Medications That Cause Dry Mouth As an Adverse Effect in Older People: A Systematic Review and Metaanalysis

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OBJECTIVES: To assess and quantify the risk of drug-induced dry mouth as a side effect in older people.

DESIGN: Systematic review and metaanalysis.

SETTING: A search of the literature was undertaken using Medline, Embase, Cochrane, Web of Science, and PubMed from 1990 to 2016.

PARTICIPANTS: Older people (aged ≥60) who participated in intervention or observational studies investigating drug use as an exposure and xerostomia or salivary gland hypofunction as adverse drug outcomes.

MEASUREMENTS: Two pairs of authors screened titles and abstracts of studies for relevance. Two authors independently extracted data, including study characteristics, definitions of exposure and outcome, and methodological quality. For the metaanalyses, random-effects models were used for pooling the data and $I^2$ statistics for exploring heterogeneity.

RESULTS: Of 1,544 potentially relevant studies, 52 were deemed eligible for inclusion in the final review and 26 in metaanalyses. The majority of studies were of moderate methodological quality. In the intervention studies, urological medications (odds ratio (OR) = 5.91, 95% confidence interval (CI) = 4.04–8.63; $I^2 = 62\%$), antidepressants (OR = 4.74, 95% CI = 2.69–8.32, $I^2 = 21\%$), and psycholeptics (OR = 2.59, 95% CI = 1.79–3.95, $I^2 = 0\%$) were significantly associated with dry mouth. In the observational studies, numbers of medications and several medication classes were significantly associated with xerostomia and salivary gland hypofunction.

CONCLUSION: Medication use was significantly associated with xerostomia and salivary gland hypofunction in older adults. The risk of dry mouth was greatest for drugs used for urinary incontinence. Future research should develop a risk score for medication-induced dry mouth to assist with prescribing and medication management. J Am Geriatr Soc 2017.

Key words: xerostomia; dry mouth; medication; systematic review; metaanalysis

Older adults are high users of medications. It is estimated that 40% of community-dwelling and 75% of institutionalized older adults take 5 or more medications, with approximately 10% of older adults taking 10 or more. This high burden of comorbidity and polypharmacy put older adults at risk of adverse drug events. Dry mouth is one of the most common adverse effects of medication use in older adults. This includes salivary gland hypofunction (subjectively measured decrease in salivation) and xerostomia (subjective feeling of dry mouth). It has been shown that the prevalence of hyposalivation increases with the number of medications used, but few studies have investigated the severity of medication-induced dry mouth and associated sequelae. Adverse effects of salivary gland hypofunction include dental caries, dysgeusia, oral mucosal soreness, and oral candidiasis. The process of chewing and swallowing may also be affected, and this can affect the nutritional status of older people.

Drug-induced dry mouth has been attributed to a range of mechanisms. Although anticholinergic effects underlie the majority of cases, other mechanisms include sympathomimetic effects, topical effects of inhaled medications, dehydration, vasoconstriction in salivary glands, alterations in electrolyte and fluid balance, and changes in saliva composition.

There is strong evidence that certain drug classes cause dry mouth. A previous systematic review identified particular drug groups that induce salivary gland hypofunction.
and xerostomia, including those affecting the alimentary, cardiovascular, genitourinary, nervous, and respiratory systems. Examples of drug classes that induce dry mouth include antidepressants, antipsychotics, anticholinergics, antihypertensives, antihistamines, and sedatives, but there is a lack of reviews focusing on elderly adults, even though they are at greater risk of drug-induced dry mouth. Additionally, although certain drugs have been found to be associated with dry mouth, few studies have tried to quantify the risk.

Objective

The aim of this study was to systematically review the literature to assess and quantify the risk of drug-induced dry mouth as a side effect in individuals aged 60 and older.

METHODS

Protocol and Registration

The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42016040033).

Search Strategy and Information Sources

A literature search was undertaken using Medline, Embase, Cochrane, Web of Science, and PubMed from 1990 to 2016. Medical Subject Headings (MeSH), Emtree subject headings, topics and key words related to dry mouth (xerostomia, asialia, hyposalivation, salivary dysfunction, salivary flow, salivary secretion, dry mouth), medication use (drugs, polypharmacy, specific drug classes), older people (aged, elder, senior, older), and study design (controlled trials, observational studies) were used. The full search strategy is included in the supplementary material (Supplementary Table S1). Searches were limited to English-language articles and excluded conference abstracts.

