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“Association between medication-induced xerostomia and orofacial pain: a systematic review.”

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Abstract

Objective: Xerostomia, (or oral dryness), is most commonly caused by medications that affect saliva secretion and is often accompanied by symptoms of orofacial pain. Medication-induced xerostomia may or may not be associated with objectively demonstrable hyposalivation. In this study, we attempt to systematically identify an association between medication-induced xerostomia and orofacial pain.

Methods: A systematic search was conducted using the following databases: WoS, PubMed, SCOPUS, and MEDLINE. The search terms used were: xerostomia OR “dry mouth” AND medication AND (“oral pain” OR “orofacial pain” OR “craniofacial pain” OR “burning mouth” OR “glossodynia”) NOT Sjögren’s NOT cancer. Inclusion criteria were medication-induced xerostomia and reported symptoms of orofacial pain. Four researchers performed the selection process and quality assessment and two researchers conducted data extraction.

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Results: Seven studies with a total of 1,029 patients were included. These studies were conducted between 2009 – 2022 and consisted of cross-sectional studies, case-control studies, and one randomized crossover trial. The studies consisted of a total of 1029 participants. All studies included male and female participants whose mean ages ranged from 43 to 100 years.

Conclusions: A positive association was found between medication-induced xerostomia and orofacial pain. We found no associations between salivary flow measurements (hyposalivation) and medication use. Future research should focus on saliva flow measurements, standardized assessment of medication-induced xerostomia as well as the inclusion of accompanying orofacial pain diagnosis in the medical history to allow for higher level of evidence in establishing reliable predictors of medication-induced oral health damage to facilitate clinical prevention and management.

Keywords

xerostomia; dry mouth; medications; orofacial pain; oral pain

INTRODUCTION/BACKGROUND

Xerostomia is the subjective feeling of dryness in the oral cavity. Hyposalivation is the objective finding of decreased salivary production and is defined as an unstimulated salivation rate of <0.3 ml/min.^{1,2} Although there is often an association between xerostomia and hyposalivation, these terms are not interchangeable. Some patients presenting with xerostomia may still maintain normal salivary production and conversely, patients with severe hyposalivation may not complain of xerostomia.^{3,4} The etiology of xerostomia is multi-factorial and possible causes include medications, systemic diseases such as Sjögren's syndrome, diabetes, HIV and other infections, sleep apnea, radiation of the head and neck, chemotherapy, radioiodine treatment, and nerve damage.⁵⁻⁷ The most frequent cause is medication-triggered side effect.⁸ Several reports describe commonly prescribed medications, for chronic conditions, that have inadvertent anticholinergic effects, resulting in medication-induced xerostomia.⁹ The intake of medication among the US population has substantially increased in recent years and is currently at 37% in adults aged 26 to 87 years.¹⁰ Over 600 medications have anticholinergic effects and these medications have the potential to bind cholinergic receptors and inhibit the action of acetylcholine which, among other effects, ultimately causes a reduction in saliva production.¹¹

The prevalence of xerostomia in the adult population ranges widely between 14–46% and is more prevalent in women. The frequency of xerostomia is also higher among older adults.³ Two studies reported prevalence of medication-related xerostomia as 27 – 30 % while the same studies reported the prevalence in non-medicated patients as 14–16 %.^{12,13} The consequences of xerostomia include high prevalence of caries, oral discomfort, taste disturbances, increased risk of oral infections, difficulty in mastication, swallowing, and speech.^{1,14,15} Xerostomia has a prominent, negative impact on oral health and quality of life.¹⁶

The International Association for the Study of Pain defines orofacial pain as “a frequent form of pain perceived in the face and/or oral cavity. It may be caused by diseases or

disorders of regional structures, dysfunction of the nervous system, or through a referral from distant sources".¹⁷ Terms such as oral pain, craniofacial pain, and facial pain have also been used in the literature to describe similar conditions. Orofacial pain is one of the most common causes of chronic pain affecting 10–15% of the adult population and has been shown to significantly impact the quality of a patient's life.^{18,19 20}

There is limited research investigating the association between medication-induced xerostomia and pain in the orofacial region. Evidence based on scientific reports is lacking regarding the impact of medication-triggered xerostomia and orofacial pain on oral and general health. Therefore, the objective of the current study was to systematically identify whether an association exists between medication-induced xerostomia and orofacial pain.

METHODS

Design

This systematic review was reported according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA).²¹ All studies published in the English language that investigated the association of medication-induced xerostomia with orofacial pain were included.

Focused Question

Is there an association between xerostomia and orofacial pain in patients taking medications?

Patient, Intervention, Comparison, Outcome (PICO) Question

P (Population): Patients taking medications that cause xerostomia

I (Intervention): Medications causing xerostomia

C (Comparison): Patients without xerostomia (xerostomia vs no xerostomia)

O (Outcome): Orofacial pain

SEARCH METHODS FOR IDENTIFICATION OF STUDIES - STUDY SELECTION

Databases.

A systematic search was conducted using the following electronic bibliographic databases to identify potential studies for inclusion in the systematic review:

- Web of Science (WoS) via Nova Southeastern University Library
- PubMed via National Library of Medicine
- SCOPUS via University of Iowa Libraries
- MEDLINE via Ovid

The reference lists of included studies were searched for additional eligible studies not retrieved by our search. The searches were re-run immediately prior to final analyses to retrieve the most recent studies eligible for inclusion.

Search terms.

The terms for medication-induced xerostomia and orofacial pain used in the search included the following: “medication” AND “xerostomia OR dry mouth” AND “oral pain OR orofacial pain OR craniofacial pain” NOT “Sjogren’s” NOT “cancer”. The search strategies and databases used are listed in Table 1. The references from articles that met the inclusion criteria were also searched.

