

# Oral drug reactions

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**ABSTRACT:** Drug-induced side effects are a frequent occurrence. Many commonly available drugs are capable of causing untoward reactions. Such adverse effects may be seen in all age groups and present in many different forms. The oral drug reactions are often nonspecific, but they may mimic specific disease states such as pemphigus, erythema multiforme, or lichen planus. In such cases a high index of suspicion is required to make a correct diagnosis.

**KEYWORDS:** angioedema, drug eruption, oral ulcers, stomatitis, xerostomia.

Drug-induced side effects are a frequent occurrence. Many commonly available drugs are capable of causing untoward reactions. Such adverse effects may be seen in all age groups and present in many different forms. The oral drug reactions are often nonspecific, but they may mimic specific disease states such as pemphigus, erythema multiforme, or lichen planus. In such cases a high index of suspicion is required to make a correct diagnosis. Side effects may be quite characteristic, as is the case with phenytoin and gingival hyperplasia (Table 1). Oral drug reactions manifest in a variety of patterns (Table 2). This article will briefly describe the common presentations and mechanisms of oral drug reactions. Table 3 highlights some of the prominent mechanisms of oral drug reactions. The drugs most commonly responsible for these reactions will then be discussed, along with specific treatments. Finally, general clinical management and therapies will be addressed.

## Reaction patterns

### Stomatitis

Stomatitis or oral inflammation is a nonspecific term that describes many oral drug reactions. Stomatitis can be classified as stomatitis venenata or stomatitis medicamentosa. The former refers to

an irritant or allergic reaction from topical medications. The latter refers to stomatitis resulting from systemically administered medications.

Stomatitis venenata presents as a localized stomatitis with a variable clinical picture ranging from mild erythema to vesiculation and necrosis. This reaction should be identified as a primary irritation reaction, fixed drug reaction, or an allergic contact stomatitis. An irritant reaction is characterized by rapid onset and confinement of the stomatitis to the area of application (Fig. 1). Allergic contact stomatitis may be associated with cutaneous reactions or systemic symptoms and may worsen with repeat exposures (Fig. 2). Patch testing may be useful to help determine the offending agent. A fixed drug reaction occurs as a well-demarcated, round, erythematous plaque with or without vesiculation and necrosis (Fig. 3). The eruption occurs in the same area after each administration of the offending agent. The lesions may be asymptomatic or associated with burning and pain.

The clinical appearance of stomatitis medicamentosa ranges from nonspecific generalized erythema, vesicles, and ulcers to more specific oral reaction patterns. These patients typically complain of tingling, burning, or severe pain with mild to moderate systemic complaints.

### Ulceration

Oral ulcerations may occur in a variety of different settings, including local irritation, chemotherapy, opportunistic infections, fixed drug reactions, and lichen planus-like reactions. Local application of a

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**Table 1.** Characteristic oral drug reactions

Reaction	Drug
Gingival hyperplasia	Phenytoin, calcium channel blockers
Lichen planus-like stomatitis	Gold, D-penicillamine
Black hairy tongue	Antibiotics, griseofulvin
Thrush	Antibiotics, aerosol corticosteroids
Oral ulcerations	Aspirin, antimetabolites, NSAIDs
Enamel staining	Iron, fluoride, tetracycline, minocycline
Metallic taste disturbance	Griseofulvin, metronidazole
Xerostomia	Antihistamines, anticholinergics, tranquilizers, antidepressants

variety of agents including aspirin and pancreatic supplements may lead to ulceration because of their caustic or enzymatic activity (Fig. 1).

Aphthous-like ulcerations may occur from a variety of medications, including captopril and nonsteroidal anti-inflammatory drugs (NSAIDs). It is unclear as to the mechanism leading to this reaction pattern.

Chemotherapy-associated mucositis and ulceration can be quite profound. Widespread sloughing and erythema may occur within days of initiating therapy and may be so painful as to require opioid analgesia. Many chemotherapeutic regimens have been implicated, particularly those utilizing methotrexate, 5-fluorouracil, doxorubicin, melphalan, mercaptopurine, or bleomycin.

