

A Review of Drug-Induced Oral 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.

The knowledge about drug-induced oral adverse effects helps health professionals to better diagnose oral disease, administer drugs, improve patient compliance during drug therapy, and may influence a more rational use of drugs.

Keywords: Oral reactions, drug reactions, adverse drug effects, side effects, oral mucosal reactions

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Etiology and Pathogenesis of Oral Adverse Drug Reactions^{1,3}

Although the skin is more commonly involved in adverse reactions to drugs, the oral mucosa is also frequently affected. Virtually any drug has the potential to cause an untoward reaction, but some have a greater ability to do so than others. Pathogenesis of drug reactions may be related to either immunologic or nonimmunologic mechanisms. Most adverse reactions to drugs are mediated by the immune system and are drug allergies. Three mechanisms have been proposed for drug allergies. Firstly, IgE-mediated reactions



occur when the drug reacts with IgE antibodies bound to mast cells. Secondly, drug allergies can involve a cytotoxic reaction in which an antibody binds to a drug that is already attached to a cell surface. The third mechanism in a drug allergy involves circulation of the antigen for extended periods allowing

sensitization of the patient's immune system and production of a new antibody. Nonimmunologic drug reactions are not antibody dependent and may directly affect mast cells causing the release of chemical mediators. Also some nonimmunologic drug-induced reactions result from a drug overdose or toxicity.

Clinical Features of Oral Adverse Drug Reactions^{1,2}

Manifestations of drug reactions are dependent on the type of drug, drug dose, and individual patient differences. These reactions can be seen either rapidly or several days after drug use. Acquired angioedema is an IgE-mediated drug allergy that is commonly observed as drug and food reactions. Other cutaneous manifestations of drug reactions include urticaria, maculopapular rash, erythema, vesicles, ulcers, and target lesions. An unusual form of drug reaction is known as fixed drug reaction during which an erythematous lesion appears in the same location with each antigenic challenge. Oral manifestations of drug reactions may be erythematous, vesicular, or ulcerative in nature. They may also

mimic erosive lichen planus known as lichenoid drug reactions.

Histopathology of Oral Adverse Drug Reactions^{1,2}

Histologic features or findings of drug reactions include nonspecific features as spongiosis, apoptotic keratinocytes, lymphoid infiltrates, eosinophils, and ulceration. Also, mononuclear or polymorphonuclear infiltrations in a subepithelial or perivascular distribution, basal cell destruction, edema, and keratinocyte necrosis are seen.

Diagnosis of Adverse Drug Reactions^{1,2}

The diagnosis of drug reactions requires a high index of suspicion and careful history taking. Recent use of a drug is important. Withdrawal of the suspected drug should result in improvement, and reinstitution of the drug should exacerbate the patient's condition. The clinical expression of lesions in drug reactions is generally allergic in nature that can help with the diagnosis.

Effects of Drugs on Oral Mucosa and Tongue^{1,2,4}

Oral mucosal membranes may be the sole site of involvement, or they may be a part of a more generalized skin reaction to the offending drug. The main type of hypersensitivity reaction that affects oral mucosa is a delayed reaction mediated by sensitized T-lymphocyte. Stomatitis medicamentosa, or fixed drug eruption, occurs with systemic drug usage and stomatitis venenata appears with contact hypersensitivity. Lesions associated with fixed drug eruption are erythematous in mild cases and appear ulcerated in severe cases. The reactions usually appear in 24 hours post-ingestion of the drug. Delayed reaction (up to two weeks) has been noted after use of ampicillin.² Withdrawal of the causative drug results in resolution of the lesions. Drugs with the potential to cause fixed drug eruptions are shown in Table 1.

Contact stomatitis is a local reaction of the mucosa after repeated contact with the causative agent. Reactions can be seen as erythematous to ulcerative lesions. The patient may complain of a burning sensation in the mouth together with xerostomia. The reaction may develop from days to years post-exposure to the causative agent. Compounds with potential to cause contact stomatitis are shown in Table 2.

Table 1. Drugs with potential to cause fixed drug eruptions	
Barbiturates	Lidocaine
Chlorhexidine	Penicillamine
Gold	Salicylates
Indomethacin	Sulphonamides

Aphthous Stomatitis⁵

Aphthous stomatitis (canker sores) is commonly observed and is mediated by the immune system. Lesions usually appear as painful, tiny, discrete, or grouped papules and vesicles. These lesions are small in diameter with round, shallow ulcerations predominantly seen over the labial and buccal mucosa. The reactions heal without scarring in 10-14 days, however, recurrence is common. Drugs with potential to cause aphthous stomatitis are shown in Table 3.