Inclusion/Exclusion Criteria

Studies were considered eligible for inclusion if the PICO criteria were met. This review considered original research articles written in English that reported on/tested medication-induced xerostomia and orofacial pain. Studies were eligible for inclusion if they analyzed patients with and without xerostomia. Studies that did not report outcomes for orofacial, oral, craniofacial pain, or xerostomia were excluded, as well as studies that reported exclusively on burning mouth syndrome. Conference, abstracts or review articles, and books that did not contain new research data were excluded. There was no restriction on year of publication.

Outcome measures

Assessments of xerostomia and assessments of pain were considered as primary outcomes. Assessments of xerostomia included a Visual Analog Scale (VAS) and different kinds of xerostomia questionnaires. Assessments of pain included scales such as Visual Analog Scale and Numeric Rating Scale (NRS), as well as questionnaires assessing pain complaints and characteristics.

Additional outcome measures observed were characteristics of medications taken by the study population and assessments of hyposalivation such as whole saliva flow rate.

Data collection and analysis

Selection of studies and data extraction.—All references identified were exported to reference manager software (Endnote 20) for tracking and removal of duplicates. The screening was performed in two phases, initial screening based on the title and abstract (phase 1), followed by a full-text screening of the eligible articles for final inclusion (phase 2). Phase 1: Two independent reviewers (DK and NM) assessed the titles and abstracts of the articles obtained from the electronic database searches to determine if the articles met the inclusion criteria. Articles that did not fulfill the inclusion criteria were removed sequentially. Disagreements were resolved through a discussion or by consulting a third reviewer (OAK) and a fourth reviewer (SA). Phase 2: Subsequent to the title and abstract review, full text was obtained for the articles that appeared to meet the inclusion criteria based on the title and/or abstract or for which there was insufficient information in the title or abstract. Two primary reviewers independently assessed the full text of each paper that appeared to meet the inclusion criteria. Any disagreements between the two primary

reviewers over the eligibility of a particular study were resolved through a discussion and if a consensus could not be reached, the third reviewer (OAK) was consulted to determine the eligibility of the article.

Prioritization of the exclusion criteria.

Phase 1: Title-abstract screening

1. Not an original full research paper
2. No reports of xerostomia
3. No reports of orofacial pain
4. Xerostomia secondary to BMS (burning mouth syndrome)
5. No appropriate control group was used

Phase 2: Full-text screening: As above, with the addition of:

1. No relevant outcome measures were reported for the assessment of pain
2. No relevant outcome measures were reported for the assessment of xerostomia
3. Xerostomia reported, however, no medications/systemic illness associated
4. Entire study population exclusively diagnosed with BMS

Data extraction and management.—Data were extracted from each paper that met the inclusion criteria as determined by the two primary reviewers. Microsoft Excel (Microsoft Office Professional Plus 2016) was used to create the data extraction form. Two reviewers independently extracted the data from each article. Numerical data from tables, text, or figures were extracted first; when these were not reported, this data was estimated from graphs and appropriately specified in the data extraction form. The following data were recorded: author and year of publication, number of subjects, gender, age, study groups, assessment of xerostomia, assessment of pain, reported medications/systemic illnesses, and assessment of salivary flow.

Additional data related to the assessment of xerostomia, assessment of pain, assessment of salivary flow, and medications were also recorded.

A narrative report of the results is provided to summarize the association between medication-induced xerostomia and orofacial pain based on the systematic review of the literature.

Assessment of Risk of Bias of Individual Studies

The Newcastle – Ottawa Scale was used to assess the methodological quality of the studies included in this review. Criteria of Selection (S), Comparability (C), and Exposure (E), were systematically assessed and graded with star allocation when satisfying the sub-criteria (detailed in Table 2). The overall score was calculated as the sum of the subcriteria scores.

RESULTS

Study selection

A total of seven studies were included in the present review. These studies were conducted between 2009 – 2022 and consisted of cross-sectional studies, case-control studies, and one randomized crossover trial. Results of the electronic bibliographic database searches and the application of the selection criteria are shown in Figure 1.

Study characteristics

The studies consisted of a total of 1029 participants. All studies included male and female participants whose mean ages ranged from 43 to 100 years. All studies were published in English. The study characteristics including author and year of publication, number of subjects, gender, age, study groups, assessment of xerostomia, assessment of pain, reported medications/systemic illnesses, and assessment of salivary flow are summarized in Table 3.

Results of individual studies

We considered two main outcome measures: assessment of xerostomia and pain. The assessment of salivary flow and details of characteristics of medications was also reported. The results of individual studies are briefly summarized in terms of the association of medication-induced xerostomia and orofacial pain. A detailed summary of these results is provided in Table 3. Michalak, P., et al. (2022)²² found that the population of Institutionalized Care Seniors reports oral and mucosal complaints like dryness, swallowing problems, lack of saliva, etc. The authors assessed xerostomia by using Fox questionnaire, Challacombe Scale, Clinical Oral Dryness Score (CODS) (over 65 % CODS with a 4–10 score), and mirror sliding to assess dry mouth. For assessment of pain, the authors reported VAS, oral and mucosal complaints like pain, burning, and mucosal burning. The most reported oral complaints were dryness 36%, lack of saliva 30%, and pain 13.8%, while the mucosal complaints were decreased saliva 45%, and difficulty in taking food 23.8%. Patients with significant resistance to the dental mirror sliding test, which was indicative of dryness, reported higher VAS scores for oral pain ($p=0.018$). Van de Rijt, L.L., et al (2020)²³ found that orofacial pain was more prevalent in patients with dementia than residents without dementia. 48.8 % of dementia patients reported orofacial pain with an Orofacial-Pain Scale for Non-Verbal Individuals (OPS-NVI) while self-reported orofacial pain was present in 37.8%. The summated xerostomia inventory score for patients with dementia is reported as median 6 (IQR 5–10). The authors report having xerostomia (apart from other factors) as one of the significant predictors of orofacial pain in residents with dementia (OR 1.04, $p < 0.05$). Yuen, H.K., et al (2009)²⁴ found that adults with SCI reported a high prevalence of oral problems including experiencing oral pain in the past 12 months (42%) and around 60% patients reported xerostomia. The authors report that oral pain was positively associated with dry mouth. The results of each method of assessment of xerostomia and pain in each study are summarized in Table 4 and 5 respectively.

