REVIEW ARTICLE

# Adverse Effects of Drugs on Salivary Glands

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## ABSTRACT

Saliva plays a critical role in maintenance of oro-pharyngeal health. Salivary gland secretion is mainly under autonomic nervous control, although various hormones may also modulate salivary composition. Secretion appears to be dependent on several modulatory influences which act via either a cyclic AMP or calcium dependent pathway. Indeed, hundreds if not thousands of drugs can be xerogenic: some cause a subjective complaint of dry mouth, many can induce hyposalivation and there appear to be multiple mechanisms whereby drugs can produce xerostomia, but few drugs have been submitted to serious scientific examination. This paper reviews the most commonly reported xerogenic drugs, and drug effects on salivary glands.

**KEYWORDS**: Adverse Drug Effects, Dry Mouth, Salivary Glands, Sialosis

## INTRODUCTION

Salivary function plays a pivotal role in providing protection and in digestion. Without adequate salivary output, oral and pharyngeal health declines along with a person's quality of life. The complaint of a dry mouth (xerostomia) and the objective finding of salivary dysfunction are common occurrences in older individuals, producing transient and permanent oral and systemic problems. Salivary dysfunction, however, is not a normal consequence of growing older, and is due to the systemic diseases, medications, and head and neck radiotherapy.[1,2]

The most common cause of salivary disorders is the use of prescription and non-prescription medications. Sreebny and Schwartz reported in their study that 80 percent of the prescribed medications cause xerostomia, and more than 400 medications are associated with salivary gland dysfunction.[3] Dry mouth is a common complaint in patients treated for hypertension, psychiatric, or urinary problems and in the elderly, mainly as a consequence of polypharmacy.[4] About 63% of hospitalized patients and 57% of outpatients complained of dry mouth, and in all patients, the use of psychiatric drugs was the main cause.[5] In the elderly using non-prescription products—most frequently, dimenhydrinate(21%), acetaminophen (paracetamol) (19%), diphen-hydramine (15%), alcohol (13%), and herbal products (11%)—mild ADRs were reported by 75%, the most common complaint being dry mouth.[6]

Even though dry mouth is the most commonly observed adverse effect of drugs, salivary gland is affected in various ways. These review intendeds to throw light on the arena of salivary gland dysfunctions associated with drug use.

## PHYSIOLOGY

Saliva consists of two components that are secreted by independent mechanisms. First a fluid component which includes ions, produced mainly by parasympathetic stimulation and secondly a protein component released mainly in response to sympathetic stimulation. Salivary gland secretion is

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mainly under autonomic nervous control, although various hormones may also modulate salivary composition. Secretion appears to be dependent on several modulatory influences which act via either a cyclic AMP or calcium dependent pathway. Parasympathetic stimulation produces copious saliva of low protein concentration while sympathetic stimulation produces little saliva but of high protein concentration and may thus give a sensation of dryness.[7] Drugs modulate either of these autonomic influences in most of the cases causing ADRs.

## DRUG INDUCED SALIVARY DYSFUNCTION

These can be as follows

- Drug induced xerostomia
- Drug induced sialorrhoea
- Drug induced saliva discoloration
- Drug induced salivary gland enlargement
- Drug induced sialolithiasis

## DRUG INDUCED XEROSTOMIA

Dry mouth or xerostomia has a variety of possible causes. Common habits such as tobacco smoking, alcohol use (including in mouthwashes), and the consumption of beverages containing caffeine (coffee, some soft drinks) can cause some oral dryness. The drugs most commonly implicated include: alpha receptor antagonist for treatment of urinary retention; amphetamines; anticholinergics; antidepressants, antihistamines, antihypertensive agents, antipsychotics such as phenothiazines, appetite suppressants, bronchodilators nasal decongestants, proton pump inhibitors, retinoids and skeletal muscle relaxants.

Several different mechanisms account for drug-related dry mouth, but an anticholinergic action underlies many: The M3 muscarinic receptors (M3R) mediate parasympathetic cholinergic neurotransmission to salivary (and lacrimal) glands, but other receptors may also be involved.[4] Drugs may also exert their neural effects in the higher centers of the brain; stimulation of certain adrenoreceptors in the frontal cortex can produce inhibitory effects on salivary nuclei but can also cause xerostomia without affecting the neural pathways. Drugs can also decrease salivary flow by causing vasoconstriction in the salivary glands.[8] Salient features of some implicated drugs are discussed below:

***Antidepressants:***

Traditional antidepressant medications such as tricyclic antidepressants (TCAs) unfortunately blocked histaminic, cholinergic, and alpha1-adrenergic receptor sites, causing ADRs such as dry mouth. The ultrarapid metabolizer phenotype of the enzyme cytochrome P450 2D6 may be a cause of non-responsiveness to antidepressant drug therapy, and the subsequent prescribing of high doses of antidepressants to such patients leading to an increased risk for ADRs. The newer generation antidepressants like selective serotonin re-uptake inhibitors (SSRIs) and multiple-receptor antidepressants (such as venlafaxine, mirtazapine, bupropion, trazodone, and nefazodone) target one or more specific brain receptor sites without causing unwanted histaminic side effects.[4]

***Antipsychotics:***

Long-term drug treatment of schizophrenia with conventional phenothiazine antipsychotics such as fluphenazine is commonly associated with dry mouth.[9]

However, newly developed antipsychotic drugs with more potent and selective antagonistic activity against the dopamine D(2) receptor may not necessarily be associated with a lower incidence of dry mouth. Olanzapine is an atypical antipsychotic which appears to produce dry mouth.[10]

***Antihistaminics:***

The first generation antihistaminics like chlorphenarime are known to produce xerostomia due their anticholinergic action. Non-sedating antihistamines—most of which are histamine H1 receptor antagonists, such as acrivastine, astemizole, cetirizine, ebastine, fexofenadine, loratadine, mizolastine, and terfenadine, are not entirely free from ADRs, though there may be less complaints of dry mouth with these drugs.[4]

***Cardiovascular Drugs:***

Diuretic agents are almost equally potent in reducing mean salivary flow rate when compared to psychotropic agents. The ganglion blockers and particularly the beta-blockers (beta adrenoceptor antagonists) may cause dry mouth thought to be associated with activation of CNS and salivary gland alpha 2-adrenergic receptors. Such antihypertensive drugs,orsympatholytics (reserpine, methyldopa, and clonidine), are seldom used because of ADRs like dry mouth.Angiotensin converting enzyme (ACE) inhibitors, which block the ACEenzyme in the renin angiotensin-aldosterone system, produce dry mouth in about 13% of patients.[4]

Some anti-hypertensive medications produce the symptoms of xerostomia without actually decreasing salivary flow. Mechanism by which antihypertensive causes xerostomia is unknown it is hypothesized that xerostomia may result from decreased fluid volume and loss of electrolytes secondary to increased urination and dehydration.[8]

***Other Drugs*:**

Several appetite suppressants can cause dry mouth, including sibutramine, fenfluramine plus phentermine and the herbal Ma Huang and Kola nut supplement (containing ephedrine alkaloids/caffeine) produce dry mouth.[4]Anti-asthma drugs can be associated with dry mouth.The most common reported ADR after use of the bronchodilator tiotropium is dry mouth.[11]Didanosine and HIV protease inhibitors can cause dry mouth.[4]

***Radiotherapy:***

Radiation therapy (RT) is a common component of treatment for head and neck cancers. Head and neck RT has serious and detrimental side-effects to the oral cavity including the loss of salivary gland function and a persistent complaint of a dry mouth. In addition, patients often experience the spectrum of oral-pharyngeal problems as a result of permanent salivary gland destruction.[1]

## DRUG INDUCED SIALORRHOEA

Salivary secretion is increased by drugs that have a cholinergic action either by acting directly on parasympathomimetic receptors or by acting on cholinesterase inhibitors. Hypersalivation can be distressing to the patient disturbing sleep, can cause choking sensation.[11]

Anticholinesterases are the drugs mainly causing hypersalivation. Clozapine, an atypical antipsychotic drug with superior efficacy can cause hypersalivation.[12]

Clozapine induced sialorrhea is suggested by stimulating effect on M3 and M4 receptors present in salivary glands leading to increased saliva production. Clozapine-induced sialorrhea may also be explained through its blocking actions at α2 receptors and by blocking target receptors located in the pharynx or by disrupting vagal control of esophageal peristalsis.[11]

## DRUG INDUCED SALIVARY GLAND ENLARGEMENT

Several drugs have been reported to cause salivary gland enlargement which may resemble mumps. The salivary gland enlargement associated with drugs could be accompanying pain or painless in certain cases. Painless, usually bilateral, salivary gland enlargement (resembling sialosis) may be an occasional side-effect of phenylbutazone, oxyphenbutazone, or chlorhexidine. Clozapine may cause transient salivary gland swelling as well as sialorrhea. Antihypertensives, anti-thyroid agents, cytotoxics, ganglion-blocking agents, iodides, phenothiazines, and sulphonamides may cause salivary gland pain.[13]

