The Efficacy and Adverse Effects of Pilocarpine and Cevimeline in Patients with Hyposalivation: A Retrospective Cohort Study

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Abstract

Objective:

The efficacy and side effects vary among cholinergic receptor agonist medications that stimulate salivary flow. This retrospective cohort investigation primarily aimed to compare the efficacy of pilocarpine (Pilo) and cevimeline (Cev) in stimulating salivary flow among patients with hyposalivation. The secondary aim was to compare the medications' side effects, discontinuation rates, and reasons for discontinuations, along with subjective changes in xerostomia, subjective perception, fungal recurrence, and the frequent usage of over-the-counter (OTC) oral lubricant products among the two drugs. Patients were further categorized into subgroups based on the underlying causes of hyposalivation, including Sjögren's disease/Sicca Syndrome, polypharmacy, and radiotherapy.

Method:

A retrospective chart review was conducted for all patients seen at the Oral Medicine Clinic at Tufts University School of Dental Medicine (TUSDM) from January 1990 to January 2025 and prescribed Pilo or Cev. Patient demographics, medical history, and medications were collected. Changes in xerostomia perception over time (at 3, 6, 12, and 24 months) were evaluated using mixed linear regression. VAS scores were compared between medication groups at each time point using independent sample t-tests, while the Mann-Whitney U test was applied for non-normally distributed data. Categorical variables such as medication dosage/frequency changes, reported side effects, and drug discontinuation rates were analyzed using Fisher's exact test. Descriptive statistics were used to summarize patient demographics, baseline characteristics, and polypharmacy profiles. Significance was set at $P < 0.05$.

Result:

This retrospective cohort study evaluated 326 patients with hyposalivation treated with Pilo or Cev at Tufts University School of Dental Medicine from 1990 to 2025. Both medications significantly improved unstimulated whole saliva (USW) and reduced subjective oral dryness measured by visual analogue scale (VAS) scores at 3 and 6 months. Cev demonstrated more sustained benefits. USW stimulated whole saliva (SWS) showed modest, time-variable improvements with both agents. There is no statistically significant difference between Cev and Pilo regarding USW, SWS, and VAS through 24 months. Adherence rates favored Cev at baseline significantly, with higher continuation rates and fewer discontinuations observed across all follow-up periods. Although overall fungal infection recurrence was low, a statistically significant association was identified between Cev use and a higher recurrence rate. No significant difference in OTC oral lubricant use was observed between the two groups. Baseline adverse effects were infrequent and mild, and both medications exhibited a strong long-term safety profile. A statistically significant association between female gender prevalence and four etiologies of hyposalivation was observed, with Sjögren's disease being predominantly female.

Conclusion:

Both Pilo and Cev are effective and well-tolerated treatments for hyposalivation. However, Cev may offer superior long-term adherence, more consistent improvements in salivary flow, and greater relief of subjective dryness. Pilo showed a lower fungal recurrence rate.

DEDICATION

To my beloved parents, Faizah Abalghunaim and Mohammed Alyousef—thank you for your unwavering support, unconditional love, and constant prayers, which have always brought me peace and strength. Your pride in me has been my greatest motivation.

To my husband, Osama—thank you for the countless sacrifices you've made to help me pursue my dreams. Your belief in me and your steady presence throughout this journey have meant everything.

To my son, Talal—your eyes give me the courage to achieve the impossible. You are my greatest inspiration.

To my dear siblings, Deemah, Sulaiman, and Abdulmohsen—thank you for your heartfelt encouragement and emotional support every step of the way.

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SWS: Stimulated salivary flow

USW: Unstimulated salivary flow

SjD: Sjögren's Disease

Pilo: Pilocarpine

Cev: Cevimeline

Introduction and Background:

Definition and prevalence of hyposalivation:

Saliva is a complex fluid produced mainly by major salivary glands, including the parotid, submandibular, and sublingual glands, and to a lesser extent by minor salivary glands. It is 99% water that serves as a solvent for other components, aids in moisturizing the mouth, and facilitates speech, chewing, and swallowing. It also contains many organic and non-organic components crucial for oral health, teeth remineralization, digestion, and immunity.[1,2]

Saliva aids in mastication, which influences the masticatory performance, and mastication forces will decline in response to a reduction in salivary secretions. It affects swallowing; the swallowing process is composed of three phases. The first voluntary phase is when saliva lubricates food and prepares the food bolus to be swept by the tongue to the posterior oral cavity. Without a saliva bolus, lubrication and movement will be impaired.[3] This is followed by a second phase of swallowing, which could be affected, and the suffocation sensation rises without adequate saliva.[3] Finally, followed by the pharyngeal phase, where the persistent movement of musculature moves the bolus in the caudal direction, with the epiglottis sealing the larynx, where saliva facilitates bolus movement during musculature contraction.[3]

Saliva buffers pH and neutralizes acids as it contains proteins and electrolytes, including sodium, potassium, calcium, magnesium chloride, phosphate, and bicarbonate; the latter is the most important as it reduces oral acidity and increases the pH level, which indirectly reduces the fungal thrive and activation and prevent teeth demineralization that mainly occurs in an acidic environment. [3]

Furthermore, it aids digestion; it contains proteins and enzymes, including amylase (Ptyalin), that are secreted mainly by the parotid glands. It is essential in converting polysaccharides to maltose and dextrin and initiating digestion in the oral cavity. Salivary amylase accounts for about 30-40% of total carbohydrate digestion, and the rest, 60-70%, will be completed by pancreatic amylase in the small intestines. [2,4]

Although it has a minor role in adults and is mainly abundant in the neonate, Lipase helps in fat digestion by breaking lipids into fatty acids and glycerol. [2,4]

The saliva contains antimicrobial proteins like lysozyme, which breaks down the bacterial cell wall; lactoferrin, which binds to iron and inhibits bacterial growth; and peroxidases. The immunological components in the saliva play a significant role in protecting the mucosal surfaces by neutralizing pathogens by secretory immunoglobulin A (sIgA).[2]

Saliva also supports wound healing and maintains mucosal integrity; it contains organic molecules, such as epidermal growth factor (EFG), which aids in wound healing by accelerating and enhancing the repair mechanism of mucosal lining following injury. If there is insufficient saliva production, EGF levels will drop, delaying the healing of mucosal tissue. [4,5] It stimulates epithelial cell proliferation, promoting rapid tissue renewal and its ability to contribute to wound healing by activating specific signaling pathways (MAPK/ERK pathway) that initiate epithelial migration and re-epithelialization. [4,5] Also, it protects mucosal cells from programmed cell death during stress conditions, helping preserve mucosal integrity and supporting the formation of tight junctions between epithelial cells, maintaining the protective barrier of the oral mucosa against pathogens and toxins. [4,5] Saliva also contains nerve growth factor (NGF), a neurotrophin produced by salivary glands in addition to epithelial cells, fibroblasts, and immune cells. It supports oral tissue repair by facilitating wound healing, stimulating fibroblast migration and

angiogenesis at the wounded site, and collagen production. It further helps regulate inflammation during mucosal repair by modulating the activity of immune cells. [4,5]

Saliva plays a critical role in protecting teeth from damage and remineralizing enamel after a high acid attack by several mechanisms. [2,6] One of the mechanisms is mechanical cleansing, where the saliva washes food debris, bacteria, and sugars away from the tooth surface, thus helping reduce plaque buildup and lower bacterial load. The electrolytes and proteins that saliva contains, mainly bicarbonate, phosphate, and proteins, aid in buffering acids and make the oral cavity acidity level pH above 5.5, protecting enamel from demineralization, they also supply the teeth with calcium and phosphate in addition to fluoride; these minerals essential for remineralization, where lost minerals are reincorporated into the enamel. [2,6] The microscopic damage in teeth will be repaired by saliva saturated with these ions before caries formation. The last essential mechanism of teeth protection is the formation of an acquired enamel pellicle (AEP). This thin protective protein film is a physical barrier against acid attacks and modulates bacterial adhesions by preventing harmful bacteria from adhering to the teeth' surface. The AEP comprises 130 proteins, and approximately 90% of the AEP is made of proteins, glycoproteins, and enzymes derived from saliva. The composition of pellicles is mainly mucins (especially MUC5B and MUC7), proline-rich proteins statherin, histatins, and cystatins. Other sources, represented by 10%, include gingival crevicular fluid (GCF) and desquamated epithelial cells. [2,6] Lastly, saliva may play a role in taste sensitivity; its primary role includes the transport of taste substances to and the protection of taste receptors. Saliva is a solvent for taste substances and diffuses them to taste receptor sites.[7] During transportation, it interacts chemically with taste substances by decreasing hydrogen ions by binding to bicarbonate, thus reducing sour taste, and some salivary proteins bind with bitter taste substances. Also, it can continuously stimulate taste,

resulting in modifications of taste sensitivity; for instance, the taste detection threshold for sodium chloride is slightly higher than the concentration of sodium in saliva, indicating ongoing stimulation of salt taste receptors.[7] In addition, saliva is protective in shielding taste receptors from damage due to dryness, bacterial infection, and atrophy, which might occur if the transport of taste stimuli to the receptor site is impaired. [7]

The condition of hyposalivation triggers serious oral complications that affect patients' quality of life. This includes challenges in essential daily functions, such as speech and eating, that can be further complicated by burning mouth sensations and dysgeusia/ageusia in addition to recurrent bacterial and fungal infections and increased tooth decay rates. [8,9]

The global prevalence of xerostomia worldwide varies depending on age group, geographic location, method of assessment, and study population. However, the overall estimate ranges from 5% to 46% of the general population suffering from dry mouth. [10]A systematic review (Villa et al. 2015) indicated that global xerostomia in the general population is 22%, and the prevalence is higher in women than men and increases with age secondary to medications and systemic diseases. [11]

Hahnel et al. showed that xerostomia affected 16% of the elderly, while hyposalivation impacted 31%. The quality of life of study cohorts diminished mainly because of the severity of xerostomia rather than hyposalivation. [12]

The National Health and Nutrition Examination Survey 2013-2016 found that 14.8% of adults reported xerostomia, and the prevalence markedly increased with polypharmacy and older age. [1] With one in five adults experiencing xerostomia, risks double to triple with the elderly, polypharmacy users, and those with certain systemic diseases.