Barbe, AG., et al. (2018)²⁵ and da Silva, L.A., et al. (2011)²⁶ were the only two studies that performed the assessment of salivary flow. Both studies used different ways to measure salivary flow. The whole stimulated salivation rate was measured in ml/min by Barbe, AG.,

et al. (2018)²⁵ at a mean of 0.3–0.4 ml/min, indicating the presence of hyposalivation associated with xerostomia.

da Silva, L.A., et al. (2011)²⁶ quantified salivary flow by measuring the weight of cotton balls placed intraorally and soaked in saliva for 5 minutes. They reported a mean of 0.125 ± 0.05 g/min in patients with orofacial pain and 0.175 ± 0.05 g/min in patients without. It is unclear whether there was a cut-off value indicative of hyposalivation with this method of assessment, but the authors stated salivary flow was lesser in patients than in the controls. Table 6 summarizes the assessment of salivary flow in two aforementioned studies.

Four out of the seven studies included in this review reported the medications being used by their study population which was used to establish the possibility of medication-induced xerostomia.^{22,23,26,27} These medications ranged from antidepressants, antihypertensives, and antihistamines, which are known to have anticholinergic effects that limit the production of saliva. Unsurprisingly, Beker, N., et al. (2019)²⁷ observed xerostomia was positively associated with the use of medications ($p=0.001$) taken by the population, namely antidepressants, and diuretics. According to da Silva, L.A., et al. (2011), 78% of patients were on medications.²⁶ Medications taken by patients with orofacial pain included amitriptyline (35%) and antihypertensives (16%) that are likewise known to have anticholinergic side effects and appeared to be associated with more frequent dry mouth complaints ($p=0.007$). Michalak, P., et al. (2022)²² observed patients with higher resistance to the dental mirror sliding test also took more medications ($p=0.014$).

de Siqueira, SRDT., et al. (2021)²⁸ reported the types of systemic illness the study population had, suggesting that these were being controlled by medication. These systemic illnesses included cardiovascular and psychiatric conditions. A weak, but positive correlation between the number of medications and dry mucosa score ($0.249 < 0.001$) was observed. Although the types of medications were only grouped as analgesic and non-analgesic, patients with craniofacial pain were taking more medication ($p < 0.001$) than the control group. The control group reportedly only took pain analgesics, while 46% of patients with craniofacial pain took medications that were not pain analgesics.

Two studies did not report medications being taken by the population. However, Barbe, AG., et al. (2018)²⁵ reported that their entire population had an established diagnosis of medication-induced xerostomia. Yuen, H.K., et al (2009)²⁴ likewise stated all patients included in the study had spinal cord injuries. The authors in their introduction established that such patients (with SCI) are usually on medications to reduce muscle spasms and to regulate neurogenic bladder problems. Details of the available data related to medication in each study can be found in Table 7.

DISCUSSION

In this systematic review, we aimed to clarify the relationship between xerostomia and orofacial pain in patients taking medications. The results of our systematic review suggest presence of a positive association between medication-induced xerostomia and orofacial pain.

Medication-induced xerostomia is the subjective feeling of dry mouth secondary to medication. Drug-induced hyposalivation is when there is a measurable, objectively demonstrable reduction of salivation associated with the use of medications. The former may be associated with a change in the property of saliva or change in the patient's perception mechanism. Xerostomia with hyposalivation is caused by both salivary gland dysfunction and salivary innervation disorder. It has been postulated that medication-induced hyposalivation may be a result of a disorder in salivary innervation.²⁹ In the current article, the authors focused on medication induced xerostomia as a criterion for inclusion. If the included articles also reported medication induced hyposalivation, this was reported as an additional finding.

Salivary gland innervation is via the parasympathetic and sympathetic innervations. Bidirectional interactions have been shown to be present between the autonomic nervous system and pain. There is a considerable overlap in the brain regions involved in pain processing and modulation as well as central autonomic networks.³⁰ Xerogenic drugs have been shown to affect CNS or neuroglandular junction. Acini cells in salivary glands are regulated by muscarinic and adrenergic receptors that are stimulated during saliva secretion. Some xerogenic medications have anticholinergic effects and can centrally suppress the production of acetylcholine or block these muscarinic and adrenergic receptors in salivary glands.³¹

Most of the studies included in the review exclusively used self-administered questionnaires to determine the presence of xerostomia.^{23,24,26–28} All studies used different methods of pain assessment, the most common being VAS. Barbe, AG., et al. (2018)²⁵ found that patients with medication-induced xerostomia reported a mean oral pain score of 0.8 and a mean dryness score of 2.3–2.5 in the xerostomia questionnaire administered. Patients also reported a VAS score for dryness between 70 to 80 on average, out of 100. Beker, N., et al.(2019)²⁷ conducted a five-point xerostomia questionnaire on a group of centenarians and reported 18% of the population had symptoms of xerostomia. Results of another questionnaire conducted, reported 12% of the population complained of oral pain or discomfort. da Silva, L.A., et al. (2011)²⁶ found that patients with orofacial pain reported more complaints of xerostomia. Results from the Xerostomia Inventory questionnaire indicated 45% and 60% of patients with orofacial pain answered “yes” to statements like experiencing dry mouth and oral discomfort, respectively, compared with controls without orofacial pain (39% and 14%). Patients with orofacial pain reported a mean score of 8.01 on a 1–10 VAS and reported pain characteristics such as neckache (39%) and masticatory pain (25%). de Siqueira, SRDT., et al. (2021)²⁸ similarly conducted a Xerostomia Inventory questionnaire on patients with and without chronic craniofacial pain and found higher xerostomia scores in patients with facial pain compared with controls (7.14 vs. 5.04, $p<0.001$). 62.6% patients with craniofacial pain reported xerostomia.

