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Original Research Article

Pharmacological Versus Prosthodontic Management of Xerostomia:A Systematic Review and Meta-analysis of Pilocarpine Therapy and Saliva-Retaining Prosthetic Appliances

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Abstract: ***Background:*** Xerostomia has a strong effect on the quality of life and oral health, and its treatment methods can be split into two directions: pharmacological and prosthodontic. Although the use of pilocarpine treatment has received a lot of research focus in enhancing the remaining salivary activity, alternative mechanical treatment, especially to edentulous patients whose salivary glands are permanently damaged, is the introduction of saliva-retaining prosthetic appliances. ***Purpose***: To compare the effects of pilocarpine therapy on clinical effectiveness, safety, patient-reported outcomes, and quality of life affectively in comparison with the saliva-retaining prosthetic appliance in the management of xerostomia. ***Methods:*** We undertook extensive searching of PubMed, EMBASE, Cochrane Library, CINAHL, and local databases (inception to December 2025) following the PRISMA 2020 recommendations. The inclusion criteria were randomized controlled studies, cohort studies and cross-sectional studies comparing pilocarpine treatment (systemic or topical) with saliva retaining prostheses in adults with xerostomia with any etiology. The main outcomes were the severity of xerostomia (VAS scores), the rate of salivary flow, and OHRQoL. Meta-analyses used random-effects models which use the standardized difference of means in continuous results. ***Findings:*** A total of 28 studies were included in the study out of 3,847 records identified (n=2,156 participants). In the case of pharmacological treatment, 18 studies have assessed pilocarpine therapy systemic pilocarpine (5mg TID) was found to have significant effect on unstimulated whole salivary flow (pooled mean difference: 0.12 mL/min, 95% CI: 0.08-0.16, p<0.001) and xerostomia VAS scores (MD: -1.84 cm, 95% CI: -2.31 to -1.37 Nevertheless, there were adverse experiences on 42 percent patients, and 12 percent stopped treatment. In the case of prosthodontic management, 10 studies were evaluated on saliva retaining prostheses: the appliances enhanced denture retention, patient comfort, and speaking capacity, patient satisfaction exceeded 87 percent, and adverse effects were few. Nonetheless, there was no significant increase in the rates of salivary flow (MD: 0.03 mL/min, 95% CI: -0.02 to 0.08, p=0.24). The direct comparative studies (n=3) showed that pilocarpine was more effective than prosthetic appliances in providing good symptom relief when patients had residual salivary functioning (MD: 2.1 points on XI scale, p=0.003), and the opposite occurred in patients with complete salivary dysfunction (satisfaction rate: 89% vs 61%, p<0.001). ***Conclusions:*** Residual salivary function and dental condition should be used to individualize management strategy. The pilocarpine treatment is good in patients with functional salivary glands regardless of their side effects but in patients with irreversible dysfunction of the glands, then saliva-retaining prostheses offer better results. Integrated strategies can be ideal in few situations. Both the pharmacological and prosthodontic knowledge should be incorporated into healthcare

systems in managing xerostomia.

Keywords: Xerostomia, Pilocarpine, Saliva reservoir prosthesis, Salivary gland hypofunction, Oral health-related quality of life, Systematic review, Meta-analysis

INTRODUCTION

Xerostomia, the subjective experience of dryness in the mouth, is a common and debilitating phenomenon in the whole adult population (10-46% in the general population)3, and is much more common in the elderly (as high as 43.6% in primary care)3 and in patients who receive radiotherapy of the head and neck (up to 80% at 12 months follow-up)2. The condition has a significant effect on oral health, nutrition, and quality of life by causing effects such as high caries in the mouth, oral infections (especially candidiasis), dysphagia, dysgeusia, and poor denture retention in edentulous patients[15].

The causation of xerostomia is multifaceted which includes medication-induced hyposalivation (of above 500 medications implicated[68,69,70]), autoimmune disorders (mainly Sjoerren syndrome impacting 0.5-5% of the population[56,57]), radiation damage of the salivary glands[2,54.55,] systemic disorders (diabetes mellitus, HIV/AIDS)[58.59], age-related physiological changes[61,62,6] The existing management paradigms are divided into two main therapeutic strategies: pharmacological intervention based on stimulation of residual functioning of salivary glands and prosthodontic strategies which are aimed at mechanically holding and distributing artificial salivary replacements all over the mouth[50,51,52.]

The gold standard pharmacological intervention of xerostomia[5,22] is pilocarpine hydrochloride, a non-selective muscarinic acetylcholine receptor agonist with a higher affinity of M3 receptors in salivary gland epithelium[5,22]. Pilocarpine has been approved by FDA to treat radiation-induced xerostomia and Sjogren syndrome-related dry mouth and acts directly at the exocrine glands by directly stimulating glandular secretions[16,17,22.] The standard treatment program is 5mg per orally thrice a day, and the dosage is increased to 10mg per orally thrice a day in non-responders[5,16,17].

Although various randomized controlled trials have shown the effectiveness of pilocarpine to enhance rate of salivary flow and decrease the subjective xerostomia symptomatology[5,16,17,25,] its clinical potential is negated by severe cholinergic xerostomia. They are excessive sweating (reported in 29-68% of the patients), nausea (13-17%), rhinitis (7-14%), and urinary frequency (9-12)[5,16,17]. Discontinuation in clinical trials is found to be 6-29%[5,16,17,25,22] and cardiovascular contraindications continue to decrease its utility in the elderly with comorbidities.

The image has recently changed with topical preparation of pilo-carbamines (mouthwashes, mucoadhesive tablets, lozenges) to limit systemic absorption and adverse effects as local therapeutic effects are maintained[7,9,10,20,27]. Initial results indicate similar local efficacy and better tolerability profiles[9,10,20,] but there is less long-term comparative effectiveness data[7].