Hyposalivation and xerostomia:

In healthy individuals, the daily production of saliva ranges from 0.5 to 1.5 L, comprising 99% water and less than 1% solids. Under normal conditions, salivary flow reaches between 1.5 and 2.0 mL/min during stimulation and remains between 0.3 and 0.4 mL/min without stimulation .[3] Hyposalivation is defined as an objective reduction in salivary flow, specifically an unstimulated whole saliva (UWS) rate of ≤0.3mL/min or a stimulated whole saliva (SWS) rate of ≤1.2 mL/min.[3,14]

Individuals start feeling dry mouth when saliva production drops significantly to about 50% of the normal unstimulated level or when the USW rate is below 0.1 mL/min. [11] Xerostomia is a subjective sensation of dry mouth that can present with reduced or normal salivary flow rate. [14] The prevalence of xerostomia affects nearly half of the geriatric population and about approximately one-fifth of younger adults. [15] Another study by Fornari et al. self-reported xerostomia prevalence among the elderly population with systemic diseases and who are taking multiple medications is 19%. [16]

Potential adverse effects of dry mouth:

Saliva protects against caries by four main mechanisms; the first mechanism is by diluting and eliminating sugars and other substances, which washes out the remaining dietary substances and microorganisms on the tooth surfaces.[17] It reduces the amount of sugar using amylase that starts the digestion of carbohydrates in the oral cavity and break it to monosaccharides. The amount of saliva during USW is ~ 0.8 mL after sugar ingestion, will rise within minutes to be 1.1 mL, thus aiding in the clearance of sugar. With insufficient saliva, the sugar level will be high and contribute to caries formation. Another mechanism is acid buffering, where normal salivary pH

ranges from 6.2 to 7.6, and demineralization of enamel occurs at a pH of 5.5. Salivary bicarbonate concentration increases from 5 mM at rest to 70 mM under maximal stimulation, neutralizing oral acid and preventing teeth from being demineralized. The rapid pH recovery (Stephan's curve) within 20-40 minutes after sugar exposure prevents sustained acid-mediated demineralization, thus reducing saliva, reducing buffering capacity and significantly increasing the caries susceptibility. [17] The third mechanism balances demineralization and remineralization; saliva supports dynamic mineral exchange to repair early enamel lesions. It is supersaturated with calcium (~1.5 mM) and phosphate (~5 mM) under resting conditions. Fluoride concentration in saliva (with regular fluoride toothpaste use) can range from 0.02 to 0.05 ppm, where all these minerals contribute to enhancing the remineralization process with the presence of regulatory proteins that prevent spontaneous crystal precipitation, including statherin, proline-rich proteins, and histatins. With low salivary flow, the supersaturation for early demineralized enamel will be disrupted. [17] The final mechanism is the antimicrobial defense by direct antimicrobial activity and biofilm regulations. Saliva contains lysozyme in the concentration of ~10-30-10 µg/mL, which hydrolyzes bacterial cell walls, lactoferrin at a concentration ~1-2µg/mL that sequesters ion, inhibiting bacterial growth, secretory IgA at concentration ~50-200µg/mL, neutralizes pathogens and inhibit microbial adhesion, in addition to the presence of peroxidase that it is toxic to microbes.[17]

Xerostomia indirectly contributes to gingivitis and periodontitis.[18] Mizutani et al. indicated that xerostomia was reported by 8.8% of the young population secondary to nasal congestion sprays, coffee, and tea consumption. It was found to be significantly associated with increased dental plaque formation, with a higher percentage of bleeding on probing (BOP), with no significant

relationship observed with probing depth ≥ 4 mm. It was concluded that xerostomia indirectly increased gingival disease activity by promoting dental plaque accumulation. [18]

Low salivary flow-prone oral mucosa to sensitivity and damage. Continuous friction results from a low salivary flow rate, which can cause a burning sensation. [19]

The association between fungal infection and xerostomia is intensely examined in the literature, with conservational results. The most updated systematic review by Molek et al. indicates that xerostomic patients are at greater risk of oral candidal growth. Candida albicans was the most prevalent type, although other non-albicans species were found to be correlated with xerostomia in patients undergoing radiotherapy for head and neck cancer. [20]

Finally, reduced salivary flow contributes to halitosis; saliva plays a crucial role in oral health protection and antibacterial function by continuously removing bacteria and food debris while mediating antimicrobial properties by several chemicals and proteins. Under normal conditions, saliva maintains a slightly acidic pH of 6.5, suppressing the growth of gram-negative and anaerobic bacteria, inhibiting the enzymatic breakdown of sulfur-containing amino acids, and thus preventing the formation of malodorous volatile sulfur compounds. [21] In the xerostomic state, a reduction in salivary flow impairs the self-cleansing mechanism, accumulating bacteria and debris. Additionally, xerostomia causes mucin precipitation and alkalization of the oral environment, which favors the proliferation of proteolytic bacteria responsible for increases in volatile sulfur compounds. [21]

Formation of saliva and regulation of salivary gland secretions:

Saliva is produced by both major and minor salivary glands located throughout the oral cavity and by the gingival crevicular sulci. The major salivary glands include a pair of parotids, submandibular, and sublingual glands.[22] Under stimulated conditions, such as mechanical stimulation, gustatory stimuli, or olfactory stimuli, salivary secretions are predominantly from the parotid gland. In contrast, during unstimulated (resting) conditions, the submandibular gland is the primary source of saliva. [3]

The regulation and initiation of salivation is achieved by the integrated activity of both the parasympathetic and sympathetic nervous systems. [23]

The parasympathetic final motor neurons responsible for stimulating saliva secretion are located in the otic, submandibular, and submaxillary ganglia. These ganglia are associated with the facial nerve (cranial nerve VII) and the glossopharyngeal nerve (cranial nerve IX) and are distributed along the salivary ducts. [23]

Within the central nervous system, the parasympathetic preganglionic neurons that regulate salivary glands are found in the rostral medulla, and the caudal pons are dispersed within the reticular formation in the dorsomedial region to the facial motor nucleus.

Inputs from the forebrain to these brainstem parasympathetic neurons are thought to mediate conditioned salivation, the reflexive salivary response that occurs upon visual, olfactory, or cognitive anticipation of food. [23]

Causes of Hyposalivation:

The occurrence of xerostomia can result from multiple underlying diseases. SjD's disease results in dry mouth because the immune system attacks and damages the glands that produce saliva. [15] The ability of diabetes mellitus patients to produce saliva diminishes due to dehydration and nerve damage, resulting in dry mouth. Both HIV/AIDS and hepatitis C create salivary gland dysfunction through mechanisms that involve both direct pathways by infecting the salivary gland epithelial and lymphoid tissue, leading to local inflammation and dysfunction, and indirect pathways where those viruses create immune deregulations causing immune like- response targeting glandular tissue, and the medications used to treat the viral infection contribute to xerostomia.[15] Sarcoidosis leads to dry mouth through gland infiltration and fibrosis, while amyloidosis causes this condition by depositing amyloid protein in glands, accumulating and further damaging the glands. The salivary flow control mechanism gets disrupted by neurological disorders such as Parkinson's disease and Alzheimer's disease, causing xerostomia. The mucus produced by cystic fibrosis clogs the salivary duct pathways. Autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE) result in impaired salivary function by causing secondary SjD's syndrome. Chronic Graft-versus-Host Disease (GVHD) leads to severe oral dryness in bone marrow transplantation patients, where the immune cells from the donor attack the recipient's salivary gland tissue. The condition arises due to metabolic disorders, which include chronic kidney disease, known as uremia, and hypothyroidism. Facial nerve damage caused by Bell's palsy, together with other neurological injuries, results in salivation regulation disorders. [15]

In addition to systemic diseases, individuals using multiple medications (polypharmacy) also experience xerostomia with high frequency among elderly women. The literature supports that

xerostomia severity is proportional to the number of drugs taken. Patients undergoing treatment for anxiety and depression frequently experience xerostomia as a common medication side effect. SSRI and antipsychotic medications work mainly by blocking nerve signals that stimulate salivary production, leading to reduced stimulation of salivary glands. The combination of antihistamines with antidepressants and other anticholinergic medications, as well as antihypertensive drugs, is a primary non-disease sources that cause dry mouth. [24] Head and neck radiation therapy, in conjunction with some chemotherapy treatments, serves as the leading cause of oral dryness. [25]

Sicca Syndrome, SjD's disease, radiation therapy, and polypharmacy:

Sicca syndrome is a broad term used to describe dry eye and dry mouth; Henrik Sjögren used the term "sicca syndrome" to describe the disease he studied extensively during his lifetime. This led, over time, to the terms Sicca syndrome and SjD's disease becoming interchangeable and confusing physicians. [26]

However, it is now recognized that Sicca syndrome and SjD's disease are not synonyms, while Sicca syndrome refers to nonspecific ocular and oral dryness, SjD's disease is defined as a systemic autoimmune disease, characterized by immune-mediated inflammation of lacrimal and salivary glands. Sicca syndrome can result from a variety of other causes. This distinction is crucial in identifying patients with the autoimmune basis for Sicca symptoms and allows clinicians to consider immunomodulatory therapy. [26]

The evaluation of Sicca syndrome involves measuring unstimulated whole saliva flow rates, which are typically low in the case of primary SjD, with flow rates that fall often below

0.1ml/min. Individuals with non-SjD sicca generally have slightly higher salivary flow rates than those with primary SjD, indicating differences in pathophysiology. [27]

SjDwas discovered and named after the Swedish ophthalmologist Henrik SjD. It is a systemic autoimmune disease that mainly affects lacrimal and salivary glands. In addition to systemic manifestations that include constitutional symptoms, fatigue, musculoskeletal involvement including arthralgia 53% and myalgias 22%, cutaneous manifestations including xerosis, pruritic over 50%. [28] Respiratory tract manifestation affecting both upper and lower respiratory tract resulting in hoarseness, dry cough, nasal dryness, and crusting, in addition to lymphocytic alveolitis, lymphocytic interstitial pneumonitis, and fibrosis, with 33% having subclinical pulmonary disease. [29] Gynecologic manifestations, including vulvovaginal dryness, pruritus that may be complicated by bacterial and fungal infection. [30] Renal involvement, including tubulointerstitial of the kidney affecting tubules, the central nervous system, including alteration in endoneurial microvessels, and peripheral neuropathy. [31] Gastroenterological involvement includes malabsorption due to lymphocytic infiltrate, and esophageal dysmotility has been reported 36% to 90% of patients. Hepatic involvement was recognized in 7% of patients with SjD by the presence of antimitochondrial antibodies. [32]

SjD poses a high risk of developing non-Hodgkin lymphoma, with an estimated lifetime risk ranging between 5% and 10%, which is 5 to 44% higher than that of the normal population. A systematic review of seven studies showed that the prevalence of lymphoma after diagnosis is 4% during the first 5 years, followed by 10% at 15 years, and the risk increases to 18% in 20 years. [33]

The pathophysiology of SjD includes chronic immune activation by both B and T lymphocytes, although the exact initiating mechanism is unknown. The B-cell hyperactivity is noticed by the

presence of hypergammaglobulinemia and circulating antibodies that could target any tissue, including salivary and lacrimal ducts, thyroid, gastric mucosa, erythrocytes, pancreas, prostate, and nerve tissue. Nonorganic specific antibodies are represented by a rheumatoid factor, antinuclear antibodies, anti-Ro/SS-A, and anti-La/SS-B antibodies, which are present in approximately 60% of SjD patients. [32]

The histopathology and cellular infiltration hallmark are the presence of focal lymphocytic infiltrates, predominantly around the gland ducts. The infiltrates consist of CD4+ helper T cells, plasma, and B cells. T cells secrete proinflammatory cytokines including IL 2, IL4, IL6, IL1ß, and TNFα .[32.]

The diagnosis of primary SjD is guided by the 2016 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) classification criteria. According to these criteria, a diagnosis is established when the patient achieves a total score of 4 or more based on five specific measures. [34]A labial salivary gland biopsy showing focal lymphocytic sialadenitis with a focus score of ≥1 focus per 4 mm^2 is weighted with 3 points. Similarly, positive anti-SSA/Ro antibodies also carry 3 points. Additional findings contribute to 1 point each, including an ocular staining score of ≥5 in at least one eye, a Schirmer's test result of ≤5 mm in 5 minutes in at least one eye, and an unstimulated whole saliva (USW) flow rate of ≤0.1 mL/min. Importantly, before confirming the diagnosis, it is necessary to exclude other conditions that can mimic SjD, such as HIV and hepatitis C infections, sarcoidosis, amyloidosis, graft versus host disease, IgG4-related disease, and a history of head and neck radiation therapy. Proper exclusion ensures accurate diagnosis and appropriate management of patients with sicca symptoms. [34]

The management of SjD requires a multidisciplinary approach involving collaboration between several specialists; an ophthalmologist who addresses the ocular manifestations, while a rheumatologist manages the systemic autoimmune aspects of the disease. Additionally, oral medicine specialists are critical in managing the oral complications associated with SjD, including recurrent infections, increased dental caries, and persistent oral dryness. Each specialist contributes equally to patient care, and coordinated efforts are essential to prevent disease progression, reduce complications, and maintain the patient's quality of life. [34]

Radiation induces hyposalivation, which leads to a marked reduction in both stimulated and USW rates. Parotid gland function suffers noticeable impairment with radiation doses exceeding 24-26 Gy, as SWS is often reduced below 25% of the baseline level. [35,36]

Measurement of salivary flow rates:

The salivary flow rates are not constant, with varied ranges of stimulated parotid and submandibular salivary gland flow rates proven with repeated collection. [37] The assessment of salivary flow rate is achieved after patients fast overnight or wait two hours following a meal. Clinicians commonly assess the unstimulated whole saliva (UWS) flow rate with the patient in an upright position. Patients use the traditional draining method by letting saliva flow from their lower lip into a graduated container for 15 minutes without interruption. Leal et al. Introduced a pre-weighed cotton roll method as an alternative technique, which requires placing cotton rolls at major salivary ducts' openings, followed by weighing before and after saliva collection. The method involves placing graduated absorbent strips on the floor of the mouth to collect measurements at the one-minute, two-minute, and three-minute marks.