None of the studies included both dry mouth and pain as their primary outcomes. Only one of the seven studies was a randomized control trial, limiting the ranking of scientific evidence gathered. In most studies, data collection of xerostomia and orofacial pain relied heavily on patient's recall ability. Additionally, medication use was reported in all studies as a covariant and not an explanatory variable. Important pharmacological factors like

dosage and duration of use were not provided and therefore not considered. This again, further limits the strength of the association between orofacial pain and medication-induced xerostomia.

Assessment of xerostomia

Yes/No format questionnaires were used to assess the presence of xerostomia by da Silva, L.A., et al. (2011)²⁶ using Xerostomia inventory, by de Siqueira, SRDT., et al. (2021)²⁸ using Reported xerostomia, by Michalak, P., et al. (2022)²² using Oral cavity complaints, Oral mucosa complaints, Fox's questionnaire, and Challacombe Scale and by Yuen, H.K., et al (2009)²⁴. Some of the questions asked were common to different questionnaires, however, a lack of standardization limits their comparability.

Barbe, AG., et al. (2018)²⁵, Beker, N., et al.(2019)²⁷, de Siqueira, SRDT., et al. (2021)²⁸, Van de Rijt, L.L., et al (2020)²³ used multiple-point summated questionnaires to determine and compare the presence of xerostomia within their study populations. Because these studies chose different points or did not mention the scale in their questionnaires, their summated scores could not be compared.

Michalak, P., et al. (2022)²² was the only included study to also use the mirror sliding test and Clinical Oral Dryness Score (CODS) to assess the severity of xerostomia. Likewise, Barbe, AG., et al. (2018)²⁵ also used a 0–100 VAS for the question, “How dry is your mouth?” to subjectively quantify the presence of xerostomia.

Assessment of pain

Beker, N., et al.(2019)²⁷, Michalak, P., et al. (2022)²² and Yuen, H.K., et al (2009)²⁴ used only Yes/No format questionnaires to determine the presence of orofacial pain in study participants. Yuen, H.K., et al (2009)²⁴ established the presence of pain by asking if certain adverse events had occurred in the last 12 months. da Silva, L.A., et al. (2011)²⁶ and de Siqueira, SRDT., et al. (2021)²⁸ however, used a combination of Yes/No and open questionnaires to collect information about pain complaints and characteristics. Barbe, AG., et al. (2018)²⁵ used mean oral pain score derived from the xerostomia questionnaire and the OHIPG-14 summated questionnaire to determine the presence of pain.

da Silva, L.A., et al. (2011)²⁶, Michalak, P., et al. (2022)²² and Van de Rijt, L.L., et al (2020)²³ used scales such as VAS, NRS, and OPS-NVI to quantify orofacial pain, although each study's scale was calibrated differently and therefore not directly comparable.

Only two studies^{26,28} specified the diagnoses of orofacial pain patients recruited that included neuralgias, temporomandibular disorders, atypical facial pain, and neuropathies. The remaining studies did not distinguish the types of orofacial pain. The pain outcomes for each study are elaborated further in Table 5.

Characteristics of Medications

Barbe, AG., et al. (2018)²⁵ and Yuen, H.K., et al (2009)²⁴ were the only two studies in this review that did not specify the medications taken by the population, nor any systemic illnesses in the population. Yuen, H.K., et al (2009)²⁴ however, did mention that their

study population of SCI patients typically take medications that reduce muscle spasms and regulate neurogenic bladder problems, some of which have anticholinergic side effects. Moreover, the authors also did not mention what percentage of the current study population was on these medications.

de Siqueira, SRDT., et al. (2021)²⁸ was the only study that reported types of systemic illnesses. They also reported medications in two categories: medications that were pain analgesics, and medications that were not. Both outcomes included respective percentages of the study population.

Beker, N., et al.(2019)²⁷, da Silva, L.A., et al. (2011)²⁶, Michalak, P., et al. (2022)²² and Van de Rijt, L.L., et al (2020)²³ specified the types of medications taken by their populations and reported their respective percentages. The percentage of participants taking antidepressants was mentioned in all four studies.

Assessment of salivary flow

Two studies utilized another clinical measure of hyposalivation: salivary flow. Barbe, AG., et al. (2018)²⁵ measured the whole stimulated salivation rate at 0.3 ± 0.2 ml/min (mean \pm SD) participants in the Gum Hydral group and 0.4 ± 0.2 ml/min (mean \pm SD) in the Biotene group. da Silva, L.A., et al. (2011)²⁶ measured quantitative salivary flow which was significantly lower in patients with orofacial pain than controls (0.125 g/min vs. 0.175 g/min, $p=0.008$).

LIMITATIONS

There are several limitations associated with this review. First, none of the studies included a control group without xerostomia. Barbe, AG., et al. (2018)²⁵ is the only study that exclusively enrolled patients with medication-induced xerostomia. Pain assessments were performed indiscriminately on the entire study population, thus the determination of whether the same subject with xerostomia also reported pain was not possible unless a direct correlation was reported.

With regard to outcome measures, most studies assessed only the presence or absence of xerostomia. Using validated xerostomia questionnaires could allow quantification of the correlation with the severity of pain. Only two studies reported objective measures of hyposalivation. Measuring hyposalivation would allow association with medication-induced dry mouth.

Furthermore, few studies specified the category of medications or the drugs taken by the study groups. It is well known that side effects from medications are dose-dependent, but no dosages were reported. Duration of drug intake was not included, which could also have an effect on xerostomia. Most studies included the combination of xerogenic and non-xerogenic medications. Therefore, a low correlation was found in those studies between xerostomia and medications, as non-xerogenic medications were combined with xerogenic medications. The risk of bias within the studies cannot be assessed as there was only one randomized controlled trial included, limiting the weight of the conclusions derived.