Many drugs, acting locally or systemically, can alter the ecosystem of the oral cavity or depress the immune system of the patient, increasing susceptibility to oral infections. Most of these

**Table 2.** Oral drug reaction patterns

Stomatitis
Ulceration
Bullous disorders
Swelling/angioedema
Salivary gland enlargement
Xerostomia
Gingival hyperplasia
White patches
Abnormal pigment
Hemorrhage
Paresthesia
Halitosis

**Table 3.** Mechanisms of oral drug reactions

Reaction	Mechanism	Drug
Gingival hyperplasia	Idiosyncratic	Calcium channel blockers
Bleeding	Overdose	Anticoagulants
Gingival pigmentation	Accumulation	Silver salts
Bleeding	Drug-drug interaction	Warfarin
Ulceration	Toxic	Antimetabolites
Thrush	Ecological imbalance	Antibiotics
Pemphigus	Unmasking disease	D-penicillamine
Stomatitis medicamentosa	Hypersensitivity	Antibiotics
Xerostomia	Pharmacologic	Anticholinergics

infections are caused by overgrowth of organisms that are part of the normal oral flora. Bacterial, fungal, and viral superinfections are all seen as a result of drug therapy. Bacterial infections are most commonly seen in patients undergoing chemotherapy. These infections are related to drug-induced alterations of normal host response. Immunosuppression is caused by induction of leukopenia, which inhibits antibody response, blocks mononuclear cell reactions, and inhibits development of delayed hypersensitivity. Destruction of the natural mucosal barrier and reduced salivary secretion also increases the susceptibility to infection. Gram-negative bacilli (e.g., *Pseudomonas*, *Klebsiella*, *Escherichia coli*, *Enterobacter*, *Proteus*) are the most common agents of bacterial



**Fig. 1.** Irritant contact stomatitis. Aspirin placed in the buccal sulcus adjacent to a painful tooth causes a primary irritant contact stomatitis reaction. A mucosal ulcer is produced.



**Fig. 2.** Allergic contact stomatitis. Erythema, edema, and tenderness develops at the site of an allergic contact stomatitis reaction. This is a delayed hypersensitivity reaction to a flavoring in a dentifrice.

superinfection in chemotherapy patients. These infections usually present as painful erosions or ulcerations involving any portion of the oral cavity, including the labial commissures and the tongue. These lesions are all indistinguishable except for those caused by *Pseudomonas*, which have the characteristic ecthyma gangrenosum appearance. Therefore cultures are needed to identify the causative organism. Immediate treatment is necessary to avoid gram-negative sepsis.

The yeast, *Candida albicans*, is the most common cause of infections of the oral cavity. Drug-induced oral candidiasis often presents as acute pseudomembranous candidiasis (thrush) (Fig. 4). This is usually asymptomatic, but it may have an associated erythematous, ulcerated base. In addition, candidiasis may present as a tender, atrophic to eroded, erythematous patch, particularly over the tongue and labial commissures (acute atrophic candidiasis). This often follows the use of broad-spectrum antibiotics or the use of corticosteroid inhalers. A chronic form may be seen in denture wearers with the lesion situated about the dental prosthesis. The diagnosis is aided by clinical history and examination and can be confirmed by culture or microscopic examination.

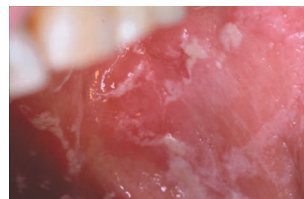
Opportunistic viral infections can occur as well. Herpes simplex virus is the most common organism, but varicella zoster and cytomegalovirus can be frequent offenders as well.

Fixed drug eruptions can manifest as ulcerations, particularly with repeated exposure. A wide range of drugs can cause fixed drug reactions, including barbiturates, sulfonamides, and tetracyclines (Fig. 3).

Lichen planus (LP) is a relatively common papulosquamous disorder involving the skin and mucous membranes. The oral lesions have a



**Fig. 3. Fixed drug reaction.** The repeated inflammatory cheilitis is the result of a tetracycline fixed drug reaction.



**Fig. 4. Thrush.** Acute pseudomembranous candidiasis is characterized by erythema, edema, and white curds of yeast covering a superficial erosion. The patient received a course of broad-spectrum antibiotics.



**Fig. 5. Drug-induced lichenoid tissue reaction.** A lichen planus-like drug reaction may develop from numerous drugs. Lesions may exhibit hyperkeratosis surrounding an erythematous plaque.