Prosthetic appliances which hold saliva: This is a mechanical means of managing xerostomia, which is useful in patients who have dentures which need denture rehabilitation[11,12,13,14,88,90,91]. They have intraoral reservoirs (which are usually in the palatal region of maxillary dentures or lingual flanges of mandibular prostheses) that are designed to deliver artificial saliva substitutes into the oral cavity by pressure-activated or gravity-driven systems[11,12,13,14.]

Compared to the mandibular designs, palatal reservoir designs are chosen because of their higher capacity potential (usually 5-8mL), lesser food debris retention and better distribution patterns to cover the entire oral mucosa[11,13,14]. Contemporary reservoir systems make use of different release mechanisms such as: (1) elastic diaphragm systems whose release is controlled by pressure; (2) multiple-outlet systems with orifice sizes adjusted through calibration; (3) simple access to reservoirs by split-denture systems; and (4) two-piece systems with precision attachments which enable easy access to the reservoirs in cleaning as well as refilling[12,13,14.]

The types of clinical outcomes reportedly obtained with reservoir prostheses are a decrease in mucosal soreness and ulceration, better speech articulation, and the continued lubrication of oral tissue (usually 2-4 hours per reservoir fill)[11,13,14,88,90,91]. Acceptance of patients differs significantly, dependent on aspects such as palatal vault anatomy, initial thickness tolerance, manual dexterity of reservoir maintenance and compliance of twice-daily refilling protocols[13,14.]

Knowledge Gaps and Clinical Equipoise.

Although there is much written on the modalities of

individual management[5,23,48,49], it is evident that no systematic synthesis has ever compared pharmacological and prosthodontic modalities. This poses a clinical uncertainty in the choice of an optimal treatment especially to those patients who may be eligible under either option. The principle questions which are still unresolved are:

1. Comparative effectiveness: Which modality is better in symptom relief in the various etiologies of xerostomia?
2. Patient-centered outcomes: What are the differences in quality of life improvements within interventions?
3. Safety profiles: Which are the risk-benefit ratio of each method in different patient groups?
4. Clinical choice: Which patient and disease factors are to be used in selecting treatment?
5. Potential to combine therapy: Can the combination therapy be optimal in selected patients?

Additionally, healthcare systems with resource-constrained resources (which is especially true of the situation in the Pakistani setting and other low- to middle-income nations) need some evidence-based information on the costs-efficiency and implementation possibilities of various management approaches.

Study Objectives

This meta-analysis and systematic review is intended to:

6. In depth review evidence on clinical efficacy (reduction in xerostomia symptoms, increase in salivary flow) of pilocarpine treatment compared to saliva-retaining prosthetic appliances.
7. Compare patient-reported outcomes and oral health related impacts of quality of life between management methods.
8. Compare safety profiles, adverse event rates, and discontinuation rates in interventions.
9. Determine the best treatment choices depending on the characteristics of the patient, etiology of xerostomia, and the condition of the teeth.
10. Determine practicability and generalizability of results to resource-limited health care environments.

By answering these goals, we hope to leave evidence-based advice to clinicians to deal with xerostomia, and eventually enhance patient outcome by informed and personalized treatment choice.

MATERIAL AND METHODS

The study was a systematic review and a meta-analysis that was done in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses, version [20,20,96.] The review is based on Cochrane Handbook methodological standards of intervention review.

Eligibility Criteria

We included randomized controlled trials (RCTs), quasi-randomized trials, controlled before-after studies, cohort studies (prospective and retrospective), and cross-sectional studies with appropriate comparison groups. Case reports, case series without control groups, narrative reviews, editorials, and conference abstracts without full-text availability were excluded.

Population

Studies were eligible if they enrolled adult participants (age ≥18 years) with clinically diagnosed xerostomia, defined as either: (1) subjective complaint of oral dryness confirmed by validated questionnaires (Xerostomia Inventory [XI], Clinical Oral Dryness Score [CODS], or similar validated instruments), or (2) objective hyposalivation documented by sialometry (unstimulated whole salivary flow rate <0.1 mL/min or stimulated flow <0.7 mL/min). Studies including participants with xerostomia of any etiology were eligible, including medication-induced, radiation-induced, Sjögren's syndrome-associated, or idiopathic presentations. Studies focusing exclusively on pediatric populations or patients with acute, reversible causes of dry mouth were excluded.

Interventions

Pharmacological interventions: Studies evaluating pilocarpine hydrochloride in any formulation (systemic tablets/capsules at standard doses 5-10mg TID, or topical preparations including mouthwashes, mucoadhesive tablets, lozenges, or sprays) administered for minimum 2 weeks. Studies on other parasympathomimetic agents (e.g., cevimeline, bethanechol) were documented but analyzed separately.

Prosthodontic interventions: Studies evaluating saliva-retaining prosthetic appliances including: complete dentures with integrated palatal reservoirs, mandibular dentures with lingual flange reservoirs, partial dentures with reservoir components, and two-piece/split denture systems designed for saliva substitute delivery. Minimum intervention period of 4 weeks was required for inclusion.

Comparators

Eligible comparators included: (1) direct head-to-head comparisons between pilocarpine and prosthodontic appliances, (2) placebo-controlled or no-treatment control groups for pharmacological studies, (3) conventional dentures without reservoirs for prosthodontic studies, or (4) artificial saliva delivered via standard methods (e.g., sprays, gels) without reservoir systems. Studies comparing different pilocarpine dosing regimens or different reservoir designs were analyzed in subgroup analyses.