Eligibility Criteria

Studies were included in the review if they were original research published as a scientific peer-reviewed article from 1990 onwards; were intervention studies or observational studies (case-control studies, cohort studies, before-after studies and cross-sectional studies, conducted in humans); included persons aged 60 and older (if studies included subjects <60, data had to have been extractable for those ≥60); included a group exposed to drugs, including specific drugs and drug classes or number of drugs; included a comparator or control group that did not receive drugs or the drug of interest (studies that involved active comparators or persons who acted as their own controls were eligible); and reported on xerostomia, hyposalivation, or salivary gland hypofunction as adverse drug effects, measured in exposed and unexposed groups.

Study Selection

The titles and abstracts of studies were screened independently for relevance by two pairs of authors (ET and GS, DL and KJ). Full-text copies were obtained if a study appeared to meet the inclusion criteria or it was unclear whether it would meet the criteria. Two authors (ET and DL) independently reviewed the full texts to assess each study’s suitability for inclusion. Disagreements or uncertainties about study inclusion were resolved by discussion in the presence of the two other authors (GS and KJ).

Data Extraction and Validity Assessment

Two authors (ET and DL) independently extracted data using a standardized data abstraction form. Data extracted included year of publication; study design; country; study setting; follow-up duration (for dry mouth outcome); study sample characteristics (age and relevant comorbidities); sample size; analytical sample size; year of data collection; definition of drug exposure, including name, dose, dose form, duration of use, and method used to determine drug exposure; definition of xerostomia or salivary gland hypofunction outcome; method used to determine presence of the outcome; and proportions in exposed and unexposed groups.

Methodological quality of studies was assessed using the Jadad score for randomized controlled trials (RCTs) and an adapted version of the Newcastle-Ottawa Scale modified for cross-sectional studies. For studies reporting pooled analyses, the original studies were assessed for quality. If at least one study did not meet a particular quality criterion, the pooled study was assigned a 0 for that quality criterion.

Metaanalysis

If 2 or more studies reported a similar drug exposure and primary outcome measure with appropriate extractable data, a metaanalysis was undertaken. Metaanalysis was performed using Review Manager version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Random-effects models were used for pooling the data, and I² statistics were used to explore heterogeneity. The effect size for the metaanalysis was calculated as odds ratios (ORs) and risk differences (RDs). Significance was tested using Z-statistics.

RESULTS

Study Selection

The search of electronic databases retrieved 2,591 articles. After removing duplicates, the titles and abstracts of 1,544 studies were reviewed, of which 867 were excluded because they clearly did not meet the inclusion criteria. The full-text versions of 677 articles were obtained and scrutinized, and 624 were excluded after independent review by at least two authors (Figure 1). A total of 52 studies were included in the final review and are summarized below and in Supplementary Tables S2 and S3.

Study Characteristics

Of the included studies, 33 were experimental studies, including 25 placebo controlled and 8 with active...
comparators\(^{(29)}\)\(^{-40}\) (1 pooled analysis\(^{(29)}\) included both). Six studies were pooled analyses of multiple trials.\(^{(15,20,25,28,29,32)}\) The remaining 19 studies were observational and used a cross-sectional study design.\(^{(41-59)}\) The majority of studies were conducted in North America (n = 19),\(^{(11,18,19,23,26,34-36,39,40,42,43,46,48,52-54,59)}\) followed by Europe (n = 13)\(^{(9,13,14,16,22,30,31,41,44,49,51,56,58)}\) and Asia (n = 7).\(^{(12,38,45,50,55-57)}\) Thirteen studies were undertaken across multiple continents as part of large, multinational trials.\(^{(10,15,17,20,24,25,27-29,32,33,37)}\) Study sample sizes ranged from 11 to 13,508 subjects. Most studies included older individuals who were generally healthy or without specific comorbidities (n = 19).\(^{(9,18,19,41,44-53,55-59)}\) The most common disease states investigated were urological, including urinary incontinence (n = 15);\(^{(12,13,15,16,18-20,22,29-33,36,40,43)}\) mental health, including major depression (n = 8);\(^{(11,17,25,26,34,35,38,39)}\) generalized anxiety disorder (n = 2);\(^{(10,24)}\) psychosis (n = 2);\(^{(37,42)}\) cognitive impairment (n = 1);\(^{(31)}\) and insomnia (n = 2);\(^{(21,23)}\) neuralgia (n = 1);\(^{(18)}\) and hypertension (n = 2).\(^{(14,54)}\)