CONCLUSION

This is the first review to summarize current knowledge on the association between xerostomia and orofacial pain in patients taking medications. This review highlights the lack of high level of evidence studies investigating orofacial pain and medication-induced dry mouth. Similarly, there is a lack of sufficient evidence regarding the characteristics of medications responsible for xerostomia and orofacial pain. The inability to perform a meta-analysis due to the limited number and quality of studies addressing this topic requires that the reader rely on the conclusions of this study with prudence. Both chronic orofacial pain and xerostomia have been shown to negatively impact quality of life. Healthcare professionals including medical providers and the dental community are encouraged to investigate symptoms of orofacial pain and dry mouth within the scope of their practice. Future research should focus on saliva flow measurements, standardized assessment of medication-induced xerostomia as well as the inclusion of accompanying orofacial pain diagnosis in the medical history to allow for higher level of evidence in establishing reliable predictors of medication-induced oral health damage to facilitate clinical prevention and management.

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LIST OF ABBREVIATIONS

BMS	Burning mouth syndrome
SCI	Spinal Cord Injury
VAS	Visual analogue scale
OHIP-14	Oral Health Impact Profile-14
OPS-NVI	Orofacial-Pain Scale for Non-Verbal Individuals
NRS	Numeric Rating Scale
CODS	Clinical Oral Dryness Score

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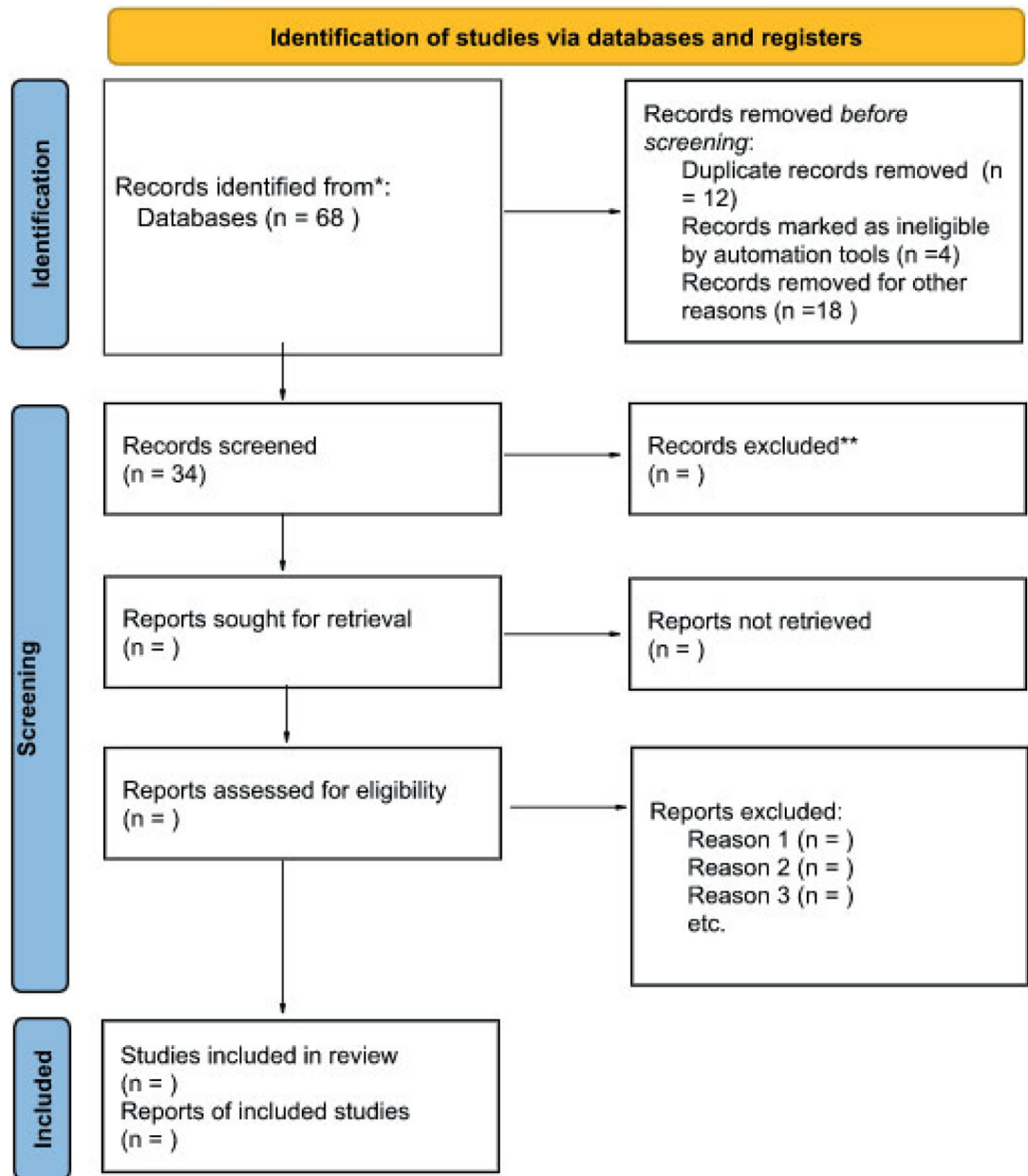


Figure 1.
PRISMA flow diagram

Table 1.

Finalized search strategy table

Database	Search Strategy
PubMed	medication AND (xerostomia OR “dry mouth”) AND (“oral pain” OR “orofacial pain” OR “craniofacial pain”) NOT sjogren’s NOT cancer
WoS	(ALL=(xerostomia) OR ALL=(“dry mouth”)) AND ALL=(medication) AND (ALL=(“oral pain”) OR ALL=(“orofacial pain”) OR ALL=(“craniofacial pain”)) NOT ALL=(Sjogren’s) NOT All=(cancer)
SCOPUS	ALL ((xerostomia OR “dry mouth”) AND medication AND (“oral pain” OR “orofacial pain” OR “craniofacial pain”) NOT sjogren’s NOT cancer)
MEDLINE	(xerostomia OR “dry mouth”) AND medication AND (“oral pain” OR “orofacial pain” OR “craniofacial pain”) NOT sjogren’s NOT cancer

Search Strategy

Database

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Table 2.