To measure USW, researchers use the spitting method, where patients spit into a container occasionally, and the suction method, where the saliva is continuously drawn into the device. [11] The usual method for measuring stimulated whole saliva (SWS) flow rate requires patients to chew an unflavored gum base or paraffin wax (1-2g) for one minute to promote salivation. Salivary flow stimulation can also be achieved by applying a 2% citric acid solution to the tongue bilaterally every 30 seconds and collecting saliva into a graduated cylinder over five minutes. [11]

It is feasible to collect saliva from each of the major salivary glands individually. The standard procedure for collecting parotid gland secretion involves positioning a Lashley or Carlson-Crittenden cup over the Stensen duct and using a suction device. Direct measurement of the submandibular gland function is achieved through cannulation of Warthin's duct. Wolff et al. developed a combined method to measure sublingual and submandibular gland flow separately. The flow of minor salivary glands can be measured using micropipette methods or absorbent paper systems, including the Periotron® technique. [11] Researchers measure the flow rates of minor salivary glands in microliters per minute per square centimeter of mucosal area ($\mu L/min/cm^2$). [11]

Current Management strategies:

Dry mouth treatment protocols typically implement a structured multi-step approach. The first recommendation for managing dry mouth whenever possible is to avoid the offending drug that causes xerostomia, and attention should be given to the amount of water intake, with a minimum of 2 L/day. [38] Salivary stimulants and substitutes are the second line of therapy, where OTC products are used; this includes a salivary substitute where artificial saliva can relieve a dry

mouth by neutralizing pH and containing electrolytes that approximately resemble normal saliva composition. Mucin-based products are reported to have a longer duration of action and better tolerability than aqueous-based products.[38]

Saliva substitutes are available in many forms, including sprays, gels, and lozenges. [38] On the other hand, the salivary stimulants category enhances saliva production, like chewing gum, by stimulating taste receptors and is advantageous in that it lacks side effects. [38] Ascorbic acid is also used to treat xerostomia. A study comparing the effectiveness of ascorbic acid versus artificial saliva found that vitamin C is subjectively more effective than artificial saliva but less effective than other salivary stimulants, with the main disadvantage being demineralizing the enamel over long-term use. [39] Malic acid, which exists in many fruits, including apples and pears, effectively alleviates xerostomia symptoms; however, it can affect the enamel with long-term use. [38] Another approach is mechanical parasympathomimetics, which has been gaining attention in the Western world, such as acupuncture, with an increasing number of studies now being conducted on its effect. [38] A Swedish study concluded that subjects who received traditional acupuncture in the glandular area showed a significant increase in salivary flow rate lasting up to a year in its efficacy compared to the placebo group. [40]

This local mechanical and chemical intervention provides palliative relief through oral mucosa lubrication yet fails to significantly increase saliva production. When OTC therapies prove ineffective in relieving symptoms, sialagogue prescriptions, such as Pilo, Cev, and, less commonly, bethanechol, come into play. Pilo is a muscarinic receptor agonist that targets M3 receptors to promote secretion from salivary glands. [42] Patients with SjD, along with those suffering from radiation-induced xerostomia, experience better salivary flow and reduced dry mouth symptoms after treatment. [42] The most common adverse effects of Pilo treatment are

sweating accompanied by flushing and gastrointestinal discomfort. [42,43] Research demonstrates that Pilo exerts pharmacological effects across a wide range while directly impacting M1 and M3 muscarinic receptors. [44] Pilo stimulate receptors in salivary glands, other exocrine glands, lacrimal and sweat glands, and goblet cells in the respiratory and digestive linings. [44]

Cev functions as a muscarinic receptor agonist that, although it binds to M1, has a higher affinity to M3 receptors, yielding better success in treating hyposalivation with fewer side effects (nausea and gastrointestinal upset are the predominant ones). [45]

Bethanechol possesses nonspecific muscarinic and, to a lesser extent, nicotinic cholinergic receptor agonists, working on abundant muscarinic receptors. [46] Bethanechol has fewer side effects and statistically showed increases in USW and SWS. [46]

An open-label crossover study conducted at the University of California, UCSF, US, evaluated the effectiveness of Pilo against bethanechol and Cev in treating xerostomia in twenty patients. The study administered each medication for one to two weeks, followed by a seven-day treatment washout period. Researchers evaluated both stimulated and unstimulated saliva flow rates alongside symptom relief and treatment side effects. The bethanechol treatment produced a statistically significant increase in stimulated saliva flow compared to Pilo ($p = 0.0272$) and demonstrated better tolerance with fewer side effects. Despite its effectiveness in improving xerostomia symptoms, as shown by p-values of 0.046 and 0.0078, Pilo treatment generated more side effects, especially increased sweating. Cev generated inconsistent outcomes with a moderate level of side effects. Bethanechol demonstrated superior effects for saliva production and patient tolerance, whereas Pilo enhanced symptom relief; both drugs exhibited statistically significant benefits in their respective domains. [41]

Despite their effectiveness and widespread use for treating hyposalivation cases, Pilo and Cev produce systemic side effects, including sweating, flushing, headache, and gastrointestinal disturbances. Although uncommon, serious adverse effects like bradycardia can develop in individuals who are predisposed to them. Non-pharmacological treatments typically cause fewer adverse effects, although their effectiveness diminishes with severe cases. [31]

Among all the above-suggested treatments, the main treatments for xerophthalmia and xerostomia are two sialagogues, Pilo and Cev. Unfortunately, these two drugs, although commonly used, remain unstudied deeply and lack comprehensive evaluations of their effectiveness and side effects among specific populations, including those with SjD disease, patients on polypharmacy, Sicca Syndrome with an unspecific diagnosis, and radiotherapy-induced hyposalivation. Future studies should extend their outcome measures to cover medication latency, effect on subjective perception of oral dryness, incidence of oral infections (e.g., oral candidiasis), and need for OTC oral lubricants, as well as medication side effects and discontinuation rates. An in-depth analysis of these aspects will enable a better comprehension of these treatments' relative efficacy and side effects among different patient groups.

Besides sialagogues medication, which is used for xeropthalmia and xerostomia, refractory cases may be developed, and additional experimental therapeutic options such as electrostimulation devices, immunomodulatory, and gene therapy may be explored.

Devices that use electrostimulation to target lingual nerves appear to effectively enhance salivary function. Such noninvasive devices offer a new treatment option for patients who show intolerance to pharmaceutical therapies. Research has demonstrated substantial enhancement of salivary flow and positive patient responses while maintaining minimal side effects. [47]

Managing systemic inflammation in SjD disease can benefit from introducing immunomodulatory drugs with a curative aim. One of the immunomodulatory treatments was tested by Mutha et al., who recommended using Rebamipide, a quinolone derivative known to stimulate mucin glycoprotein synthesis and exhibit both anti-inflammatory and immunomodulatory effects. [48] They suggested administering 100 mg twice daily, alongside topical 0.5% carboxymethylcellulose (CMC), to treat xerostomia and xeropthalmia; subjects experienced significant improvement in symptoms of dry eye and mouth with this systemic medication, in SjD's patients. However, further large-scale studies are required for benefit verification. [48]. Another medication is Ianalumab, a monoclonal antibody that targets and depletes B cells, binding to B cell-activating receptor (BAFF-R), a receptor in mature B cells, and blocking it to reduce abnormal B-cell activity. Bowman et al tested this drug on subjects who received varying doses of Ianalumab (5mg, 50 mg, or 300 mg). The treatment showed statistically significant dose-related reduction in disease activity (measured by ESSDAI EULAR SjD's Syndrome Disease Activity Index score), with the most significant improvement in the 300 mg Ianalumab group. Rare serious side effects make it one of the promising treatments in reducing further progression of SjD disease in terms of exocrine gland destruction. [49]

Lastly, there is a treatment that has a protective activity against further glandular destruction: the use of cytoprotective agents such as Amifostine, which medical professionals administer to protect salivary glands from radiation-induced damage during radiotherapy.[50] Another medication that has protective properties and prevents further glandular damage from radiation is recombinant human erythropoietin (rhEPO), whose primary role is stimulating red blood cell (RBC) production. However, it has another role by protecting salivary glandular tissue, as erythropoietin receptors are overexpressed in glandular tissue after radiation therapy. rhEPO

increases salivary flow rates with upregulation of aquaporin-5 in a rat model. The promising results needed further exploration of the same efficacy in human subjects. [51]

Aim and Hypothesis

Primary Aim:

To compare the efficacy of Pilo versus Cev in stimulating salivary flow among patients with hyposalivation by objectively measuring the change in SWS and UWS flow at baseline and follow-ups. Patients were further categorized into subgroups based on their underlying causes of hyposalivation, including Sjögren's disease, Sicca Syndrome, polypharmacy, and radiotherapy.

Secondary Aims:

To evaluate latency, subjective perception of oral dryness using Visual Analog Scale (VAS 1-10) scores, side effects, incidence of oral fungal infection recurrence, and OTC oral lubricant products use, medication discontinuation rates, and reasons for discontinuation among users of both medications. Subgroup analysis will also be conducted.

Hypothesis:

We hypothesize that Cev demonstrates superior efficacy over Pilo by objectively enhancing both stimulated and USW rates, with notable differences in side effects and discontinuation rates, as supported by clinical observations and prior studies, given its targeted affinity for M3 receptors.

Materials and methods:

This retrospective cohort investigation included all patients seen at the Oral Medicine Clinic at Tufts University School of Dental Medicine (TUSDM) who were prescribed either Pilo or Cev as a treatment for their hyposalivation between January 1990 and January 2025. Patient data from January 1990 to March 2018 were obtained from Dr. Farag's prior retrospective study (IRB #12300). Records before 2016 were extracted from paper charts, while those from 2016 to March 2018 were obtained from axiUm electronic records. Data from April 2018 through January 2025 were retrieved from the axiUm electronic health record system. A total of 452 patient records were reviewed in this study.

The Tufts Health Sciences Institutional Review Board (IRB #5773) approved the study on March 14, 2025. The research team examined medical records of individuals treated at the Oral Medicine Clinic at TUSDM who received Cev or Pilo prescriptions from January 1990 to January 2025.

Inclusion criteria:

1. **Date range:** Tufts Dental Chart Records from 01/01/1990 to 01/31/2025
2. **Age Range:** Adult patients aged 18 and up
3. **Subjective reporting of dry mouth**: severity measured using Visual Analog Scale (VAS) scores. Those with severity of subjective oral dryness above 3/10 on VAS (where zero indicates no dryness and 10 is the maximum dryness) will be included
4. **Objective Diagnosis of Hyposalivation via Unstimulated Salivary Flow Rate:**

An unstimulated salivary flow rate of 0.3 mL/min or less, measured prior to the prescription of sialagogues (i.e., baseline), with existing records for a minimum of one follow-up after the initiation of the sialagogues (i.e., at 3 months).