Outcomes

Primary outcomes:

1. Xerostomia severity: measured using validated visual analog scales (VAS, 0-10 cm), Xerostomia Inventory (XI, 11-55 scale), or Clinical Oral Dryness Score (CODS, 0-10 scale) at minimum 4-week follow-up
2. Salivary flow rates: unstimulated whole salivary flow rate (UWS, mL/min) and stimulated whole salivary flow rate (SWS, mL/min) measured by standardized sialometry
3. Oral health-related quality of life: measured by validated instruments (OHIP-14, GOHAI, or condition-specific QoL questionnaires)

Secondary outcomes:

4. Adverse events: frequency, severity, and type of treatment-related complications
5. Treatment discontinuation rates and reasons for withdrawal
6. Patient satisfaction: measured by validated satisfaction scales or global assessment questionnaires
7. Functional outcomes: chewing ability, swallowing function, speech quality assessed by standardized instruments
8. Denture retention and stability (prosthodontic studies only)
9. Oral mucosal health: incidence of ulceration, candidiasis, or other oral complications
10. Cost-effectiveness metrics when reported

Information Sources and Search Strategy

Electronic Database Searches

Comprehensive electronic searches were conducted in the following databases from inception to November 28, 2025:

- MEDLINE (via PubMed, 1946-present)
- EMBASE (1947-present)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- Web of Science Core Collection
- Scopus
- LILACS (Latin American and Caribbean Health Sciences Literature)
- SciELO (Scientific Electronic Library Online)

The search strategy was developed iteratively by the research team in consultation with a medical librarian experienced in systematic review methodology. Medical Subject Headings (MeSH) terms and text words were combined using Boolean operators (AND, OR) to capture four concept domains: (1) xerostomia and related conditions, (2) pilocarpine and parasympathomimetic agents, (3) prosthetic appliances and denture-related terms, and (4) clinical outcomes and quality of life measures.

Sample PubMed search strategy:

(xerostomia[MeSH] OR "dry mouth"[tiab] OR hyposalivation[tiab] OR "salivary gland hypofunction"[tiab]) AND (pilocarpine[MeSH] OR pilocarpine[tiab] OR salagen[tiab] OR "cholinergic agonist"[tiab] OR parasympathomimetic*[tiab] OR "denture*"[tiab] OR "complete denture*"[MeSH] OR "dental prosthes*"[tiab] OR "saliva reservoir"[tiab] OR "palatal reservoir"[tiab] OR "denture retention"[tiab]) AND ("quality of life"[MeSH] OR "treatment outcome"[MeSH] OR "patient satisfaction"[MeSH] OR effectiveness[tiab] OR efficacy[tiab])*

No language, date, or publication status restrictions were applied during the search phase. The complete search strategies for all databases are provided in Appendix A (Supplementary Material).

Study Selection Process

All databases were searched and the results were imported to EndNote X9 (Clarivate Analytics) to remove duplicates and then transferred to Covidence systematic review management software (Veritas Health Innovation) to be screened. Titles and abstracts were screened by two reviewers (1ST and 2nd Authors) against pre-specified eligibility criteria with any disagreements being resolved by discussion or referral to the third reviewer (3rd Author). Potentially eligible studies were moved to a full-text review.

The same two reviewers were used to evaluate full-text articles based on a standardized eligibility assessment form. The reasons why people were excluded on full-text stage were recorded. Cohen was used to determine inter-rater agreement during both screening stages on the basis of kappa coefficient. The conflicts at full-text level were solved by discussing them in a team until an agreement was reached.

Data Management and collection

A pilot-tested data extraction form in Microsoft Excel was created. Data were extracted by two reviewers (4th and 5th Authors) of included studies with discrepancies settled after discussion with a third reviewer (6th Authors). In the case of studies that had inadequate detail, the respective authors were contacted through email (up to 3 contact attempts in 4 weeks) with a request to provide further details.

The data elements that were extracted were:

- Characteristics of the study: First author, year of publication, country of study, study design, setting (hospital, clinic, university), source of funding, conflict of interests.
- Participant characteristics: sample size, age (mean SD), gender, etiology of xerostomia, dental condition (dentate/partially edentulous/edentulous), baseline salivary flow rates, baseline xerostomia severity, comorbid conditions, concomitant drugs.
- Intervention: pilocarpine formulation (systemic vs. topical), dose schedule,

duration of therapy, methods of compliance, prosthetic appliance design (maxillary/mandibular, reservoir volume, release mechanism), artificial saliva formulation, fabrication method, guidelines on maintenance;

- Intervention: pilocarpine formulation (systemic vs. topical dosage), schedule, duration of treatment, compliance, artificial saliva formulation, fabrication procedure, maintenance procedures; design of prosthetic appliances (maxillary/mandibular), reserv
- Comparator: composition of control group, interventions administered to the controls.
- Outcome data: baseline and all follow up time period mean values and standard deviations (or medians and interquartile ranges) of continuous outcomes; the number of events and participants of dichotomous outcomes; description of measurement tools and timing of assessment.
- Statistical information: effect sizes, confidence intervals, p-values, statistical tests used.
- Loss to follow-up: attrition rates, withdrawal causes, intention-to-treat as compared to per-protocol analysis.
-

For studies with multiple follow-up assessments, we extracted data from time points closest to 4 weeks (short-term), 12 weeks (medium-term), and 24+ weeks (long-term) for sensitivity analyses examining temporal effects.

Risk of Bias Assessment

Risk of bias was independently assessed by two reviewers (1st and 6th Authors) using appropriate tools based on study design:

- Randomized controlled trials: Cochrane Risk of Bias tool version 2 (RoB 2), evaluating bias arising from randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting
- Non-randomized studies: ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions), assessing confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting

Each domain was judged as low risk, some concerns, or high risk of bias. Overall study-level risk of bias was determined according to tool-specific algorithms. Disagreements between reviewers were resolved through discussion or adjudication by a third reviewer (3rd Authors).

Results

Study Selection

The systematic search identified 3,847 unique records after duplicate removal. Title and abstract screening excluded 3,654 records (inter-rater agreement κ=0.89). Full-text assessment of 193 articles resulted in the inclusion of 28 studies meeting eligibility criteria (Figure 1, PRISMA flow diagram). Primary reasons for exclusion were: inappropriate comparison groups (n=87), short follow-up duration <2 weeks (n=34), case series/reports without controls (n=26), review articles (n=18), and studies on pediatric populations (n=8).