Quality of reporting of including studies using the Newcastle-Ottawa Assessment criteria

Newcastle-Ottawa Assessment criteria	Barbe et al. (2018)	Beker et al. (2019)	da Silva et al. (2011)	de Siqueria et al. (2021)	Michalak et al. (2022)	Van de Rijt et al. (2020)	Yuen et al. (2009)
SELECTION							
• Is the case definition adequate?	*	*	*	*	-	*	-
• Representativeness of the cases	*	-	*	*	-	*	-
• Selection of controls	-	*	*	-	*	*	*
• Definition of controls	-	-	*	*	*	*	-
COMPARABILITY							
• Comparability of cohorts	-	-	-	-	-	*	**
EXPOSURE							
• Ascertainment of exposure	*	*	-	-	*	*	*
• Same method of ascertainment for cases and controls	-	*	-	*	-	*	*
• Non-response rate	*	*	*	*	-	*	-
TOTAL	4	5	5	5	3	8	5

A study can be awarded a maximum of one star (*) for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. Good studies: 7–8 points Satisfactory studies: 5–6 points Unsatisfactory studies: 0 to 4 points

Table 3. Summary of characteristics of studies reporting on medication-induced xerostomia and orofacial pain

Index	Author (Year)	Number of subjects	Gender	Age (Mean)	Groups (N)	Assesment of xerostomia	Assessment of pain	Reported Medications/ Systemic Illnesses	Assessment of Salivary Flow
1	Barbe, A.G., et al. (2018)	40	14M, 26F	61	Xerostomia and GUM Hydral Xerostomia and Biogene	VAS, Xerostomia Questionnaire	OHIPG-14, XQP-art 1	Not specified	Whole stimulated salivation rate
2	Beker, N., et al. (2019)	162	38 M, 120 F	100.9	NA	Xerostomia Questionnaire	Questionnaire	Reported medications	NA
3	da Silva, L.A., et al. (2011)	138	41 M, 97 F	N/A	Patients with orofacial pain (82) Control (56)	Xerostomia Inventory	VAS, Pain characteristics	Reported medications	Salivary Flow
4	de Siqueira, SRDT., et al. (2021)	306	89M, 217F	52.32	Patients with facial pain (174) Control (132)	Xerostomia Inventory	Pain complaints, Pain characteristics	Reported systemic illnesses	N/A
5	Michalak, P., et al. (2022)	80	28 M, 52 F	72.05	Institutionalised center MHCOD (50) Institutionalised center DMCH (30)	Oral and mucosal complaints, Fox's questionnaire, Challacombe Scale, CODS and Mirror sliding test	VAS, Oral Cavity Complaints, Oral Mucosal Complaints	Reported medications	N/A
6	Van de Rijt, L., L., et al (2020)	111	42 M, 69 F	83.9	Group 1: Patients with dementia (84) Group 2 : Patients without dem	Summated Xerostomia Inventory	NRS, OPS-NVI	Reported medications	N/A
7	Yuen, H.K., et al (2009)	192	115 M, 77 F	43.9	N/A	Questionnaire	Questionnaire	Not specified	N/A

Abbreviations

M Male

F Female

VAS Visual Analogue Scale

OHIPG-14 Oral Health Impact Profile

OPS-NVI Orofacial-Pain Scale for Non-Verbal Individuals

NRS Numeric Rating Scale

CODS Clinical Oral Dryness Score

Table 4.

Assessment of xerostomia

Index	Author (Year)	Assesment of dry mouth	Outcome	Scale	Group(s)	Mean \pm SD	N (%)
1	Barbe, AG., et al. (2018)	Visual Analogue Scale (VAS)	How dry is your mouth?	0–100	Gum Hydral	80	
					Biotene	70	
		Xerostomia Questionnaire Part I	Mean oral dryness score		Gum Hydral	2.5 \pm 0.6	
					Biotene	2.3 \pm 0.6	
2	Beker, N., et al (2019)	Xerostomia Questionnaire	My mouth feels dry when eating	5–15	Yes (scores 8)		30 (18)
			My mouth feels dry				
			I have difficulty eating dry foods				
			I have difficulties swallowing certain foods				
			My lips feel dry				
3	da Silva, L.A., et al. (2011)	Xerostomia Inventory	Difficulty of chewing due to xerostomia	Yes/No	Patients with orofacial pain		11 (13.4)
					Control		2 (3.6)
			Dry mouth sensation		Patients with orofacial pain		45 (54.9)
					Control		22 (39.3)
			Needs of liquids to swallow		Patients with orofacial pain		17 (20.7)
					Control		5 (8.9)
			Avoiding food due to xerostomia		Patients with orofacial pain		8 (9.8)
					Control		0 (0)
			Abnormal saliva		Patients with orofacial pain		30 (36.6)
					Control		11 (19.6)
			Discomfort at the oral cavity		Patients with orofacial pain		60 (73.2)
					Control		8 (14.3)
			Lost in taste due to xerostomia		Patients with orofacial pain		24 (29.3)
					Control		6 (10.7)
Difficulty to use dentures due to xerostomia	Patients with orofacial pain		4 (4.9)				
	Control		1 (1.8)				
4	de Siqueira SRDT., et al. (2021)	Xerostomia Inventory	Dry mucosa score		Patients with facial pain	9.76 \pm 4.488	
					Control	6.69 \pm 3.535	
			Xerostomia score		Patients with facial pain	7.14 \pm 3.482	