**Fig. 6. Drug-induced lichenoid tissue reaction.** This patient has developed an erosive, ulcerative form of lichen planus-like drug reaction.

distinct clinical and histologic appearance whether the etiology is drug-related or idiopathic. Often these lesions are asymptomatic. The primary hyperkeratotic papules may coalesce to form a reticular pattern most often on the buccal mucosa and tongue (Fig. 5). Occasionally erosions and ulcerations may develop (Fig. 6). There are no clinical or histologic features to reliably differentiate drug-induced from idiopathic LP. It is suggested, however, that drug-induced LP may more likely demonstrate eosinophils, plasma cells, and a more diffuse lymphocytic infiltrate (1). A number of drugs have been implicated in LP-like eruptions, including NSAIDs and angiotensin converting enzyme (ACE) inhibitors (Table 4). Some of the agents that cause LP-like eruptions are of potential therapeutic benefit in the management of LP (e.g., dapsone, tetracycline, hydroxychloroquine). The pathogenic mechanism by which drugs cause LP-like drug eruptions is not clear.

### Bullous disease

Drug reactions may mimic a number of disorders associated with blistering, including pemphigus vulgaris, pemphigoid, linear immunoglobulin A bullous disease (LABD), erythema multiforme (EM), and toxic epidermal necrolysis (TEN). Drug-induced pemphigus is not rare. Pemphigus-like drug reactions have been reported to have similar clinical, histologic, and immunofluorescent patterns as pemphigus vulgaris. Clinically it may resemble pemphigus vulgaris, with flaccid bullae and erosions occurring on noninflamed skin, particularly over the scalp, chest, and intertriginous areas. Oral erosions are common, but less common than in pemphigus vulgaris.

**Table 4.** Drugs causing lichen planus

Allopurinol	Methyldopa
Amitriptyline	Naproxen
Arsenic	Omeprazole
Captopril	Penicillamine
Chlorpropamide	Penicillin
Chloroquine	Phenytoin
Captopril	Prazosin
Dapsone	Procainamide
Furosemide	Propranolol
Gemfibrozil	Psoralens
Gold	Quinidine
Griseofulvin	Quinine
Hydralazine	Simvastatin
Hydroxyurea	Spirolactone
Imipramine	Streptomycin
Indomethacin	Sulfasalazine
Interferons	Sulindac
Isoniazid	Tetracycline
Labetalol	Tolbutamide
Lithium	Ursodiol

Thiols are commonly implicated drugs. They may lead to a decrease in levels of plasminogen activator inhibitor, which accordingly leads to an increase in plasminogen activation and epithelial damage, thereby exposing epithelial antigens (e.g., desmoglein 1 and 3) (2–4). Thiols may also disrupt cell membrane cysteine links, revealing epithelial antigens (5).

Drug-induced pemphigoid can occur in the setting of a number of drugs. Like drug-induced pemphigus, thiol drugs (e.g., D-penicillamine) and nonthiol agents can be responsible for the eruption. Distinguishing drug-induced pemphigoid from idiopathic bullous pemphigoid can be challenging, as patients from each group can present in the seventh and eighth decades with tense bullae on erythematous skin. Drug-induced pemphigoid patients may be younger and have more frequent oral involvement, however. Laboratory evaluation may not provide insight, as the histopathology, immunofluorescence, and antibody profile may be identical in both cases. Therefore an accurate drug history and a high index of suspicion is paramount.

LABD is a heterogeneous group of bullous disorders that can be drug induced. LABD patients can have IgA antibodies to several different antigens, including bullous pemphigoid antigen-1 (6,7). A number of drugs have been reported to induce this condition, including vancomycin (6).

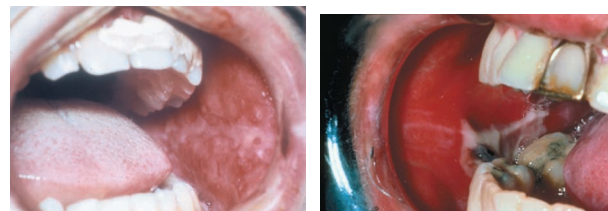
Erythema multiforme is a syndrome consisting of symmetrical mucocutaneous lesions that have a

predilection for the oral mucosa, hands, and feet. Initial bullae may rupture, giving rise to widespread superficial ulceration (Fig. 7). A spectrum of disease can be seen ranging from a benign cutaneous eruption to a severe mucocutaneous eruption. Stevens–Johnson syndrome (SJS) represents a severe manifestation of EM. Other mucous membrane surfaces may commonly be involved, including the bulbar conjunctivae, nasopharynx, and respiratory and genital mucosae (Fig. 8). A myriad of agents have been implicated in provoking EM/SJS. Drugs are a common cause, especially for the more severe mucocutaneous SJS reactions. They typically occur 1–3 weeks after ingestion of the offending drug.

