



Review

Salivary Secretory Disorders, Inducing Drugs, and Clinical Management

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Abstract

Background: Salivary secretory disorders can be the result of a wide range of factors. Their prevalence and negative effects on the patient's quality of life oblige the clinician to confront the issue.

Aim: To review the salivary secretory disorders, inducing drugs and their clinical management.

Methods: In this article, a literature search of these dysfunctions was conducted with the assistance of a research librarian in the MEDLINE/PubMed Database.

Results: Xerostomia, or dry mouth syndrome, can be caused by medication, systemic diseases such as Sjögren's Syndrome, glandular pathologies, and radiotherapy of the head and neck. Treatment of dry mouth is aimed at both minimizing its symptoms and preventing oral complications with the employment of sialogogues and topical acting substances. Sialorrhea and drooling, are mainly due to medication or neurological systemic disease. There are various therapeutic, pharmacologic, and surgical alternatives for its management. The pharmacology of most of the substances employed for the treatment of salivary disorders is well-known. Nevertheless, in some cases a significant improvement in salivary function has not been observed after their administration.

Conclusion: At present, there are numerous frequently prescribed drugs whose unwanted effects include some kind of salivary disorder. In addition, the differing pathologic mechanisms, and the great variety of existing treatments hinder the clinical management of these patients.

The authors have designed an algorithm to facilitate the decision making process when physicians, oral surgeons, or dentists face these salivary dysfunctions.

Key words: Saliva, Drugs, Xerostomia, Sialorrhea, Drooling

Introduction

Saliva is an aqueous, hypotonic solution which protects all the tissues of the oral cavity. It is secreted by the major salivary glands – the parotid, submandibular or submaxillary, and sublingual. In the oral cavity there are also a large number of minor salivary glands found on the surfaces of the buccal, palatine, and labial mucosa, as in the tongue, sub-lingual area, and in the retromolar region [1].

The salivary gland structure is made up of acinar cells, accessory ducts (intercalated and intralobular),

striated ducts, and the principal duct (Stensen, Wharton, Bartholin, and Rivinus) [1].

Both afferent and efferent stimuli modulate neural control of salivation. Apart from taste and mastication, which play a key role, the former also include smell, sight, and thought. Input to the solitary nucleus from afferent stimuli is integrated via the facial (VII) and glossopharyngeal (IX) nerves [2-4].

Parasympathetic efferent pathways for the sublingual and submandibular glands are from the facial

nerve via the submandibular ganglion; and for the parotid gland from the glossopharyngeal nerve via the otic ganglion. The parasympathetic nervous system, through the liberation of acetylcholine, acts upon the muscarinic M3 receptors and produces an abundant secretion of aqueous saliva. Sympathetic post-ganglionic pathways are from the cervical ganglion of the sympathetic chain. Stimulation of the sympathetic nervous system by the binding of norepinephrine to β -adrenergic receptors produces a thicker and less abundant secretion [1,4-6].

Saliva formation and secretion is considered to be a two-step process [1,7]:

Stage 1. Secretion of the isotonic plasma-like primary saliva fluid takes place in the secretory end-pieces, also called acinar cells. There is a functional coupling mechanism between salt and fluid secretory processes. Ion channels and transporters promote a vectorial ion transport in the secretory direction from the serosal (basolateral) to luminal (apical) side. Water movement in the salivary glands requires the transcellular secretion of Cl⁻. The Cl⁻-transporting proteins expressed at the basolateral membrane must, therefore, accumulate Cl⁻ at a quantity superior to its equilibrium potential.

Stage 2. The NaCl-rich fluid is modified during its passage along the duct system, where most of the NaCl is reabsorbed. The K⁺ concentration in saliva is higher than that found in plasma due to KHCO₃ secretion. The final saliva is usually hypotonic because the ductal epithelium is poorly permeable to water and, moreover, NaCl reabsorption is greater than KHCO₃ secretion.

Saliva is primarily made up of water (99%) and a number of electrolytes which include sodium, potassium, calcium, magnesium, bicarbonate, and phosphate. In addition, there are organic components: immunoglobulins (IgA, IgG, IgM), proteins, enzymes, mucins, and nitrogenized products (urea and ammonium). The pH values of this biological fluid basically vary from 6 to 7. Whilst saliva is initially isotonic, during its ductal trajectory it becomes hypotonic. We can distinguish between glandular saliva, which comes directly from a gland, and total saliva or oral fluid, glandular saliva with contaminating elements from the mouth itself [1,5,8,9]. The latter has an effect on the oral cavity structures and plays a role in digestion (Table 1) [8,10].

The major glands are primarily responsible for salivary volume and electrolyte content; the minor ones produce a smaller quantity with a high content of substances from the ABO blood group, neutrophils and other leukocytes [8]. Over 90% of unstimulated salivary secretion is produced by the major salivary glands: 20% from the parotid glands, 65% from the

submandibular ones, 7-8% from the sublingual ones, and approximately 10% from the minor salivary glands. With stimulated saliva the percentages differ considerably, the parotid glands being responsible for more than 50% of secreted saliva [8].

Table 1: Saliva composition and functions: Relations and roles among the various salivary constituents.

INFLUENCED AREAS	FUNCTIONS	SALIVARY CONSTITUENTS
Teeth	Inhibition of demineralization	Mucins
	Remineralization / Buffering	Proline-rich proteins Statherin Calcium Bicarbonate Phosphate Proteins
	Lubrication, viscoelasticity	Proline-rich glycoprotein Mucins
	Digestion	Amylase DNase, RNase Lipase Protease
Food	Taste	Zinc
	Bolus	Mucins
	Antiviral	Mucins Immunoglobulins Cystatins
Microbes	Antifungal	Immunoglobulins Mucins Histatins
	Antibacterial	Mucins Lysozyme Lactoferrin Lactoperoxidase Histatin Agglutinin Cystatins VEGh

There is a wide inter-individual variation of salivary fluid rates. Values of 0.3 to 0.5 ml/min are considered normal for unstimulated salivary flow; and values between 0.01 and 0.1 ml/min are considered hyposalivation. Stimulated salivary flow is considered normal when values are from 1 to 2 ml/min; <0.7 ml/min is considered reduced [11]. Average daily saliva flow is from 0.8 l to 1.5 l [1,8].