Study Characteristics

The 28 included studies enrolled 2,156 participants (range: 18-207 per study) across 15 countries. Publication years ranged from 1984 to 2025, with 64% published after 2015. Eighteen studies (n=1,387 participants) evaluated pharmacological interventions: 15 focused on systemic pilocarpine tablets, 3 on topical pilocarpine formulations. Ten studies (n=769 participants) assessed prosthodontic interventions with saliva-retaining appliances. Three studies directly compared pharmacological and prosthodontic approaches head-to-head (n=294 participants).

Participant Characteristics

Mean participant age was 62.4 years (SD 8.7, range 18-89), with 68% female. Xerostomia etiology included: radiation-induced (39%, n=841), Sjögren's syndrome (28%, n=604), medication-induced (21%, n=453), mixed/idiopathic (12%, n=258). Dental status was: fully dentate (18%), partially dentate (27%), completely edentulous (55%). Baseline mean unstimulated whole salivary flow was 0.08 mL/min (SD 0.05), mean stimulated flow 0.34 mL/min (SD 0.21). Mean baseline xerostomia severity was VAS 6.8/10 (SD 1.4) and XI score 32.6/55 (SD 8.2).

Intervention Characteristics

Pharmacological studies: Systemic pilocarpine was administered at 5mg TID (n=12 studies), 10mg TID (n=2), or dose-titration protocols 2.5-10mg TID (n=3). Mean treatment duration was 11.3 weeks (range 4-52). Topical pilocarpine studies used mouthwash formulations (0.1-2% concentration, 5mL for 1 minute, 3-4 times daily) for mean 8.2 weeks duration.

Prosthodontic studies: All reservoir prostheses incorporated palatal reservoirs (no mandibular-only designs met inclusion criteria). Mean reservoir capacity was 6.2mL (range 4-10mL). Release mechanisms included: elastic diaphragm (n=4), gravity-driven outlets (n=3), split-denture systems (n=2), precision attachment two-piece (n=1). Artificial saliva substitutes used were carboxymethylcellulose-based (n=7), mucin-based

(n=2), or mixed polymer formulations (n=1). Participants refilled reservoirs median 2 times daily. Mean follow-up duration was 16.8 weeks (range 4-104).

Risk of Bias Assessment

Among 11 RCTs evaluating pharmacological interventions: 4 demonstrated low overall risk of bias, 5 had some concerns (primarily inadequate allocation concealment or selective outcome reporting), and 2 were at high risk (lack of blinding for subjective outcomes, >20% attrition). Among 7 RCTs assessing prosthodontic interventions: 2 showed low risk, 4 some concerns, 1 high risk. Non-randomized studies (n=10, all cohort designs) showed moderate to serious risk of bias using ROBINS-I, primarily due to confounding and participant selection issues. Publication bias assessment via funnel plot asymmetry and Egger's test suggested possible small-study effects for pilocarpine efficacy outcomes (p=0.04), though trim-and-fill analysis indicated minimal impact on pooled estimates.

Synthesis of Results

Primary Outcome: Xerostomia Severity

Pilocarpine versus placebo/control: Meta-analysis of 15 studies (n=1,203 participants) revealed systemic pilocarpine significantly reduced xerostomia VAS scores compared to placebo at 4-12 weeks follow-up (MD: -1.84 cm on 10cm scale, 95% CI: -2.31 to -1.37, p<0.001, I^2=58%). This represents a clinically meaningful improvement exceeding the minimal important difference of 1.5cm. Sensitivity analysis excluding high risk of bias studies strengthened effect size (MD: -2.12 cm, 95% CI: -2.68 to -1.56, p<0.001, I^2=42%). Subgroup analyses demonstrated greater efficacy in radiation-induced xerostomia (MD: -2.23 cm) versus Sjögren's syndrome (MD: -1.47 cm, p for interaction=0.02). XI scores showed similar improvements (MD: -8.4 points, 95% CI: -10.2 to -6.6, p<0.001, I^2=47%).

Studies of topical pilocarpine mouthwash (n=3, 186 subjects) showed a small xerostomia effect (VAS MD: -0.88 cm, 95% CI: -2.72 to 0.95, p=0.34, I 2 =76%), with large heterogeneity and no significant statistically significant pooled effect, although each patient study showed significant benefits in 47-62%.

Reservoir prostheses versus conventional dentures: Seven articles (n=418 participants) were comparing reservoir-equipped versus standard complete dentures. The meta-analysis indicated that xerostomia symptoms were significantly reduced in support of reservoir prostheses (VAS MD: -1.62 cm, 95% CI: -2.14 to -1.10, p<0.001, I 2=34%). Patient-reported comfort and satisfaction were constantly in support of reservoir designs in all researches. Patients receiving reservoir prostheses had a better improvement in Clinical Oral Dryness Scores (MD: -2.3, 95% CI: -3.1 to -1.5, p<0.001, I 2=28%).

Direct comparison studies: Three studies that directly compared pilocarpine to reservoir prostheses (n=294) found that they are context-dependent as better. Pilocarpine was more effective in reducing the symptoms in dentate/partially dentate subjects who retained salivary functionality (UWS >0.05 mL/min) (XI score difference: 2.1 points, 95% CI: 0.8-3.4, p=0.003). On the other hand in edentulous participants who experienced severe hyposalivation (UWS <0.05 mL/min), reservoir prosthesis proved to be more successful (patient satisfaction: 89 vs 61, p=0.001; VAS improvement: -2.4 vs -1.3 cm, p=0.008).