5. **One of the following causations:**

   - Sjögren disease: Proven diagnosis based on meeting 4 scores of the 2016 ACR-EULAR classification criteria[15]. These criteria include anti-SSA/Ro antibody positivity (3 points), histopathologic evidence of focal lymphocytic sialadenitis with a focus score ≥1 foci/4 mm^2 on labial salivary gland biopsy (3 points), an ocular staining score (OSS) ≥5 (1 point), a Schirmer's test result ≤5 mm/5 minutes (1 point), and an unstimulated whole salivary flow rate ≤0.1 mL/min (1 point).
   - Sicca syndrome (i.e., history of xerostomia and xeropthalmia, with negative minor salivary gland biopsy and/ or blood test of SS-A).
   - Radiotherapy History: History of radiotherapy in the head and neck region
   - Polypharmacy: Concurrent use of one or more medications known to cause dry mouth when the diagnosis of hyposalivation was established.

     Eligibility for inclusion in polypharmacy or post-radiation subgroups was determined through chart review in the axiUm electronic health record. Patients with confirmed Sjögren's disease (via positive SS-A serologic or minor salivary gland biopsy) and those with Sicca syndrome but negative for serologic or histopathologic markers were included.

6. **Prescription of Sialagogues:**

Patients must have received prescriptions for either:

- Pilo (5 mg or 7.5 mg) dosed QD, BID, TID, or QID.
- Cev (30 mg) dosed QD, BID, or TID.

7. **Follow-Up Duration:**

   Patients must have completed at least three months of follow-up after initiating sialagogue therapy.

Exclusion criteria:

1. **Pregnancy and Nursing:**

   Women who were pregnant or nursing during the period of sialagogues treatment as there could be too many confounding factors that could impact the data analysis.

2. **Concurrent Chemotherapy or Radiation:**

   Patients records indicating active chemotherapy or receiving ionizing radiation will be eliminated.

3. **Salivary Gland Aplasia:**

   Patients with congenital or acquired absence of salivary glands.

4. **Xerostomia Due to other Underlying Conditions:**

   Patients with xerostomia secondary to conditions including HIV, Hepatitis C, sarcoidosis, SLE, graft-versus-host disease, pre-existing lymphoma, amyloidosis, IgG4-related disease.

5. **Other Factors:**

   Any additional factors that, in the investigator's opinion, could compromise the quality or reliability of the collected data.

Data collection:

This study gathers patient demographics (age, race, sex, and ethnicity) and medical history, which includes autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary biliary cirrhosis, along with systemic diseases such as diabetes mellitus and diabetes insipidus, which are known contributors to xerostomia. These conditions were categorized under the Sicca syndrome group, which also included patients reporting nonspecific symptoms of dry eyes and mouth.

The study assessed the etiologies of hyposalivation, including Sicca syndrome, Sjögren's disease, polypharmacy (with documentation of xerogenic medications), and a history of head and neck radiation therapy. Salivary flow rates, both stimulated and unstimulated, were measured at baseline and after 3 months as a mandatory follow-up, with optional evaluations at 6, 12, and 24 months.

The study also evaluated adverse effects such as sweating and gastrointestinal disturbance, atrial fibrillation, urinary incontinence, and worsening of symptoms in general. Prescription data were reviewed to capture dosing schedules and adjustments in sialagogue therapy. Medication discontinuation rates, transitions to alternative sialagogues, and subjects reported oral dryness using a visual analog scale (VAS). were also recorded. Additional outcomes included the frequency of over-the-counter oral lubricant products usage and the recurrence of fungal infections among patients taking Pilo or Cev.

All data were handled in accordance with confidentiality standards and applicable legal protections.

Saliva collection:

As part of routine clinical care in the Oral Medicine Clinic, salivary flow rates were collected and documented at baseline and follow-up visits. This retrospective chart review included data on UWS and SWS whole salivary flow rates recorded prior to the initiation of sialagogue therapy, with follow-up assessments at approximately 3, 6, 12, and 24 months, as available. According to institutional protocol, saliva collection was performed during scheduled visits. At the initial visit, UWS was measured over 15 minutes, and SWS over 5 minutes. At subsequent follow-ups, UWS collection was limited to 2 minutes, while SWS remained at 5 minutes. Patients were advised to abstain from food, drink, oral hygiene, or moisturizing agents for at least 90 minutes prior to the visit. Saliva collection followed a standardized approach: UWS was gathered while patients sat upright, remained silent, and expectorated into pre-weighed tubes every minute. For SWS, patients chewed a standardized, tasteless 1×1 cm paraffin wax square and expectorated saliva similarly. Saliva weights were measured using an Adam Equipment PGW 253e analytical balance, with salivary flow rates calculated and recorded via axiUm electronic health record software.

Statistical Analyses:

All statistical analyses were conducted using SPSS version 30 (IBM Corp., Armonk, NY) and Stata 18 (Stata Corp LLC, College Station, TX, USA). A p-value of less than 0.05 was considered statistically significant. Continuous variables were summarized as means with standard deviations (SD) when normally distributed, and medians with interquartile ranges (IQR) when not. Categorical variables were presented as counts and percentages. The assumption of normality for continuous data was assessed using both visual inspection (histograms and Q–Q plots) and the Shapiro–Wilk test.

To assess the associations between categorical variables, the Fisher Exact test was used.

To assess between-group differences in salivary flow rates, the Mann–Whitney U test was used due to the non-normal distribution of these measures. However, for comparing Visual Analogue Scale (VAS) scores, which followed a normal distribution, the independent samples t-test was applied at each time point between the two medication groups.

To evaluate longitudinal treatment effects over time while adjusting for repeated measurements, mixed linear regression models were used for each outcome variable—unstimulated whole saliva, stimulated whole saliva, and VAS. These models included time as a fixed factor and provided coefficient estimates, standard errors, 95% confidence intervals, and p-values to assess statistical significance at each follow-up compared to baseline.

Associations between treatment discontinuation and medication type over time were analyzed using the Fisher's exact test, due to small sample sizes in some categories. All analyses were based on complete-case data, and no imputation was performed for missing values. A p-value of less than 0.05 was considered statistically significant. Statistical methods were selected based on the nature and distribution of each variable and the study design.

Results:

This retrospective cohort investigation included a total of 326 patients diagnosed with hyposalivation, of which the majority received Cev (57.7%) or Pilo (42.3%). A notable finding is the predominance of female patients (82.8%), ~~aligning with known epidemiological patterns of hyposalivation and Sjögren's disease, which disproportionately affect women.~~

The racial distribution:

The racial distribution was heavily skewed toward white individuals (94.8%), with minimal representation from black (2.6%), hispanic (1.3%), and other racial groups (1.3%).

From a clinical perspective, the most frequently documented diagnosis was SjD disease (42.3%), followed by Sicca syndrome (21.2%), polypharmacy-induced hyposalivation (10.1%), and radiation-induced xerostomia (8.6%). Interestingly, 17.5% of cases lacked a specified diagnosis, which may reflect gaps in documentation or undetermined etiologies. Only a single patient (0.3%) had a dual diagnosis of SjD and polypharmacy, and while rare, such overlap cases are clinically significant. (Table 1)

Nearly all patients (98.2%) had insurance coverage, ensuring comparable access to pharmacologic treatment across the cohort, thus minimizing socioeconomic confounding. The relatively even split between medication groups and diversity in etiological subgroups sets a strong foundation for both primary and secondary outcome comparisons across diagnostic categories. The Demographic and Clinical Characteristics of the Study Population, including gender, race, and insurance coverage (N = 326) are represented in Table 1.

The Age Distribution:

The age distribution across different hyposalivation subgroups reveals a predominantly older patient population, which is consistent with the pathophysiology of hyposalivation, particularly in cases related to autoimmune conditions, polypharmacy, and post-radiation effects. The overall median age was 68 years (IQR: 18), highlighting the relevance of this condition in the geriatric population.

Among the subgroups, patients with radiation-induced hyposalivation exhibited the highest median age at 74.5 years (IQR: 15), followed closely by the polypharmacy group, with a median age of 73 years (IQR: 16). These findings are expected, as both radiation therapy and the use of multiple medications are more common in elderly individuals. Similarly, the SjD's (median: 68, IQR: 18) and Sicca (median: 68, IQR: 14) groups presented with comparable age profiles, suggesting overlapping age-related risk for autoimmune and idiopathic salivary dysfunction. The group with unreported diagnosis had a slightly younger median age of 65 years (IQR: 17), which may imply less typical or undocumented etiologies. A single patient with a dual diagnosis of SjD's and polypharmacy was 59 years old, though the n=1 limits the interpretation of the findings. Table 2 shows the median and IQR of the age distribution among the hyposalivation groups.

Comparison of USW, SWS, and VAS Scores Between Pilo and Cev Groups Over Time:

Comparative Analysis of SWS & UWS Flow and Subjective Perception of Oral Dryness Between Pilo and Cev: Across all time points, no statistically significant differences in SWS, UWS, and perception of xerostomia using VAS, were observed between the two medication groups, as indicated by p-values > 0.05 in all comparisons.

USW and SWS Scores: Median values for both USW and SWS fluctuated slightly over time but remained comparable between the two groups. At 3 months, the median USW was 0.08 mL/min for Pilo and 0.13 mL/min for Cev ($p = 0.225$), while the median SWS for Pilo and Cev were 0.79 and 0.90 mL/min, respectively ($p = 0.209$). Similar patterns of non-significant differences were noted at 6, 12, and 24 months These findings suggest that both medications have a similar effect on salivary output, with no evidence of superiority.

VAS Scores: The VAS, reflecting patients perceived oral dryness (i.e., xerostomia), also showed no statistically significant differences between groups at any time point. Although Cev users consistently reported slightly lower VAS scores at follow-up (indicating less perceived dryness) than Pilo users, the differences were not statistically significant. Notably, at 6 months, the VAS score was numerically lower for Cev (mean = 3.15) compared to Pilo (mean = 4.33), but the p-value approached significance only marginally ($p = 0.082$), suggesting a potential trend worth further exploration in a larger sample.

Overall, the findings reported in Table 3' indicate that Pilo and Cev yield similar clinical outcomes in objective salivary secretion and subjective symptom relief, with no consistent or statistically significant advantage of one agent over the other throughout the two-year follow-up period.

Polypharmacy Profile of the Study Participants:

The polypharmacy profile of participants in this cohort reveals significant variability in exposure to medications known to exacerbate hyposalivation, such as antihistamines, antihypertensives, and anticholinergic agents. The findings highlight the complex pharmacologic landscape often encountered in hyposalivation management, especially among older adults.

Antihistamine use was relatively infrequent, with 88.3% of participants not using any, and only a small subset using one or more agents (11.7% combined). This suggests that antihistamines, despite their known xerogenic potential, may not be a dominant contributor in this population. Similarly, the majority of patients (71.2%) were not on antihypertensive medications, though nearly 29% used one or more, which is clinically relevant given the known salivary-inhibiting effects of certain blood pressure medications.

Focusing specifically on anticholinergic/antimuscarinic agents—among the most potent xerogenic drug classes—data from 217 patients indicate that 93.1% had no recorded exposure. This low prevalence may reflect either conservative prescribing practices in this vulnerable population or potential underreporting. Nevertheless, even minimal use can have cumulative effects on salivary gland function in predisposed individuals.

The profile of medications known to cause dry mouth paints a clearer picture: among the 217 patients with available data, 52.5% were exposed to at least one xerogenic agent. While 47.5% had no exposure, a considerable number were taking between 1 and 4 such medications, and a few (n=3) were on five or more. This high level of polypharmacy underscores the need for clinicians to routinely review and optimize medication regimens in patients presenting with hyposalivation, particularly those not responding adequately to salivary stimulants like Pilo or Cev. Medication percentages are presented in Table 4.

Baseline Frequency of Reported Side Effects Among Study Participants:

At baseline, a relatively low frequency of adverse effects was reported among study participants, indicating that most patients were clinically stable prior to, or after, starting Pilo or Cev therapy. Notably, only 6.8% (n=22) of patients reported a general worsening of symptoms, mainly

worsening of GERD, the most frequently documented issue, which may reflect underlying systemic disease fluctuations after any of the drug usage, or pre-treatment symptom burden rather than specific drug effects.