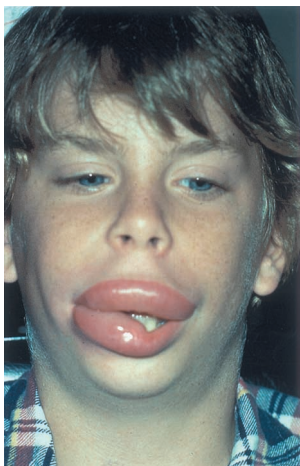
Toxic epidermal necrolysis is characterized by extensive mucocutaneous epidermolysis. Through-out the oral mucosa there may be diffuse painful blistering. TEN has been associated with antimicrobials, analgesics, and allopurinol among others.

### Swelling/angioedema

Oral or facial swelling may represent allergic angioedema (type I hypersensitivity) or hereditary angioedema (deficiency of C1 esterase). The swelling is acute and is often transient (Fig. 9). Lesions typically last for only several hours, but may last for days. There is the potential for airway obstruction. There are many potential causes of angioedema. Provocation may stem from a non-allergic reaction to food (direct liberation of histamine), as well as allergic reactions to foods, additives, or inhalants (e.g., pollens, infectious agents, drugs). A host of drugs can elicit this condition, particularly histamine-releasing drugs,



**Fig. 7. Erythema multiforme.** A generalized stomatitis may develop in the form of erythema multiforme patient. Gingival and buccal involvement is confluent with erosions and ulcerations (Courtesy Carl Allen, developing as the blisters slough away.)



**Fig. 9. Angioedema.** Acute swelling of the lips and occasionally of the tongue and oral mucosa may occur as a type I hypersensitivity reaction to foods or drugs.



**Fig. 10. Gingival hyperplasia.** Marked gingival hyperplasia is seen in patients on anticonvulsant therapy. The enlargement may cover the entire tooth.

aspirin, penicillins, and ACE inhibitors. Drug-induced mucosal swelling predominantly affects the lips and tongue (8). Rarely isolated uvula swelling occurs (Quinke's disease) (9).

Oral swelling with ACE inhibitors typically occurs in the early weeks of therapy, but may occur within several hours to several years after initiation of therapy. African Americans as well as those previously suffering from idiopathic angioedema may be at particular risk for this side effect (10). The tissue swelling associated with ACE inhibitors may be related to elevated bradykinin levels or altered C1 esterase levels or functions.

Angioedema resulting from drugs is probably not IgE mediated. Therefore antihistamines and inhaled or systemic corticosteroids may not alleviate airway obstruction (11).

### Salivary glands/xerostomia

Salivary gland enlargement may be painless or associated with tenderness. The causes of salivary gland swelling are numerous, but they can be viewed as local causes (e.g., neoplasm, duct obstruction), systemic causes (e.g., mumps, HIV parotitis, Sjogren's syndrome, sarcoidosis), or drug related (e.g., thiouracil, sulfonamides, NSAIDs, phenothiazines). Table 5 lists the causes of salivary gland enlargement.

There are many causes of xerostomia. Pharmacologic therapy is a common cause. Table 6

highlights pharmacologic agents and the mechanism by which they cause xerostomia. The parasympathetic division of the autonomic nervous system controls secretion by the salivary glands. Drugs can cause parasympatholytic activity in several ways, including competitive inhibition of acetylcholine at the parasympathetic ganglia and at the effector junction. Drugs may also influence parasympathetic response indirectly via interactions with the sympathetic and central nervous systems (12).

Numerous conditions can cause xerostomia (Table 7). History is of prime importance when attempting to make a diagnosis of drug-induced xerostomia. There is usually a close temporal relationship between beginning a drug and the development of symptoms. In addition, some patients may experience xerostomia with a recently increased dose of a medication they had taken for some time without any difficulties.