Sialometry encompasses a range of diagnostic tests aimed at evaluating the rate of salivary secretion (quantitative sialometry) and analyzing its composition (qualitative sialometry). When quantitative sialometry is employed it should be specified whether the saliva is mixed or uni-glandular, and whether the figures have been obtained at unstimulated state or after stimulating the secretion. Endogenous and exogenous salivary constituents are determined through qualitative sialometry: the former to assess physiological states and diagnose salivary gland diseases and systemic metabolopathies, and the latter to confirm treatment compliance and intoxication [12].

Salivary secretory disorders, xerostomia and sialorrhea, can be caused by a wide range of factors

including drugs [8].

Xerostomia is the term used for the subjective sensation of dry mouth. This syndrome is a combination of signs and symptoms associated with a decrease in the secretion of saliva [13-15]. The reported prevalence of xerostomia ranges from 17-29%, and in a recent cross-sectional study approximately 20% was observed. Women have a significantly higher rate than men. The most frequent causes of dry mouth among dental patients are the use of xerogenic medications, head and neck radiotherapy, and Sjögren syndrome. It is generally accepted that xerostomia results in a lower quality of life for all affected patients [15-18].

Sialorrhea is a salivary hyper-secretion clinically diagnosed by quantitative sialometry. Drooling in many cases is not accompanied by an increased salivary flow, generally the flow of saliva is normal or reduced and only the handling of saliva is disturbed. However, some drooling in infants and toddlers is normal and it may occur with teething [14-19].

To the best of our knowledge, there are no data concerning sialorrhea prevalence rates in the literature. However, some authors have reported a drooling prevalence of approximately 14% in their control group, and 56% in the Parkinson's disease one. In children with cerebral palsy the range of drooling prevalence was between 45-58% [20-23].

The objectives of the present review were:

- 1- Study different causes of xerostomia, sialorrhea and drooling.
- 2- Review the most important drug-effects involved in these disorders.
- 3- Provide a clinical approach to the current management strategies for these entities.

Methods

A literature search was conducted with the assistance of a research librarian in the MEDLINE/PubMed Database. The primary outcome was to identify all literature containing original and review data describing (a) causes of xerostomia, sialorrhea and drooling, (b) the drugs related with xerostomia, sialorrhea and drooling, and (c) management strategies of these salivary gland disorders.

The following terms were covered in the search were covered the terms: xerostomia (MeSH), sialorrhea (MeSH), drooling (MeSH), and "AND" - combined with terms: "causes", "ethiology", "drugs", "drug induced", "Sjögren's syndrome", "head and neck radiation", "management", "therapy", "bioengineering" (MeSH).

Selection of studies

The selection of qualified studies was performed

in three stages. First stage: assessment of the title alone. Second stage: based on the abstract, they were reviewed and irrelevant citations were removed. Third stage: selection based on the review of full-text article. The selected articles were distributed to the reviewer team along with a customized evaluation form for reviewing xerostomia, sialorrhea and drooling.

Xerostomia

This disorder may be caused by medication, systemic diseases, pathologies of the salivary glands, and head and neck radiotherapy (Table 2) [15-24].

Drug induced xerostomia

From an etiological perspective, xerostomia is most frequently associated with medication. It is the side effect of a large number of drugs and 70% of adults taking some kind of medication can suffer from it [24].

Anticholinergic and antimuscarinic agents are drugs with the capacity to reduce or block the effects produced by acetylcholine on the central and peripheral nervous system. They are generally competitive reversible antagonists of some of the two types of acetylcholine receptors, and are classified according to the receptor they block. Most anticholinergic agents affect muscarinic gland receptors producing a decrease in salivary secretion [5].

Antidepressants, such as fluoxetine, with a serotonergic action have xerostomia as a common side effect. Xerostomia is also observed in other kinds of antidepressants (monoamine-oxidase inhibitors, tricyclics, heterocyclics, and others) and antipsychotics, many of which are anticholinergic agents [5].

Within the group of diuretics the loop and potassium-sparing ones are noteworthy as their target molecules include Na^+ , Cl^- and K^+ , electrolytes present in the production-secretion process of saliva [15,25,26].

Table 2: Main causes underlying xerostomia.

Drugs	See table 3
Systemic diseases	Sjögren's syndrome (primary and secondary) Granulomatous diseases (sarcoidosis, tuberculosis) Graft-versus-host disease Bone marrow transplantation Renal dialysis Malnutrition (anorexia, bulimia, dehydration)
Radiation and radioisotopes	External beam radiation Internal radionuclide therapy Radioactive iodine (I-131) Head and neck radiation

Table 3: Some drugs known to be associated with drug-induced xerostomia.

