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Xerostomia: Understanding the Diagnosis and the Treatment of Dry Mouth

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Abstract

Xerostomia, commonly referred to as dry mouth syndrome, is a result of reduced or absent salivary flow producing mucosal dryness. It can subsequently cause oral discomforts and alterations in taste, cracked and peeling lips, dry nasal passages, and a painful tongue. Its symptoms make tasks such as swallowing, speaking and sleeping difficult and painful, as well as increasing the risk of gum disease and tooth loss through increased formation of plaque and dental caries. Xerostomia is often caused by systemic autoimmune diseases, including diabetes, thyroid disorders and Sjögren's Syndrome, however dry mouth itself has been associated with a variety of mood and anxiety disorders and their treatments; as well, several therapeutic medications are reported as causing xerostomia in at least 10% of users. Treatment options include agents that act as artificial saliva which mimic and provide temporary relief of xerostomia, however they do not stimulate salivary gland production and are thus solely considered replacement therapy. Research is currently working towards developing agents that facilitate saliva production and provide a replacement for natural antimicrobials.

Keywords

Xerostomia, Dry mouth, Treatment, Adverse effect, Psychiatric medications, Antidepressant

Introduction

Saliva can reflect the current condition of ones body and is a very important health indicator [1]. It is a clear, watery, viscous fluid with a pH of 6-7, secreted from the parotid, submaxillary, sublingual and small mucous glands of the mouth [2]. Saliva is composed of fluid ions (potassium, bicarbonate, sodium and chloride ions) and both serous and mucous proteins [2]. Serous secretions contain digestive enzymes, including ptyalin, while mucous secretions contain mucin, a lubricating aid [2], as well as thiocyanate, lysoszyme, immunoglobins, lactoferrin and transferring [2,3]. These play an essential role as antimicrobial constituents, acting to maintain optimal health of an individual by managing lubrication, pH, cleanliness and integrity of the oral cavity [4] and mucosa [1,2].

Saliva secretion happens through a complex process controlled by the autonomic nervous system, and specifically through receptors present in the salivary gland [1]. Secretion occurs subsequent to neurotransmitter stimuli and is derived from both sympathetic and parasympathetic innervations [1]. Sympathetic stimulation mainly affects protein content and composition, whereas parasympathetic stimulation acts to increase the volume of secreted saliva [5]. Normal salivary function is controlled by parasympathetic cholinergic neurotransmission mediated through the muscarinic M3 receptor [2,6]. Stimulating this receptor results specifically in increased watery flow of salivary secretions, as has been shown in human trials [6,7]. This system regulates the secretory function on the acinar cell level and controls the reabsorption process in the striated ducts of salivary glands [1].

Xerostomia, commonly referred to as dry mouth syndrome, is a result of reduced or absent salivary flow [2,8]. Patients with xerostomia report symptoms such as mucosal dryness, oral discomforts and alterations in taste [7,9], cracked and peeling lips, and dry nasal passages [2,10]. These symptoms can result in simple tasks such as swallowing, speaking and sleeping becoming more difficult and painful [2,7,9,11,12]. If left untreated, xeros4tomia can decrease oral pH significantly, thus increasing the formation of plaque and dental caries [2,7,13]. In fact, 3 out of 10 adults experience gum disease and tooth loss as a result of xerostomia [2,14]. Xerostomia is also the leading cause of oral candidiasis, a common oral infection [2,9] and is reported to be more prevalent amongst women than men [15], as well as more prominent in the elderly [2,6,9,10,13-16], where approximately 1 in 5 report the condition [9].

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A major cause of xerostomia is systemic diseases, including diabetes, thyroid disorders, cystic fibrosis and a variety of autoimmune connective tissue diseases which all affect salivary gland function [6,10,13,16]. Sjögren's syndrome is the most prominent chronic, inflammatory autoimmune condition that causes xerostomia [2,13,16,17], as a result of infiltration of salivary and lacrimal glands [16]. Sjögren's syndrome itself affects approximately 1.3 million adults in the United States [18] and is primarily manifested in postmenopausal women [19]. In fact, up to 90% of individuals experiencing this condition are women [10] with a mean age of diagnosis of 50 years [2]. Xerostomia is also a common condition associated with radiation therapy to the head and neck for the treatment of cancer, often as a result of injury to the salivary glands resulting in reduced salivary output [2,7,20]. The prevalence of xerostomia among patients with Sjögren's syndrome and those who have received neck and head radiation is nearly 100% [20,21] with those exposed to neck and head radiation developing permanent xerostomia [13,21].

