



## **Adverse Drug Reactions in Terms of Dentistry**

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### **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## **ABSTRACT**

There is a wide range of drugs and their clinical applications that can cause adverse drug reactions (ARD) due to dose, duration, age, and gender. Drugs like ACE inhibitors, which can cause xerostomia, lichen planus, which is caused by NSAIDs and anti hypertensive drugs, ulceration, pigmentation, and osteonecrosis are not only caused by bisphosphonates but also antiangiogenic agents, and malignancy is targeted by rapamycin in the oral cavity. Changes in taste sensation, angioedema, and infection are also some of the side effects of drugs that have been reported. Immunosuppressed patients show more advanced and complex lesions. A clinician should look for adverse effects of medicine.

*Keywords: Drug reactions; anti hypertensive drugs; ulceration; pigmentation.*

## **1. INTRODUCTION**

Drug-induced adverse effects are common. Drug-induced lesions affect at least 5% of patients who attend a dermatological clinic. Drug-induced lesions can be discovered in people of all ages and in every country on the planet.

We define an adverse drug reaction (ADR) as "an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of

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the dosage regimen, or withdrawal of the product [1].

Most of the drugs are immune mediated and non-dose related in nature. Time and dose are risk factors (as in the classic case of bisphosphonate-related jaw osteonecrosis).

ARD is comprised of three components: (1) drug-related harm, (2) drug-related damage caused by improper drug use, and (3) medication errors.

It's crucial to understand the dissimilar among ADR and an allergy: An immune-mediated reaction to a drugs, such as anaphylaxis are allergy, whereas in adverse drug reaction (ADR) its result that is no medically sought, such as drowsiness. An ADR can be an allergy, but not all allergies are ADRs. True drug allergies can be distinguished by the presence of any specific immunological mechanism among dissimilar [2].

The most commonly used pharmacological agents in modern dental practise are local anaesthetics drugs (LA), central nervous system depressants (e.g. N<sub>2</sub>O, benzodiazepines, & general anaesthetic), analgesics (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids), and antibiotics (e.g. penicillin, clindamycin, and metronidazol. Drug-induced cutaneous responses are frequent and diverse, whereas just a few reaction patterns occur in the mouth cavity [3].

There are numerous types of oral lesions that will be described.

## 2. XEROSTOMIA / HYPOSALIVATION

The name "xerostomia" is derived from the Grecian word "xerostomia." Which means

"xeros" (dry) and "stoma" (mouth), and is used to describe a state in which there is insufficient saliva to keep the mouth wet. Many mid - aged group & older age group patients in the United States are taking many drugs, and even medications with minor anticholinergic effects may act synergistically in combination to elicit oral sensations of dryness and pain [3].

A variety of short-term and long-term diseases can impair salivary production, resulting in hyposalivation. These include psychological issues (stress and anxiety), autoimmune illness (Sjögren syndrome), and head and neck chemotherapy or radiation. The most frequent adverse oral medication response in the oral cavity is dry mouth.

Antidepressants, antipsychotics, antihistamines, muscarinic receptor and α-receptor antagonists, antihypertensives (e.g., diuretics, b-blockers, and ACE inhibitors), bronchodilators, and skeletal muscle relaxants are the most regularly reported pharmacological classes that cause hyposalivation. Chemotherapy drugs, appetite suppressants, decongestants, antimigraine pharmaceuticals, opioids, benzodiazepines, hypnotics, histamine 2 (H<sub>2</sub>) receptor antagonists and proton pump inhibitors, systemic retinoids, anti-human immunodeficiency virus treatments, and cytokine therapy are some of the other possible causes [4].

Candidiasis, dental caries, and bacterial sialadenitis are all infections caused by persistent hyposalivation. The loss of lubrication causes erythema and exposes the mucosa to tooth friction, resulting in acute pain and burning [4].

**Table 1. ADR are grouped under six heading**

Sr. No.	Types	Feature related to	Related to dose	Related to time
1.	Dose related	Associated with a drug's MOA	Yes	No
2.	Non dose related	Not associated with a drug's	No	No
3.	Dose and time related	Associated with cumulative dose	Yes	Yes
4.	Time related	Occurs after some time	Generally	Yes
5.	Withdrawal	Occurs immediately after drug withdrawal	No	No
6.	Therapeutic failure	Common	Yes	No

### 3. LICHENOID REACTION / LICHEN PLANUS (LP)

LP, an inflammatory illness that affects the skin and oral mucosa, is one of the most common. On the buccal mucosa, tongue, and gingiva, white striations or papules with erythema, erosion, and ulcers are mostly bilaterally symmetrical [5]. Clinically and histopathologically, it's often difficult to tell the difference between this and idiopathic cutaneous LP [6].

