the multivariate model. The generally close agreement between the two approaches suggests that the essentially data-driven CART method can be useful for investigating the association of medications and dry mouth; nevertheless, it is prudent to use an alternative approach, as well.

Generalizing about medications and dry mouth among older populations from the findings of this study is problematic. While the baseline sample was representative of noninstitutionalized South Australians aged 60 years or older, it is evident from the data in Table 1 that those remaining at five years were no longer so, being younger, less highly medicated, and having better dental self-care and service-use patterns than the general population of community-dwelling older South Australians. However, it certainly can be stated that, among participants in this study, unstimulated flow rate was higher among current users of hypolipidemic drugs and among current cigarette smokers, and lower among people who were exposed to antidepressants at both data collections. Xerostomia symptoms were more severe among those taking anginals at five years without a concomitant betablocker, and among those taking thyroxine and a diuretic at five years; and among those who were exposed to antidepressants, anginals, or antiasthma drugs at both data collection stages.

Explaining the medication findings is another challenge: while some are relatively simple—for example, the association between antidepressants and low unstimulated salivary flow rate has long been hinted at in cross-sectional studies, and their emergence as predictors was consistent with those results (particularly with those of the other study to have used an exploratory approach) (2)—others are considerably less so. The apparent positive effect of hypolipidemic medications on flow rate was an unexpected finding that cannot be explained on the basis of our current knowledge of the physiology of salivation, but that hints at a possible therapeutic use for these preparations among people with low salivary flow rates. They might also have a role in the prevention of lowered flow rates in individuals or groups who are known to be at high risk of developing the condition. Nevertheless, replication of this study's findings and more research into the apparent sialogenic properties of those preparations (such as Simvastatin and Pravastatin) are indicated before this conclusion can be considered seriously. Determining whether hypolipidemics cause unstimulated flow rates to increase or if individuals taking them are likely to have higher flow rates anyway is not possible with this study.

Possible reasons for some of the associations with xerostomia severity are relatively easy to find. For example, the thyroxine-diuretic interaction may be due to a dehydrating effect of both of those medication types, although neither produced the effect independently. The antidepressant-xerostomia association has been discussed above. The increased severity of xerostomia symptoms among individuals taking antiasthma drugs at baseline and five years may possibly be due to the dehydrating effect of mouth breathing, which is a common feature of their everyday breathing. The lack of a robust association of xerostomia and HRT is intriguing. The published literature in this area is equivocal, with one recent study reporting no difference (32), but another reporting higher salivary flow rates among women in a longitudinal study who began using HRT (33). The latter study measured the symptoms of dry mouth, but did not report on whether they had improved or worsened since the commencement of HRT. Finally, it is difficult to account for the association of anginal use and xerostomia; however, it is a strong relationship meriting further research.

There were a number of drug categories for which cross-sectional studies have reported an association with dry mouth, but for which none was apparent in the current study. These include antiulcer drugs (11), anxiolytics (10,11,13), anticholinergics (10,16), and antihistamines (2,10). Insufficient numbers of people were taking antihistamines for the approach taken in this study to be used successfully: antihistamine prevalence was 1.6 percent at baseline and 1.5 percent at five years. The other categories did not have an association with either dependent variable, which suggests either that the putative relationships do not exist, or that perhaps they may be more apparent when stimulated salivary flow is being measured.

In summary, this investigation has shown that polypharmacy can be allowed for to a certain extent by using Classification and Regression Tree analysis, with regression analysis as a useful complementary technique. Different medication types and combinations are associated with dry mouth, depending upon whether salivary flow rate or the symptoms of xerostomia are examined. While it is not possible to generalize from the findings of this cohort study to the wider South Australian older population, they offer a useful insight into the complex association of medications and dry mouth.

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