While it can be part of a variety of diseases, xerostomia is often seen as a common side effect of many medications, such that, medication use is the most prevalent cause of xerostomia [6,9,13] due to specific effects on salivary hypofunction in the mouth [1,10,22,23]. It has been reported that 25 million people in the United States have experienced this uncomfortable side effect in association with medication use [2,6,24]. Xerostomia is noted to be more prevalent in individuals who take a large number of drugs [9,25-29] and/or take medication with higher frequency [1,22]. In previous studies medication has actually been shown to be a better predictor of dry mouth than age or gender [2,6,30]. However, at present we have not been able to predict differences between medications in terms of how xerogenic they are.

Thomson and colleagues [31] reported that severity of dry mouth was higher amongst females or individuals taking: an anti-anginal, an anti-anginal without a concomitant beta-blocker, thyroxine and a diuretic, antidepressants or anti-asthma drugs. As well, due to normal salivary function being modulated by parasympathetic cholinergic neurotransmission through the muscarinic M3 receptor [2,6], anticholinergic activity against the M3 muscarinic receptor is often observed to result in reduced salivary flow [6,7].

For this reason, several classes of over 500 commonly used drugs [8] can cause xerostomia, likely through the M3 receptor [2,6], including antihistamines, antidepressants, antipsychotics, diuretics and sedatives [2,6,8,9,12].A list of the various common medications that have xerostomia reported as a side effect are listed in table 1. Furthermore, several medication complications, both minor and severe, have been associated with xerostomia and are listed in table 2.

As such, dry mouth can also be associated with a variety of pharmaceutical treatment options for mood and anxiety disorders, often leading patients to report dry mouth as a symptom of their disorder, rather than as a side effect of treatment [2,7,8]. While antidepressant medications causing xerostomia were originally thought to be a short-term side effect, it has been demonstrated that the problem may persist over longer periods of time, resulting in a variety of dental problems [1,12]. However, additional research suggests that the physiological effects of depression may also contribute to changes in the amount and nature of salivary production regardless of antidepressant medication [6], due to stimulation of the sympathetic nervous system [1,33]. Patients with depression demonstrate heightened activation of the sympathetic nervous system [34,35], which is responsible for decreasing salivary flow. Furthermore, treatment of depressive symptoms through antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs), has been found to significantly reduce sympathetic activation [36], suggesting the role of depressive physiology in xerostomia.

Due to behavioural consequences in relation to mental health, this syndrome is considered to hinder the capacity of practicing good oral hygiene, reducing ones overall health, as the absence of saliva negatively impacts one's emotional well-being, as well as causing significant morbidity [1,37]. Patients suffering from psychiatric disorders typically experience symptoms of fatigue, lethargy, and lack of motivation, as well as impairments in memory and motor control. These impairments may result in decreases in ones likelihood of establishing good oral hygiene techniques [38,39].

Symptom Management

There are many simple ways to help alleviate and prevent the symptoms of xerostomia from getting worse on a day-to-day basis. Drinking water is a primary option as it will relieve dryness, ease swallowing, hydrate tissues and cleanse the mouth just as saliva does [2,7,9]. Using oral mouthwashes, gels, sprays and artificial saliva may help to reduce the discomfort and improve function momentarily [11]. Oral care products specifically formulated for dry mouth (containing no detergents, have a mild taste, contain antimicrobial proteins) are also recommended for use and are well-tolerated [11]. Sugarless chewing gum and hard candies [7,9], as well as some commercially available lozenges and sprays [2] are also suggested for quick symptomatic relief, but must be sugar-free and non-acidic [1,7,37,40]. Vitamin C tablets have also been recommended to stimulate salivary flow as it acts as a reducing agent, breaking disulfide bonds between cysteine residues in proteins leading to a decrease in saliva viscosity [11]. Frequent use of vitamin C tablets is not recommended, as citric acid and sweeteners are often added to reduce the bitter taste of vitamin C, which have erosive effects on dental enamel [11]. The use of a bedside humidifier during sleep can help alleviate some of the symptoms of xerostomia as well as often associated dry eyes and nasal passages [10]. A diet that contains moisture-rich foods, in addition to staying away from dry foods, foods of temperature extremes, and spicy and sugary flavours may also be helpful [2]. Alcohol [7], caffeine [2], and smoking [2,41,42] should be avoided as they can further irritate and dry out the mucosa.

To help reduce adverse side effects of medications that cause xerostomia, switching medications to a similar drug with fewer xerostomic side effects is an option for patients [10,13]. For example, SSRIs cause less dry mouth than do tricyclic antidepressants [6]. Furthermore, altering the timing and dosing schedule of the medication such as avoiding taking medications at nighttime when salivary flow is usually at its lowest can help minimize the effects of xerostomia [13]. Patients should also be encouraged by their physician to lubricate their mouth with water prior to ingesting medications, followed by a full glass of water. Additionally, dividing drug doses to smaller portions can help avoid the xerostomic side effects caused by a large single dose [13], as well as informing patients what medications can and cannot be crushed for ingestion.