Burning Mouth Syndrome

This syndrome may occur due to psychogenic factors, hormonal withdrawal, folate, iron, pyridoxine deficiency, or hypersensitivity reactions to the materials utilized in dental prostheses.¹ There is a case report of burning mouth syndrome after taking clonazepam.⁶ Cases of “scalded mouth” caused by captopril, lisinopril, and enalapril have been described.⁷⁻⁹ The mechanism of ACE-inhibitor “scalded mouth” is uncertain, but it may be a subclinical manifestation of lichen planus.

Glossitis⁵

Glossitis is inflammation of the tongue that is characterized by swelling and intense pain that may be referred to the ear area. Salivation, fever, and enlarged regional lymph nodes may develop during an infectious disease or after a burn, bile, or other injury. Drugs that have potential to cause glossitis are shown in Table 4.

Erythema Multiforme (Stevens–Johnson Syndrome)^{1,5,10-12}

Erythema multiforme, which when severe is termed Stevens–Johnson Syndrome, is a mucocutaneous disorder characterized by various clinical types of lesions. Young male adults are predominantly affected. The lips are swollen, crusted, and bleeding. Widespread erythema can be seen within the mouth. The oral lesions disappear within 14 days of drug withdrawal. Only 4% of erythema multiforme reactions are caused by

drugs, however, 80% of cases occur in Stevens–Johnson Syndrome. Drugs with potential to cause erythema multiforme are shown in Table 5.

Oral Ulceration^{1,13-16}

A number of chemicals used by dental surgeons can cause “burns” of the oral mucosa, i.e., trichloroacetic acid used in the treatment of pericoronitis. Others that may cause local irritation or ulceration of the mouth include those listed in Table 6.



Vesiculo–bullous Lesions¹

The exact mechanism of this reaction is unclear, but it seems to be the consequence of a direct irritant effect. Patients using steroid inhalers for more than 5 years are more prone to the development of oral blistering. This type of reaction has also been reported for naproxen and penicillamine.

Lichenoid Eruptions^{1,2}

Unlike true lichen planus, drug-induced lichenoid eruptions disappear after drug withdrawal. Lichenoid drug eruptions rarely affect the buccal mucosa. A characteristic white lace pattern may be present. It is thought that drugs causing lichenoid reactions only uncover the latent disease of lichen planus, or amplify a previous disorder, rather than inducing the disease de novo. Such drugs are listed in Table 7.

Color Changes of Oral Mucosa and Teeth

Discoloration can occur after direct contact with or following systemic absorption of a drug. Historically, exposure to metals like silver, bismuth, gold, lead, mercury, zinc, and copper were the main causative agents of tissue discoloration. Color changes are typically seen along the gingival margins and are caused by the formation of metallic sulphides as a result of reactions with plaque products in gingival pockets. The exact

Table 2. Compounds with potential to cause contact stomatitis include^{1,2}

Antibiotics	Iodine
Antiseptic lozenges	Mouthwashes
Chewing gum	Toothpastes (especially those containing cinnamonaldehyde, formalin and herbal components)
Cosmetics	Topical anesthetics
Dental materials (amalgam, steel wires, beryllium, palladium, platinum, acrylic components)	Topical steroids
Food additives	

Table 3. Drugs with potential to cause aphthous stomatitis

Azathiopurine	Losartan
Captopril	NSAIDs
Cyclosporine	Olanzapine
Fluoxetine	Penicillamine
Gold compounds	Sertraline
Indinavir	Sulfonamides
Interferons	

Table 4. Drugs that have potential to cause glossitis

Atrovastatin	Etidronate	Penicillamine
Benzodiazepines	Fluoxetine	Penicillins
Bleomycin	Fluvoxamine	Rivastigmine
Captopril	Gabapentin	Sertraline
Carbamazepine	Gold compounds	Sildenafil
Cephalosporines	Imipenem/cilastatin	Sulfonamides
Chloramphenicol	Lansoprazole	Tacrine
Chlorhexidine	Mefenamic acid	Tetracyclines
Clarithromycin	Mercaptopurine	Triamterene
Clomipramine	Methotrexate	Tricyclic antidepressants
Cyclosporine	Metronidazole	Trihexyphenidyl
Doxepin	NSAIDs	Venlafaxine
Enalapril	Olanzapine	

Table 5. Drugs with potential to cause erythema multiforme

Allopurinol	Ginseng	Penicillins
Barbiturates	Gold compounds	Phenothiazines
Carbamazepine	Iodine-containing mouth washes	Phenytoin
Chlorpropamide	Sulphonamides	Rifampicin
Clindamycin	Minoxidil	Tetracyclines
Combination of antimalarial drugs (chloroquine and sulfadoxine-pyrimethamine)	NSAIDs	Tolbutamide
Estrogens/Progestins	Penicillamine	Verapamil
Ethambutol		