Other side effects were rare. Sweating was the second most common symptom, reported by 4.6% (n=15) of patients—relevant given the parasympathomimetic nature of both Pilo and Cev, which can exacerbate autonomic responses. Flushing (2.8%), allergic reactions (0.9%), and dizziness (0.9%) were reported with low frequency and likely reflect non-specific symptoms that are important to track but are not uncommon in chronic conditions or polypharmacy contexts. Clinically significant but infrequent adverse events included urinary incontinence (0.6%), atrial fibrillation (0.6%), frequent urination (0.3%), and worsening asthma (0.3%). These are particularly important in risk stratification, as they may be exacerbated upon initiation of treatment with cholinergic agonists and warrant close monitoring in vulnerable individuals. Overall, the low rate of side effects reporting at baseline supports the assumption that any increase in adverse events following treatment initiation can be more confidently attributed to the pharmacologic intervention itself rather than underlying comorbidities or pre-existing conditions. These findings set the stage for a meaningful comparison of post-treatment adverse event profiles between Pilo and Cev users. Table 5 presents the percentages of reported side effects.

Laboratory Tests Reported Among Study Participants:

Laboratory investigations pertinent to autoimmune etiologies—particularly SjD's disease—were selectively performed, reflecting variable diagnostic work-up strategies across patients. The SSA antibody test, a cornerstone in SjD's disease diagnosis, was the most commonly reported laboratory investigation, with 25.1% (n=81) of participants undergoing the test. This aligns with

the clinical suspicion for autoimmune involvement in a substantial subset of the hyposalivation population.

The SSB antibody test and lip biopsy, both also indicative of SjD's disease, were each reported in 17.6% (n=57) of patients. This consistency in proportions suggests that when autoimmune etiology was suspected, a combination of serologic and histopathologic confirmation was often pursued. However, these rates also indicate that a large fraction of the cohort did not undergo these evaluations, potentially due to established diagnoses, clinical judgment, or external factors like referral patterns or resources availability.

The ANA profile, a broader marker of autoimmune activity, was performed in 17.3% (n=56) of participants, supporting its utility as a general screening tool in systemic autoimmune disorders. The Rheumatoid Factor Test (RFT) was the least frequently reported among autoimmune-related investigations, conducted in only 9.3% (n=30) of cases, perhaps reflecting its lower direct relevance to SjD disease unless overlapping rheumatoid arthritis was suspected. Laboratory test percentages are summarized in Table 6.

Association Between Gender and Hyposalivation Group:

An analysis of gender distribution among the various hyposalivation etiological groups revealed a statistically significant association between gender and hyposalivation subgroup classification (Fisher's exact test, $p < 0.001$), indicating that specific underlying causes of hyposalivation are strongly skewed in relation to gender. Most notably, SjD's disease was overwhelmingly prevalent among females, with 95.6% (n = 132) of affected individuals being women. This finding is consistent with the established autoimmune epidemiology, where SjD's disease

predominantly affects middle-aged and older females due to hormonal and immunological factors. Similarly, the Sicca group, often encompassing undifferentiated or non-autoimmune dryness syndromes, also demonstrated a female predominance (75.4% female), though to a lesser extent.

In contrast, polypharmacy-related hyposalivation exhibited a more balanced gender distribution, with 39.4% male and 60.6% female, suggesting that medication-induced salivary dysfunction affects both sexes, but still with a mild female majority. Interestingly, the radiation-induced group had the highest proportion of male participants (42.9%), which may reflect treatment patterns related to head and neck cancers, historically more common in males due to behavioral and occupational exposures.

The “not reported” group, while unclassified in terms of etiology, also followed the overall cohort trend, with 86.0% female, suggesting that even among cases lacking documented diagnostic categorization, the burden of hyposalivation remains disproportionately higher among women.

These findings underscore the importance of recognizing gender-specific patterns in the pathophysiology and etiology of salivary gland dysfunction. Tailoring the Association Between Gender: Tailoring evaluation and management. Hyposalivation Group management approaches based on these distributions may enhance diagnostic precision and therapeutic outcomes. The association between gender and hyposalivation groups is presented in Table 7.

Drug adherence and its association with medication at baseline:

This analysis highlights a significant association between baseline medication (Pilo vs. Cev) and patient-reported drug adherence levels (Fisher's exact test, $p < 0.001$), emphasizing that the type of sialagogue may influence adherence behavior in this cohort.

Among the 278 participants (85.3%) who continued their medication without modification, Cev was more commonly used (60.1% vs. 39.9% for Pilo), suggesting a possible preference or better tolerability profile. This dominance of Cev use among adherent patients may reflect differences in side-effect burden, dosage frequency, or perceived effectiveness between the two drugs.

Conversely, non-adherent patterns, including reduced dose/frequency or discontinuation, were more often observed among Pilo users. For instance, 62.5% of participants who reduced their dose/frequency were on Pilo, and a striking 66.7% of those who stopped the medication entirely were also taking Pilo. These findings could suggest tolerability or satisfaction issues with Pilo, leading to suboptimal adherence.

Interestingly, medication switching behavior further supported this pattern: 90% of participants who switched to Cev were initially taking Pilo, whereas all 10 participants who switched to Pilo had been on Cev. This bi-directional switching behavior may reflect individual variability in response or side-effect profiles, but the unidirectional skew toward switching to Cev raises questions about its perceived superiority or better tolerability.

The data underscore that while both medications are used to treat hyposalivation, Cev may be associated with higher adherence and fewer discontinuation events compared to Pilo. Table 8 shows the percentages of Pilo versus Cev users.

Fungal Infection Recurrence and OTC Lubricant Usage over all timepoints:

The frequency of recurrent fungal infections among participants was relatively low, with a median of zero recurrences and an interquartile range (IQR) of 1, indicating that most participants did not experience repeated infections. This finding may suggest effective management of oral fungal infections or a low prevalence of conditions that predispose patients to recurrence at the time of assessment.

In contrast, OTC lubricant use was more prevalent, with a median of 2 products used and an IQR of 1, reflecting a common reliance on non-prescription agents to manage symptoms of dryness. The narrow IQR suggests a consistent pattern of OTC product use across the population, possibly pointing to routine self-management strategies adopted by participants to alleviate xerostomia.

Together, these results indicate a population actively engaging in symptom management, with limited evidence of severe or persistent fungal complications. However, the notable use of OTC lubricants implies ongoing discomfort and highlights the importance of monitoring patient-reported outcomes and supporting symptom control beyond pharmacologic therapies. Median and Interquartile Range (IQR) of fungal infection recurrence and OTC lubricant use are presented in Table 9.

Fungal Infection Recurrence by Medication Over Time Points:

The distribution of recurrent fungal infections among participants using either Pilo or Cev was recorded. A significant association was observed between the type of medication and the number of fungal infection recurrences, as indicated by both the Fisher's exact test ($p = 0.001$) and the Mann-Whitney U test ($p = 0.016$).

Among participants who reported no recurrence of fungal infections, the distribution was nearly equal between Pilo (48.9%) and Cev (51.1%). However, as the number of recurrences increased, a clear shift toward higher prevalence among Cev users was observed. For instance, in those with 4 or more episodes of recurrence, the vast majority were on Cev (e.g., 100% for 4 recurrences, and 85.7% for 5 recurrences). Conversely, the fungal infection recurrence in Pilo use declined progressively, suggesting a potentially protective or less aggravating profile of Pilo regarding fungal overgrowth.

This pattern underscores a statistically significant and clinically potentially meaningful association, raising considerations for fungal infection risk as a possible adverse event in patients using Cev. The results warrant further investigation into the microbiological impact of salivary stimulants and call for enhanced monitoring of oral health, especially among Cev users. Table 10 summarizes the distribution of recurrent fungal infections among participants using either Pilo or Cev, and a graph of fungal infection recurrence over two years.

Number of Over-the-Counter (OTC) Oral Lubricants Used at All-Time Points:

The findings indicate no statistically significant association between the type of medication and the number of lubricants used, as reflected by both the Fisher's exact test ($p = 0.365$) and the Mann-Whitney U test ($p = 0.405$).

Participants who reported no use of OTC lubricants were 48.0% for Pilo and 52.0% for Cev users. Similarly, among users of one or two products—the most commonly reported usage levels—Cev was slightly more represented (64.8% and 58.7%, respectively), but the difference did not reach statistical significance. Interestingly, at higher usage levels (≥ 3 products), the

distribution began to lean slightly more toward Pilo, but again, without a meaningful trend or statistical significance.

These results suggest that OTC lubricant use is comparable between the two medication groups and does not appear to be influenced by the choice of sialagogue. Therefore, lubricant selection and usage may be more closely related to individual symptom burden or patient preference rather than the pharmacologic profile of the prescribed medication. Table 11 presents the distribution over two years of OTC oral lubricant use among participants according to their medication type (Pilo vs. Cev).

Medication Type, Dose, and Frequency Across Timepoints:

In terms of medication type, Cev usage consistently exceeded that of Pilo at all timepoints. While Pilo users declined from 41.7% at baseline to 36.7% at 24 months, Cev users increased from 58.3% to 63.3%, suggesting greater long-term adherence or tolerance for Cev compared to Pilo.

Regarding dosage, most participants were on 30 mg Cev, increasing modestly over time (from 58.3% to 63.3%). Among Pilo users, the 5 mg dose was predominant and relatively stable, albeit showing a slight decline over time (38.3% to 33.6%). The use of the 7.5 mg Pilo dose declined slightly over the course of the study, ranging from 3.4% to 3.1%.

As for frequency of use, the three-times-daily regimen was by far the most common pattern and remained consistently high across all timepoints (ranging from 82.5% to 84.4%). The usage of four-times-daily dosing increased slightly at 6 months (13.6%) but gradually declined afterward. Interestingly, once-daily usage, though minimal, slightly increased at 3 months (2.0%) and increased to 2.2% in 12 months before tapering off again.

These trends may reflect efforts to optimize symptom control while balancing tolerability and adherence, particularly as participants continue therapy over extended periods of time. The decline in overall sample size by 24 months also suggests potential drop-out or discontinuation, which should be explored further to understand medication sustainability in this population. Table 12 shows the evolution of medication usage, dosing, and frequency among study participants across five time points from baseline to 24 months.

Side Effects and Discontinuation Over Time:

The discontinuation rates remained low across all timepoints, with a slight decrease from the three months (2.3%), (1.6%) at 6 months, (1.5%) at 12 months, and (0.0%) at 24 months. Regarding side effects, most patients reported no adverse effects, with the percentage increasing from 76.3% at 3 months to a peak of 98.4% at 24 months. The reduction in reported side effects over time suggests either better tolerance, resolution of initial adverse reactions, or potential reporting fatigue in long-term follow-up.

Individual side effects were rare. The most consistently reported symptoms included gastrointestinal (GI) upset (ranging from 1.81.3% to 2.121%) and sweating (0.606% to 2.1%). Other effects, such as dizziness and gastroesophageal reflux disease, occurred in ≤ 1% of participants. Notably, no cases of heart palpitations were reported at 3 months, and no cases of frequent urination were reported at any time point. The "Other" category included a small proportion of events, peaking at 2.9% after 12 months before dropping to 0% at 24 months. Collectively, these findings underscore the good safety profile and long-term tolerability of the studied medications, with minimal adverse effects and low discontinuation rates supporting their

use in long-term management. Table 13 presents longitudinal data on reported side effects and medication discontinuation at four follow-up intervals over two years.