Anticholinergic/antimuscarinic agents	Atropine, belladonna, benztropine, oxybutynin, scopolamine, trihexyphenidyl
Diuretic agents	Chlorothiazide, furosemide, hydrochlorothiazide, triamterene
Antihypertensive agents	Captopril, clonidine, clonidine/chlorthalidone, enalapril, guanfacine, lisinopril, methyl dopa
Antidepressants and antipsychotics	Selective serotonin-reuptake inhibitors: citalopram, fluoxetine, paroxetine, sertraline, venlafaxine Tricyclic antidepressants: imipramine, amitriptyline, desipramine, nortriptyline Monoamine oxidase inhibitors (MAO): phenelzine Other antidepressants: bupropion, nefazodone, mirtazapine Typical (first generation) and atypical (second generation) antipsychotics: haloperidol, pimozide, clozapine, olanzapine
Antihistamines	Astemizole, brompheniramine, chlorpheniramine, diphenhydramine, loratadine, meclizine
Sedative and anxiolytic agents	Alprazolam, diazepam, furazepam, temazepam, triazolam
Muscle relaxant agents	Cyclobenzaprine, orphenadrine, tizanidine
Opioids analgesic agents	Central nervous system: codeine, meperidine, methadone, pentazocine, propoxyphene, tramadol
Nonsteroidal anti-inflammatory agents	Diflunisal, ibuprofen, naproxen, piroxicam
Other drugs	Anorexiant: diethylpropion (amfepramone), sibutramine Antiacne agents (retinoids): isotretinoin Anticonvulsants: carbamazepine Antidysrhythmics: disopyramide Anti-incontinence agent -anticholinergics-: tolterodine Antiparkinsonian agents: carbidopa / levodopa Bronchial dilators-anticholinergics-: ipratropium Ophthalmic formulations: brimonidine (alpha-2 adrenergic agonist) Smoking cessation agents: nicotine Adrenergic agents: Amphetamine Drugs of abuse: MDMA, cannabis

Antihypertensive drugs such as the inhibitors of the angiotensin-converting enzyme (captopril and enalapril) may cause the accumulation of bradykinin-tissular mediator which is responsible for a large number of adverse reactions. Up to 8% of patients taking captopril, enalapril, and lisinopril present xerostomia [27,28].

Anxiolytic, sedative, and opiate drugs may provoke xerostomia as a secondary effect in patients who are taking them chronically [29,32].

Some *antihistamines*, particularly those of the first generation and some of the third, for instance, desloratadine, have an antimuscarinic effect which may lead to xerostomia and sedation. Second and third generation antihistamines effectively antagonize H1 receptors without any special affinity for the muscarinic receptors [33,34].

A number of *non-steroidal analgesic and anti-inflammatory drugs* (diflunisal, ibuprofen, naproxen,

and piroxicam), *anorexigens, anti-acne, anti-parkinsons, and anti-smoking agents* amongst others, may cause a decrease in salivary secretion as a secondary effect (Table 3) [35].

Adrenergic agents may induce dry mouth syndrome. Amphetamine and MDMA (also known as ecstasy) can act directly or indirectly on a number of receptors, including the α 2-adrenergic one, thus causing xerostomia. Occasionally, this effect may also lead to an acute localized periodontal pathology. Several reported cases of necrotizing ulcerative gingivitis (NUG) have been associated with the consumption of MDMA. The possible mechanism may be due to a direct contact between the drug and the oral mucosa, the acid components of the tablet, and the dry mouth induced by MDMA [36].

Other illicit drugs, for example cannabis, produce short-term hyposalivation due to the action of delta-9-tetrahydrocannabinol (THC) [37].

Xerostomia and Sjögren syndrome

Sjögren Syndrome (SS) is a multisystem autoimmune disease which causes lymphocytic infiltration in the exocrine glands, particularly the salivary and lacrimal ones leading to the characteristic features of dry eye and salivary dysfunction (xerostomia). In addition, approximately one third of the patients present systemic extraglandular manifestations [38].

Focal lymphocytic sialoadenitis (FLS) of the labial salivary glands (minor glands) has long been associated with SS. Daniels *et al.* [39,40] observed that the focus score of FLS is strongly associated with the ocular and serologic components of SS and reflects SS autoimmunity.

Broadly accepted classification norms were developed and validated between 1989 and 1996 by the European Study Group on Classification Criteria for SS. The most widely accepted classification criteria for SS are the American-European Consensus Group (AECG) revised version [38]. Recently, the Sjögren's International Collaborative Clinical Alliance (SICCA) published new classification criteria following the American College of Rheumatology guidelines [41]. This consensus criticized the inclusion of subjective tests (symptoms), physiological measures that lack specificity, and alternate objective tests that are not diagnostically equivalent to the AECG classification criteria [39,41,42]. However, the final classification criteria might be a mix of the AECG and the SICCA.

Head and neck radiation

Radiotherapy (RT) of the head and neck region may cause acute side-effects such as mucositis, dysphagia, hoarseness, erythema, and desquamation of the skin [43,44]. Later may appear chronic injuries to

vasculature, salivary glands, mucosa, connective tissue, and bone. The severity of these complications depends on radiation dosimetry, and treatment duration [45].

Xerostomia is the main complication in these irradiated patients as it usually involves a high radiation dose to both salivary gland [46].

Radiation-induced xerostomia has an early onset: in the first week, half the patients present a decrease in salivary flow. After 7 weeks of head and neck RT the salivary flow diminishes up to 20% [47]. Salivary function continues to decline after RT, and there is minimal long-term recovery [45].

With respect to the mean radiation dose, some authors have indicated that less than 25-35 Gy will probably prevent long-term injury. However, the issue as to whether there is a threshold dose for initiating injury versus a gradual dose-complication remains controversial. After head and neck RT, salivary glands have a limited capacity for repair especially with mean doses above 40 Gy [48].

Sialorrhea and Drooling

Salivary hypersecretion/sialorrhea and drooling, may be caused by medication, systemic diseases, psychiatric disorders, oral pathologies, and toxic substances (Table 4) [14].

In healthy subjects drugs may increase saliva secretion but usually not result in drooling, the produced saliva can be easily handled. On the other hand, drooling is generally accompanied by insufficient handling of saliva and not by hypersalivation.