The clinical finding of a reaction is largely subjective; it can be unilateral and erosive, but these characteristics are not always present. Histology reveals a widespread lymphocytic infiltrate with eosinophils and plasma cells, as well as the presence of colloid bodies, although there are no distinguishing features. Though basal cell cytoplasmic antibodies have been discovered, they have not been confirmed and occur far less frequently than cutaneous drug reactions [7].

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Drugs related LP  
Antimalarials  
NSAIDs  
ACE inhibitors  
Antihypertensive  
Phenothiazines  
sulphonamides  
HIV protease inhibitors  
Tetracyclines

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### 4. APHTHOUS - LIKE AND NON - APHTHOUS LIKE ULCERS

Idiopathic aphthous ulcers appear as ovoid to circular ulcers 1 cm or smaller in size with a yellowish fibrinous surface and surrounding erythema affecting the nonkeratinized mucosa in the first two decades of life. Mouth ulcers with a known cause are said to as "aphthous-like," because they disappear once the underlying aetiology is addressed [7].

NSAIDs are well-known and widely used. Several recent publications, however, have linked oral ulcers to relatively new medicines used to treat chronic conditions like diabetes, angina pectoris, rheumatoid arthritis, and osteoporosis.

Mouth ulcers have been associated to trimethoprim-sulfamethoxazole, cyclooxygenase-2 inhibitors (e.g., refecoxib), naproxen, and the angiotensin-converting enzyme inhibitor cozaar. Chemotherapy drugs are stomatotoxic, resulting in mouth ulcers and ulcerative mucositis.

### 5. BULLOUS DISORDERS

Autoimmune disease caused by drugs illnesses of the skin are prevalent, while autoimmune disorders of the mouth are uncommon. The use of thiol radical-containing medicines like penicillamine and NSAIDs has been linked to the onset of oral and cutaneous pemphigus vulgaris at the same time.

Erythema multiforme (EM) can affect the skin as well as the mucous membranes. It manifests as irregular mouth ulcers with widespread erythema and cutaneous target lesions. The use of infliximab and adalimumab has been linked to EM of the oral mucous membranes and skin [4].

Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are reaction to necrolytic enzymes (severe necrolytic hypersensitivity responses that, in contrast to EM, are more commonly related to pharmaceutical usage and can be fatal. SJS and TEN virtually always, and sometimes severely, affect mouth, eye, and genital mucous membranes [8]. The condition has been connected to antimicrobials and anti - convulsants. Anti - microbials (27.1%), antivirals (23.3%), antiseizure medications (8.4%), and analgesics (8.4%) were the most frequently associated pharmaceuticals. Nevirapine (97.6%) and cotrimoxazole (41.6%) were the most prevalent causal medicines among the 12 (30%) HIV - reactive patients. Among HIV-positive people, males (75%) were impacted more than females (25%) were. In HIV-positive individuals, the incubation time was substantially longer. Corticosteroids were given to 30 individuals (75%) in total. The most commonly utilised steroids were dexamethasone (90%) and prednisolone (26.6%). There was no discernible difference between cases treated with or without corticosteroids.

### 6. PIGMENTATION

Most of the superficial discoloration of mucous tissue, soft tissue, and hard tissue may be caused by food, beverages, habits, and drugs. It's dubbed "black hairy tongue" when the darkening is apparent on the posterior dorsum of the tongue and the filiform papillae are excessively lengthy and tinted dark brown or black but it is less prevalent than other superficial discolorations. Antimalarial phenothiazines and phenytoin can cause mucosal pigmentation in the form of brown, blue, or blue-grey [4].

Blue	Brown	Black	Grey	Green
Amiodarone	Aminophenazone	Amiodiaquine	Amiodiaquine	Copper
Antimalarials	Busulphan	Bismuth	Chloroquine	
Bismuth	Cyclophosphamide	Methyldopa	Fluoxetine	
Minocycline	Diethylstilbestro	Minocycline	Hydroxychloroquine	

## 7. GINGIVAL HYPERPLASIA

Gingival hyperplasia is developed within few months caused by Ca channel blockers, in specific nifedipine, amlodipine, & other anti-hypertensive agents [9]. As it is highly fibrous, widespread, generalised, and frequently nodular in overgrowth of gingival tissue, which results in gingival enlargement, made worse by plaque-induced inflammation, as well as the possibility of a hereditary predisposition.