Changes in unstimulated whole saliva (USW), stimulated whole saliva (SWS), and visual analogue scale (VAS) scores over time:

Unstimulated Whole Saliva (USW):

Both Pilo and Cev were associated with statistically significant increases in USW at 3 and 6 months compared to baseline. For Pilo, the most significant effect was seen at three months ($\beta = 0.223$, $p < 0.001$), and the benefit tapered off by 12 months ($\beta = 0.122$, $p = 0.032$), with no significant improvement at 24 months ($p = 0.538$). Cev also showed a robust increase at 3 months ($\beta = 0.267$, $p < 0.001$), followed by a smaller but still significant gain at 6 months ($\beta = 0.125$, $p < 0.001$), with borderline significance at 12 months ($p = 0.052$), and a modest but statistically significant increase persisting at 24 months ($\beta = 0.089$, $p = 0.044$). These results suggest that both agents significantly improve unstimulated salivary output early in treatment, though Cev may offer slightly more sustained effects.

Stimulated Whole Saliva (SWS):

Effects on SWS were more variable. In the Pilo group, a statistically significant increase was only observed at 12 months ($\beta = 1.629$, $p = 0.004$), with no significant changes at other timepoints. In contrast, Cev demonstrated a modest but statistically significant increase at 6 months ($\beta = 0.172$, $p = 0.009$), and borderline trends at 3 and 12 months. Neither group showed significant improvement at 24 months. These findings indicate that improvements in stimulated saliva flow were inconsistent, but Cev showed earlier and more stable benefits.

Visual Analogue Scale (VAS):

Both medications produced marked and statistically significant reductions in VAS scores at all follow-up timepoints, indicating improvements in subjective dryness. Pilo resulted in reductions ranging from $\beta = -2.013$ at 3 months to $\beta = -2.700$ at 12 months, all $p < 0.005$. Cev showed even greater VAS reductions, especially at 6 months ($\beta = -3.652$, $p < 0.001$) and 12 months ($\beta = -3.850$, $p < 0.001$). This suggests that Cev may provide superior subjective symptom relief over time.

Overall, both Pilo and Cev demonstrated significant improvements in USW and VAS, with more modest effects on SWS. Notably, Cev showed a stronger and more sustained reduction in subjective dryness (VAS scores), and slightly more consistent improvements in both USW and SWS, especially at longer follow-up intervals. These findings may suggest a potential clinical preference for Cev in long-term management, although both agents are effective.

Table 14 presents the results of mixed linear regression models examining changes in USW, SWS, and VAS scores over time, with separate models fitted for Pilo and Cev groups.

Association Between Discontinuing Medication and Medication Type Over Time:

At the 3-month mark, the discontinuation rates were low for both medications. Among the patients using Pilo, only 3.9% (5 out of 127) discontinued the medication, while Cev had an even slightly lower discontinuation rate of 0.6% (1 out of 174). The p-value of 0.086 indicates that there was no statistically significant difference in the discontinuation rates between the two medications at this time point, suggesting that both Pilo and Cev had similar retention rates early in the treatment period.

By the 6-month mark, the rate of discontinuation increased for Pilo, with 1.1% (1 out of 89) of patients discontinuing the medication. In contrast, Cev demonstrated a lower discontinuation rate

of 1.4% (2 out of 145). Despite the difference, the p-value of 1.000 suggests no statistically significant difference between the two medications in terms of patient discontinuation rates. This indicates that, although Pilo showed a higher rate of discontinuation, the difference between the two medications was not significant.

At 12 months, the discontinuation rate for Pilo decreased significantly, with 0.0% (0 out of 51) showing absent discontinuation of Pilo in 12 months, while Cev had two cases discontinuing (2 out of 86). The p-value of 0.529 suggests that this difference was not statistically significant, implying that both medications showed favorable adherence at the 12-month mark, with Cev slightly outperforming Pilo in retention.

At the 24-month time point, there was no absent discontinuation for both Pilo and Cev.

Both Pilo and Cev demonstrated low discontinuation rates across the 24-month period. However, Pilo showed a higher rate of discontinuation at the 3-month mark, while Cev showed a higher rate of discontinuation at the 6-month and 12-month follow-up periods. Despite these trends, the differences in discontinuation rates between the two medications were not statistically significant, suggesting that both medications are well-tolerated, with Cev potentially offering a slight advantage in patient adherence, particularly in the long term. Table 15 presents the discontinuation rates of Pilo and Cev over a 24-month period, comparing the proportion of patients who continued versus discontinued their prescribed medication. Fisher's exact test was used to assess the statistical significance of these differences.

Discussion

This retrospective study provides comprehensive insights into the use, tolerability, and effectiveness of Pilo and Cev in managing hyposalivation over a 24-month period. The findings underscore important clinical and pharmacologic considerations for the long-term management of xerostomia, particularly in medically complex populations.

The study sample consisted of 326 patients, where females constituted the majority (82.8%), which line up with the typical epidemiological patterns observed in hyposalivation and autoimmune conditions like SjD. Systematic review and meta-analysis by Alani et al. regarding gender distribution in SjD disease reveals that 82-100% of females are affected, which aligns with our findings [53]**.** The racial makeup was heavily weighted toward white participants, who made up 94.8% of the study population, while other racial groups had limited representation, which constrained the study's generalizability. SjD's disease appeared in 42.3% of cases as the leading diagnosis, followed by Sicca syndrome and hyposalivation associated with polypharmacy and radiation therapy. The diagnostic distribution represents both the foundational physiological mechanisms and typical causes observed in clinical settings. The study achieved nearly complete insurance coverage (98.2%), which minimized socioeconomic bias and improved internal validity.

Age-related findings demonstrated that the majority of patients were older adults, with a median age of 68 years (IQR: The median age data from older adults (IQR: 18) solidifies the connection between aging and diminished salivary gland function, other reference indicated older ages affected by hyposalivation, however, SjD has bimodal age distribution, first one at thirties and second at fifties which indicated younger age group than reported in our study [54]**.** Radiation-

induced and polypharmacy subgroups exhibited the highest median ages, which matched clinical expectations for head and neck cancer patients and those with multiple health conditions.

During comparative analysis, researchers found no significant statistical differences between Pilo and Cev groups concerning USW, SWS, or VAS scores measured at all study timepoints. Users of Cev consistently showed marginally reduced VAS scores, which implies a slight trend toward better subjective relief from dryness that is not statistically significant. Existing studies suggest that patients perceive Cev as better tolerated and more effective. One of these studies is a study conducted by Farag et al. [52] Her findings are that SWS at three months was significantly improved in Cev than Pilo group; however, it aligns with our study that SWS and USW differences between Pilo and Cev were insignificant at the 6 months. Other study by Chainani et al. [41] found that subjective sensation of improvement were reported significantly with Pilo group, in contrast to our study where was no difference between both medication groups in terms of VAS. More than half of the study participants received at least one medication that causes dryness. The research data showed minimal anticholinergic and antihistamine consumption yet demonstrated that antihypertensives appeared in approximately 30% of the cases. It is crucial to examine patient medication records to reduce treatment-induced causes of xerostomia. Low anticholinergic exposure did not prevent many patients from developing symptoms, demonstrating that hyposalivation involves multiple factors.

The baseline side effects manifested infrequently since only 6.8% of patients experienced symptom deterioration, mainly from GERD and sweating. Patients presented clinical stability during therapy start, which allows subsequent symptom burden alterations to be attributed reliably to medication effects.

The research laboratory findings confirmed that certain patients' autoimmune process (SjD) drives hyposalivation. Among serologic markers, SSA antibodies emerged as the most prevalent finding at 25.1% in the diagnosis of this disease, but SSB antibodies and ANA results, along with lip biopsies, occurred much less often. The diagnostic work-up variation suggests that the SSA blood test is the most widely used method of testing SjD compared to the lip biopsy, this align with study conducted by Engelke et al. that most widely used test for SjD is SSA which found by 40 to 60% positive in this population, and if not, then the more complex second line lip biopsy should be obtained for confirmation. [55]

The gender analysis displayed a substantial imbalance throughout different causative subgroups. The conditions SjD and Sicca showed a strong female predominance, but radiation-induced hyposalivation exhibited the greatest number of male patients. The findings correlate with extensive epidemiological trends, highlighting the necessity for diagnostic and therapeutic procedures that account for gender differences.

According to adherence data at baseline, continuation rates displayed a statistically significant relationship with different types of medication. The medication Cev demonstrated higher patient adherence and fewer instances of treatment discontinuation. This result was also found by the Faraj et al. study [52], where the discontinuation rate was found to be higher in the Pilo group, thus confirming Cev favorable tolerability profile. Most patients who changed medications transitioned from Pilo to Cev, which indicates a preference pattern that could result from perceived differences in treatment effectiveness or side effect profiles and dose frequency requirements.

While fungal infection recurrence remained low across all patients, those who used Cev experienced a significantly higher recurrence rate when the number of episodes reached four or more. Prolonged therapy with Cev may lead to changes in oral flora or salivary composition, necessitating proactive antifungal monitoring for affected users. Pilo could be prescribed for subjects who suffered from recurrent episodes of fungal infection, as it works on multiple muscarinic receptors, including M1 and M3, that increase saliva production for a shorter period than Cev, which produces more sustained saliva amounts for a more extended period with high affinity for M3.

Data from longitudinal monitoring of medications demonstrated an uptick in Cev usage while Pilo usage saw a decrease over time. Patients most frequently administered the 30 mg Cev dose, while TID dosing continued to be the standard pattern for both medications. Treatment patterns indicate Cev provides a more sustainable option for prolonged management.

According to mixed regression analyses, both drugs effectively enhanced USW and VAS scores throughout the study period, but Cev provided more persistent and stronger results. The SWS results showed greater fluctuation since Cev demonstrated improvement at 6 months, whereas Pilo reached its peak effectiveness at the 12-month mark. The data demonstrate that salivary stimulation has complex dynamics, and both pharmaceuticals can be suitable treatments based on individual patient needs.

Throughout the study periods, discontinuation rates remained low without significant statistical distinctions between the different medications. Pilo had a slightly higher rate of early discontinuation, and Cev exhibited modest mid-term discontinuation, although neither reached

statistical significance. The results demonstrate that both drugs are well-tolerated, which enables doctors to prescribe them according to individual patient needs and reactions.

Limitations

1. Selection Bias

This retrospective cohort study may represent selection bias. Data obtained prior to April 2018 lack specific subgroups for the distribution of subjects to SjD, Sicca, polypharmacy, or radiation therapy, as it was decided to include SjD or non-SjD hyposalivation groups, which might affect the result of subgroup analysis in terms of efficacy and adverse effects.

2. Variable Data Quality

The use of historical data over three decades (1990-2025) introduces inconsistencies in record practices. Earlier data were extracted from paper charts, which may lack completeness compared to those in the most recent medical records. And evolving of assessment protocol over time could affect the heterogeneity and accuracy of data across the cohort.

3- Lack of Standardized Diagnostic Protocols

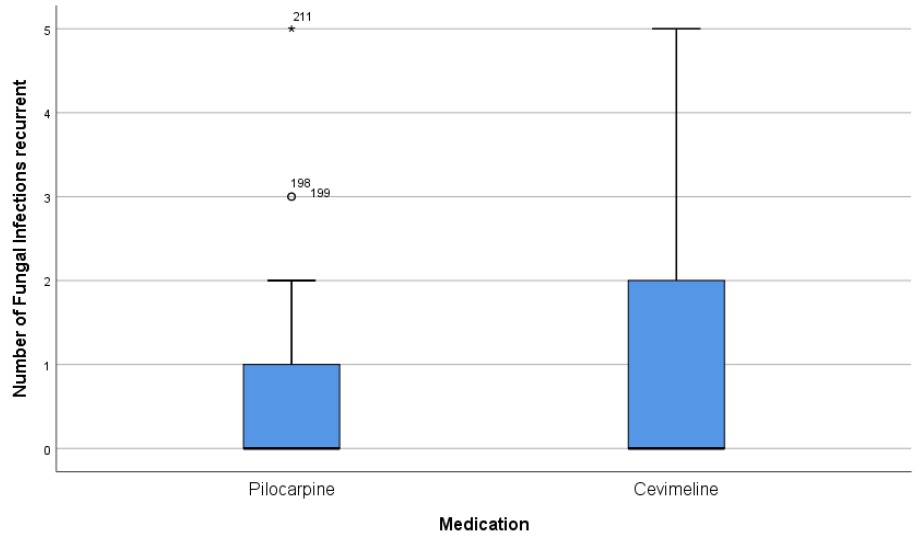
The diagnosis and classification of hyposalivation into four groups (SjD's disease, polypharmacy-related dryness, Sicca Syndrome, and post-radiation effects) were based on clinical judgment and chart documentation, without standardized diagnostic criteria. This, which may limit the consistency of correct subgrouping and, that could affect the comparison across them all.