Index	Author (Year)	Assesment of dry mouth	Outcome	Scale	Group(s)	Mean \pm SD	N (%)
					Control	5.04 \pm 2.698	
		Reported xerostomia		Yes/No	Patients with facial pain, yes		109 (62.6)
					Control, yes		45 (34.1)
5	Michalak, P., et al. (2022)	Oral cavity complaints	Dryness	Yes/No	Both groups, yes		29 (36.3)
			Swallowing problems	Yes/No	Both groups, yes		11 (13.8)
			Lack of saliva	Yes/No	Both groups, yes		24 (30)
		Oral mucosa complaints	Decrease in saliva	Yes/No	Both groups, yes		36 (45)
			Difficulty in taking food	Yes/No	Both groups, yes		19 (15.2)
		Fox's questionnaire	Do you experience mouth dryness during the night or upon wakin up?	Yes/No	Both groups, yes		34 (42.5)
			Do you experience mouth dryness during the day?	Yes/No	Both groups, yes		33 (41.3)
			Do you keep a glass of water next to your bed?	Yes/No	Both groups, yes		30 (37.5)
			Do you drink fluids while swallowing dry foods?	Yes/No	Both groups, yes		37 (46.3)
			Do you experience mouth dryness during meals?	Yes/No	Both groups, yes		30 (37.5)
			Do you experience problems with swallowing foods?	Yes/No	Both groups, yes		17 (21.3)
			Do you use chewing gum on a daily basis to eliminate a feeling of mouth dryness?	Yes/No	Both groups, yes		7 (8.8)
			Do you use hard fruit or mint candies on a daily basis to eliminate a feeling of mouth dryness?	Yes/No	Both groups, yes		18 (22.5)
			Do you perceive the volume of saliva in your mouth as too small/ excessive, or do you just not notice it?	Yes/No	Both groups, yes		42 (52.5)
			Do you need to moisten your mouth frequently?	Yes/No	Both groups, yes		29 (36.3)
		Challacombe Scale	Mirror sticks to buccal mucosa	Yes/No	Both groups, yes		41 (51.3)
			Mirror sticks to tongue	Yes/No	Both groups, yes		49 (61.3)
			Saliva frothy	Yes/No	Both groups, yes		17 (21.3)
			No saliva pooling in floor of mouth	Yes/No	Both groups, yes		49 (61.3)
			Tongue shows generalised shortened papillae (mild depapillation)	Yes/No	Both groups, yes		53 (66.3)
Altered gingival structure (i.e., smooth)	Yes/No		Both groups, yes		43 (53.8)		

Index	Author (Year)	Assesment of dry mouth	Outcome	Scale	Group(s)	Mean \pm SD	N (%)	
			Glassy appearance of oral mucosa, especially palate	Yes/No	Both groups, yes		17 (21.3)	
			Tongue lobulated/fissured	Yes/No	Both groups, yes		53 (66.3)	
			Cervical caries (more than 2 teeth)	Yes/No	Both groups, yes		11 (13.8)	
			Debris on palate or sticking to teeth	Yes/No	Both groups, yes		24 (30)	
		Clinical Oral Dryness Score (CODS)		1-10	1-3			28 (35)
					4-6			42 (52.5)
					7-10			10 (12.5)
		Mirror sliding test		1-3	1 - No Resistance			29 (36.2)
					2 - Slightly Resistance			31 (38.8)
					3 - Significant Resistance			20 (25)
6	Van de Rijt, L. L., et al (2020)	Summated Xerostomia Inventory			Group 1	6 (5-10)*		
					Group 2	7 (5.5-13)*		
7	Yuen, H.K., et al (2009)	Questionnaire	Do you sip liquids to aid in swallowing dry foods?	Yes/No	Yes		59.90%	
			Does your mouth feel dry when eating a meal?					
			Do you have difficulties swallowing any foods?					
			Does the amount of saliva in your mouth seem to be too little?					

* Median (IQR)

Table 5.

Assessment of orofacial pain

Index	Author (Year)	Assessment of pain	Outcomes	Scale	Group(s)	Mean (±SD)	N (%)	
1	Barbe, AG., et al. (2018)	OHIPG-14	Pain in oral area	0–4	Gum Hydral	No score available		
					Biotene	No score available		
		Xerostomia Questionnaire Part 1	Mean Oral Pain score	0–3	Gum Hydral	0.8 ± 0.9		
					Biotene	0.8 ± 1.0		
2	Beker, N., et al. (2019)	Questionnaire	Do you experience pain or discomfort in your mouth	Yes/No/Sometimes	Patients with orofacial pain, Yes		7 (4)	
					Patients with orofacial pain, Sometimes		13 (8)	
3	da Silva, L.A., et al. (2011)	VAS		0–10	Pt with Orofacial pain	8.01 ± 2.72		
					Control	NA		
			Pain in mandibular movements			Pt with Orofacial pain, Present		15 (18.3)
						Control, Present		1 (1.8)
			TMD			Pt with Orofacial pain, Present		36 (43.9)
						Control, Present		2 (3.6)
			Pain at facial palpation			Pt with Orofacial pain, Present		26 (31.7)
						Control, Present		0 (0)
			Neckache			Pt with Orofacial pain, Present		32 (39.0)
						Control, Present		7 (12.5)
			Masticatory pain			Pt with Orofacial pain, Present		21 (25.6)
						Control, Present		1 (1.8)
4	de Siqueira SRDT., et al (2021)	Pain complaints	Pain (except at the craniofacial region)	Yes/No	Pt with facial pain, Yes		152 (87.4)	
					Control, Yes		80 (60.6)	
			Pain when waking up	Yes/No		Pt with facial pain, Yes		101 (58.0)
						Control, Yes		41 (31.1)

