

# Oral Manifestations of Drug Reactions

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**Abstract:** Every drug can produce untoward consequences, even when used according to standard or recommended methods of administration. Adverse drug reactions can involve every organ and system of the body and are frequently mistaken for signs of underlying disease. Similarly, the mouth and associated structures can be affected by many drugs or chemicals. Good oral health, including salivary function, is very important in maintaining whole body health. Regarding different parts of the oral system, these reactions can be categorized to oral mucosa and tongue, periodontal tissues, dental structures, salivary glands, cleft lip and palate, muscular and neurological disorders, taste disturbances, drug-induced oral infection, and facial edema. In this article, the drugs that may cause adverse effects in the mouth and related structures are reviewed.

**Keywords:** oral manifestations, drug reactions

## 1. Introduction

The clinical patterns of adverse drug reactions of the oral cavity include xerostomia, swelling, non specific ulceration, vesiculobullous or ulcerative mucositis that mimics other disease states, non specific vesiculoulcerative mucositis, pigmentation, gingival enlargement, and bisphosphonate related osteonecrosis of the jaws.

### **Xerostomia:**

Xerostomia or dry mouth is the most common adverse drug related effect in the oral cavity. Xerostomia has been associated with more than 500 medications. The synergistic effects of medications have been recognized and are increasingly common in elderly patients taking multiple medications. In addition, habits such as smoking, alcohol may contribute to xerostomia.

General drug classes that are strongly associated with xerostomia include antidepressants and antipsychotics (benzodiazepines), antihypertensives (beta blockers), antihistamines and anticholinergics.

### **Swelling:**

Several drugs can induce type I hypersensitivity reactions or disease mediated by immunoglobulin E mast cells. The lips are the most frequently involved site followed by the tongue. Among the most common offending agents are ACE inhibitors, penicillin and penicillin derivatives, cephalosporins, barbiturates and aspirin and other NSAIDs. Affected mucosa typically appears edematous and erythematous within minutes or hours after exposure.

### **Nonspecific Ulceration and Mucositis:**

Epithelial necrosis and ulceration may result from direct application of medications such as aspirin, hydrogen peroxide, potassium tablets and phenol-containing compounds to the mucosa. The affected mucosa appears whitish and corrugated with erosion and ulceration of the most severely damaged areas. Fixed drug eruptions in the oral cavity often initially appear as areas of edema and erythema that lead to localized, non specific ulceration. A number of drugs are implicated in the development of nonspecific ulceration and oral mucositis. These include barbiturates, beta-blockers, dapsone, NSAIDs, phenazone derivatives, thiazide derivatives, phenolphthalein,

sulfonamides, and tetracyclines. Ulceration of the oral mucosa is a common adverse effect of a wide variety of antineoplastic agents, including methotrexate, 5-fluorouracil, doxorubicin, and melphalan.

### **Vesiculobullous Or Ulcerative Lesions That Mimic Other Immunologic Diseases:**

These drug reactions bear striking clinical, histopathologic and immunopathologic resemblance to idiopathic lichen planus, erythema multiforme, pemphoid, pemphigus, and lupus erythematosus.

### **Lichen planus-like (lichenoid) reactions:**

Initially described in association with antimalarial medications, lichen planus-like or lichenoid drug reactions have subsequently been reported in association with many other agents. Both papuloreticular and erosive manifestations may be observed; the latter is characterized by shallow irregular ulcerations or erosions with a peripheral border of fine keratotic striae that often appear to radiate from the center of the lesion. Currently, NSAIDs and ACE inhibitors appear to be among the most frequently cited offenders. Interestingly, agents used in the treatment of lichen planus (eg, hydroxychloroquine, dapsone, levamisole) have themselves led to adverse lichenoid eruptions.

### **Erythema multiforme-like reactions:**

Drug-induced erythema multiforme is frequently linked to agents such as sulfonamides, sulfonyleureas, and barbiturates. Oral lesions start as erythematous macules or patches that lead to short-lived vesicles or bullae, followed by ragged and shallow ulcerations that may become extensive. Hemorrhagic ulceration and crusting of the labial vermilion zone is common.