Conclusion

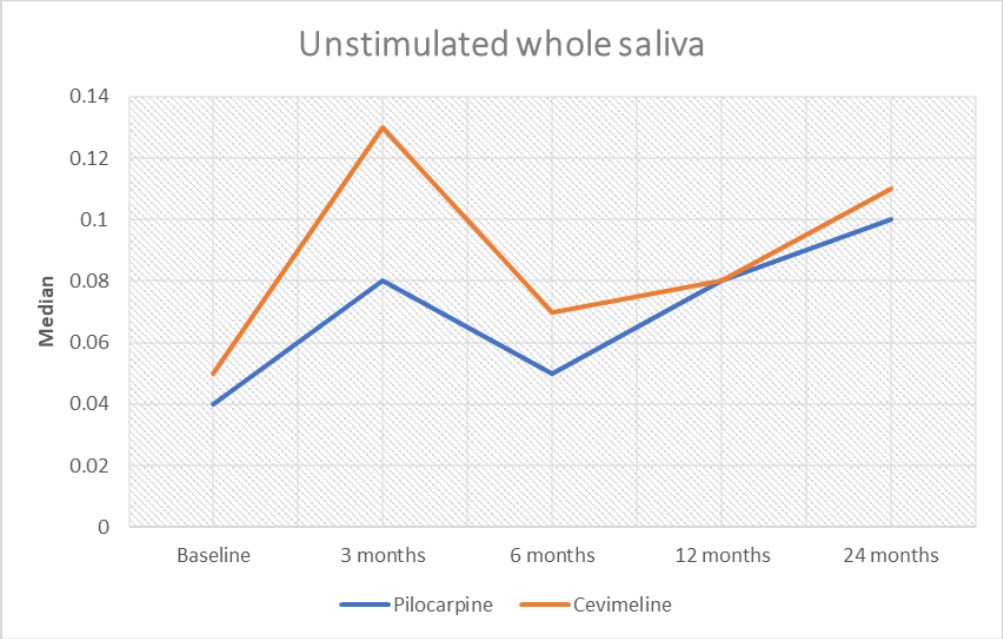
Pilo and Cev serve as effective and well-tolerated options to treat hyposalivation. Patients may experience better long-term adherence to Cev treatment along with more reliable enhancements in saliva production and stronger relief from subjective dry mouth symptoms. The study results show that Cev is the primary treatment option for xerostomia management in patients experiencing ongoing symptoms. Pilo is associated with a lower fungal recurrence rate. The choice of medication requires evaluation of patient tolerance levels alongside their existing comorbidities and total medication load.

Appendix A (Graphs)

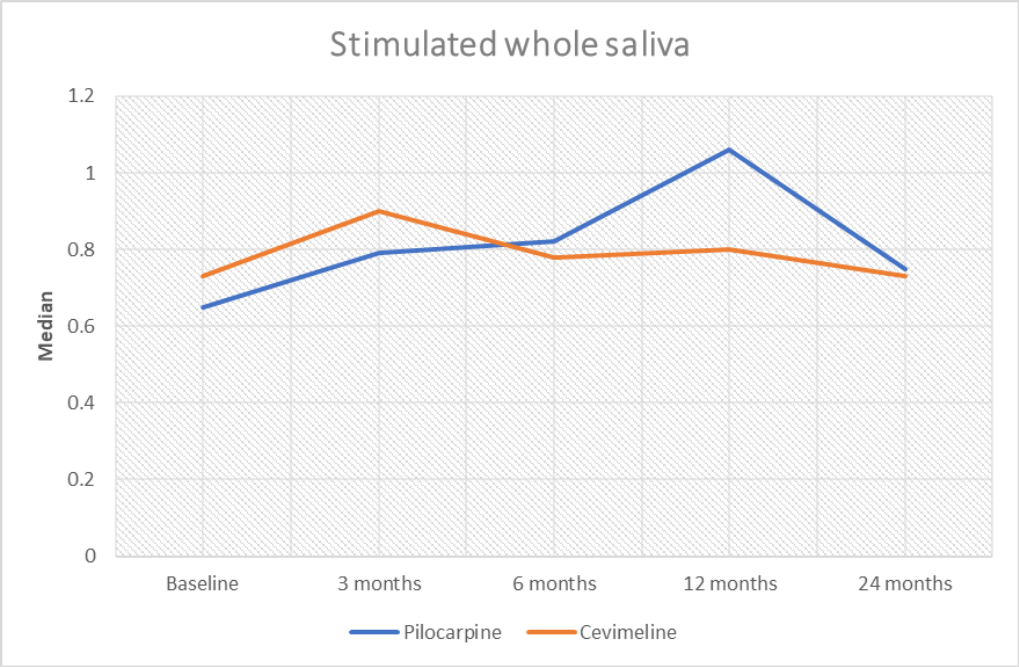
Graph 1: Fungal Infection Recurrent by Medication at Baseline



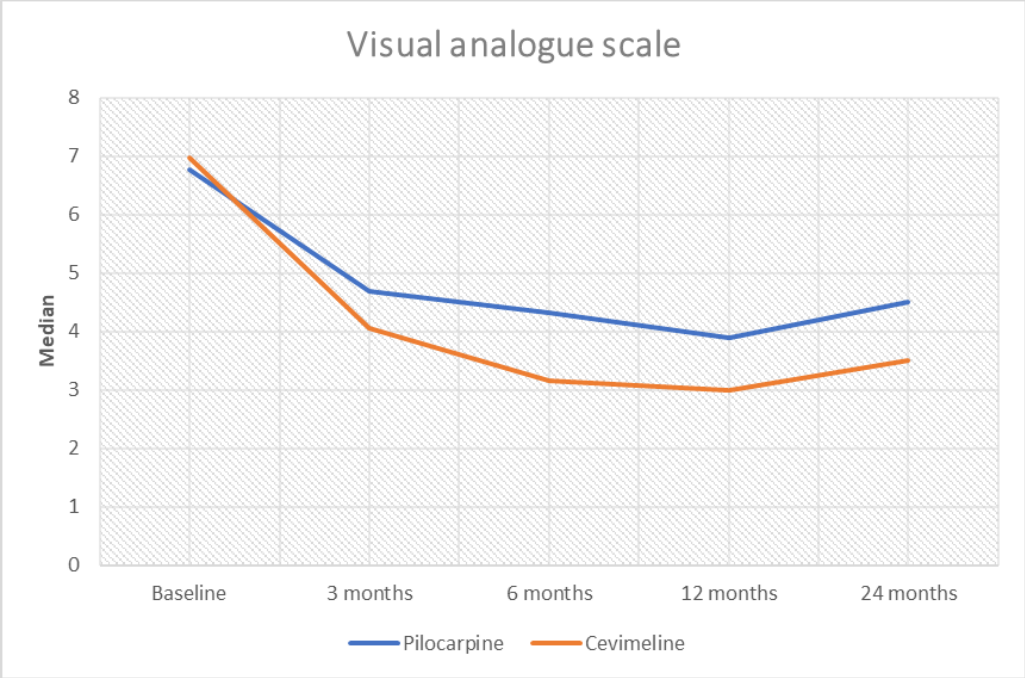
Graph 2: Unstimulated whole saliva through the time in Pilo and Cev medication groups



Graph 3: Stimulated whole saliva through the time in Pilo and Cev medication groups



Graph 4: Visual analogue scale through the time in Pilocarpine and Cev medication groups:



Appendix B (Tables)

Table 1: Demographic and Clinical Characteristics of the Study Population (N = 326)

Variable	Category	N	%
Diagnosis Group	Not reported	57	17.5
	Sjögren's	138	42.3
	Polypharmacy	33	10.1
	Sicca	69	21.2
	Radiation	28	8.6
	Sjögren's and Polypharmacy	1	0.3
Medication	Pilocarpine	138	42.3
	Cevimeline	188	57.7
Gender	Female	270	82.8
	Male	56	17.2
Race	Whie	292	94.8
	Black	8	2.6
	Hispanic	4	1.3
	Other	4	1.3
Insurance Coverage	No	6	1.8
	Yes	320	98.2

Table 2: Age Distribution Across Hyposalivation Groups

Hyposalivation Group	N	Median	IQR
Not reported	57	65	17
Sjogren's	138	68	18
Polypharmacy	33	73	16
Sicca	69	68	14
Radiation	28	74.5	15
Sjogren's + Polypharmacy	1	59	0
Total	326	68	18

Note: Due to the non-normal distribution or presence of small subgroup sizes (e.g., n=1), data represented as median and IQR.

Table 3: Comparison of USW, SWS, and VAS Scores Between Pilocarpine and Cevimeline Groups Over Time

Time	Measure	Medication	N	Median/Mean	IQR/SD	p-value
Baseline	USW	Pilocarpine	138	0.04	0.110	0.563[a]
		Cevimeline	188	0.05	0.130	
	SWS	Pilocarpine	138	0.65	0.940	0.378[a]
		Cevimeline	188	0.73	1.059	
	VAS	Pilocarpine	46	6.78	2.032	0.627[b]
		Cevimeline	39	6.97	1.496	
3 months	USW	Pilocarpine	125	0.08	0.28	0.226[a]
		Cevimeline	173	0.13	0.36	
	SWS	Pilocarpine	125	0.79	1.03	0.209[a]
		Cevimeline	174	0.90	1.10	
	VAS	Pilocarpine	43	4.69	1.858	0.193[b]
		Cevimeline	35	4.06	2.449	
6 months	USW	Pilocarpine	88	0.05	0.26	0.485[a]
		Cevimeline	145	0.07	0.22	
	SWS	Pilocarpine	89	0.82	1.008	0.319[a]
		Cevimeline	145	0.78	1.380	
	VAS	Pilocarpine	18	4.33	2.425	0.082[b]
		Cevimeline	27	3.15	2.013	
12 months	USW	Pilocarpine	50	0.08	0.290	0.554[a]
		Cevimeline	86	0.08	0.280	
	SWS	Pilocarpine	50	1.06	1.580	0.748[a]
		Cevimeline	86	0.80	1.420	
	VAS	Pilocarpine	10	3.90	2.331	0.209[b]
		Cevimeline	10	3.00	2.108	
24 months	USW	Pilocarpine	47	0.10	0.190	0.476[a]
		Cevimeline	81	0.11	0.310	
	SWS	Pilocarpine	47	0.75	1.090	0.616[a]
		Cevimeline	81	0.73	1.290	
	VAS	Pilocarpine	6	4.50	1.516	0.282[b]
		Cevimeline	10	3.50	1.841	

Note: [a]Mann-Whitney U test, [i]ndependent t-test, USW; unstimulated whole saliva, SWS; stimulated whole saliva, VAS; visual analogue scale.