Drug-induced sialorrhea and/or drooling

Direct muscarinic agonists are parasympathomimetic and, therefore, increase cholinergic tone and induce sialorrhea. Pilocarpine, used to treat wide-angle glaucoma, causes salivary hypersecretion as one of its adverse effects. The muscarinic agonist, arecoline, is an alkaloid with parasympathomimetic properties (see also at the end of this section the betel nut comment). Bethanechol is a cholinergic drug that selectively stimulates the parasympathetic nervous system across muscarinic receptors. It is sometimes given orally or subcutaneously to treat urinary retention resulting from a general anesthetic, diabetic neuropathy of the bladder, or to treat gastrointestinal atony (lack of muscular tone). Cevimeline is also a parasympathomimetic and muscarinic agonist with particular effect on M_3 receptors [13,49].

Table 4: Main causes underlying drooling or sialorrhea.

Drugs	See table 5
Neurological diseases	Myasthenia gravis Cerebral palsy Facial paralysis Guillain-Barré syndrome Motor neuron disease, notable amyotrophic lateral sclerosis (ALS) Moebius syndrome Cerebrovascular accidents Parkinson's disease Congenital suprabulbar palsy Hydrocephalus Hypoxic encephalopathy Freeman-Sheldon syndrome Psychosis Brain tumors Seizures Severe mental retardation, Down syndrome Worster-Drought syndrome Landau-Kleffner syndrome Encephalitis Angleman syndrome
Systemic diseases	Nasal obstruction Heavy metal poisoning Hyperhydration Digestive pathologies: Oesophageal spasms, tumors and ulcerations, gastric disorders accompanied by nausea and vomiting, pancreatitis, bladder processes, intestinal infections
Oral conditions	Mucosal ulcerations Teething Ulcerative lichen planus Herpetic ulceration Traumatic ulceration Oral pain: pulpitis, periodontitis, stomatitis Pharynx and tonsillar Inflammation, irritative and ulcerative lesions

Table 5: Some drugs known to be associated with drug-induced drooling or sialorrhea.

Direct cholinergic/muscarinic agonists	Bethanechol, pilocarpine, arecoline, cevimeline
Indirect cholinergic/muscarinic agonists (acetylcholinesterase inhibitors)	Edrophonium, neostigmine, physostigmine, pyridostigmine, metrifonate, donepezil, galantamine, rivastigmine, tacrine
Antipsychotics	Typical (first generation) antipsychotics: haloperidol, fluphenazine Atypical (second generation) antipsychotics: clozapine, risperidone, olanzapine Reserpine
Sedative medications	Anticonvulsants-antiepileptics Benzodiazepines
Adrenergic antagonists (peripheral)	Yohimbine
Medications irritating the esophagus	Doxycycline, tetracycline, iron preparations, quinidine, potassium, nonsteroidal anti-inflammatory drugs
Poisons and toxins	Heavy metals: arsenic, manganese, mercury (inorganic volatile), thallium Organophosphates: insecticides, nerve gases (sarin, tabun, soman, VX) Food poisoning: <i>Amanita muscaria</i> Illicit drugs: phencyclidine (PCP)
Herbal and fruit preparations	Betel nut, jaborandi, yohimbine, citric acid, red pepper

Indirect muscarinic stimulants are primarily inhibitors of the acetylcholinesterase enzyme, they increase acetylcholine to stimulate muscarinic and nicotinic receptors which results in an increased saliva flow. Donepezil, galantamine, and rivastigmine, the main clinical acetylcholinesterase inhibitors, are used in the treatment of Alzheimer's disease. Despite its compelling mechanism, drooling is rarely considered to be a clinical problem with this class of drugs [50-52]. Other inhibitors of acetylcholinesterase are edrophonium, neostigmine, and physostigmine, mainly employed in the diagnosis and treatment of myasthenia gravis [53].

Antidopaminergic drugs can all potentially lead to drooling if they cause clinical bradykinesia which results in a low rate of swallowing. This is usually clinically quite evident as patients appear to have extrapyramidal side effects. Antipsychotic drugs can, therefore, produce sialorrhea due to:

1. Induced parkinson symptoms.
2. Blockage of the α 2-adrenergic receptors or decrease of noradrenaline.
3. Direct agonism of the M3 and M4 muscarinic receptors.

Typical (first generation) antipsychotic drugs, such as haloperidol and fluphenazine, are stronger inducers for extrapyramidal symptoms than those of the atypical (second generation) antipsychotics, for instance clozapine, risperidone, and olanzapine. Another mechanism that interferes with swallowing is excessive sedation, a side effect of many antipsychotics [13].

Clozapine is the atypical *antipsychotic* prototype. It can cause sialorrhea due to its agonist effect on the M3 and M4 glandular muscarinic receptors which leads to an increase in salivary secretion through the parasympathetic nervous system, and also because of its antagonism with the α 2-adrenergic receptors of the sympathetic nervous system [54,55].

In some cases, *benzodiazepines* may cause drooling, indicating a change in the underlying swallowing process due to excessive sedation, particularly at high doses [13].

Drooling can also result from an esophagus mucosal inflammation induced by tetracycline, doxycycline, iron preparations, quinidine, potassium, and non-steroidal anti-inflammatory drugs which might impair swallowing either functionally or from pain [13,14].

Drooling is a hallmark of some toxins such as organophosphate insecticides and related nerve agents which irreversibly block the acetylcholinesterase enzyme, thus producing signs and symptoms from the overstimulation of the muscarinic and nicotinic receptors. Pro-cholinergic toxins from mushrooms such as the muscarine (*Amanita muscaria*) can

produce sialorrhea in acute intoxication. Poisoning from mercury, thallium, manganese, and arsenic can also induce drooling [56-60], and it is also a clinical sign of some illicit drugs such as phencyclidine (PCP) [13].

A number of preparations based on herbs, for instance jaborandi which contains pilocarpine, and yohimbine supplements (alkaloids) considered to be peripheral adrenergic α 2 antagonists, may stimulate salivary secretion [61,62]. In addition, the betel nut, a widely used drug chewed by millions of people in Southeast Asia, contains arecoline a direct muscarinic agonist which can cause "betel nut drooling", whilst both citric acid and red pepper can stimulate saliva flow (Table 5) [13].

