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Antidepressant xerogenic medications and restoration rates

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Abstract – Objectives: This report examines the association between xerogenic antidepressant medication use and dental restorations (a proxy for dental caries). *Methods:* Data for this study was collected from the electronic databases of two large dental group practices associated with two managed care organizations. The population examined was at least 55-year-old on the reference date and had at least 48 months of concurrent dental, medical and pharmacy coverage. We identified 915 individuals whose only exposure to a xerogenic medication was to an antidepressant. This group was compared with a group not on any medications and to a group on medications without any known xerostomic side effect. *Results:* Poisson regression was used to compare restoration occurrence and restoration rates among the three groups. The antidepressant medication and the no xerogenic medication groups were more likely to have restorations than the no medication group but there was no difference in restoration rates between the two medication groups. The mean restoration rates were significantly different between the three groups with the antidepressant group having the highest restoration rate. The no xerogenic group also had a higher rate than the no medication group but not as high as the antidepressant group rate. *Conclusions:* This study provides objective quantification of the long-term effects that anti-depressant medications have on restoration use.

Key words: antidepressants; caries; depression; rates; restorations; xerostomia

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Medications with a xerogenic side effect are suggested as contributing to higher caries rates (1). Our research looked at the various classes of xerogenic medications utilizing tight controls on the use of other xerogenic medication. This paper is reporting on the results of the antidepressant class of xerogenic medications.

Xerostomia is a reduction of the salivary flow resulting in a subjective complaint of mouth dryness. Saliva has an important protective effect for the dentition because of its remineralization, antibacterial, and buffering actions. Xerostomia can result (2) from several causes including autoimmune diseases, head and neck radiation, depression (3, 4), anxiety, dehydration, and taking medications with an effect on the autonomic nervous system (5–7). Antidepressants are a very commonly prescribed class of drugs that have been shown to alter salivary flow. Approximately 6% of the population is exposed to antidepressant medications annually based on pharmacy data from our HMOs. It has been reported (8) that 63% of patients on tricyclic antidepressants complained of dry mouth and that 35% of the patient on selective serotonin-reuptake inhibitors (SSRIs), had a similar complaint.

Many medications have long been identified as potentially contributing to xerostomia and subsequent dental caries among dentate older adults. Papas et al. (9) evaluated the caries rates for adults taking xerogenic medications (prescription or over the counter) ($n = 60$) versus medication-free adults ($n = 60$). For the medicated group, the coronal caries rate was higher for all ages than the medication-free group. Active root-surface decay was more than three times higher in the medicated group than the non-medicated group for subjects aged 60 and older. The numbers were small but the difference was statistically significant. In another study (10) 848 non-institutionalized elderly subjects

were evaluated for prescription medication usage and associations between those medications and dental caries experience. A significantly higher prevalence of root caries was found in those subjects taking specific kinds of medications (antidepressants, anti-ulcer, or anti-angina drugs). Investigators also found that subjects taking multiple medications had a root caries attack rate that was significantly higher than those taking only one or two medications. No relationship was found between medication usage and coronal caries or missing teeth. These results would suggest that recession was the primary reason for the increased caries rates.

Other studies have failed to find associations between caries rates and xerostomic antidepressant drugs. Persson et al. (11) found no significant relationship between xerostomia-related medication usage and decayed, missing, and filled teeth. They measured the stimulated whole salivary flow rate (SWSFR) in a group of elderly nursing home patients taking one or more potentially xerostomic medications and compared them to a group taking medications not known to affect SFRs. Although they found that the SWSFR was significantly reduced among patients taking potentially xerostomic medications, they did not find a relationship to caries experience. In a different small controlled trial on older adults in a long-term care facility Saunders and Handelman (12) found that subjects taking xerogenic medications had a lower saliva flow rate, but no significant differences for coronal and root caries prevalence than non-medicated subjects. The small sample size of both of these studies, however, may have affected the ability to detect difference.

Thomson et al. (13) followed 528 individuals for 5 years and could not show any evidence supporting a medication–caries relationship. One potential difficulty with their study may have resulted from their definition of exposure. They assumed a subject was continuously exposed if on the medication at baseline and at 5 years. In addition to this issue of misclassification bias, there is also the potential of bias arising from the losses to follow-up with 38% of individuals dropping out prior to completion of the study. The individuals lost did show a somewhat higher rate of caries and less regular oral hygiene behaviors at baseline when compared with the group followed. Janket et al. (14) saw a non-significant increase in caries when observing a population from VA clinics for caries at a clinical examination while identifying whether the subjects had been taking a xerostomic medication in the preceding 14–385 days.