The mechanism of drug-induced sialadenitis remains unclear in most cases. Either oedema or spasm of smooth muscle in the salivary gland or a hypersensitivity reaction could be responsible.[14] Sialadenitis can be of allergic origin was hypothetised after two cases were reported one after naproxen therapy and use of intravenous radiologic contrast agent.[13]

## DRUG INDUCED SIALOLITHIASIS

Drug therapy is a relatively unknown cause of

stones in the salivary glands. A solitary case report describes the occurrence of salivary gland stone following atomoxetinetheapy which was removed by massaging the gland digitallyis documented.[15]

## DRUG INDUCED SALIVARY DISCOLORATION

Discoloration of saliva (red or orange saliva) as well as other body fluids may be seen in patients treated with clofazimine, levodopa, rifampicin, and rifabutin therapy.[16]

## MANAGEMENT

While treating iatrogenic salivary disorders careful history and scrutiny of drugs that patient is receiving is of paramount importance. Discontinuation of culprit drug if symptoms are distressing is mandatory. Drug substitutions may help reduce the adverse side effects of medications that produce xerostomia if similar drugs are available that have fewer xerostomic side effects. For example, replacement of selective serotonin reuptake inhibitors causes less dry mouth than do tricyclic antidepressants.

If an older patient can take anticholinergic medications during the daytime, nocturnal xerostomia can be diminished, because salivary output is lowest at night. Divided doses can avoid the side effects caused by a large single dose. A dentist's scrutiny of drug side effects can be helpful to reduce xerostomic effect due to polypharmacy.[2]

***General Measures:***

For patients with remaining viable salivary gland tissue, stimulation techniques are helpful. Sugar-free chewing gum, candies, and mints can stimulate remaining salivary secretions, as well as enhance secretion of salivary sIgA. If the prognosis for restoration of normal salivation is poor, such as with head and neck radiotherapy for oral cancers, then use of artificial saliva and lubricants may ameliorate some xerostomic symptoms. These products tend to diminish the sensation of oral dryness and improve oral functioning. Preference of products depends on effect duration. lubrication. taste. deliverv svstem. and cost; many patients nevertheless primarily use water.[1]

Patients, particularly older adults, must be reminded to maintain hydration (water is the drink of choice) to assist with xerostomia. Several habits, such as smoking, mouth breathing, and consumption of caffeine-containing beverages, have been shown to increase the risk of xerostomia. Limiting or stopping these practices should lessen the severity of dry mouth symptoms.

***Medications:***

Treating xerostomia with medications that enhance salivation is another therapeutic option particularly in the relatively healthy person for whom polypharmacy may not be a critical concern.The U.S. Food and Drug Administration has approved two secretagogues, pilocarpine[17,18] and cevimeline[19,20] for the treatment of xerostomia and salivary hypofunction. These drugs are effective in increasing secretions by stimulating effect on salivary glands.

***Pilocarpine:***

Secretogogues such as pilocarpine can increase secretions and diminish xerostomic complaints in patients with sufficiently remaining exocrine tissue. Pilocarpine is typically given in a dosage of 5 mg orally three times a day and before bedtime. When taken 30 min before mealtime, patients may benefit from the increased salivation in eating their meal. The total daily dose should not exceed 30 mg.

***Cevimeline:***

It is approved for the treatment of dry mouth in Sjogren Syndrome in a dosage of 30 mg orally three times daily. Like pilocarpine, it is a muscarinic agonist that increases production of saliva. Cevimeline has a higher affinity for M1 and M3 muscarinic receptor subtypes. As M2 and M4 receptors are located on cardiac and lung tissues, cevimeline can enhance salivary secretions while minimizing adverse effects on pulmonary and cardiac function. Patients with uncontrolled asthma, significant cardiac disease and angle closure glaucoma should not take cevimeline.

***Bethanechol:***

It is used in dosage of 25 mg tid to stimulate saliva in post head and neck radiotherapy patients.

***Tackling complications:***

A low-sugar diet and daily use of topical fluorides and antimicrobial mouth rinses are critical to help prevent dental caries.[2]

## CONCLUSION

Oral Adverse drug effects are often less attended and can affect overall patient's quality of life. Though, benign but distressing adverse effects of drugs on salivary gland do occur. A combined approach of physician and dentist will help in tackling such problems especially in cases of radiotherapy induced xerostomia. It is incumbent upon the practitioner to try to stay abreast of this ever evolving field of drugs and their ADRs to provide holistic health.

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