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Latest Interventions and Clinical Evidence for the Prevention of Salivary Gland Hypofunction (2023–2025): A Comprehensive Review of Photobiomodulation, Electrostimulation, and Cellular/Genetic/Conservative Strategies

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ABSTRACT

This review synthesizes evidence from literature published between 2023 and 2025 regarding interventions to prevent salivary gland hypofunction. Photobiomodulation (PBM) and electrostimulation consistently demonstrated the capacity to reduce salivary gland dysfunction induced by radiation or chemotherapy, improving subjective symptoms and quality of life. Pharmacologic and topical stimulation showed significant short-term secretion enhancement. Cellular and gene therapies suggest potential for fundamental recovery, though long-term safety, cost, and standardization remain challenges. Standardized protocols and large-scale longitudinal studies are warranted.

Keywords: Xerostomia; Salivary gland hypofunction; Photobiomodulation therapy (PBM); Electrostimulation therapy; Gene therapy; Cell therapy

INTRODUCTION

Xerostomia and salivary gland hypofunction arise from diverse causes, including head and neck radiotherapy, chemotherapy, aging, and autoimmune disorders such as Sjögren's syndrome, significantly reducing patient quality of life [1,2]. Saliva plays a crucial role in oral homeostasis, digestion, swallowing, and antimicrobial defense, so hypofunction can affect systemic health [1,3]. Recent studies emphasize preventive and regenerative approaches beyond conventional palliative management (saliva substitutes and pharmacotherapy) [4,5].

Photobiomodulation therapy (PBMT)has been clinically reported to prevent salivary gland damage and maintain salivary flow during radiotherapy [6,7]. PBM enhances mitochondrial activity and suppresses oxidative stress at the cellular level, mitigating tissue damage [7].

Electrostimulation therapyhas been shown to increase natural salivary secretion by stimulating neuro-salivary reflexes [8]. Device-based approaches are noninvasive, have high patient adherence, and are suitable for repeated preventive interventions [8].

Pharmacologic approaches, particularly muscarinic receptor agonists such as pilocarpine and cevimeline, stimulate secretion but are limited by systemic side effects (e.g., sweating, gastrointestinal symptoms) [9]. Combining pharmacologic and nonpharmacologic strategies or customizing treatments per patient may optimize outcomes [9,10]. Gene and cell therapies offer potential for fundamental recovery. AAV2-hAQP1 gene therapy restores water channel protein expression in damaged salivary cells [11,12], and mesenchymal stem cell (MSC) injection or autologous transplantation shows regenerative effects [13].

In summary, a multi-modal approach is required to prevent and treat salivary gland hypofunction, with PBM, electrostimulation, and gene/cell therapy emerging as next-generation strategies [6-13]. Future research priorities include optimizing treatment parameters, evaluating long-term safety, and designing personalized interventions [6,7,10].

METHODS

This rapid systematic review included studies published between January 2023 and August 2025. Database searches were conducted in PubMed/MEDLINE, PMC, Embase, Cochrane Library, Scopus, ClinicalTrials.gov, and relevant journals (e.g., Photobiomodulation, Supportive Care in Cancer, JCI). Search terms included combinations of "salivary gland hypofunction prevention," "xerostomia prevention," "photobiomodulation AND salivary," "electrostimulation AND salivary gland," "AAV-hAQP1," and "mesenchymal stromal cells salivary."

Included study types were RCTs, prospective cohort trials, systematic reviews/meta-analyses, registered clinical trials, and major preclinical/mechanistic studies; case reports and retrospective studies were included only as supplementary evidence.

Inclusion criteria:(1) Human clinical studies (including preventive interventions), (2) reporting salivary gland function (stimulated/unstimulated salivary flow) or subjective xerostomia as primary/secondary outcomes, (3) published in English from 2023–2025 or trial registry entries.

Exclusion criteria:(1) Studies where xerostomia was a secondary outcome from other diseases, (2) studies outside the specified time range, (3) duplicate reports.

Data extracted included study design, participant characteristics (disease, prior therapy, age), intervention parameters (PBM wavelength, energy, mode; electrostimulation current, frequency, session schedule), comparator, follow-up duration, outcomes (unstimulated/stimulated saliva mL/min, xerostomia scales, QoL measures), and safety (adverse events, dropout rate). Nonstandardized parameters were narratively summarized, and RCTs with high homogeneity were evaluated for potential meta-analysis; however, this review primarily focused on qualitative integration of effect size and directionality.

ClinicalTrials.gov and corporate reports (e.g., MeiraGTx) were reviewed for ongoing gene (AAV2-hAQP1) and cell therapy trials to evaluate the current state of regenerative preventive strategies. Study quality was assessed using Cochrane Risk of Bias (RCTs) and ROBINS-I (nonrandomized studies), and evidence strength was discussed according to GRADE. Selected references (n=20) are listed in the reference section.

RESULTS

Photobiomodulation (PBM) – preventive/protective effects

Multiple prospective studies and some RCTs indicate that PBM (red to near-infrared wavelengths) mitigates reductions in salivary flow during and after radiotherapy or chemotherapy, improving subjective xerostomia and QoL. Studies using 810 nm Ga-Al-As lasers reported prevention of abrupt salivary decline, particularly when PBM was applied prophylactically (pre-/mid-treatment). Wavelengths (630–980 nm), energy density (2–8 J/cm²), irradiation site (direct vs external), and session frequency (2–3/week) varied across studies, limiting meta-analysis. Overall, PBM shows long-term protective trends but standardized protocols are needed.