Neurological diseases

Drooling is often a consequence of some centrally neurological disorders, as in patients affected by cerebral palsy or mental retardation. Nevertheless, there are some peripheral affections such as seventh or ninth cranial nerve palsies where drooling may be also present [63]. Furthermore, Lespargot *et al.* indicated that drooling is related to one or more of three abnormalities [64]:

- Incomplete lip closure during swallowing.
- Low suction pressure.
- Prolonged delay between the suction and the propulsion phase of the intra-oral, as opposed to the pharyngeal or oesophageal, stage of swallowing.

Management

Xerostomia

Xerostomia has clear, negative effects on oral-dental tissue. Some of the best known side effects include demineralization of tooth enamel, rampant decay, super-infections caused by fungal diseases (candidiasis), reactive gingival enlargement due to dehydration, and loss of salivary antimicrobial properties [15]. Xerostomia can also influence ingestion, swallowing, and speech articulation, thus negatively affecting the quality of life of people suffering from it [65,66]. Its high prevalence, 17-29% according to population samples based on salivary flow, makes it advisable that its clinical management be well-known [15]. See the algorithm (Fig 1).

Initial treatment of xerostomia is basically palliative, minimizing symptoms and preventing oral complications [15,62,66].

- The elimination of possible factors for xerostomia such as mouthwashes with an alcoholic content, diet sugar, and toxic habits including alcohol and tobacco.

- Preventive treatment for complications.
If xerostomia is an unwanted consequence of pharmacological treatment [67,68]:
- The possibility of alternative medication with different mechanism of action should be considered.
- Reduction of the prescribed dosage may, in some cases, increase salivary flow.
- There are a number of varying frequently employed drugs and strategies for the clinical management of these patients: sialogogic drugs, immunologic agents, topical medication, and complementary and alternative medicine [19,69].

Sialogogic drugs

Sialogogic drugs are substances designed to stimulate salivary secretion as they have an effect on the systemic pathway. These drugs act upon differing receptor groups:

- Direct and indirect muscarinic agonists.
- Peripheral adrenergic $\alpha 2$ antagonists.
- Centrally active agents that diminish adrenergic tone.

Pilocarpine has been shown to be efficient in SS patients, irradiated and with bone marrow transplants. Studies have reported positive results with respect to glandular function and improvement in

symptoms [19,69-73]. Pilocarpine dosage is from 5 to 10 mg 1 h before eating, 3 times a day oral route (OR). Onset of effects at 30 min with a duration between 2-3 h [72].

Cevimeline Hydrochloride is indicated for the treatment of dry mouth syndrome in patients with SS. The recommended dosage is 30 mg 3 times a day (OR). In theory, cevimeline is more specific when acting on salivary glands and thus presents less severe unwanted effects [19,69,73-75].

Bethanechol chloride has been reported in a number of studies to decrease unwanted effects caused by antidepressant and antipsychotic drugs. It is administered 4 times a day in doses from 10 to 50 mg. It has a 1h effect and its onset of action appears 30 min after being administered (OR) [76-78].

Anetholetrithione has been shown in clinical studies to improve symptoms of xerostomia. The habitual dosage is 25mg 3 times a day [79,80].

Other agents have been put forward as sialogogic drugs in spite of a lack of scientific evidence from clinical studies. They include bromhexine and other mucolytic agents such as guaiphenesin. In addition, substances such as herbal preparations, neostigmine, distigmine, yohimbine, nicotinic and malic acid have also been attributed positive effects in the treatment of xerostomia [19,81].

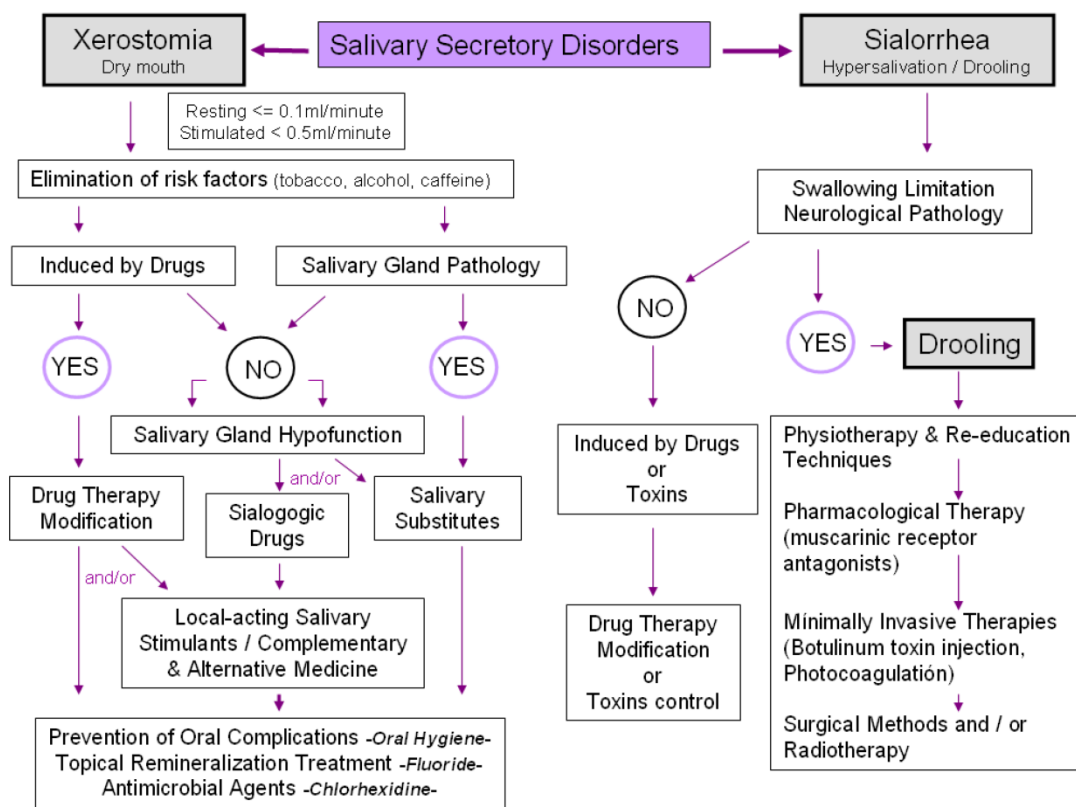


Figure 1. Algorithm of salivary secretory disorder management.