The process is thought to be due to reduced cellular folic acid absorption, which results in diminished matrix metalloproteinase activity and an inability to activate collagenase.

The enhanced collagen formation is assumed to be attributable to both reduced matrix metalloproteinase activity and increased tissue inhibitors of metalloproteinase activity.

## 8. DYSESTHESIA

Medication-induced oral dysesthesias, such as sensitivity, burning, parageusia and other altered sensations without clinical symptoms, can occur. It is caused by damage to the salivary glands, which affects saliva production [10].

The production of saliva, the solution in which chemoreceptors in tongue taste buds bind their receptor molecules, is reduced when the salivary gland is damaged. Drug receptor inhibition, altered neurotransmitter function, modification of action potentials in neurons, and faulty sensory modulation in the brain could all be part of the mechanism [11].

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Drugs related dysesthesia  
 Clarithromycin (17%)  
 Antimycotics [terbinafine (9%) and fluoroquinolones (8%)]  
 Protein kinase inhibitors  
 ACE inhibitors  
 Statins  
 Proton pump inhibitors

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**Osteonecrosis of the Jaws:** Antiresorptive drugs such as bisphosphonates and denosumab reduce bone turnover and remodelling, resulting

in increased bone density. The non-healing extraction socket and exposed alveolar bone suggest osteonecrosis in ADR. Avascular necrosis (AVN) can be induced by bisphosphonates alone or with anti-VEGF to AVN. Bisphosphonates alone can cause AVN rather when bind with anti-VEGF drugs [12].

**Infection:** Long-term immunosuppressive medication can lead to a range of opportunistic infections in the mouth. Pseudomembranous candidiasis, fungal infections, and viral infections (eg; papilloma, hairy leukoplakia), are common. TNF- $\alpha$  treatment has been associated to an enhance risk of serious infections including TB & meningitis in particular. Patients undergoing infliximab and adalimumab have shown a high risk of TB [13].

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Drugs causing infection  
 Immunosuppressive agents  
 Cytotoxic drugs  
 Immunosuppressive agents  
 Antibiotics  
 Corticosteroid  
 Drug inducing hypo-salivation

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**Angioedema:** The lips and tongue are most commonly affected by drug-induced mucosal edema. Although isolated uvula swelling is unusual, this is due to type I hypersensitivity. ACE inhibitor therapy is responsible for non-allergic oral swelling [14].

The effect may be seen within a few hours, weeks, or even long-term therapy. Side effects can be seen in the use of the stain class of drugs (e.g., simvastain, fluvastain, and atorvastain).

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Drugs cause angioedema  
 ACE inhibitors  
 Angiotensin receptor blockers  
 Ca channel blockers  
 Hydrochlorothiazide

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**World will scenario of adverse drug reaction:** In 2010, 85 effective case reports of ADR were reported. The majority of drugs are antibiotics and analgesics, and the dentist is the most frequently prescribed medication. It is

approximate fourth leading cause of death around world.

Although it is impossible to totally eliminate ADR, it is possible to limit its occurrence. To reduce the occurrence of ADR in clinical medication use, the following steps can be taken:

- (1) Pay close attention to the patient's constitution and previous medical history; use medications with caution in the elderly and minors, and rigorously follow the indications and dose.
- (2) Pay close attention to drug administration methods and compatibility: to reduce the amount of intravenous administration and drug combinations.
- (3) Strengthen anti-infective drug rational usage: to decrease or avoid protracted drug use, multiple combined medications, and extensive treatment courses.
- (4) Improve ADR event reporting and feedback, give and perfect medication safety data, and minimise or lessen the risk of potential ADR.

## 9. CONCLUSION

This article has discussed a wide range of drugs that cause several adverse reactions. Most of them are hyposalivation, lichen planus, ulceration, and pigmentation. A careful examination should be taken for oral symptoms. Therapeutic drug agents have been discovered in clinical practice to be more likely to have adverse drug reactions. A clinician's goal should always be to take a careful drug history in order to avoid this reaction.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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