Ultimately natural saliva still provides the best protection for oral tissues [11], with artificial saliva having been formulated in order to mimic the advantages of natural saliva. Still, these agents do not stimulate salivary gland production and are thus considered at best as replacement therapy [2,11,43]. Saliva substitutes, such as Biotène Oral Balance and Xialine, are all commercially available products with moistening and lubricating properties that are intended to provide prolonged wetness of the oral tissue [11]. However, financial costs of these commercially available products must be considered, as well as the risk of patient incompliance.

Future Directions

At present, research is directed at saliva substitutes that wet and lubricate but also provide protection against microorganisms. Histatins are small antimicrobial peptides found in saliva that have a broad antimicrobial spectrum. Currently a number of smaller, more active derivatives have been developed and due to their small size are financially cost effective to produce. Nieuw Amerongen and Veerman [11] have demonstrated that a cationic antimicrobial peptide retains its antifungicidal activity in Xialine, *in vitro*. The application of these compounds in saliva substitutes is currently under investigation.

Pilocarpine is a cholinergic parasympathomimetic agent with

Table 1: Commonly prescribed medications associated with xerostomia

Category	Generic Name (Brand)	Mechanism of Action
Anticholinergic Agents	Atropine (Atreza, Sal-Tropine, AtroPen) Belladonna Benztropine (Cogentin) Oxybutynin (Ditropan XL, Urotrol) Scopolamine (Scopace) Trihexyphenidyl (Artane)	Inhibit parasympathetic nerve impulses through the blockage of acetylcholine
Selective Serotonin-Reuptake Inhibitors	Citalopram (Celexa) Escitalopram (Lexapro) Fluvoxamine (Luvox) Fluoxetine (Prozac, Sarefem) Paroxetine (Paxil) Sertraline (Zoloft, Lustral)	Block the reabsorption of serotonin
Tricyclic Antidepressants	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Nortriptyline (Pamelor, Aventyl) Imipramine (Tofranil, Praminil)	Block the reabsorption of serotonin and norepinephrine
Tetracyclic Antidepressants	Mirtazpine (Remeron) Amoxapine (Ascendin)	Block the reabsorption of serotonin and/or norepinephrine
Monoamine Oxidase Inhibitors	Phenelzine (Nardil) Tranylcypromine (Parnate) Isocarboxazid (Marplan) Rasagiline (Azilect)	Increase levels of serotonin, norepinephrine, and dopamine through the inhibition of monoamine oxidase
Antipsychotic Agents	Haloperidol (Haldol) Oimozide (Oral) Olanzapine (Zyprexa) Quetiapine (Seroquel)	Primarily block D_2 receptors and/or 5-HT_{2A} receptors
Diuretic Agents	Chlorothiazide (Diuril) Furosemide (Lasix) Hydrochlorothiazide (Aquazide H, Microzide, HydroDIURIL) Triamterene (Dyrenium)	Promote the excretion of salt and water from the kidneys to increase urine volume; prevent reabsorption of chloride and sodium ions in the Loop of Henle
Antihypertensive Agents		
ACE Inhibitors	Captopril (Capoten) Enalapril (Epaned, Vasotec) Lisinopril (Prinivil, Zestril)	Inhibit angiotensin converting enzyme activity leading to decreases in angiotensin II
Beta Blockers	Atenolol (Tenormin) Carvedilol (Coreg) Propranolol (Hemangeol)	Block norepinephrine and epinephrine from binding to beta receptors on nerves
Calcium Channel Blockers	Amlodipine (Norvasc) Felodipine (Plendil) Nicardipine (Cardene)	Decrease calcium flow into heart cells and blood vessel walls
Benzodiazepines	Alprazolam (Xanax) Diazepam (Valium) Flurazepam (Dalmane) Temazepam (Restoril) Triazolam (Halcion)	Enhances response to GABA by opening GABA-activated chloride channels, allowing chloride ions into the neuron leading the a negative charge, becoming resistant to excitation
Muscle Relaxant Agents	Cyclobenzaprine (Amrix, Flexeril, Fexmid) Orphenadrine (Norflex) Tizanidine (Zanaflex)	Block nerve impulses that are sent to the brain