Electrostimulation (transcutaneous/intraoral)-functional preservation

Studies using TENS or small intraoral electrostimulation devices report immediate saliva increase and short-term symptom improvement. Some multicenter prospective trials suggest that concurrent electrostimulation during radiotherapy reduces salivary decline. Evidence for long-term (≥12 months) maintenance and optimal parameters remains limited. Current, frequency, and session schedules vary widely.

Pharmacologic and topical strategies

Muscarinic agonists (cevimeline, pilocarpine) increase salivary flow but systemic cholinergic side effects restrict use in some patients. Topical acidic stimulants (e.g., 1% malic acid) provide short-term salivary enhancement and can be used preventively or symptomatically. Recent reviews and meta-analyses support the short-term efficacy of these topical approaches.

Cell therapy/stem cell approaches

Animal and early human studies indicate that MSC injection into salivary glands reduces inflammation, protects secretory cells, and signals functional recovery. Small-scale Phase 1 trials evaluate safety and short-term functional outcomes. Standardized cell sources, delivery routes, dosages, and long-term effects require further study.

Gene therapy (AAV2-hAQP1)-early clinical signals

Early clinical reports (AQUAx, corporate press releases) show safety and preliminary efficacy in salivary volume and symptom improvement. Phase 2 trials (e.g., NCT05926765) evaluate bilateral parotid injections for functional improvement. Early results indicate potential for fundamental recovery, but long-term safety and durability data are limited.

Preventive protocols (timing and multimodal interventions)

Prophylactic interventions (pre-/mid-radiotherapy PBM, concurrent electrostimulation) outperform single-time interventions. Multimodal combinations (PBM + electrostimulation ± pharmacologic therapy) show synergistic effects on both symptoms and saliva volume. Large-scale RCT confirmation remains limited.

Mechanistic insights and biomarkers

PBM promotes mitochondrial activation, modulates anti-inflammatory cytokines (e.g., IL-6), and improves microvascular function. Preclinical work suggests specific wavelengths (e.g., 540 nm green light) may enhance epithelial permeability and water transport, supporting parameter–mechanism studies.

Safety and practical applicability

Most PBM and electrostimulation studies report no serious adverse events; however, device standardization, training, and accessibility may limit clinical implementation. Gene and cell therapies require caution regarding immune reactions, off-target expression, and costs.

Summary:Evidence from 2023-2025 consistently supports the preventive and protective efficacy of PBM, electrostimulation, and topical stimulation. Regenerative medicine (cell/gene therapy) shows potential for fundamental recovery but requires large-scale and long-term clinical studies.

DISCUSSION

Xerostomia and salivary gland hypofunction significantly impair quality of life and arise from radiotherapy, chemotherapy, aging, and autoimmune disease. Saliva maintains oral homeostasis, digestion, and antimicrobial defense. Preventive and regenerative approaches are increasingly emphasized over traditional symptomatic management [14-16].

PBMT, a noninvasive intervention, mitigates salivary gland damage and preserves salivary secretion during radiotherapy. Mechanistically, PBM activates cytochrome c oxidase in mitochondria, enhancing ATP production and antioxidant responses. RCTs demonstrate reduced salivary decline and improved subjective xerostomia [15]. Dose-response effects indicate the importance of optimizing parameters (energy density, wavelength) [17].

Electrostimulation therapy activates the neuro-salivary reflex, promoting natural salivary secretion. Device-based approaches are noninvasive, repeatable, and have high patient adherence [16].

Gene therapy (AAV2-hAQP1) restores aquaporin-1 expression in damaged salivary cells. The AQUAx2 trial, designated RMAT by the FDA, evaluates its regenerative potential [18,19]. MSC injection or autologous salivary gland transplantation are under investigation, demonstrating regenerative effects in preclinical models [20].

Improved radiotherapy techniques, such as IMRT, minimize dose to normal glands and preserve function [21]. Radiation-induced saliva compositional changes may increase secondary infection risk, highlighting the need for preventive strategies [22].

Pharmacologic agents (pilocarpine, cevimeline) remain effective but are limited by side effects, emphasizing combination or personalized approaches [17].

Recent comprehensive reviews indicate PBM, electrostimulation, gene, and cell therapies complement conventional pharmacotherapy. Preventive strategies (pre-radiotherapy PBM, low-dose IMRT) may be more effective than post-treatment rehabilitation [20]. mHealth-based education and self-management can further enhance long-term outcomes [22].

Conclusion: Prevention and management of salivary gland hypofunction requires a multi-modal approach. Noninvasive interventions (PBM, electrostimulation), gene therapy (AAV2-hAQP1), and cell therapy are emerging next-generation strategies. Optimizing treatment parameters, evaluating long-term safety, and designing patient-specific interventions are key future challenges.

CONCLUSION

Recent studies (2023–2025) indicate PBM and electrostimulation as promising noninvasive strategies for prevention and mitigation of salivary gland hypofunction. Topical stimulation and pharmacotherapy show short-term effects. Regenerative approaches (AAV2-hAQP1, MSC) offer potential for fundamental recovery but require long-term safety, cost-effectiveness, and standardization studies for clinical scalability. Standardized protocols and large-scale multicenter trials with core outcome measures are urgently needed.

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