Table 6. Drugs with potential to cause local irritation of the mouth

Anticancer drugs	Isoproterenol	Potassium chloride tablets
Aspirin	Lithium	Tetracyclines
Cocaine	NSAIDs	Toothache solutions (menthol, phenol, clove oil, camphor and chloroform)
Ergotamine Tartrate	Pancreatin	
Hydrogen peroxide	Paraquat	

Drugs with potential to cause oral ulceration^{10,17}

Alendronate	Enalapril	Naproxen
Allopurinol	Erythromycin	Olanzapine
Alprazolam	Fluconazole	Penicillamine
Aspirin	Fluoxetine	Penicillins
Atrovastatin	Ganciclovir	Phenytoin
Azathiopurine	Gold compounds	Proguanil
Barbiturates	Hydralazine	Promethazine
Bleomycin	Hydroxyurea	Propranolol
Captopril	Ibuprofen	Propylthiouracil
Chlorambucil	Imipramine	Quinidine
Chloramphenicol	Indomethacin	Ritonavir
Chloroquine	Lamotrigine	Saquinavir
Chlorpromazine	Levamisole	Streptomycin
Cisplatin	Lithium	Sulfonamides
Clofibrate	Melphalan	Terbutaline
Clonazepam	Mesalamine	Tetracycline
Codeine	Methimazole	Venlafaxine
Cyclosporine	Methotrexate	Vincristine
Cytarabine	Metronidazole	Warfarin
Disopyramide	Mitomycin	Zidovudine
Doxorubicin		

Table 7. Drugs with potential to cause oral lichenoid changes	
Allopurinol	Mercury (Amalgam)
Angiotensin-converting enzyme inhibitors	Methyldopa
Arsenical Compounds	NSAIDs
B-blockers	Palladium
Bismuth	Penicillamine
Chloroquine	Phenothiazines
Chlorpropamide	Propranolol
Furosemide	Quinidine
Gold compounds	Streptomycin
Hydroxychloroquine	Tetracyclines
Lithium Carbonate	Thiazides
Mepacrine	Tolbutamide

mechanism of tissue discoloration by many drugs is uncertain but generally resolves within weeks to months when the offending drug is withdrawn, although sometimes it is permanent. For anti-malarial drugs like quinolones including chloroquine and mepacrine, the deposit of melanin or iron in mucosal tissues has been suggested. Phenothiazines, especially chlorpromazine, in long-term use produce widespread mucosal pigmentation which is caused by accumulation of a drug metabolite in the tissue.^{1,2} Smokers' melanosis, characterized by increased melanin formation especially in the attached gingiva, has been described, but in view of the prevalence of smoking, is less common or conspicuous than might be expected.¹⁰

Pigmentation of the oral mucosa can also be caused by the use of oral contraceptives, and cessation of the drug does not produce complete regression of the pigmentation. Estrogens are well known to induce high levels of cortisol binding globulin that contribute to a decreased portion of plasma free cortisol and as a result produces a hypersecretion of ACTH and β -melano-stimulating. The later may cause the increased oral pigmentation.¹ Minocycline-induced oral pigmentation consequent to interaction of drug with the bone during its formation is most common. Almost all cases of intraoral pigmentation represent minocycline staining of the underlying bones without involvement of the overlying oral mucosa surfaces.¹⁸

Pigmented lesions of the tongue (dark macular patches) are reported to occur in heroin addicts who inhale the smoke. Histologically the lesions are packed with melanocytes but the mechanism is uncertain. Also, breakdown of methyldopa or its metabolites produce melanin, a product of dopa metabolism; biopsy material was not available to prove this suggestion. There has been no report for other drugs which may increase blood dopa levels.¹ Drugs and chemicals with potential to cause oral pigmentation are listed in Table 8.

A close correlation exists between plaque removal capability and discoloration after chlorhexidine rinses. Three possible mechanisms for chlorhexidine-induced staining include non-enzymatic browning reactions, formation of pigmented metal sulphides, and dietary factors. Drugs and chemicals with potential to cause tooth discoloration are listed in Table 9. Extrinsic stains are located on the surface of the tooth and are most easily removed by external cleaning. Intrinsic stains are located within the tooth and are accessible only by bleaching. Some extrinsic stains that remain on the tooth for a long time become intrinsic. By recognizing the likely cause of the stain, the dentist can better tell the patient the rate at which the teeth may lighten in color and the limits on the amount of improvement that can be expected after treatment.²⁰ Tetracycline can cause the most common distracting, generalized type of intrinsic discoloration. It is hypothesized to occur by the