Primary Outcome: Salivary Flow Rates

Unstimulated whole salivary flow (UWS): Systemic pilocarpine significantly increased UWS versus placebo in 13 studies (n=967 participants): pooled MD 0.12 mL/min (95% CI: 0.08-0.16, p<0.001, I^2=52%). Effect was dose-dependent: 5mg TID yielded MD 0.10 mL/min (95% CI: 0.06-0.14), while 10mg TID produced MD 0.15 mL/min (95% CI: 0.09-0.21). Effects persisted at 12-week assessment (MD: 0.11 mL/min, 95% CI: 0.07-0.15) but diminished by 24 weeks in studies with long-term follow-up (MD: 0.06 mL/min, 95% CI: -0.01 to 0.13, p=0.08, n=4 studies).

Reservoir prostheses did not significantly alter salivary flow rates (UWS MD: 0.03 mL/min, 95% CI: -0.02 to 0.08, p=0.24, I^2=12%, n=6 studies), confirming their mechanism operates through saliva substitute retention rather than glandular stimulation.

Stimulated whole salivary flow (SWS): Pilocarpine increased SWS modestly (MD: 0.28 mL/min, 95% CI: 0.17-0.39, p<0.001, I^2=61%, n=11 studies). However, baseline SWS >0.5 mL/min predicted better response (MD: 0.41 mL/min) compared to severe baseline hyposalivation (MD: 0.14 mL/min, p for interaction=0.01).

Primary Outcome: Oral Health-Related Quality of Life

Ten studies (n=734 participants) reported OHRQoL outcomes using validated instruments (OHIP-14, GOHAI, or condition-specific questionnaires). Both interventions demonstrated significant QoL improvements from baseline, though with different patterns:

Pilocarpine: OHIP-14 scores (lower=better) decreased significantly (MD: -6.8 points, 95% CI: -8.4 to -5.2, p<0.001, I^2=43%, n=6 studies). Improvements were most pronounced in functional limitation and physical pain domains. However, psychosocial impact and social disability domains showed minimal change.

Reservoir prostheses: OHIP-14 improvement (MD: -5.2 points, 95% CI: -7.1 to -3.3, p<0.001, I^2=31%, n=4 studies) with particular benefits in functional domains directly related to denture function (chewing, speaking) and psychosocial impact of edentulism. Patient satisfaction with prostheses was consistently high (pooled rate: 87%, 95% CI: 81-92%).

GOHAI scores improved with both interventions: pilocarpine MD +4.6 points (95% CI: 3.1-6.1, p<0.001, I^2=38%); reservoir prostheses MD +5.8 points (95% CI: 4.2-7.4, p<0.001, I^2=24%). The difference between interventions was not statistically significant (p=0.28).

Secondary Outcome: Adverse Events and Safety

Pilocarpine adverse events: Pooled analysis of 16 studies (n=1,289 participants) revealed high adverse event incidence: any cholinergic effect occurred in 42% (95% CI: 36-48%, I^2=65%). Specific events included: excessive sweating 29% (95% CI: 24-34%), nausea 13% (95% CI: 10-17%), rhinitis 9% (95% CI: 6-13%), urinary frequency 8% (95% CI: 5-12%), diarrhea 7% (95% CI: 4-10%), headache 11% (95% CI: 7-15%). Most events were mild to moderate severity. Treatment discontinuation occurred in 12% (95% CI: 9-16%, I^2=47%), primarily due to sweating or gastrointestinal symptoms. Serious adverse events (cardiovascular events, bronchospasm) occurred in <1% but necessitated permanent discontinuation.

Prosthetic adverse events: Eight studies (n=612 participants) reported complications: any device-related problem occurred in 18% (95% CI: 14-23%, I^2=28%). Specific issues included: reservoir clogging requiring maintenance 8% (95% CI: 5-12%), initial gagging/discomfort with increased thickness 12% (95% CI: 8-17%, resolved with adaptation in 75% within 2 weeks), minor mucosal irritation 6% (95% CI: 3-10%), difficulty with refilling mechanism (elderly patients with dexterity limitations) 4% (95% CI: 2-7%). Prosthesis fracture or structural failure occurred in 2% (95% CI: 0.5-4%). Treatment discontinuation was rare (3%, 95% CI: 1-6%), primarily due to inability to adapt to increased palatal thickness. No serious adverse events were reported. Candidiasis incidence was lower with metal-based reservoir components versus acrylic (4% vs 11%, p=0.04).

Secondary Outcomes: Functional Parameters

Denture retention and stability: There were five studies that evaluated the retention of dentures in xerostomic patients. Reservoir prostheses were also found to have much better retention than standard dentures (retention force gain: mean 0.8N, 95% CI: 0.5-1.1, p<0.001). The reservoir designs were also better in patient-reported denture stability (VAS improvement: 3.2 cm, 95% CI: 2.4-4.0, p<0.001). Pilocarpine trials on denture-wearing patients revealed significant reductions in retention in participants with residual flow response (mean 0.3N increase, 95% CI: 0.1-0.5, p=0.03).

Masticatory: Chewing: The ability to chew is measured using masticatory performance tests or validated questionnaires with both interventions showing improvement. With pilocarpine (95% CI: 18-30%, p<0.001, n=4 studies), color-changeable chewing gum tests improved 24% and with reservoir prostheses (95% CI: 24-38%, p<0.001, n=3 studies), they improved 31%. Pilocarpine and reservoir prostheses grew in self-reported chewing ability (VAS 0-10) by mean 2.1 and 2.8, respectively (P 95% CI 1.5-2.7 and 2.1-3.5).

Speech function: Speech intelligibility tests (n=4 studies) demonstrated better speech intelligibility with reservoir prostheses (means phoneme recognition improvement: 12, 95% CI: 7-17, p=0.001) and pilocarpine (means phoneme recognition improvement: 8, 95% CI: 412, p=0.002). But, early adaptation period of speech with reservoir prostheses (mean 2.3 weeks) was necessitated by palatal contours.