Patients with xerostomia often complain of a dry, "cotton mouth." Other problems include difficulty with speech and mastication, altered taste, poor denture fit, paresthesia, and burning mouth syndrome. Examination may reveal a dry, erythematous oral mucosa. Thinning, ulcerations, and erosions are sequelae. Xerostomia is primarily a nuisance, but its persistence may foster the development of bacterial infections, candidiasis, angular stomatitis, and dental caries, particularly at the gingival margins.

Ptyalism, or excess salivation, is much less frequent than xerostomia. More often it is due

**Table 5.** Causes of salivary gland swelling

Local
Duct obstruction
Neoplasm
Sialadenitis
Systemic
HIV parotitis
Mumps
Sarcoidosis
Sialosis
Sjogren's syndrome
Drugs
Catecholamines
Iodine
Methyldopa
Phenothiazines
Phenylbutazone
Pyrazolone derivatives
Sulfonamides
Thiouracil

**Table 6.** Mechanisms and drugs causing xerostomia

Mechanism	Drug class	Drug
Anticholinergic effect		
Parasympathetic ganglia	Antihypertensives	Pentolinium, mecamylamine, pempidine
Parasympathetic effector junction	Atropine	Atropine
	Atropine-like antispasmodic	Dicyclominehydrochloride, oxyphenonium, poldine, propantheline
	Antidepressants: tricyclic	Amitriptyline
	Antidepressants: tetracyclic	Maprotiline hydrochloride
	Antihistamines	Phenothiazines, phenothiazines derivatives
	Antiparkinsonian drugs	Benzhexol, biperiden, benzotropine mesylate, orphenadrine, levadopa, trihexylphenidyl
	Muscle relaxants	Orphenadrine, cyclobenzaprine
Sympathomimetic effect	Amphetamines/appetite suppressants	Ephedrine, fenfluramine chloride
Other	Antipsychotics	Chlorpromazine, promazine, thioridazine
	Antiemetics	Metoclopramide
	Narcotics	Meperidine, morphine
	Anticonvulsants	Carbamazepine
	Diuretics	Hydrochlorothiazide, furosemide
	Anxiolytics	Meprobamate
	Mood stabilizer	Lithium carbonate

to abnormalities in swallowing which results in drooling rather than an actual overproduction of saliva. Drooling is also quite common in those patients who have ulcers of the mouth or foreign bodies such as new dentures. Drugs rarely cause salivary overproduction, but they do so by stimulating a cholinergic response. Drugs may stimulate cholinergic receptors or may act upon cholinesterase inhibitors. Several other drugs are reported to increase salivary production, including aldosterone, bromide, captopril, lithium, ketamine, nitrazepam, and mercurial salts.

**Table 7.** Causes of xerostomia

Medication
Dehydration
Diabetes
Diarrhea and vomiting
Organic disease
Cytotoxic injury
Graft-versus-host disease
Parotitis
Radiation injury
Sarcoidosis
Sjogren's syndrome
Psychogenic
Fear/stress
Hypochondria

### Gingival enlargement

Gingival enlargement is seen in periodontal disease, systemic disorders (e.g., hereditary gingival fibromatosis, sarcoidosis, Crohn's disease, Wegener's granulomatosis, amyloidosis, leukemia, pregnancy, and scurvy) and drug-induced states. The drugs most commonly implicated are cyclosporine, anticonvulsants (e.g., phenytoin, sodium valproate), calcium channel blockers (e.g., nifedipine, diltiazem, verapamil, amlodipine), and large doses of progesterone. Patients receiving both cyclosporine and calcium channel blockers (e.g., renal and cardiac transplant patients) may be particularly susceptible. Gingival enlargement often begins within several months of drug therapy; it is usually generalized. The swelling is often firm, painless, and most prominent in the interdental papillae (13). The extent of gingival swelling varies. It may be slight or it may be severe enough to cover the entire tooth crown (Fig. 10). Occasionally the gingival enlargement may have a prominent inflammatory component. This gingivitis will be more likely to present with erythema, pain, and bleeding. Rarely Kaposi's sarcoma and squamous cell carcinoma (SCC) arise within areas of cyclosporine-induced gingival enlargement (14). Gingivectomy may be required, but recurrences occur unless the offending agent is withdrawn.

Tartar-control toothpastes and other contactants (e.g., cinnamon) may give rise to a

plasmacytosis of the oral mucosa (atypical gingivostomatitis) (15). This most often manifests as gingival enlargement. Histopathologically it is characterized by a polyclonal plasma cell infiltrate (16,17).