Table 8. Drugs and chemicals with potential to cause oral pigmentation^{1,2,19}		
Drug/chemical	Color	Site
Amalgam	Gray	Gingiva
Amalgam	Brown (Tattoo)	Tongue
Amodiaquine	Blue-gray/black	Palate
Arsenic	Brown	Tongue
Aspirin	White	-
Bismuth	Blue-gray/Blue-black/Brown	Gum lines/mucosa/tongue
Bromine	Brown	Tongue
Busulfan	Brown	Mucosa
Chlorhexidine	White	Tongue
Chloroquine	Blue-grey	Hard Palate, gingiva, lip
Coal	Metal dust dark	Mucosa
Copper salts	Blue-green	Gum lines
Cyclophosphamide		-
Doxorubicin	Dark/Brown	Mucosa/Tongue
Gold	Purple	Gingiva
Heroin inhalation	Dark macular patch	Tongue
Iron	Dark	-
Lead	Blue-gray/Blue	Gum Lines/tongue
Manganese	Dark	-
Mepacrine	Yellow	Mucosa
Mercury	Blue-gray/Blue-black	Gum Line/Buccal
Methyldopa	Darkening	Tongue
Oral contraceptives	Dark	Mucosa
Phenolphthalein	Brown	Tongue
Phenothiazines	Blue-grey	Mucosa
Quinacrine	Gray/Brown	Palate/tongue
Quinidine	Blue-Black	Palate
Quinine	Brown	-
Silver Salts	Gray	Gingiva
Thallium	Blue-gray	Gum lines
Tin	Dark	-
Tobacco	Hazy gray or Brown	-
Vanadium	Green	Tongue
Zidovudine	Dark	Soft palate, gingival, lips, tongue

Table 9. Drugs and chemicals with potential to cause tooth discoloration^{1,19,22}	
Drugs/Chemical	Color
Cadmium	Yellow ring
Chlorhexidine	Yellow – brown
Chlortetracycline	Gray-brown
Ciprofloxacin	Green
Copper salts	Green
Iron in combination with tea	Brown
Isoproterenol	Chalky white
Minocycline	Gray-black
Other tetracyclines	Brown-yellow
Oxytetracycline	Yellow
Tetracycline	Yellow
Tobacco	Yellow-brown
Tooth paste containing Stannous fluoride	Black or green
White wine	Black

Table 10. Drugs and chemicals with potential to cause black tongue	
Amitriptyline	Lansoprazole
Benzotropine	Methyldopa
Cephalosporines	Maprotiline
Chloramphenicol	Nortriptyline
Clarithromycin	Penicillins
Clomipramine	Streptomycin
Clonazepam	Sulfonamides
Corticosteroids	Tobacco
Desipramine	Tetracyclines
Fluoxetine	Thiothixene
Griseofulvin	Tranylcypromine
Imipramine	Vegetable dyes

Table 11. Other drugs with potential to cause gingival hyperplasia	
Cotrimoxazole	Phenobarbital
Cyclosporine	Primidone
Erythromycin	Sertraline
Ethosuximide	Sodium valproate
Ketoconazole	Topiramate
Lamotrigine	Vigabatrin
Lithium	

joining of the tetracycline molecule with calcium through the chelation process and a subsequent incorporation into the hydroxyapatite crystal of the tooth during the mineralization stage of development. A second theory maintains the discoloration involves a binding of the tetracycline to the tooth structure by a metal organic matrix combination of the tetracycline complex.²¹

Black Hairy Tongue (*Lingua villosa nigra*)^{1,5,10,19}

In this condition there is an elongation of the filiform papillae of the tongue to form hair-like overgrowth that becomes stained brown or black due to proliferation of chromogenic microorganisms. Black hairy tongue can be seen with the administration of oral antibiotics, poor dental hygiene, and excessive smoking in adults. Drugs and chemicals with potential to cause black tongue include those listed in Table 10.

Postmortem Pink–Red Coloration¹⁹

Tooth coloration of this nature is due to hemolysis and exudation of hemoglobin to dental pulp and is enhanced in the presence of moisture and increased venous pressure. Specific conditions of death associated with this phenomenon include drowning, aspiration pneumonitis, and suffocation. Overdoses with barbiturates and carbon monoxide also demonstrate similar findings.