**Drug Exposure**

A wide range of drug treatments was assessed across the included studies. Experimental studies tested specific drugs, the most common being those used for urinary frequency and incontinence (Anatomical Therapeutic Chemical code G04BD, n = 16),\(^{(12,13,15,16,18-20,22,29-33,36,40,43)}\) antidepressants (N06A, n = 10)\(^{(10,11,21,25-27,34,35,38,39)}\) and antipsychotics (N05A, n = 3).\(^{(17,24,37)}\) One study each assessed cardiovascular drugs (C03A\(^{(14)}\) and C07A\(^{(54)}\)), hypnotics and sedatives (N05C),\(^{(3)}\) and antiepileptics for neuropathic pain (N03A).\(^{(28)}\)

The cross-sectional studies mainly investigated broad or nonspecific groups of drugs as exposures. Eight studies assessed number of drugs,\(^{(45,47,49,51,53,56,58)}\) and two studies assessed use of any medication.\(^{(44,52)}\) Six studies assessed different types or classes of drugs,\(^{(35,47,50,51,56,58)}\) 3 studies assessed xerogenic or hyposalivation-inducing drug use,\(^{(46,53,59)}\) and 2 studies assessed anticholinergic drug use.\(^{(41,48)}\) When a duration of drug exposure was reported, this ranged from use within the previous 2 weeks to 1 year.\(^{(14,47)}\)

**Outcomes**

All experimental studies assessed xerostomia as a dichotomous outcome, without further description on how this was assessed. Follow-up duration for the assessment of xerostomia in experimental studies ranged from 1 week to 3 years.\(^{(14)}\) Eleven cross-sectional studies had xerostomia as an outcome,\(^{(41-51)}\) and eight had salivary gland hypofunction.\(^{(52-59)}\) One study differentiated between daytime and nighttime xerostomia,\(^{(44)}\) 2 studies assessed severity of xerostomia,\(^{(47,50)}\) and 2 studies objectively assessed oral exposure to medications.
Risk of Bias Within Studies

The majority of experimental studies (n = 15) received a Jadad score of 3 out of 5,9–11,13–15,17–37,40 with 6 studies scoring the maximum 5 out of 5.9,15,17,19,24,31,33 The main limitations of included RCTs were their failure to report appropriate methods of randomization sequence generation (I2 = 12–14,16,20,22,23,25–30,32,34,35,37–40 and double blinding10–13,16,18,20,21,23,25–29,32,34,35,37–39 (n = 21 for each). The majority of cross-sectional studies scored 4 stars out of 10 on the adapted Newcastle-Ottawa Scale,52,55–57 one study assessed parotid and submandibular gland secretion rate;58 and one study assessed minor salivary gland output.53

Results of Individual Studies

In the experimental studies, a greater proportion of those undergoing drug treatment reported xerostomia than of those receiving placebo. In the cross-sectional studies, medication use, number of medications, and using a wide range of medication classes were significantly associated with xerostomia, salivary flow rate, and salivary gland hypofunction. In studies investigating number of drugs as the exposure, all except 141 reported a significant association between number of drugs and dry mouth in older people. Main findings are summarized in Supplementary Tables S4 and S5 and Supplementary Texts S1 and S2.

Metaanalysis

Twenty-two placebo-controlled RCTs were deemed eligible for further inclusion in the metaanalysis.10–12,15–17,19–27,29–33

Of the RCTs, included trials investigated drugs used for urinary frequency and incontinence (ATC code G04BD) (n = 13),12,15,16,19,20,22,29–33 antidepressants (N06A) (n = 6),10,11,21,23–27 and psycholeptics (N05) (n = 3).17,23,24 Statistical heterogeneity was substantial across the trials assessing drugs used for urinary frequency and incontinence (I2 = 62%). The main drugs assessed in this group included tolterodine (n = 4)12,22,29,33 and oxybutynin (n = 3).16,19,30 Of the tolterodine studies, 1 investigated twice-daily administration of the immediate-release preparation,22 with the remainder assessing extended-release formulations. All oxybutynin studies included in the metaanalysis assessed immediate-release oral preparations. The metaanalysis found that urological medications were significantly associated with xerostomia (OR = 5.91, 95% CI = 4.04–8.63; RD = 0.25, 95% CI = 0.13–0.36) (Figure 2, Supplementary Figure S1a). When examining specific urological drugs, oral immediate-release oxybutynin was associated with the greatest risk of dry mouth (RD = 0.56, 95% CI = 0.43–0.70), whereas the risk with mirabegron was negligible (RD = 0.00, 95% CI = −0.01–0.02). Statistical heterogeneity was low across trials investigating antidepressants (I2 = 21%). The main drug assessed in this group was duloxetine (n = 4). Antidepressant use was significantly associated with xerostomia (OR = 4.74, 95% CI = 2.69–8.32; RD = 0.09, 95% CI = 0.04–0.14) (Figure 3, Supplementary Figure S1b). Statistical heterogeneity was low across trials assessing psycholeptics (I2 = 0%). Psycholeptics were more likely than placebo to cause xerostomia (OR = 2.59, 95% CI = 1.79–3.95; RD = 0.09, 95% CI = 0.05–0.12) (Figure 4, Supplementary Figure S1c).