Because of the limitations of smaller cross-sectional studies and the conflicting results in the current literature, larger population-based longitudinal studies have been needed to clarify the relationships between xerogenic medication usage and caries experience. The current report details the results of an investigation into the antidepressant medication class of medications; a group that as a whole have often been reported to have a high prevalence of xerogenic side effects.

Subjects and methods

Subjects

This investigation was carried out using the electronic databases of two large dental group practices associated with medical managed care organizations. Study subjects at both sites were required to fulfill the following criteria: have both dental and medical coverage with pharmacy benefits for an overlapping period of at least 48 months without interruption of coverage (this period had to fall between 1990 and 2000). If a potential subject had more than one eligible period during this interval only the first period was used. Contiguous gaps in coverage up to 90 days were not considered as breaks in coverage. Because of the differences in the stability of enrollment between the two sites there were substantial differences in the distributions of the lengths of the eligibility periods (Table 1).

Because the rate of chronic conditions increases with age, to increase the likelihood of exposure to xerogenic medications only study subjects who were 55 years of age or older on December 31, 2000 were considered for inclusion (Table 2). Fifty-two percent of the study subjects at site 1 were male, while at site 2 this was 48%. The subjects at site 2

Table 1. Distribution of enrollees by site and length of eligibility period

	Eligibility counts [*n* (%)]	
Length in years	Site 1	Site 2
4	1433 (27)	2097 (9)
5	2430 (47)	1962 (9)
6	383 (7)	1974 (9)
7	629 (12)	1837 (8)
8	231 (4)	1471 (6)
9	71 (1)	1446 (6)
10	39 (1)	12266 (53)
Total	5216	23053

Table 2. Distributions of subject ages by study site

	Eligibility counts [*n* (%)]	
Age	Site 1	Site 2
55–59	2072 (40)	6952 (30)
60–64	1367 (26)	4840 (21)
65–69	814 (16)	3312 (14)
70–74	524 (10)	2758 (12)
75–79	241 (5)	2294 (10)
80–84	116 (6)	1439 (6)
85–89	42 (1)	921 (4)
90–94	18 (<1)	403 (2)
95–99	18 (<1)	111 (<1)
100–104	4 (<1)	22 (<1)
105–109	0	1 (<1)
Total	5216	23053

were also slightly older than those at site 1 ($P <= 0.0001$).

There were two control groups, a no medication group and a non-xerogenic medication group. The first consisted of 1183 subjects without any pharmacy fills during the study period. They had a mean age of 59 and were 67% male. In which, 95% had a record of dental services utilization during the observation period. This group was included to control for a possible undetermined affect of being on non-xerogenic medication. The second control group contained 5622 subjects with a history of medication use, but with no exposure to the medications on the study xerogenic list. The mean age of this group was 61. The percentage of male was 52% and 99% of this group had a record of dental services utilization.

The study subjects consisted of 915 individuals whose only xerogenic medication exposure was to one or more of the antidepressants within the xerogenic list. The anti-depressant class comprised 12% of the xerogenic medications we examined in this project. Within these study subjects 328 (36%) were male. The average age was 62 years and 99+% of this group had a record of dental services utilization. Only two individuals had exposure to xerogenic tetracyclics, 259 to xerogenic-modified cyclics, 272 to xerogenic SSRIs, 517 to xerogenic tricyclics, and 41 to xerogenic miscellaneous antidepressants. Because exposure to multiple classes of antidepressants was common no effort was made to do a sub-analysis by antidepressant xerogenic medication class.

Xerogenic medications

Our classification of xerogenic medications relied on three approaches.

The first approach used a drug categorizations based on anticholinergic mechanisms developed by Summers (15) and Han et al. (16).

The second approach assembled lists of drugs that were known to have xerogenic potential – either by means of their clinical manifestations, with special attention to dry mouth (13, 17) or because they were so classified (based on their pharmacodynamics) in fundamental pharmacology textbooks, such as Goodman and Gilman's (18). These lists were subsequently reviewed by two practicing clinicians (an internal medicine specialist and a psychiatrist) and two pharmacists and merged into a single list.

The third approach was to conduct an electronic search of any drug with a 3% or greater reported rate of xerostomic side effects in the 2002 Physician's Desk Reference™ (19). While coarse, such an arbitrary threshold is set by current standards of reporting industrial specifications. To obtain a final classification for data analysis, we created a subset of medications that included all drugs that were derived from the above three approaches. This final list contained 190 different putative xerogenic medications with some level of usage in the study population. Each medication was coded by generic product identifier (GPI) group and class to facilitate clustering by usage.

The rationale to identify all medications with a xerostomic effect was twofold. The first reason was to exclude from the control population any patients on xerogenic medications. The second was to allow the identification of a sub-population whose only xerogenic medication experience were with the drug class of interest – in this case, antidepressants.