Drug Induced Gingival Hyperplasia^{1,2,5,10,19,17,23}

The growth starts as a painless, beadlike enlargement of the interdental papilla and extends to the facial and lingual gingival margin. The enlargement is usually generalized throughout the mouth but is more severe in the maxillary and mandibular anterior regions. Plaque removal and good oral hygiene may benefit in a fast recovery and limits the severity of the lesion but the lesion does not completely resolve. It is hypothesized that in non-inflamed gingiva, fibroblasts are less active or even quiescent and do not respond to circulating drugs; fibroblasts within inflamed tissue are in an active state as a result of inflammatory mediators and the endogenous growth factors. It is known that causative drugs inhibit Ca^{2+} uptake on gingival fibroblasts that correlates with the rate of fibroblast proliferation. Drug variables, plaque-induced inflammatory changes in the gingival tissues, and genetic factors should be considered. The last determines the heterogeneity of the gingival fibro-

blast and could also influence drug pharmacokinetics and pharmacodynamics.

Phenytoin, cyclosporine-A, calcium channel blockers, and oral contraceptives are the main causative agents of gingival hyperplasia. Several mechanisms have been suggested for drug-induced gingival hyperplasia. Cyclosporine-A has been shown to increase the fibroblast production of collagen and protein, leading to extracellular collagen and matrix formation and to decreased collagenase activity. The increased levels of interleukin-6 and TGF- β and the decreased levels of gamma-interferon observed during cyclosporine-A therapy may favor the fibroblast synthesis of collagen.²⁴ Also, it has been reported the keratinocyte growth factor receptor is up-regulated by cyclosporine-A²⁵, and there is evidence that cyclosporine-A regulates cytokine expression in gingival tissue.²⁶

There is evidence that mast cell mediated androgen action in the gingiva in response to phenytoin could contribute to gingival overgrowth.²⁷ The incidence of phenytoin-induced gingival overgrowth is approximately 50 percent, but it is higher in both teenagers and institutionalized epileptics. Gingival overgrowth usually becomes apparent during the first 3 months after starting phenytoin and is most rapid in the first year. Unlike phenytoin hyperplasia, cyclosporine-induced hyperplasia is reversible following cessation of drug use.²⁸

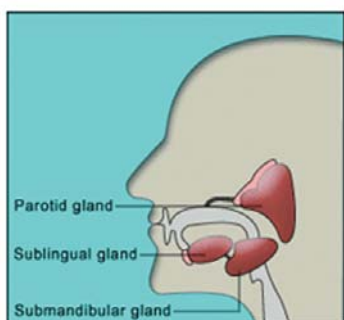
Nifedipine, the most commonly used calcium channel blocker, induces gingival enlargement in 20% of the cases. Amlodipine, diltiazem, felodipine, nitrendipine, and verapamil also induce gingival overgrowth. The dihydropyridine derivative isradipine does not induce gingival overgrowth. Inhibition of apoptosis by nifedipine and resultant epithelial hyperplasia has been reported.²⁹ There is also evidence that nifedipine inhibits both adherence- and lipopolysaccharide-stimulated macrophage-induced death of fibroblasts which results in gingival overgrowth.³⁰ Nifedipine is frequently prescribed to organ transplant patients to reduce the nephrotoxic effects of cyclosporine and, thus, an additive effect on the gingival tissues is usually observed.³¹

The incidence of gingival overgrowth by oral contraceptives is not rare and resolves when the drug

is withdrawn. There is evidence the accumulation of metabolic products of the naturally occurring sex hormones in gingiva is an important factor in the pathogenesis of chronic gingivitis. The prevalence and percentage of incidence is uncertain. Maintenance of adequate plaque control is important for gingival health during the administration of oral contraceptives. Other drugs with potential to cause gingival hyperplasia are listed in Table 11.

Salivary Glands^{1,5,32-48}

The salivary glands are under control of the autonomic nervous system, mainly the parasympathetic division. Salivary gland function can be affected by a variety of drugs that can produce xerostomia or ptyalism. It is suggested this is due to both the reduced salivary flow rate and to a decrease in salivary calcium and phosphate concentration caused by such drugs as amphetamines.



Submandibular and parotid glands, the major salivary glands of the body, have important roles in maintaining the health of the oral cavity and gastrointestinal tract. Altered salivary flow rate and levels of secretory proteins or enzymes

may cause destructive effects on oral and dental health and wound healing rates directly through lower levels of specific growth factors being present. It is known that salivary mucins and growth factors are involved in the maintenance of mucosal integrity due to their ability to trap water, thereby, preventing injury through desiccation; growth factors may assist in tissue regeneration. The epidermal growth factor that is secreted from salivary glands has a potential role in oral wound healing.⁴⁹ Common oral manifestations resulting from decreased salivary flow include increased dental caries, fungal infections, bacterial infec-

tions, aphthous lesions, and dysphagia. Systemic drug therapy can also produce pain and swelling of the salivary glands.⁵⁰ Table 13 lists drugs and chemicals with potential to inhibit the function of salivary glands.