Oral mucosal health: Oral mucosal lesions (ulcerations, denture trauma) were less common during the reservoir prosthesis than the conventional denture in xerostomic patients (17% vs 34% at 12 weeks, RR: 0.50, 95% CI: 0.33-0.75, p=0.001). Pilocarpine trials demonstrated a lower incidence of candida than the placebo (9% and 18%, respectively, RR= 0.51, 95% CI=0.31-0.84, p=0.008).

Subgroup and Sensitivity Analyses.

Heterogeneity sources were investigated in pre-specified subgroup analysis:

By xerostomia etiology: Pilocarpine was most effective in the radiation-induced xerostomia (VAS MD: -2.23 cm) than in the medication induced (MD: -1.72 cm, p=0.04) or Sj ogren syndrome (MD: -1.47 cm, p=0.02). Prostheses Reservoir prostheses demonstrated uniform advantage in all etiologies (p interaction=0.68).

By the salivary function at the baseline: Pilocarpine response was significantly correlated with residual flow (baseline UWS >0.05 mL/min: VAS improvement -2.41 cm vs UWS <0.05 mL/min: improvement -0.89 cm, p<0.001). Reservoir prostheses were found to have a steady advantage over different baseline flow.

By the condition of the denture status: among edentulous subjects, the reservoir prostheses were superior (VAS improvement: -2.41 cm vs pilocarpine: -1.34 cm, p=0.003). Pilocarpine was superior in

dentate/partially dentate (-2.12 cm vs prosthetic methods: -1.21 cm, p=0.01).

By age: Among older participants (70 years and above), the discontinuation rates of pilocarpine were higher (18% vs 8% in younger patients, p=0.02) but the effectiveness in completers was the same. The prostheses that incorporated reservoirs demonstrated results that did not depend on the age of the user but those that were aged with dexterity issues needed to have simplified refilling systems.

Follow-up: There were no differences in interventions in terms of short term benefits (4-8 weeks). At medium-term follow-up (12-24 weeks), pilocarpine was a better option than reservoir based on symptom relief but not functional outcome and satisfaction. The long-term results (more than 24 weeks, 6 studies) revealed a long-term benefit of the use of reservoir prostheses and a decline in the effects of pilocarpine in the absence of dose changes.

Primary outcome conclusions were not significantly different in sensitivity analyses that omitted high risk of bias studies (n=3). Outlier studies (detected through standardized residuals of more than 2.5) decreased heterogeneity of pilocarpine VAS results (I 2 shrinkage of 58 per cent to 34 per cent), with no alteration in direction or statistical significance.

Evidence Quality Assessment (GRADE)

Certainty of evidence was measured with the help of GRADE methodology:

- Reduction of xerostomia using pilocarpine: MODERATE certainty (downgraded because of inconsistencies in baseline characteristics and timing of measurement)
- Pilocarpine safety profile: HIGH level of certainty (unanimity in multiple high-quality randomized clinical trials)

Concerns: Efficacy of reservoir prosthesis MODERATE (downgraded due to study design limitations of non-randomized studies, but RCT data concordant)

Moderate certainty (highly stable adverse events rates, however with little long-term follow-up): reservoir prostheses safety.

- Direct comparative effectiveness: LOW certainty (limited number of direct comparison studies, limited sample sizes, limited time to follow-up studies)

The comparatively weak assurance of direct comparisons evidences the necessity of the well-conceptualized head-to-head trials to reinforce evidence-based treatment choice advice.

Discussion

This is a rigorous systematic review and meta-analysis of 28 research studies with 2,156 participants, which presents the first to compare the effects of pharmacological (pilocarpine) against prosthodontic (saliva-retaining appliances) management of xerostomia. As we have shown, the two methods have considerable clinical advantages, but the choice of treatment strictly relies on the features of a patient, especially the salivary gland functions that remain and the condition of teeth.

Among the major findings are: (1) Systemic pilocarpine has moderate-certainty efficacy in improving symptoms and stimulating salivary secretions in patients with residual gland activity5,16,17,7 with substantial cholinergic adverse effects in 42% patients, and discontinuation of 12%. (2) Saliva-retaining prosthetic appliances have acceptable symptomatic good results with minimal complications (18% minor, 3% discontinuation)[11,13,14] yet demand edentulous status and manual dexterity in maintenance of the reservoirs. (3) There are context-dependent superiority hints in direct comparative data, which are limited (15), which indicate pilocarpine in dentate patients with quantifiable salivary flow (>0.05 mL/min) and reservoir prostheses in edentulous patients with severe hyposalivation79. (4) The two interventions are effective in improving oral health-related quality of life[80,81,83], and the different patterns within their responses provide evidence of the mechanism, wherein pilocarpine enhances fluid production, and prostheses improves mechanical functionality and retention.

We have evidence to suggest an individualised, stratified management of xerostomia depending on patient phenotype[50,51,52]:

Pilocarpine as first-line treatment of:

Patients with residual salivary function (UWS >0.05 mL/min) who are dentate or partially dentate[6576]; Patients who are post radiation within 24 months (remaining gland recovery potential)[5455]; Patients who need rapid alleviation of symptoms (responses occurring within days to weeks)[16,17].

Reservoir prostheses as preferential treatment of:

It is necessary when patients are completely edentulous, when they are requiring denture rehabilitation[79]; When patients have severe and irreversible hyposalivation (UWS <0.05 mL/min) irrespective of the etiology[76]; When patients have unacceptable adverse effects with pilocarpine or computerized contraindications[22]; When patients are elderly and have multiple comorbidities limiting pharmacological choice[95]; When patients have long-term mechanical function goals and long-term relief[11,13,14].

This stratification aligns with emerging personalized medicine principles[52], moving beyond one-size-fits-all approaches toward precision targeting based on pathophysiology and patient preferences. Importantly, baseline salivary flow measurement—

readily performed via simple sialometry[65]—emerges as a critical biomarker guiding treatment selection.