DISCUSSION

Summary of Evidence

Our systematic review found that medication use was significantly associated with xerostomia and salivary gland hypofunction in older individuals. Findings of the metaanalyses confirm that specific drugs, including those from therapeutic classes used for urinary incontinence, antidepressants, and psycholeptics are significantly associated with xerostomia. The risk was greatest in drugs used for urinary incontinence, for which the odds of xerostomia were almost 6 times as great as with placebo. Methodological limitations of current studies were related to sample selection, randomization, and blinding.

The most common ATC categories associated with xerostomia were agents acting on the genitourinary and nervous systems, with the most cited drugs being tolterodine (4 studies), duloxetine (4 studies), and oxybutynin (3 studies). This finding is reflected in a previous review.4 Most of the drugs used for urinary incontinence are antimuscarinics and exert dry mouth through this antimuscarinic mechanism. Oxybutynin, tolterodine, and fesoterodine are nonselective antimuscarinic agents. Darifenac and solifenac are M3-selective receptor antagonists and may be more bladder-specific and less prone to causing anticholinergic side effects, such as dry mouth. Mirabegron, assessed in one study, is a beta-3 adrenergic receptor agonist and an alternative to antimuscarinic drugs. It is less likely to cause dry mouth, and this is reflected in our metaanalysis in that it was not significantly different from placebo.

Our metaanalysis of antidepressants included 3 classes of antidepressants: duloxetine, a selective serotonin and noradrenaline reuptake inhibitor (SSNRI); escitalopram, a selective serotonin-reuptake inhibitor (SSRI); and doxepin, a tricyclic antidepressant (TCA). TCAs enhance the actions of noradrenaline and serotonin by blocking their reuptake at the neuronal membrane, but they also block histaminic, 51-adrenergic, and muscarinic cholinergic receptors,
resulting in adverse drug reactions such as dry mouth. Although SSRIs and SNRIs can cause dry mouth, they are generally less likely to cause anticholinergic side effects than TCAs.

Several psycholeptic medications, including particular antipsychotics, anxiolytics, and hypnotics, are also prone to causing dry mouth. Quetiapine, an atypical antipsychotic, works through antagonism at D2 receptors in the mesolimbic pathway and 5HT2A receptors in the frontal cortex. Quetiapine also has a strong affinity for histaminergic and α1-adrenergic receptors, which may be responsible for dry mouth. Eszopiclone, a nonbenzodiazepine
hypnotic, interacts with the gamma-aminobutyric acid-benzodiazepine receptor complex. The most common adverse effect of eszopiclone is unpleasant taste, although it may also produce dry mouth.

There were considerable differences in the magnitude of the likelihood of xerostomia between different drug classes. This is probably because of variations in the mechanism of actions between and within drug classes. The greatest likelihood of xerostomia was seen with drugs used for urinary frequency and incontinence (G04BD) (OR = 5.91), which is probably related to their antimuscarinic properties. This was equivalent to a 25% greater absolute risk of dry mouth and is clinically significant given that 1 in 4 individuals treated with a urological medication developed dry mouth. Orally administered immediate-release oxybutynin was associated with the greatest risk of dry mouth (56% absolute risk increase) of the drugs in the same therapeutic class. The second largest likelihood was seen with antidepressants (N06A) (OR = 4.74), which mainly consisted of antidepressants

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Figure 3. Forest plots for randomized controlled trials of antidepressants (N06A) vs placebo.

Figure 4. Forest plots for randomized controlled trials of psycholeptics (N05) vs placebo.
with fewer anticholinergic side effects. Lastly, the psycholeptics (N05) in our metaanalysis had the lowest likelihood of causing xerostomia (OR = 1.60), because they were newer agents with more selective receptor activity. Antidepressants and psycholeptics were associated with a 9% greater absolute risk of dry mouth, indicating that, for every 11 people treated, one would experience drug-induced dry mouth.