Sjogren's Syndrome includes parotid swelling. However, parotid enlargement in Sjogren's Syndrome occurs relatively late in the course of rheumatoid arthritis. Its sudden appearance in the early stages of the disease may well indicate an adverse reaction to an anti-inflammatory drug since the H²-receptor antagonists have been reported to aggravate the disease. The swelling is quite common in rheumatoid arthritis, for which NSAIDs are frequently used, therefore, salivary gland swelling could be part of the disease rather than a complication of its treatment. Sjogren's Syndrome is often (30%) seen in association with other autoimmune rheumatic diseases.⁵⁵

Effects on Dental Structure^{1,32-34,56-58}

Systemic drug therapies can also affect the oral environment, most notably when causing xerostomia. Xerostomia is the reduction of salivary flow as well as a change in the quality of the saliva, both of which increase the risk of dental caries. A large number of drugs including tricyclic antidepressants, benzodiazepines, lithium, and morphine may cause xerostomia. Some of the common problems associated with dry mouth include a constant sore throat, burning sensation, problems in speaking, difficulties in swallowing, hoarseness or dry nasal passage. Left untreated, dry mouth can damage teeth structure. Without adequate saliva to lubricate mouth, wash away food, and neutralize the acids produced by plaque, extensive decay can occur. Dryness of mouth and severely dry lips are also the side effects of isotretinoin therapy for acne. Table 12 lists other agents with the potential to affect dental structures from reduced saliva flow rate.

Table 12. Other agents with potential to affect dental structures^{1,10,39,54}

Antineoplastic agents	Maternal smoking
B-Blockers	Phenytoin
Cocaine	Radiotherapy
Doxapram	Sympathomimetics or corticosteroids
Local anesthetics	as inhaled powders or aerosols

Table 13. Drugs and chemicals with potential to inhibit the function of salivary glands including secretion of proteins and enzymes into saliva	
Benzodiazepines	Morphine
Cadmium	Nifedipine
Cyclosporine	Nitric oxide inhibitors
Diltiazem	Ofloxacin
Gentamicin	Rubidium
Lead	Verapamil
Lithium	
Drugs that can cause dryness of mouth	
Amphetamine	Omeprazole
Anticholinergics	Ondansetron
Antihistamines	Selective serotonin reuptake inhibitors
Antineoplastic drugs	Thiabendazole
Anti-HIV protease inhibitors	Tramadol
Didanosine	Tricyclic antidepressants
Levodopa	
Drugs that can cause sialorrhea	
Alprazolam	Levodopa
Amiodarone	Lithium
Bethanechol	Mefenamic Acid
Buspirone	Mercurial salts
Clozapine	Niridazole
Diazoxide	Pentoxifylline
Edrophonium	Pilocarpine
Gentamycin	Risperidone
Guanethidine	Rivastigmine
Imipenem/Cilastatin	Succinylcholine
Iodides	Tacrine
Kanamycin	Tobramycin
Ketamine	Venlafaxine
Lamotrigine	Zaleplon
Drugs that have potential to cause swelling and/or pain in salivary	
Bretylium	Naproxen
Catecholamine inhalation	Nifedipine
Chlorhexidine	Nitrofurantoin
Cimetidine	Phenytoin
Clonidine	Ranitidine
Deoxycycline	Ritodrine
Famotidine	Sulfonamides
Iodine	Trimipramine
Methyldopa	Warfarin

Table 14. Drugs reported to cause sensation of numbness, tingling, or burning in the face or mouth

Acetazolamide	Nicotinic acid
Amitriptyline	Nitrofurantoin
Chlorpropamide	Pentamidine
Ergotamine	Polymyxin B
Gonadotropin-releasing-hormone analogues	Propranolol
Hydralazine	Streptomycin
Isoniazid	Tolbutamide
Nalidixic acid	

Muscular and Neurological Disorders¹

Tardive dyskinesia that affects the elderly, particularly women, taking antipsychotic drugs for many years, is an uncommon and sometimes unrecognized cause of orofacial pain. Tardive dyskinesia is a painless syndrome in itself, but secondary orofacial pain can result from chronic mild trauma between a denture-bearing mucosa and dentures with abnormal movement.

Facial pain has also been reported following the use of a controlled-release theophylline preparation. Table 14 lists drugs reported to cause sensation of numbness, tingling, or burning in the face or mouth.