Integration with Existing Management Paradigms

Our results are complementary and not contradictory of the current xerostomia management recommendation[50,51,52,93,94,] that focus on multimodal interventions. Our pedagogical approach to a stepped-care model is:

Step 1: Generally preventive interventions (review and optimization of medicines95, prevention against dehydrating substances, fluoride prophylaxis94, frequent sips of water).

Step 2: Mild cases (sugar-free gum[33,34,35,36,37,38,] sialagogue lozenges) are to be stimulated mechanically with saliva.

Step 3: Phenotype-based intervention (pilocarpine with residual function, reservoir on severe cases with edentulous)

Step 4: Refractory cases Refractory cases Combined therapy or other options (topical pilocarpine formulations[7,9,10,20], emerging regenerative therapies)

Three of these studies (with combined pilocarpine and reservoir prostheses) also demonstrated beneficial effects (added) in the chosen patients (edentulous with partial residual function), although the sample size was small (n=47 overall). This should be investigated further because it may be possible to maximize results on an intermediate phenotype.

Resource-Constrained Setting Implications.

In terms of health systems (which would be especially true in low- to middle-income nations such as Pakistan), there are a number of considerations:

Pilocarpine: The cost of medication is relatively cheap (generic pilocarpine 15-25 per month in Pakistan), but systematic prescription needs the following: (1) physician willing to prescribe and follow-up use of cholinergic agents, (2) patient education about coping with side effects and adherence, (3) follow-up to optimize dosage, (4) discontinuation management. These requirements can also be a limiting factor in scaled healthcare systems that are fragmented.

Reservoir prostheses: The initial cost of fabrication is more (about 200-400 in the Pakistani private sector), including need of prosthodontic knowledge and laboratory facilities. The benefit, however, is longer-lasting (one-time investment with maintenance which lasts 5-7 years) and there is no need to spend money on drugs every day. Such critical barriers as: (1) the lack of capacity in terms of workforce (prosthodontists) (estimated in 1 prosthodontist per 500,000 population in Pakistan vs 1 per 50,000 in high-income countries), (2) patient out-of-pocket expenditure in a system with limited denture coverage, (3) the necessity of access to artificial saliva substitutes to perform refills, [46,47,48] are identified.

Pragmatically, resource-constrained systems may focus on: (1) educating general dentists in simplified methods of fabricating reservoirs13, (2) devising low-cost artificial saliva formulas with domestically available polymers (caroxymethylcellulose-based)[46,47], (3) creating cost-sharing programs of fabricating dentures, (4) holding back pilocarpine to a few cases in which prosthodontic solutions are not possible or adequate.

Correlation with Existing Literature.

Past systematic reviews have been conducted on the management of pharmacological and prosthodontic xerostomia separately but have not been directly synthesized comparatively. Our results are consistent with and go beyond previous literature:

Cheng et al. (2015)5 meta-analyzed pilocarpine effectiveness in 752 head and neck cancer patients but found no difference in effect sizes between xerostomia reduction (VAS MD: -1.76 cm vs our -1.84 cm), but more discontinuation rates (15% vs our 12%) as they targeted a population more likely to have high baseline symptom burden, i.e. post-radiation. They did not analyze topical pilocarpine formulations nor they discussed comparative effectiveness in their analysis.

In a Cochrane review, Riley et al. (2017)[23] concluded that pharmacological interventions (pilocarpine, cevimeline) have moderate quality evidence of the xerostomia improvement but the authors note that there is little evidence on how to select patients. This is furthered in our work where baseline salivary flow is identified as one of the predictive biomarkers.

Case series and small cohort studies have been the only literature on prosthodontics[11,12,13,14,88,90,91]. Jensen et al. (2010)[2] offer a comprehensive overview of radiation-induced xerostomia management, but synthesized the information only in a narrative manner without quantitative pooling of the prosthodontic strategies. The meta-analysis of 10 prosthodontics studies we did is the first synthesis of evidence that shows a substantial and clinically meaningful impact.

Our study is the first review to compare pharmacological and prosthodontic methods directly a gap in the literature that has been filled by both indirect comparison meta-analysis and the inclusion of three direct comparison trials. Such a comparative framework is fundamental to clinical decision-making that is based on evidence.

Strengths and Limitations

Our systematic review has the following strengths: (1) Search strategy was extensive and covered 8 major databases with no language limitations, which reduced publication bias. (2) Strict methodology based on PRISMA 2020[96] and Cochrane requirements including prospective protocol registration. (3) Both

RCT and observational data, trade-offs in internal validity and real-world applicability. (4) First quantitative synthesis of comparison of management paradigm. (5) Open disclosures of sources of heterogeneity in large subgroups used to select the treatment. (6) GRADE evidence quality judgement99 giving transparency of certainty of conclusions.

Nevertheless, there are a number of limitations that should be mentioned:

Evidence limitations Evidence is mostly indirect, with the majority of research being head-to-head comparisons of two interventions, and most having similar populations and measure of outcomes (similar populations, comparable outcome measurement). Pooling was difficult because of heterogeneity in the baseline characteristics, protocols of intervention and outcome measures[64]. The information on long-term follow-up (>24 weeks) was limited, and it was not possible to draw conclusions regarding the long-term effectiveness. The majority of prosthodontic research has assessed narrow designs of reservoirs; it is not clear how the same design can be broadened to other designs.

Limitations of the methodology: In non-randomized prosthodontic studies, risk of bias was high (inherent confounding, selection bias)98. The assessment of publication bias indicated that there is a potential of small-study effects of pilocarpine results, but the trim-and-fill analysis revealed that the effect is minimal. Reservoir studies could not be evaluated on reporting bias because of lack of enough number of studies. Multiplicity of comparisons and post-hoc character of some of them should be taken cautiously as subgroup analysis.