The antidepressant medications for study were identified as those medications on the xerogenic list that also had a GPI group code of 58 (the GPI antidepressant group). This resulted in four SSRIs, nine tricyclics, one tetracyclics, three MAO inhibitors, two modified cyclics, and three miscellaneous antidepressants. We also considered the possible effect of non-prescription medication but tracking their use under this study design was impossible. In addition, we concluded that the use of non-prescription medications would be similar across groups.

In order to reduce the likelihood that patients were on antidepressants prior to the start of the eligibility period any subjects with fills within the first 100 days of initial eligibility were excluded. This period was chosen because it was found that less than 1% of the fills or refills for an

antidepressant within both medical groups were for greater than 100 days. Seventy-three patients were excluded by this criterion.

In order to create common data structures for analysis, dental procedure-coding systems from both sites were translated into a single common structure. To obtain the best available proxy for caries activity, events were restricted to amalgam or resin restorations. A random audit of 517 study subject charts at site 2 found that 62% of all restorations were associated with caries. Because 'all restorations' included crowns it might be reasonable to assume that this percentage would be even higher if it were restricted to amalgams and resins. No distinction was made between amalgams/resins and crowns.

Results

In the first stage of the analysis we examined the relationship between having restorations (yes versus no) during the observation period and exposure to medications (antidepressant xerogenic medication exposure, non-xerogenic medication exposure only, or no medication exposure) while controlling for medical site, age, and gender. Poisson regression analysis was used because it contains an adjustment for the varying observation (eligibility) periods among the subjects. The observation period used in this Poisson analysis is the time from the study entry until the first restoration. For individuals with no restorations, the observation period consists of the time from the study entry until the end of the members' eligibility within the study period. As our focus was on the relationship between restoration occurrence and exposure and expecting that this relationship may be different for different sites, ages, or genders, we examined interactions between exposure group and each of these other covariates. None of these interactions were statistically significant. In other words, there was no evidence to indicate that the effect of drug exposure differed between men and women, between the two sites, or for different age groups. Therefore, we present results from the model containing only main effects.

Estimated yearly restoration occurrence rates are 0.29, 0.26, and 0.20 for the antidepressant, non-xerogenic medication, and no medication groups, respectively. As can be seen in Table 3, there does appear to be a significant association between use of xerogenic antidepressants and occurrence of restorations. The group dispensed antidepressants had an approximate 40% increase in the occurrence rate for restorations compared with that for individuals taking no medications. The difference between the antidepressant medication group and the group taking non-xerogenic medications is small (and not significant).

We next wanted to examine whether the total number of restorations (relative to observation time) was significantly greater for individuals on xerogenic antidepressant medications than for each of the other two groups. Again we used Poisson regression, incorporating the varying observation times, but now our response variable was the total number of restorations observed rather than just the occurrence of a restoration during the observation period. The observation time used here is the

Table 3. Poisson regression results for estimation of restoration occurrence rates as a function of exposure group, gender, site, and age ($n = 7717$*)

Effect	*P*-value for testing effect	Estimated ratio of restoration occurrence rates adjusted for covariates	95% CI for estimated restoration occurrence ratio
Exposure	<0.0001		
Antidepressant relative to no medications	<0.0001	1.40	1.22–1.62
Antidepressant relative to non-xerogenic medications	0.1376	1.08	0.97–1.21
Non-xerogenic relative to no medications	<0.0001	1.30	1.17–1.44
Gender: Male/Female	0.1077	1.06	0.99–1.14
Site: Site 2/Site 1	0.0746	1.07	0.99–1.16
Age**	0.4223	0.98	0.93–1.03

*Date of first restoration is missing for three subjects.
**The estimated ratio for age refers to the estimated occurrence rate of restorations for individuals of a given age relative to individuals 10 years younger, after adjustment for covariates.

Table 4. Poisson regression results for estimation of mean restoration rates as a function of exposure group, gender, site, and age ($n = 7720$)

Effect	*P*-value for testing effect	Estimated ratio of mean restoration rates adjusted for covariates	95% CI for estimated restoration rate ratio
Exposure	<0.0001		
Antidepressant relative to no medications	<0.0001	1.60	1.46–1.76
Antidepressant relative to non-xerogenic medications	<0.0001	1.16	1.09–1.23
Non-xerogenic relative to no medications	<0.0001	1.38	1.28–1.49
Gender: Male/Female	<0.0001	1.24	1.18–1.30
Site: Site 2/Site 1	<0.0001	1.38	1.31–1.47
Age*	<0.0001	1.10	1.06–1.13

*The estimated ratio for age refers to the estimated mean rate of restorations for individuals of a given age relative to individuals 10 years younger after adjustment for covariates.

total length of eligibility for each individual during the study period. Again, we did not observe any significant interaction effects and hence present results from the main-effects' model.