Taste Disturbance^{1,48}

Many drugs induce abnormalities of taste by processes not yet fully understood. The alteration in taste may be simply a blunting or decreased sensitivity in taste perception (hypogeusia), a total loss of the ability to taste (ageusia), or a distortion in perception of the correct taste of a substance, for example, sour for sweet (dysgeusia). A wide-range of drugs give rise to dysgeusia or hypogeusia either by interfering in chemical composition or flow of saliva, or, more specifically, affecting taste receptor function or signal transduction. Sulfhydryl compounds are a common cause of taste disturbance. Drugs with the potential for affecting taste are listed in Table 15.

Taste Disturbance^{1,48}

In many patients, penicillamine causes partial or total loss of taste. It seems there is a marked difference in the frequency of this effect between patients being treated for Wilson's disease and

those being treated for other conditions. In patients treated for Wilson's disease, frequency is much lower. Loss of taste has been found to be dose related. It appears that taste disturbance is reversible within a period of 8-10 weeks, whether or not penicillamine is discontinued.⁵

An impaired salty taste is a frequent complaint associated with Captopril. The extent of Captopril-induced dysgeusia seems to be related to dose and renal function and can be compounded by smoking. Taste disturbances tend to be self-limiting and reversible in 2-3 months even if the drug is continued. ACE inhibitors can also cause a persistent chronic dry cough.

Systemic griseofulvin can render certain foods profoundly tasteless, the effect gradually worsening for as long as the patient takes the drug. Furthermore, the effect may take some months to disappear after the drug is withdrawn. In addition, other drugs especially those used for gastrointestinal disorders may cause some degree of loss of taste or altered taste as follows: tripotassium dicitrate bismuthate chelate, Clarithromycin, lansoprazole, anti-HIV protease inhibitors, terbinafine, intravenous pentamidine, and isotretinoin.⁴⁸

Halitosis¹

Halitosis is the offensive breath resulting from poor oral hygiene, dental or oral infections, ingestion of certain foods, use of tobacco, and some systemic diseases. Disulfiram and sublingual isosorbide dinitrate can cause halitosis. Drugs causing xerostomia, discussed earlier, may indirectly cause or aggravate this problem.

Table 15. Drugs with potential to cause ageusia ^{1,5,19}		
Acarbose	Dicyclomine	Pentamidine
Acetazolamide	Enalapril	Phenytoin
Amitriptyline	Etidronate	Propantheline
Aspirin	Fluoxetine	Propylthiouracil
Atrovastatin	Fluvoxamine	Rifabutin
Captopril	Indomethacin	Ritonavir
Ceftirizine	Isotretinoin	Rivastigmine
Cisplatin	Levodopa	Spiroglactone
Clidinium	Losartan	Sulfadoxine
Clomipramine	Methimazole	Topiramate
Cocaine	Penicillamine	Venlafaxine
Diazoxide		
Drugs with potential to cause dysgeusia ^{1,5}		
Acetaminophen	Dipyridamole	Minoxidil
Acetazolamide	Donepezil	Naratriptan
Acyclovir	Dorzolamide	Nifedipine
Albuterol	Doxepin	Nortriptyline
Alendronate	Deoxycycline	Ofloxacin
Allopurinol	Enalapril	Olanzapine
Alprazolam	Etidronate	Omeprazole
Amiloride	Famotidine	Pamidronate
Amiodarone	Fenfluramine	Penicillamine
Amitriptyline	Fentanyl	Penicillins
Amlodipine	Flecainide	Pentazocine
Amoxicillin	Fluconazole	Pentoxifylline
Aspirin	Fluorouracil	Pergolide
Atrovastatin	Fluoxetine	Perindopril
Atropine sulfate	Flurazepam	Phytonadione
Baclofen	Fluvastatin	Pilocarpine
Benzotropine	Fluvoxamine	Potassium iodide
Bromocriptine	Gancyclovir	Procainamide
Buspirone	Gemfibrozil	Propantheline
Busulfan	Glyburide	Propranolol
Calcitonin	Gold compounds	Propylthiouracil
Captopril	Granisetron	Pyrimethamine
Carbamazepine	Griseofulvin	Quinidine
Cephalosporines	Hydrochlorothiazide	Ranitidine
Celecoxib	Hydroxychloroquine	Ribavirin

Table 15 (continued)