Outcome limitations: Long-term quality of life, cost-effectiveness and treatment burden were patient-important outcomes, which were inconsistently reported. None of the studies compared the feasibility of implementation in resource-constrained conditions. The reporting of adverse events was inconsistent and may not have accurately reflected the complications of prosthodontic work (i.e. maintenance needs, long-term reservoir failures). Functional outcomes (mastication, speech) applied a variety of measurement methods restricting meta-analysis[71,78].

Applicability constraints: Research articles were mainly carried out in high-income health care environments (64% North America/Western Europe); it is not clear how the research can be generalized to low-resource environments with different disease patterns, healthcare systems, and patient expectations. There was an underrepresentation of elderly patients (>80 years) and severe comorbidities848586 and thus a constraint of the conclusions to these vulnerable groups. Subgroups based on etiology were not very large (e.g., 3 studies in diabetes-related xerostomia only)[58].

Future Research Priorities

According to our review, there are a number of important gaps in research that need to be filled:

1. Head-to-head randomized trials: Huge, sufficiently powered RCTs with direct comparison of pilocarpine vs. reservoir prostheses in stratified groups (based on dental status and baseline salivary functioning) with 12-month follow-up or longer. These trials must have a full outcome measure (symptoms, salivary flow, QoL, functional measures, adverse events, costs) and economic analysis.
2. Combination therapy trials: Phase II adequacy of combination pilocarpine and reservoir prostheses in patients with intermediate phenotypes (partial edentulism,moderate residual function) with a hypothesis of synergistic effect between the two glandular stimulation and mechanical retention.
3. Predictive biomarker validation: Prospective trials that validate baseline salivary flow as a treatment-selection biomarker6576, determine optimum levels through which patients are guided to either a pharmacological or a prosthodontic treatment option. Personalization may be narrowed down by including more predictors (salivary composition, gland imaging, genetic markers).
4. Optimization of prosthodontic designs: Comparative effectiveness studies of reservoir designs (palatal vs. mandibular, single- vs. dual-reservoir, different release mechanisms)[11,12,13,14], artificial saliva-formulations (polymer types, additive compositions)[46,47], and maintenance strategies. Standardization and testing of standard quality measures on reservoir prostheses.
5. Topical pilocarpine development: Additional work on topical preparations (mouthwashes, mucoadhesible tablets, sublingual sprays)[7,9,10,20,43,44] as a middle-ground with pilocarpine efficacy with decreased systemic exposure. Pharmacokinetics of local versus systemic absorption systems of various formulations.
6. Implementation research Pragmatic trials at a variety of healthcare facilities (including low-resource environments) assessing the real-world effectiveness, cost-efficiency, and barriers/facilitators to implementation. Shared decision-making can be promoted by development of clinical decision support tools and patient decision aids.
7. Long-term outcomes: Sustained benefit, pattern of treatment adherence, late adverse events, and time-related requirement to change or upgrade their interventions are evaluated in long-term follow-ups (>2 years).
8. Special populations: Special studies in under-represented groups such as very elderly (>80 years)[84,85,86,] severe comorbidity patients and specific etiology (diabetes58, autoimmune conditions beyond Sjogren57), and heterogeneous socioeconomic

backgrounds.

9. New treatment: Comparative effectiveness studies involving the addition of new treatments (regenerative therapies to restore glands, gene therapy, acellular therapies, nerve stimulation devices) into the treatment algorithm with traditional ones.

10. Patient-centered outcome development: Testing xerostomia-specific quality of life instruments 64 that capture domains with greatest patient importance; inclusion of patient preferences and treatment burden measurement in comparative effectiveness analyses.

Conclusions

This meta-analysis and systematic review offers medium-certainty evidence that both pharmacological (pilocarpine) and prosthodontic (saliva-retaining appliances) are of clinical relevance in the management of xerostomia, but the choice of the best treatment option is highly dependent on patient phenotype. However, pilocarpine is better effective in patients whose salivary gland is not completely lost[5,16,17] but has critical cholinergic side effects that hamper adherence22. Salivary-retaining prosthetic devices have been demonstrated as an effective stress reliever with few adverse effects in edentulous patients[11,13,14] only when the dental condition allows denture rehabilitation and the patient abilities of supporting the device.

We suggest the use of an individualized, stratified approach to treatment: pilocarpine as first-line treatment of dentate patients with quantifiable salivary flow (>0.05 mL/min UWS)6576, and reservoir prostheses as the treatment of choice in patients with severe, irreversible hyposalivation[79.] This individualized paradigm goes past the archaic one size fits all models to accuracy targeting based on pathophysiology and patient factors[52.] The pharmacological and the prosthodontic knowledge in the management pathways of xerostomia should be incorporated in healthcare systems as formalizing them as complementary and not competing interventions.

Research wise, head-to-head trials with rigorous outcome evaluation and long-term follow-ups are strongly required to enhance the level of evidence certainty. Combination therapy methods and biomarkers of the selection of treatment should be investigated and validated. In resource-constrained environments (such as Pakistan and other such like scenarios), implementation research assessing the feasibility, cost-effectiveness, and scalability of various management interventions is necessary to help transform evidence into better patient care.

Finally, the best xerostomia management is an individualized grasp of the condition with a combination of preventative approaches[94,95,33,34,35,36,37,38,39,40,41,42,43,44,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,] Through treatment strategy-patient phenotype concord, clinicians are able to benefit the patient with minimal harm and treatment burden, thus enhancing quality of life to the millions of sufferers of this debilitating disorder in the world today1,50,83.

Conflicts of Interest

The authors do not identify any conflict of interest with respect to this work.

Author Contributions

The study was conceived by 1st Author, designed by 1 st Author, and searched by 1st Author, 1 st Author screened studies, 1st Author extracted data, and 1st Author critically revised the manuscript, risk of bias was assessed by 2nd Author and 3rd Author, and critical revising of the manuscript was done by 4th Author and 5th Author. The final manuscript was accepted by all the authors.

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