The estimated mean yearly restoration rates for the antidepressant, non-xerogenic medication, and no medication groups were 0.78, 0.67, and 0.49, respectively.

We see, in Table 4, that individuals taking antidepressant medications sometime during the observation period had a restoration rate approximately 60% greater than those taking no medications at all. The antidepressant group had a 16% higher restoration rate than the non-xerogenic mediation group. We observed larger restoration rates for males, older members, and those at site 2.

Discussion

This study performed two analyses. The first analysis looked at whether individuals on antidepressant xerogenic medications are at increased risk of experiencing one or more restorations. The second set of analyses dealt with whether patients exposed to xerogenic antidepressant medications have a higher number of restorations than those without any xerogenic medication exposure.

In the first analysis both the xerogenic, antidepressant exposed study group and the no xerogenic medication group were significantly more likely to have a restoration than the no medication group but not significantly different in their risk from each other. This suggests that exposure to xerogenic, antidepressant medications does not provoke any greater risk of a restoration than a spectrum of non-xerogenic medication usage. Conversely, one would conclude that being on an antidepressant does increase the risk of having restorations when compared with not being on any medication. The differences between the medication usage groups and the no medication group may be explained by a profile of overall better health for the no medication group. Healthier people may choose a lifestyle that includes better nutrition and healthier self-care behaviors. One might suspect that improved oral hygiene and a less cariogenic diet are mediating this effect. A prospective study would be needed to measure these factors in order to determine if these are the mediating factors that explain these differences.

The second analysis tells a different story. All three groups are significantly different from each other. In this analysis the xerogenic, antidepressant medications group had a higher restoration rate than both the control groups with the no xerogenic medication group having a higher rate than the no medication group but a lower rate than the antidepressant group.

The results of this study suggest that xerogenic, antidepressant medications do not produce an increase in the overall restoration risk (a proxy for caries risk) level when compared with a group on non-xerogenic medication. Rather, that antidepressant medication increases the amount of disease for individuals already at risk. The clinical impact of this information is to first look at the overall caries risk level of the patient on xerogenic medications. If the patient is already at risk of caries, the dentist should consider a more aggressive preventive intervention for the patient

and monitor more frequently the onset of new caries.

Other considerations

It might be suggested that antidepressant medication is really a proxy for poor oral health behaviors associated with depression. Poor oral health behaviors, such as reduced oral hygiene and frequent eating of cariogenic foods, increase the risk of developing caries. This explanation needs to be considered when trying to understand these results. We have seen similar results (not presented in this paper) when examining other classes of medications with a xerostomic side effect. These results suggest the impact of xerogenic medication is significant. This study was not able to determine if other factors are also mediating the results we see. These questions call out for a study that is able to sort out the impact of depression, differences in oral hygiene and dietary factors and the xerostomic side effects of the medication.

Among the control covariates the largest effect found was for the difference between the sites. This might be explained in part by the fact that site 1 had fluoridated water systems and site 2 did not. In addition, women and younger patients had a slightly lower numbers of restorations.

Methods and issues

Two control groups were used. The first group had all the same medical, dental and pharmacy coverage as the study group but no history of any pharmacy usage during their eligibility period. The advantage of this group is that there is no evidence of exposure to any medication that might have a xerogenic impact. As indicated previously, a potential bias may be introduced because this is probably a medically and orally healthier group than the one with non-xerogenic medication usage, resulting in an overall lower risk of developing caries. Also, the second group using a non-xerogenic medication might be unknowingly contaminated with medications having xerogenic side effects that fell outside our definition.

Limitations

This report has not dealt with the length of exposure to antidepressants, which are increasingly being prescribed for a long period of time. We do not know if length of exposure would affect the results. We looked at the duration of a fill episode and found that 35% of the individuals were on an antidepressant for greater than 60 days. In the study, 75% of individuals had three or more fill episodes during the time we observed them in this study. Clearly a number of individuals go on and off the medications over time.

This study was not able to distinguish the effect that depression may have on the development of restoration/caries rates when compared with the medication used to treat the depression. Also, we do not know if depressed individuals utilize dental services differently. And finally, it may be that depressed individuals who are properly treated have better oral care habits and see their dentist more frequently than those who are not being adequately treated.

Additionally, we were not able to determine the use of over the counter medications within each of the groups. Some of these medications, such as anti-histamines, have xerostomic side effects. Possibly this could have influenced our results.

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