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Index	Author (Year)	Assessment of pain	Outcomes	Scale	Group(s)	Mean (\pm SD)	N (%)
			Sensation of tired face	Yes/No	Pt with facial pain, Yes		81 (46.6)
					Control, Yes		20 (15.2)
			Pain in mandibular movements	Yes/No	Pt with facial pain, Yes		64 (36.8)
					Control, Yes		5 (3.8)
		Pain characteristics	Number of cranial areas with headache		Pt with facial pain	0.90 \pm 0.761	
					Control	0.50 \pm 0.704	
			Number of pain areas (except at the craniofacial region)		Pt with facial pain	1.61 \pm 0.995	
					Control	0.80 \pm 0.766	
			Number of pain areas when waking up		Pt with facial pain	1.83 \pm 2.000	
					Control	0.54 \pm 1.087	
			Number of areas with "tired" sensation		Pt with facial pain	0.70 \pm 0.954	
					Control	0.16 \pm 0.369	
		Number of painful mandibular movements		Pt with facial pain	0.85 \pm 1.404		
				Control	0.04 \pm 0.193		
Number trigger points		Pt with facial pain	2.69 \pm 2.379				
		Control	0.25 \pm 0.651				
5	Michalak, P., et al. (2022)	VAS		Not specified	No resistance	1.1	
					Slight resistance	1.42	
					Significant resistance	3.05	
		Oral complaints		Yes/No	Both groups, Yes		11 (13.75)
					Burning	Yes/No	Both groups, Yes
		Yes/No	Both groups, Yes		3 (3.75)		
Oral mucosal complaints	Mucosal burning	Yes/No	Both groups, Yes		10 (12.5)		
6	Van de Rijt, L.L., et al (2020)	NRS			Verbal participants of Group 1 (37)		14 (37.8)
					Group 2		4 (14.8)
		OPS-NVI			Group 1		41 (48.8)

Index	Author (Year)	Assessment of pain	Outcomes	Scale	Group(s)	Mean (±SD)	N (%)
					Group 2		4 (14.8)
7	Yuen, H.K., et al (2009)	Questionnaire	In the past 12 months, have you had any of the following incidents as a result of your teeth or gums hurting?	Pain medication used	Yes/No		43 (22.4)
				Eating disrupted	Yes/No		38 (19.8)
				Dentist visited	Yes/No		35 (18.2)
				Sleep disrupted	Yes/No		17 (8.8)
				Work or school missed	Yes/No		3 (1.6)
				Emergency room visited	Yes/No		1 (0.5)

Abbreviations

VAS Visual Analogue Scale

OHIPG-14 Oral Health Impact Profile

OPS-NVI Orofacial-Pain Scale for Non-Verbal Individuals

NRS Numeric Rating Scale

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Table 6.

Assessment of salivary flow

Index	Author (Year)	Salivary flow measure	Scale	Group(s)	Mean (\pm SD)
1	Barbe, AG., et al. (2018)	Whole stimulated salivation rate	ml/min	Gum Hydral	0.3 \pm 0.2
2	Beker, N., et al. (2019)	NA	NA	Biotene NA	0.4 \pm 0.2 NA
3	da Silva, L.A., et al. (2011)	Salivary flow	g/min	Patients with orofacial pain	0.125 \pm 0.05 *
4	de Siqueira, SRDT., et al. (2021)	NA	NA	Control NA	0.175 \pm 0.05 * NA
5	Michalak, P., et al. (2022)	NA	NA	NA	NA
6	Van de Rijt, L.L., et al (2020)	NA	NA	NA	NA
7	Yuen, H.K., et al (2009)	NA	NA	NA	NA

* Estimated

Table 7.

Characteristics of medications and illnesses reported

Index	Author (Year)	Group	Types of medications	Known side effect of xerostomia	Percentage of patients taking medication (%)	Number of medication (Mean ± SD)	Type of systemic illness (N%)		
1	Barbe, AG., et al. (2018)		Not specified		NA				
2	Beker, N., et al. (2019)	NA	Cardiac medication		53.00				
			Diuretics	Y	47.00				
			Anti-coagulants		45.00				
			Antacids		41.00				
			Analgesics		25.00				
			Sedatives		16.00				
			Laxatives		18.00				
			Antidiabetics		5.00				
			Antidepressants	Y	3.00				
			Iron supplements		7.00				
Other		49.00							
3	da Silva, L.A., (2011)	Patients with orofacial pain	Amitriptyline	Y	35.30				
			Carbamazepine		26.80				
			Antihypertensive	Y	15.90				
			Common analgesics		4.90				
		Others		14.60					
Control	Anti-hypertensive	Y	53.60						
4	de Siqueira, SRDT., et al. (2021)	Patients with facial pain	Including pain analgesics		82.80	1.91 ± 1.491	Cardiovascular (39.2) Otorhinolaryngologic (20.9)		
			Excluding pain analgesics		46.60	0.76 ± 1.068	Gastric (19.0) Psychiatric (14.7)		
		Control	Including pain analgesics		43.20	0.64 ± 1.006	Endocrine (12.1) Rheumatologic (13.1)		
			Excluding pain analgesics		43.20	0.64 ± 1.006	Nephrologic (3.3) Neurologic (3.3)		
		5	Michalak, P., et al. (2022)	Both groups	Anticholinergics	Y	5.65	MHCOD: 6.32 ± 2.34 DMCH : 6.23 ± 3.13	
					Antihistamines	Y	9.65		
Antihypertensive	Y				71.00				
For Parkinson's disease					10.65				
Cytotoxic					4.65				
Sedative					55.00				

Index	Author (Year)	Group	Types of medications	Known side effect of xerostomia	Percentage of patients taking medication (%)	Number of medication (Mean \pm SD)	Type of systemic illness (N%)
			Relaxants		9.35		
			Antidepressants	Y	34.65		
			Anticoagulants		28.00		
			Bone resorption inhibitors		3.65		
			Other		78.00		
6	Van de Rijt, L. L., et al (2020)	Both groups	Analgesics		82.90		
			Regular		58.10		
			Anti-depressants	Y	26.10		
			Anti-epileptics		17.10		
			Anti-psychotics		16.20		
7	Yuen, H.K., et al (2009)	NA	Reduce muscle spasms (eg, phenytoin and baclofen)				
			Regulate neurogenic bladder problems (eg, bethanechol and oxybutynin)				