Table 4: Polypharmacy Profile of the Study Participants

Medication Category	Number of Medications	N	%
Antihistamines	0	288	88.3
	1	29	8.9
	2	7	2.2
	3	2	0.6
Antihypertensives	0	232	71.2
	1	62	19.0
	2	27	8.3
	3	4	1.2
	4	1	0.3
Anticholinergic/Antimuscarinic Agents (N = 217)	0	202	93.1
	1	7	3.2
	2	6	2.8
	3	2	0.9
Medications Causing Dry Mouth **(N = 217)**	0	103	47.5
	1	40	18.4
	2	18	8.3
	3	29	13.4
	4	15	6.9
	5	8	3.7
	6	2	0.9
	7	1	0.5
	9	1	0.5

Note. Anticholinergic and dry mouth medication data were available for 217 participants.

Table 5: Baseline Frequency of Reported Side Effects Among Study Participants (N = 326)

Side Effect	Reported (Yes)	N	%
Urinary incontinence	Yes	2	0.6
Sweating	Yes	15	4.6
Worsening Asthma attacks	Yes	1	0.3
Flushing	Yes	9	2.8
Allergic reaction	Yes	3	0.9
Worsening of symptoms in general	Yes	22	6.8
Heart A fibrillation	Yes	2	0.6
Dizziness	Yes	3	0.9
Frequent urination	Yes	1	0.3

Note. Only participants reporting the presence of the listed side effects are presented in the table.

Table 6: Laboratory Tests Reported Among Study Participants (N = 326)

Laboratory test	Reported (Yes)	N	%
SSA blood test (for Sjogren's disease)	Yes	81	25.1
SSB Blood test (for Sjogren's disease)	Yes	57	17.6
ANA profile	Yes	56	17.3
Rheumatoid Factor Test (RFT) test	Yes	30	9.3
Lip Biopsy	Yes	57	17.6

Note. Percentages are calculated based on the total number of participants.

Table 7: Association Between Gender and Hyposalivation Group

Hyposalivation Group	Male N (%)	Female N (%)	Sig.
Not reported	8 (14.0%)	49 (86.0%)	0.000[a]
Sjogren's	6 (4.3%)	132 (95.6%)	
Polypharmacy	13 (39.4%)	20 (60.6%)	
Sicca	17 (24.6%)	52 (75.4%)	
Radiation	12 (42.9%)	16 (57.1%)	
Sjogren's + Polypharmacy	0 (0.0%)	1 (100.0%)	
Total	**56** (17.2%)	**270** (82.8%)	

Note: [a]Fisher's exact test, $p < 0.001$, indicates a significant association between gender and hyposalivation group.

Table 8: Drug adherence and its association with medication at baseline

Adherence Group	Pilocarpine N (%)	Cevimeline N (%)	Total N (%)	p-value
Continue	111 (39.9%)	167 (60.1%)	278 (85.3%)	0.000[a]
Reduced Dose/Frequency	10 (62.5%)	6 (37.5%)	16 (4.9%)	
Stop Medication	8 (66.7%)	4 (33.3%)	12 (3.7%)	
Switched to Cevimeline	9 (90.0%)	1 (10.0%)	10 (3.1%)	
Switched to Pilocarpine	0 (0.0%)	10 (100.0%)	10 (3.1%)	
Total	**138 (42.3%)**	**188 (57.7%)**	**326 (100%)**	

Note: [a]Fisher's exact test, $p < 0.001$, there is a statistically significant association between medication taken and adherence level at baseline.

Table 9: Median and Interquartile Range (IQR) of Fungal Infection Recurrence and OTC Lubricant Use Over Two Years

	Median	IQR
Number of Fungal Infections Recurrent	0	1
Number of OTC Lubricants Used	2	1

Table 10: Fungal Infection Recurrence by Medication over two years

Number of Fungal Infections Recurrent	Pilocarpine N (%)	Cevimeline N (%)	Total N (%)	p-value	P-value
0	65 (48.9%)	68 (51.1%)	133 (61.9%)	0.001[a]	0.016[b]
1	21 (50.0%)	21 (50.0%)	42 (19.5%)		
2	6 (30.0%)	14 (70.0%)	20 (9.3%)		
3	2 (25.0%)	6 (75.0%)	8 (3.7%)		
4	0 (0.0%)	5 (100.0%)	5 (2.3%)		
5	1 (14.3%)	6 (85.7%)	7 (3.3%)		
Total	**95 (44.2%)**	**120 (55.8%)**	**215 (100%)**		

Note: [a]Fisher's exact test, [b]Mann-Whitney U test, $p < 0.001$ is statistically significant.

Table 11: Number of Over-the-Counter (OTC) Oral Lubricants Used Over Two Years by Medication

Number of OTC Lubricants Used	Pilocarpine N (%)	Cevimeline N (%)	Total N (%)	P-value	P-value
0 – None	24 (48.0%)	26 (52.0%)	50 (23.3%)	0.365[a]	0.405[b]
1 – One Product	19 (35.2%)	35 (64.8%)	54 (25.1%)		
2 – Two Products	26 (41.3%)	37 (58.7%)	63 (29.3%)		
3 – Three Products	19 (51.4%)	18 (48.6%)	37 (17.2%)		
4 – Four Products	4 (57.1%)	3 (42.9%)	7 (3.3%)		
5 – Five Products	3 (75.0%)	1 (25.0%)	4 (1.8%)		
Total	**95 (44.2%)**	**120 (55.8%)**	**215 (100%)**		

Note: [a]Fisher's exact test, [b]Mann-Whitney U test

Table 12: Medication Type, Dose, and Frequency Across Timepoints

Variable	Baseline	3 Months	6 Months	12 Months	24 Months (n=128)
Medicine					
Pilocarpine	138 (42.3%)	127 (42.2%)	89 (38.0%)	51 (37.2%)	47 (36.7%)
Cevimeline	188 (57.7%)	174 (57.8%)	145 (62.0%)	86 (62.8%)	81 (63.3%)
Dose					
0 medication	-	1 (0.3%)	-	-	-
30mg Cevimeline	190 (58.3%)	174 (57.6%)	145 (62.0%)	86 (62.8%)	81 (63.3%)
5mg Pilocarpine	125 (38.3%)	119 (39.4%)	79 (33.7%)	46 (34.3%)	43 (33.6%)
7.5mg Pilocarpine	11 (3.4%)	8 (2.7%)	10 (4.3%)	4 (2.9%)	4 (3.1%)
Frequency					
zero	-	1 (0.3%)	1 (0.4%)	-	-
Once	1 (0.3%)	6 (2.0%)	4 (1.7%)	3 (2.2%)	1 (0.8%)
Twice	27 (8.3%)	25 (8.3%)	20 (8.6%)	8 (5.8%)	9 (7.0%)
Thrice	269 (82.5%)	235 (77.8%)	178 (75.7%)	114 (83.2%)	108 (84.4%)
Four Times	29 (8.9%)	35 (11.6%)	32 (13.6%)	12 (8.8%)	10 (7.8%)

Table 13: Side Effects and Discontinuation Over Time

Variable	3 Months (n=308)	6 Months (n=249)	12 Months (n=137)	24 Months (n=129)
Discontinued	7 (2.3%)	4 (1.6%)	2 (1.5%)	0 (0.0%)
Variable	**3 Months (n=312315312) [a]**	**6 Months (n=253) [a]**	**12 Months (n=140) [a]**	**24 Months (n=129) [a]**
None	238292 (92.7238 (76.3%)	238 (94.1%)	128 (91.4%)	127 (98.4%)
Heart palpitations	1 (0.3 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dizziness	2 (0.6%)	2 (0.8%)	1 (0.7%)	0 (0.0%)
Sweating	25 (12 (0.6%)	2 (0.8%)	3 (2.1%)	0 (0.0%)
GI upset	47 (2.24 (1.3%)	4 (1.6%)	3 (2.1%)	1 (0.8%)
Frequent urination	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GERD	121 (0.363%)	1 (0.4%)	1 (0.7%)	1 (0.8%)
Other	6 (1.9%)	6 (2.4%)	4 (2.9%)	0 (0.0%)

Note; [a] is Number of total side effects.

Table 14: Mixed Linear Regression Analysis of Salivary Measurements and VAS Over Time by Medication

Measure	Medication	Time (Months)	Coefficient	Std. Error	95% CI (Lower, Upper)	p-value
Unstimulated whole saliva	Pilocarpine	3	0.223	0.041	(0.141, 0.304)	<0.001
		6	0.149	0.046	(0.058, 0.240)	0.001
		12	0.122	0.057	(0.011, 0.233)	0.032
		24	0.036	0.058	(-0.078, 0.150)	0.538
	Cevimeline	3	0.267	0.034	(0.201, 0.334)	<0.001
		6	0.125	0.036	(0.055, 0.195)	<0.001
		12	0.083	0.043	(-0.001, 0.167)	0.052
		24	0.089	0.044	(0.002, 0.175)	0.044
	All sample	3	0.247	0.026	(0.197, 0.298)	<0.001
		6	0.133	0.028	(0.078, 0.188)	<0.001
		12	0.095	0.034	(0.029, 0.161)	<0.001
		24	0.058	0.034	(-0.010, 0.126)	0.094
		Medication (0= pilocarpine)	0.029	0.026	(-0.023, 0.080)	0.272
Stimulated whole saliva	Pilocarpine	3	0.028	0.428	(-0.811, 0.868)	0.947
		6	0.070	0.472	(-0.855, 0.994)	0.883
		12	1.629	0.572	(0.507, 2.751)	0.004
		24	0.147	0.586	(-1.001, 1.295)	0.802
	Cevimeline	3	0.117	0.062	(-0.006, 0.239)	0.061
		6	0.172	0.066	(0.042, 0.302)	0.009
		12	0.149	0.080	(-0.008, 0.306)	0.062
		24	0.045	0.083	(-0.117, 0.207)	0.583
	All sample	3	0.088	0.182	(-0.269, 0.444)	0.629
		6	0.154	0.195	(-0.229, 0.536)	0.431
		12	0.718	0.234	(0.260, 1.176)	0.002
		24	0.119	0.239	(-0.349, 0.587)	0.619
		Medication (0= pilocarpine)	-0.654	0.148	(-0.356, 0.225)	0.659
Visual analogue scale	Pilocarpine	3	-2.013	0.360	(-2.720, -1.307)	<0.001
		6	-2.414	0.491	(-3.378, -1.451)	<0.001
		12	-2.700	0.624	(-3.923, -1.476)	<0.001
		24	-2.396	0.795	(-3.954, -0.838)	0.003
	Cevimeline	3	-2.673	0.371	(-3.400, -1.964)	<0.001
		6	-3.652	0.406	(-4.448, -2.855)	<0.001
		12	-3.850	0.586	(-4.998, -2.702)	<0.001
		24	-3.805	0.607	(-4.995, -2.615)	<0.001
	All sample	3	-2.343	0.263	(-2.859, -1.827)	<0.001
		6	-3.102	0.320	(-3.729, -2.475)	<0.001
		12	-3.256	0.438	(-4.114, -2.398)	<0.001

		24	-3.129	0.494	(-4.098, -2.160)	<0.001
		Medication (0= pilocarpine)	-0.525	0.320	(-1.151, 0.102)	0.101
Note: $p < 0.001$ is statistically significant.						

Table 15: Association Between Discontinuing Medication and Medication Type Over Time

Time (Months)	Medication	Continued Medication	Discontinued Medication	Total	p-value
3 months	Pilocarpine	122 (96.1%)	5 (3.9%)	127	0.086[a]
	Cevimeline	173 (99.4%)	1 (0.6%)	174	
6 months	Pilocarpine	88 (98.9%)	1 (1.1%)	89	1.000[a]
	Cevimeline	143 (98.6%)	2 (1.4%)	145	
12 months	Pilocarpine	51 (100.0%)	0 (0.0%)	51	0.529[a]
	Cevimeline	84 (97.7%)	2 (2.3%)	86	
24 months	Pilocarpine	47 (100.0%)	0 (0.0%)	47	NA
	Cevimeline	81 (100.0%)	0 (0.0%)	81	

Note: [a]Fisher's exact test

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