Amongst the secondary effects produced by cholinergic drugs employed as sialogogics the following are the most noteworthy: gastrointestinal alterations, sweating, bronchospasms, altered heart rate, and blurred vision. Excessive use may produce a contrary effect in some patients, for example sialorrhea and drooling. They are contraindicated or considered to be of risk for patients with bronchial asthma, chronic obstructive pulmonary disease, cardiac disease (angina pectoris, acute myocardial infarction), hyperthyroidism, gastric ulcer, arterial hypertension, risk of intestinal obstruction, or ureteral colic [19,69,72,78].

Immunologic agents and salivary gland protectors

Biological substances which modulate immunological response; for instance, due to the fact that they aid tissue regeneration of the glandular parenchyma, they are employed in the treatment of tissue auto-immune-related xerostomia [82].

The interferons are proteins involved in a wide range of regulatory functions: cell proliferation and differentiation, enzyme induction, and the antigen expression of the cell surface [83]. **Interferon alpha (IFN- α)** has been proposed as an effective treatment for autoimmune-related xerostomia, linked to SS, in which the levels of salivary cytokines are altered leading to the destruction of glandular tissue. It could act as a modifier of the biological response thus improving salivary gland function [83-87].

Rituximab is a chimeric murine/human anti-CD20 monoclonal antibody [88,89]. Meijer *et al.*, [90] in pilot trials involving patients with some residual glandular secretory potential, described that rituximab might improve subjective and objective symptoms related to primary SS for at least 6-9 months. These authors observed that no relevant improvement in salivary gland function can be expected in patients with little or no secretory potential at baseline [90]. In the same way, Meiners *et al.* [91] reported that anti-CD20 therapy can be considered an effective treatment option in primary SS patients. However, Ramos-Casals *et al.* [92] concluded that larger controlled trials were needed to establish the efficacy of rituximab.

Amifostine is a cytoprotective agent which acts as a free radical scavenger, diminishing the cell damage caused by radiation when administered simultaneously with RT. The benefits are, however, insignificant [48].

Other treatments with dubious reliability and multiple secondary effects for SS-associated xerostomia have been reported in the literature, for instance, anti-tumor necrosis factor alpha therapy (etanercept, abatacept, infliximab, adalimumab, certolizumab

pegol, and golimumab), hydroxychloroquine, anti-inflammatory drugs, methotrexate, hormone replacement, and other monoclonal antibodies [19,69,86,93-98].

Topical medication

Salivary substitutes, local-acting salivary stimulants, lubricants, and protectors. There are a number of distinct products included within this group such as toothpaste, mouthwash, moisturizing gel, chewing gum, and salivary flow stimulating tablets (Table 6).

Table 6: Salivary substitutes, local-acting salivary stimulants, lubricants, and protectors.

Pharmaceutical Forms	Mouthwash Toothpaste Gel Spray Capsule Tablet Chewing gum
Drug Combinations	Olive oil, Betaine, Xylitol Sorbitol, Xylitol, Betaine, Allantoin, Sodium fluoride Betaine, Aloe Vera, Xylitol, Sodium fluoride Malic acid, Xylitol Malic acid, Xylitol, Sodium fluoride Triclosan, Sodium fluoride, Aloe Vera, Vitamin E Sorbitol, Xylitol, Sodium fluoride, Panthenol, Vitamin E Xylitol, Potassium chloride, calcium, magnesium Maltitol, Xylitol, Sorbitol, Lysozyme, Lactoferrin, Colostrum extract, Glucose oxidase, Aloe barbadensis, Minerals CPP-ACP (Casein Phosphopeptide-Amorphous Calcium Phosphate), Fluoride Lactoferrin, Lactoperoxidase, Lysozyme, Glucose oxidase, Sodium monofluorophosphate, Fluoride, Xylitol, Aloe Vera Stannous Fluoride(0.4% w/w), Glycerine, hydroxyethylcellulose Sodium fluoride (1.1% w/w)

They are used for the palliative treatment of patients with non-functional glandular parenchyma, many of them affected by SS, and for whom sialogogic therapy is inadequate.

The use of sugar-free chewing gum or tablet can increase salivary secretion and improve the sensation of dry mouth together with gustatory and masticatory stimulation. These products can additionally be fluoride, chlorhexidine, calcium phosphate, and xylitol releasers [99,100]. Simons *et al.* [101] observed in elderly populations the capacity of chlorhexidine-xylitol releasers, through chewing, to positively modify cariogenic microflora. Toothpastes and gels with high fluoride concentrations have also been introduced in the management of xerostomic patients [102,103].

Salivary substitutes are compounds which generally contain water, electrolytes, glycoproteins, carboxymethylcellulose, hydroxymethylcellulose, mucins, sweetening enzymes, preservatives, and some fluoride products. They are presented as solutions,

gels, tablets, or spray and administered as many times as needed with the aim of providing a prolonged humidity of the oral mucosa. In European countries, bovine- and porcine-derived mucin-containing substitutes are used, whilst in the United States, substitutes based on carboxymethylcellulose, sometimes accompanied by mucopolysaccharides and glycerol polymer gels, are employed [81,104]. Various authors have studied the sensation of comfort in xerostomia patients comparing salivary substitutes with placebo, or stimulating salivary secretion with chewing gum [105,106]. Ship *et al.* [107] demonstrated that the use of the novel topical dry mouth products containing olive oil, betaine, and xylitol (Xerostom[®] products) significantly increased non-stimulated whole salivary flow rates, reduced complaints of xerostomia, and improved xerostomia-associated quality of life.