Chlorhexidine	Imipenem/Cilastatin	Riluzole
Chlorothiazide	Imipramine	Risperidone
Cholestyramine	Indinavir	Ritonavir
Ciprofloxacin	Interferons	Rivastigmine
Citalopram	Isotretinoin	Saccharin
Clarithromycin	Ketoprofen	Selegiline
Clidinium	Ketorolac	Serteraline
Clindamycin	Labetalol	Simvastatin
Clofazimine	Lamotrigine	Sulfonamides
Clofibrate	Lansoprazole	Sumatriptan
Clomipramine	Leuprolide	Tacrine
Clonazepam	Levodopa	Tamoxifen
Clonidine	Lisinopril	Terbutaline
Clozapine	Lithium	Timolol
Codeine	Loratadine	Tocainde
Cotrimoxazole	Losartan	Tolazamide
Cromolyn	Lovastatin	Tolbutamide
Cyproheptadine	Maprotiline	Tolmetin
Dacarbazine	Mesalamine	Topiramate
Dantrolene	Mesna	Tramadol
Desipramine	Metformin	Triamteren
Dexfenfluramine	Methamphetamine	Trimipramine
Dextroamphetamine	Methimazole	Ursodiol
Diazoxide	Methocarbamol	Vancomycin
Diclofenac	Methotrexate	Venlafaxine
Dicyclomine	Metoprolol	Vinblastine
Dihydroergotamine	Metronidazole	Vincristine
Diltiazem	Midazolam	Zidovudine

Table 16. Drugs with potential to cause oral candidiasis⁵

Cephalosporins	Olanzapine
Ciprofloxacin	Omeprazole
Claithromycin	Penicillins
Griseofulvin	Riluzole
Mesalamine	Tacrolimus

Oral Infections Induced or Aggravated by Drugs¹

Many types of systemic drug therapy can alter oral flora and, therefore, predispose the mouth to bacterial or fungal infection. Drugs that have been implicated in this problem include corticosteroids, antimicrobials, anticancer drugs, immunosuppressive agents, and oral contraceptives. Drugs causing xerostomia may also potentiate the initiation of oral infections. Table 16 lists drugs with potential to cause oral candidiasis.

Alveolar Osteitis (Dry Socket)^{1,60}

The use of contraceptives has been associated with a significant increase in the frequency of dry sockets (alveolar osteitis) after removal of impacted lower third molars. The probability of dry sockets increases with the estrogen dose in the oral contraceptive. The dry sockets can be minimized by carrying out the extractions during days 23-28 of the tablet cycle.

Facial Edema/Angioedema^{1,5}

Facial edema is often a manifestation of drug-induced hypersensitivity reactions, and angiotensin converting enzyme inhibitors (ACEIs) are the most common cause. It seems that angioedema arises as a consequence of an alternation in bradykinin metabolism in susceptible patients. The most common ACEIs implicated in this reaction are captopril, lisinopril, and enalapril. Angioedema usually occurs within hours or at most weeks after starting the ACEI and reverses within hours of stopping. However, it can develop after long-term therapy. Table 17 lists drugs that can cause facial edema.

Stomatodynia⁵

Stomatodynia is pain in the mouth and can be a consequence of drug reactions. Table 18 lists drugs with the potential to cause this condition.

Cheilitis^{5,54}

Cheilitis is an abnormal condition of the lips characterized by inflammation and cracking of the skin.

This is almost always associated with fungal infections and frequently occurs with xerostomia that is drug-induced. Table 19 lists drugs with potential to cause cheilitis.

Conclusion^{54,61-64}

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. However, severe reactions necessitate rapid withdrawal of the suspected drug.

In most cases, the oral reaction will be resolved by symptomatic treatment. Readministration of the offending drug helps to establish whether the oral eruption is drug-induced.

Reactions after rechallenge may be more severe and, therefore, rechallenge should not be performed without medical supervision. Many clients take multiple medications; therefore, dentists must be aware of the issues related to drug use including indications, interactions, and adverse drug effects. The ability to evaluate these issues is necessary to accurately assess client status and prevent situations that compromise client safety. Oral side effects interfere with client function and increase risks for infection, pain, and possible tooth loss. It has been reported the most frequent side-effects of drugs are xerostomia, dysgeusia, and stomatitis.

As a final note, rapid progress in pharmacotherapeutics requires clinicians to constantly update their knowledge of drugs used by their patients. Attention must be paid to their toxic and unwanted effects that in many cases may be similar to characteristics of common diseases.



Table 17. Drugs that can cause facial edema

Adrenomimetic bronchodilators	Intravenous clindamycin
Captopril	Lisinopril
Droperidol	Mianserin
Enalapril	

Table 18. Drugs with potential to cause stomatodynia

Benztropine	Potassium Iodide
Biperidin	Ticarcillin
Griseofulvin	Triamteren
Lithium	Vitamin A
Penicillins	

Table 19. Drugs with potential to cause cheilitis include⁸

Atrovastatin	Psoralens
Busulfan	Ritonavir
Clofazimine	Saquinavir
Clomipramine	Simvastatin
Cyanocobalamin	Streptomycin
Gold compounds	Sulfasalazine
Indinavir	Tetracycline
Isotretinoin	Vitamin A
Methyldopa	

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