Analgesic Agents		
Narcotics/Opioids	Codeine	Reduce the sending of pain signals to the brain by binding to opioid receptors in the brain, spinal cord, and other regions in the body to reduce pain sensations
	Methadone	
	Pentazocine (Talwin)	
	Propoxyphene (Darvon)	
	Tramadol (Ultram, ConZip)	
	Oxycodone (OxyContin, Percocet)	
Nonsteroidal anti-inflammatory agents	Diflunisal (Dolobid)	Block cyclooxygenase enzyme and reduce prostaglandins throughout the body
	Ibuprofen (Advil, Motrin, Midol)	
	Naproxen (Aleve, Anaprox)	
	Piroxicam (Feldene)	
Antihistamines	Astemizole (Hismanal)	Inhibit histamine activity by blocking H1 and H2 receptors
	Brompheniramine (Bromax, Siltane)	
	Chlorpheniramine (Ahist, Chlor-Trimeton)	
	Diphenhydramine (Benadryl)	
	Loratadine (Claritin, Alavert)	
	Meclizine (Antivert, Bonine)	

Table 2: Complications associated with xerostomia

Dysgeusia	Taste disorder leading to distortions in ones taste, often described as metallic. Often associated with a complete loss of taste or decrease in taste sensitivity.
Glossodynia	Burning sensation in the mouth and tongue, often leading to alterations in taste and/or smell.
Cheilitis	Inflammation of the lips and surrounding skin.
Sialadenitis	Inflammation and enlargement of one or more salivary glands, associated with pain, redness, and swelling.
Halitosis	Unpleasant odor of breath as a result of poor oral hygiene.
Oral Candidiasis	Results from the accumulation of the fungus Candida albicans on the lining of the mouth, causing white lesions on the tongue and inner cheeks.
Dental Caries	Tooth decay due to bacteria that may result in inflammation of the tissue surrounding the teeth or formation of an abscess.

M3 muscarinic action that stimulates the residual functioning of salivary glands and has been shown to significantly decrease dryness of the mouth [1,2,11,44]. It has also been shown to relieve dry mouth symptoms in xerostomia induced cancer patients from head and neck radioactivity. As well, Masters [45] found that pilocarpine was an effective treatment of xerostomia induced by psychoactive medications, with side effects mainly consisting of sweating and increased urination, and no adverse effect on psychiatric symptoms in patients. Pilocarpine is available commercially in a tablet form under the brand name Salagen, with an effect duration of two to three hours, yet it is often 2 months or longer before the maximal effect is reached [2,11]. Cevimeline, a cholinergic agonist, and Anetholetrithione, a cholagogue, have also been successful medications used in the treatment of xerostomia, but reports differ regarding their efficacy [2].

Human interferon alpha (IFN-α), recognized for its role as an inducer of the differentiation and activation of dendritic cells [46], are currently undergoing clinical trials to determine their safety and efficacy as low-dose lozenges in the treatment of salivary gland dysfunction and xerostomia [2]. Other areas of research include slow-release delivery systems for pilocarpine, the development of saliva substitutes with longer mucosal surface retention, vaccination with auto-reactive T cells or T cell receptor peptides, as well as the possibility of inserting aquaporins into the cell membrane of ductal cells [2] appear to be future approaches for the management of xerostomia.

Summary

Xerostomia, or dry mouth syndrome, is the result of reduced or absent salivary flow. It may occur as a result of systemic disease, autoimmune conditions, and radiation to the head and neck or on-going drug use, with concurrent medications appearing to be the most prevalent cause of dry mouth. There are over 500 commonly used drugs that list xerostomia as a side effect, including various antihistamines, antidepressants, antipsychotics, diuretics and sedatives. Of these, antidepressants are displayed as the most outstanding class of drug associated with xerostomia. Research suggests that dry mouth, which was once thought to be a short-term side effect is more severe and persistent than originally perceived, with its associated problems leading to long-term dental-related issues. Temporary relief options include oral mouthwashes, gels and sprays, lozenges, and gum, however more prolonged treatment options such as artificial saliva with added protection from microorganisms as a result of the addition of small antimicrobial peptides are being developed and investigated. There are several future areas of research for xerostomia treatment such as slow-release delivery systems for pilocarpine, and the development of saliva substitutes with longer mucosal surface retention. Thus, xerostomia must be considered as a recognizable and extremely important undiagnosed side effect of multiple medical conditions, and is a syndrome of concern in need of direct attention.

Conflicts of Interest

IlinaRistevska has no conflicts of interest to declare.

Rosaria S. Armata has no conflicts of interest to declare.

Christina D'Ambrosio has no conflicts of interest to declare.

Melissa Furtado has no conflicts of interests to declare

Leena Anand has no conflicts of interests to declare

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Rosaria S. Armata reviewed the literature and contributed to the writing of the manuscript.

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