Stewart *et al.* [108] evaluated the preference and efficacy of three products indicated to reduce xerostomia: a salivary substitute (with a sorbitol/xylitol base), and two salivary stimulants (sorbitol/xylitol chewing gum and acidic tablets with sorbitol). No significant differences were observed between the sialometry of these products and the control group. Chewing gum, however, appeared to be a greater stimulant and in most cases gave the most relief for dry mouth syndrome.

Intraoral releasers of saliva substitutes - reservoirs. These are intraoral devices designed to deliver a salivary substitute (Oralbalance gel[®], K-Y jelly[®], Orthana[®] artificial saliva) for a prolonged period. Patients who habitually wear a dental prosthesis can have them built into the prosthetic structure [109,110]. Results from reviewed studies are contradictory and with low rates of success [111,112].

Neuroelectric stimulation. In recent years, non-pharmacological treatment based on electrostimulation has been developed for xerostomia [113]. Through the use of miniature, intraoral electrostimulators with dental splints the increase of salivary secretion and improvement of symptoms have been attempted [114,115]. Other electrostimulation systems such as transcutaneous electrical nerve stimulation (TENS) or the remote control Saliwell GenNarino device have shown an increase in salivary secretion in healthy patients [116,117].

Glandular regeneration and surgical methods

Glandular regeneration. Mechanisms to restore acinar cell function through tissue engineering and genetic therapy have been recently studied [114,118,119]. Regenerative therapy involves tissue stem cell transplantation to grow or re-grow healthy organs. Its ultimate goal is to develop fully functioning bioengineered organs to replace lost or damaged

organs that result from disease, injury or aging [118-122].

In glandular regeneration, the use of duct stem cells has been reported for salivary gland tissue repair [123]. Ogawa *et al.* [124] demonstrated the fully functional regeneration of a salivary gland through the orthotopic transplantation of a bioengineered salivary gland germ in adult mice. This recent study provides a proof-of-concept for bioengineered salivary gland regeneration as a potential treatment for xerostomia.

Surgical methods. Some authors have proposed a preventive surgical technique [125-128]. Jha *et al.* [127] described a submandibular duct transposition to the region below the chin in order to prevent radiation-induced xerostomia in patients with neoplasias of the pharynx and larynx.

Complementary and alternative medicine

Medicinal herbs, such as jaborandi (which contains pilocarpine), yohimbine supplements (with yohimbine as an active ingredient plus others alkaloids), betel nut (which contains arecholine a muscarinic agonist), citric acid, red pepper, bakumondoto, Iceland Moss (*Cetraria islandica*), and Longo Vital can all stimulate salivary secretion [129-132].

Acupuncture as a method of treatment has a physiological and psychological effect through the activation of various biological mechanisms [133-135]. There are, however, no randomized clinical trials available which can establish this method based on evidence [68].

Sialorrhoea and drooling

In patients with persistent drooling salivary incontinence may even be accompanied by perioral and/or chin dermatitis, cheilitis and on occasions, they may experience fungal infection. In severe cases of salivary hypersecretion or sialorrhoea, muscular fatigue may arise caused by continuous forced swallowing due to excess saliva. Sialorrhoea may functionally affect phonation and gustative perception. The pathological repercussions should also be taken into consideration as there is an accompanying loss of liquids, electrolytes, and proteins [13,14,63].

There are a number of distinct therapeutical alternatives which basically differ according to their degree of invasiveness and the administration or not of medication. The following strategies are the most frequently used: physiotherapy and neuromuscular re-education techniques, pharmacological therapy (anticholinergic drugs), complementary and alternative medicine, minimally invasive therapies, radiotherapy, and therapeutical surgery [13,14]. See the algorithm (Fig 1).

Physiotherapy and neuromuscular re-education techniques

Oral motor therapy. Aimed at improving oral skills such as suction, lip closing, and tongue and mandibular mobility. The speech therapist plays a crucial role in the evaluation of existing oral motor skills [14].

Behavioral modification through biofeedback. Biofeedback techniques condition the patient to swallow on hearing auditory stimulation. Such techniques have not yet been implemented in clinical practice [14,136].

Oro-facial regulation therapy. Functional appliances are employed with high success rates. In cases where the disorder is not completely eliminated it is at least reduced. This therapy can be used with other ones [137-141].

Pharmacological therapy

The muscarinic receptor antagonists, such as atropine, scopolamine (hyoscine), and glycopyrronium bromide inhibit salivary secretion and can, therefore, be employed to treat drooling. These drugs are contraindicated in patients with cardiac problems, glaucoma, prostatic hypertrophy, paralytic ileus, and pyloric obstruction. Results are still incomplete and there are considerable individual variations which can, on occasions, lead to the administration of high doses with the consequent appearances of severe secondary effects such as excessive dry mouth, constipation, urinary retention, blurred vision, irritability, confusion, and even toxic psychosis, all of which are of greater risk to the patient than the sialorrhea itself [15,142].

Atropine when administered sublingually has the capacity to reduce drooling [143,144]. Sublingual release has many advantages with respect to via parenteral administration. Atropine is not expensive, does not require special skills for its administration, and has a reversible effect. It is contraindicated in patients with cognitive deterioration, dementia, and hallucinations [14,15].