In our systematic review, a significant association was found between number of drugs and dry mouth in older people. These findings reflect the results of previous studies conducted in the general population and highlight the link between polypharmacy and dry mouth. To our knowledge, this is the first review to quantify the risk of medication-associated dry mouth in persons aged 60 and older. The odds ratio of xerostomia as a side effect of xerostomic drugs in our study would be expected to be higher than in younger individuals because salivary production declines with aging. A Swedish study also reported a greater prevalence of xerostomia with older age in nonmedicated adults, but there have been few other metaanalyses assessing the risk of dry mouth as a medication side effect in elderly adults.

Limitations
This systematic review and metaanalysis has some limitations. Although broad search strategies were implemented in a range of databases to ensure that all relevant studies were included, unpublished and non-English-language studies were not sought. Thus, the possibility of publication bias cannot be excluded. We limited the search from 1990 to 2016, so currently used medications with a strong association with dry mouth that were researched before this time were excluded. Common examples include older TCAs, potent diuretics, antihistamines, and various drugs acting on the central nervous system.

Dry mouth is usually not a primary outcome of experimental studies; hence our search may have missed certain studies that did not report dry mouth as an adverse outcome in the title or abstract. Heterogeneity in the definitions and methods used to assess dry mouth across studies may have affected the ability to compare findings and draw conclusions. Xerostomia is a subjective phenomenon, and different people may have experienced and reported xerostomia differently. Currently, there is no criterion standard method of assessing xerostomia. There may have been differences in medication exposure between studies. Treatment dose, duration, and formulation were not assessed in this review. It is likely that these factors influence the severity of medication-induced xerostomia. For ease of classification, we categorized drugs according to ATC codes, but inclusion of different drugs in each group, some of which may have different indications, may have differing effects on xerostomia. Most of the cross-sectional studies used self-reported drug use, which may underestimate total drug use. Additionally, the way drugs were classified into particular groups may have varied between studies. We addressed potential heterogeneity in sample characteristics and treatment effects in our metaanalyses by using random-effects models. Some included studies were of low methodological quality, and thus their findings should be interpreted with caution. Our systematic review included fewer studies than previous similar reviews, which probably reflects our stricter inclusion criteria, including restricting the population to older people and the years of publication.

Implications
This review has implications for practitioners treating and managing older adults using drugs. Practitioners should carefully weigh the benefits of therapy against the potential risk of dry mouth, oral complications, and treatment discontinuation. This is particularly important in people with polypharmacy. Medications should be regularly monitored and reviewed to identify potential oral side effects of medications, and dose adjustment or change of therapy should be considered when needed. Based on the quantified risk, risk scores can be developed that may be a useful guide for practitioners not only in identifying individuals at risk of dry mouth, but also in evaluating the risk grade for dental health. This can provide information on how much the risk of dental complications is for elderly adults and aid in the development and implementation of preventive programs and comprehensive therapy plans. Future studies should be conducted to develop risk scores for dental health based on the use of different drug groups and numbers of drugs used. Additional factors such as dose, duration, and formulation of treatment should also be considered. The major consequences of medication-induced xerostomia, such as the development of dental caries and need for clinical intervention, should also be explored in future research.

CONCLUSION
Our systematic review found that medication use was significantly associated with xerostomia and salivary gland hypofunction in older individuals. Findings of the metaanalyses show that the risk of xerostomia was greatest for drugs used for urinary incontinence, followed by antidepressants and psycholeptics. Future research should develop a risk score for medication-induced dry mouth to assist with prescribing and medication management.

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REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Full search strategy for each database.

Table S2. Characteristics of included experimental studies with xerostomia outcome.

Table S3. Characteristics of included cross-sectional studies with xerostomia and salivary gland hypofunction as outcomes.

Table S4. Quality assessment of experimental studies.

Table S5. Quality assessment of cross-sectional studies.

Text S1. Jadad scoring system.

Text S2. Newcastle-Ottawa Scale adapted for cross-sectional studies.

Figure S1a-c. Forest plots for RCTs with xerostomia as an outcome reported as risk differences. S1a. Drugs used for urinary frequency and incontinence (G04BD) vs placebo. S1b. Antidepressants (N06A) vs placebo. S1c. Psycholeptics (N05) vs placebo.

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