### **Pemphigoid-like reactions:**

Clinically, lesions appear as relatively sturdy vesicles or bullae that break down into shallow ulcerations. Generalized or multifocal involvement of the gingival tissues may be observed, with marked erythema and erosion of the superficial gingiva, a pattern that has been called desquamative gingivitis. Thiol-containing drugs and sulfonamide derivatives are among the most commonly involved medications, as are the therapeutic classes of

NSAIDs, cardiovascular agents, antimicrobials, and antirheumatics.

#### **Pemphigus-like reactions:**

Pemphigus like reactions can have features of either pemphigus vulgaris or pemphigus foliaceus, although pemphigus foliaceus is uncommon in the oral cavity. Thiol-containing drugs are the most common cause of pemphigus like reactions.

#### **Lupus erythematosus-like reactions:**

Drug-induced lupus erythematosus is a well-recognized adverse reaction that is most commonly associated with procainamide and hydralazine, although more than 70 medications are implicated.

#### **Pigmentation**

Discoloration of the oral mucosa after drug use may be due to direct melanocytic stimulation, the deposition of pigmented drug metabolites, or both. This reaction has long been recognized with antimalarial agents, particularly chloroquine, hydroxychloroquine, quinacrine, and quinidine. Macular or diffuse oral pigmentation may occur after the treatment of HIV disease with zidovudine, clofazimine, and ketoconazole. Minocycline use may be associated with bluish-gray to brownish mucosal pigmentation.

#### **Gingival Enlargement**

Diffuse, non-neoplastic enlargement or overgrowth of the gingival tissues was initially recognized in patients who were using phenytoin. More recently, calcium channel blockers (members of the dihydropyridine class of medications), cyclosporine, and the antiepileptic drug sodium valproate have been associated with this reaction. Within the calcium channel blocker family, nifedipine, diltiazem, verapamil, and amlodipine are among the most commonly reported causative agents. Tissue enlargement typically occurs by 1-3 months after drug therapy is initiated and begins in the superficial interdental papillae. Anterior segments are more frequently involved than posterior areas.

#### **Bisphosphonate-Related Osteonecrosis Of The Jaws:**

Osteonecrosis of the jaws (ONJ) is an adverse effect related to bisphosphonate (BP) therapy, although cases have been reported that implicate other medications or drug combinations. Clinically, ONJ is characterized by prolonged exposure and necrosis of portions of the jawbone(s). BPs are derivatives of pyrophosphate that significantly reduce the rate of bone turnover, primarily by inhibiting osteoclastic activity. Given the relatively high metabolic demands of the jaws, it is thought that sustained use of BP drugs may suppress the ability of the jawbones to fulfill normal maintenance and repair functions, especially in the presence of the dense, complex microflora found in the oral cavity.

BP drugs are widely used, most commonly in the treatment of osteoporosis and other metabolic bone diseases. The greatest risk for ONJ, however, appears to be among cancer patients. A number of malignant conditions, such as multiple myeloma and carcinoma of the breast, have a recognized propensity to involve the skeleton. BP therapy significantly reduces local and metastatic spread of these skeletal lesions,

as well as associated morbidity and mortality. More than 90% of published cases of ONJ have occurred in the setting of cancer therapy. These patients are treated with intravenous forms of BP and at much higher doses than those used for metabolic bone conditions.

## **2. Conclusion**

Since most drug reactions occur within 1 to 2 weeks following initiation of therapy, reactions seen after 2 weeks are less likely to be due to medication use. Some reactions are dependent on dosage or cumulative toxicity. The majority of drug-induced oral reactions are moderate in severity. In most cases, the oral reaction will be resolved by symptomatic treatment. Read ministration of the offending drug helps establish whether the oral eruption is drug-induced. Oral side effects interfere with client function and increase risk for infection, pain, and possible tooth loss. It has been reported the most frequent side effects are xerostomia, dysgeusia, and stomatitis. Attention must be paid to their toxic and unwanted effects that in many cases may be similar to characteristics of common diseases.

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