Scopolamine is applied through transdermal patches (Scopoderm®) for therapy of nausea associated with motion sickness. Its most common unwanted effect is dry mouth. Scopolamine has been evaluated in patients with drooling, medicated with clozapine, suffering from cerebral lesions, cerebral palsy, or major oropharyngeal resection [145,146]. The administration of scopolamine via nebulization provides a better absorption of the drug. An 800 µg dose administered two/ three times a day has been reported to be both effective and without side effects [147].

Reviews such as that by Jongerius *et al.*, [148]

which studied the efficacy of anticholinergic medication in multi-disabled children, have shown evidence that some anticholinergic medication is effective without preference for any particular one.

Complementary and alternative medicine

Tongue acupuncture techniques. Acupuncture can stimulate the complex neural network of the tongue thus improving salivary secretion and swallowing mechanisms. Wong *et al.* [149] observed that it was a treatment without complications, well tolerated by children, and that it markedly improved drooling. Whilst this technique depends a great deal on the skill and experience of the practitioner, it could be an alternative or complementary therapy for children with non-treatable drooling [14]. More longitudinal studies with long-term follow-up and quantitative evaluations are required to determine the validity of this technique.

Radiotherapy

The application of ionizing radiation for the treatment of sialorrhea, with the aim of decreasing salivary secretion, has been studied by authors such as Borg *et al* [150]. They warned that radiotherapy in children should be avoided due to the risk of inducing malignancy, delayed growth, xerostomia, mucositis, dental decay, and osteoradionecrosis [150]. This therapy might be effective in specific disorders such as amyotrophic lateral sclerosis, [151] and Parkinson [152].

Minimally invasive methods

Botulinum toxin injection. Xerostomia is one of the first signs of botulism [14]. Injecting botulinum toxin serotype A causes the inhibition of neuromuscular transmission it acts by blocking the release of acetylcholine neurotransmitter [153]. The pilot studies that have been carried out reported an improvement of the patients treated with the botulinum toxin injection in either both parotid glands or in combination with the submandibular ones [14,154,155]. The trial conducted by Lipp *et al.* [156] concluded that the greater the dose the more reduced the drooling, nevertheless, the optimum dosage has yet to be established.

Botulinum toxin serotype B presents different pharmacological properties, nevertheless, its administration has been shown to be successful in decreasing drooling in patients with Parkinson [157,158].

Photocoagulation of the salivary gland ducts. The concept of laser photocoagulation is based on the partial destruction of the gland and occlusion of the duct. Chang *et al.* [159] employed the Nd:YAG (1064nm) laser for the intra-ductal photocoagulation of both parotid glands. In their study of 48 patients

with cerebral palsy they reported, in most cases, a significant improvement in drooling with respect to severity and frequency. Postoperatively they observed transient facial swelling in all the patients. The complications were infections, cystic formations, and hematomas, all of which were of low frequency. Photocoagulation of the submandibular gland ducts is reserved for recurrent patients or for those who have had unsatisfactory results from the previously mentioned technique.

Surgical methods

Surgical control of sialorrhea is the last therapeutic option and is recommended:

- In moderate and persistent cases where conservative therapies have not been successful.
- In severe cases where there are antecedents of failure or limited results from conservative therapies.
- In moderate cases in which there is retarded cognitive development, or where conservative therapies were unsuccessful due to lack of co-operation.

Neurectomy. Sectioning of the parasympathetic nerve reduces the flow of saliva. The tympanic plexus nerve and the tympanic cord may be sectioned, uni- or bilaterally, either alone or in combination with other procedures such as exeresis of the submandibular gland [160-162]. Neurectomy of the tympanic cord reduces the rates of secretion from the sublingual and submaxillary glands, however, as an isolated procedure results have been shown to be insignificant [163]. Auditory loss could be a possible complication in addition to a decrease in gustative capacity in the anterior two-thirds of the tongue. It is, therefore, not recommended in patients with auditory problems [14,164]. Long-term results from isolated neurectomies are controversial [14,165].

Surgical procedures on the salivary duct and gland. The objective of duct ligation is to obtain gland atrophy. There are a number of different procedures which include bilateral ligation of the parotid gland ducts combined with the exeresis of the submandibular glands. This has proven to be the simplest technique with good results (85-86% success rate) as demonstrated in a total of 96 patients observed in three studies [14,166-168]. Another procedure is repositioning of the parotid gland duct to the tonsillar fossa, or the posterior tonsillar pillar, in order to initiate the swallowing reflex together with a bilateral sialoadenectomy of the submandibular glands [14,169]. Repositioning of the submandibular duct carried out alone or combined is a common procedure with a success rate of 75%-89%. Advantages include its physiological characteristics and the fact that it is a

scar-free technique with few complications. A number of studies have reported differing ductal repositioning techniques and results. It would be of interest to try to relocate the saliva exit towards the base of the tongue in order to physiologically initiate the swallowing reflex [14].

Conclusions

Quantitative alterations in salivary secretion are frequent in clinical practice. Their prevalence and negative effects on the patient's quality of life oblige the physician to confront the issue.

At present, there are numerous, frequently prescribed drugs whose unwanted effects include some kind of salivary disorder; at the same time there is medication for the clinical management of patients with these symptoms. As a result, the physician may feel disorientated by both the large quantity of trigger or influential factors for these disorders with their differing pathogenic mechanisms, and the great variety of existing treatments.

The pharmacology of most of the substances employed for the treatment of salivary disorders is well-known. Nevertheless, in some cases, depending on the parenchymal gland affection no significant improvement in salivary function has been observed after their administration.

In agreement with the level of scientific evidence which evaluates the various substances employed in the treatment or clinical management of patients with hypersalivation/xerostomia, we can conclude that more clinical studies are needed to evaluate the drugs, substances, and techniques which are presented as useful therapies for these pathologies.

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Authors' contributions

JMR and ELS carried out the literature search and selection of manuscripts to be reviewed. JMR, LBL and ELS drafted the article. JMR, LBL, MF revised critically the manuscript for important intellectual content. All the authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

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