### White patches

Pseudomembranous candidiasis, or thrush, arises with the use of broad-spectrum antibiotics, corticosteroids (inhaled or systemic), immunosuppressive agents such as cyclosporine, and cytotoxic therapies. Clinically thrush is a superficial infection of the oral mucosa consisting of creamy white patches that are easily scraped from the epithelium (Fig. 4). Rarely mucormycosis and aspergillosis may cause thrushlike areas in patients on long-term immunosuppressive therapy.

Oral hairy leukoplakia is a benign, virally induced hyperplasia of the oral mucosa. It most commonly presents as a corrugated, verrucous plaque of the inferolateral surface of the tongue in HIV patients. It may also occur in the setting of drug-induced immunodeficiency or with topical corticosteroids (18,19).

### Pigment

Abnormal oral pigmentation can result from a number of causes (Table 8) including local and systemic medications. Mucosal pigmentation is related to erythrocyte degradation products,

**Table 8.** Causes of mucosal pigmentation

Localized
Amalgam tattoo
Ephelis
Foods and beverages (e.g., tea)
Iron salts
Irritation (e.g., smoking)
Kaposi's sarcoma
Melanoma
Nevus
Peutz-Jegher's syndrome
Generalized
Addison's disease
Albright's syndrome
Drugs
Antimalarials
Oral contraceptives
Phenothiazines
Zidovudine
Hemochromatosis
Racial



**Fig. 11. Amalgam tattoo.** Amalgam may be driven into the alveolar purla. Drugs affecting gingivae or other oral mucosal tissues during the course of a dental restoration procedure.

**Fig. 12. Drug-induced oral hemorrhage and purpura.** Drugs affecting vascular permeability, coagulation, or platelet function can cause painful bleeding, petechiae, or purpura of the oral mucosa.

increased melanin production, and drug moiety association with melanosomes.

Local agents such as heavy metals or dental amalgam may cause discoloration by traumatic implantation (Fig. 11). The gingival margin is a common site of involvement.

Systemic medications may leave the patient with a bluish-gray to yellowish-brown discoloration of the buccal mucosa, tongue, or hard palate (12). Aside from the appearance, the reaction is asymptomatic. Antimalarials, phenothiazines, and phenytoin have all been implicated. Abnormal pigmentation of the teeth may be caused by tetracycline and minocycline (20,21). Minocycline may also cause discoloration of the gingivae and surrounding oral mucosa. Much of the pigmentation is due to osseous discoloration, but minocycline inherently pigments the oral mucosa (22). In HIV disease, a diffuse or macular pigmentation of the oral mucosa may develop following therapy with clofazimine, zidovudine, or ketoconazole (23). Amiodarone may cause a gray orofacial and oral mucosal discoloration. Rarely oral contraceptives, cyclophosphamide, and busulfan can cause melanotic pigmentation (24,25).

Kaposi's sarcoma of the mouth is a rare complication related to drug-induced immunosuppression. It may present as a blue, red, or purple macule, papule, nodule, or area of ulceration. Lesions typically affect the palate or gingivae, but may affect other oral mucosal sites (26).

### Hemorrhage

Drug-induced hemorrhage of the oral mucosa is caused indirectly by medications and compounded by local factors. Drugs affecting vascular permeability, coagulation, or platelet function or

number may induce bleeding. Clinically the patient presents with painless bleeding or petechiae of the oral mucosa (Fig. 12). Most drug-induced hemorrhages result from thrombocytopenia. Spontaneous bleeding rarely occurs if the platelet count is greater than 20,000/mm<sup>3</sup>. With minor trauma, hemorrhage may ensue with platelet counts approaching 40,000/mm<sup>3</sup>.

### Sensation

Facial or oral paresthesia is a reported side effect of drugs. Many different agents have been reported to cause these symptoms of burning, tingling and numbness. Chemotherapeutic agents, particularly the vinca alkaloids, monoamine oxidase inhibitors, tricyclic antidepressants, streptomycin, nitrofurantoin, isoniazid, propranolol, and nicotinic acid in large doses have all been implicated.

Numerous causes exist that can lead to a decreased ability to perceive taste or causing an unpleasant taste (Table 9). The most common cause is due to an upper respiratory infection that affects olfaction, in turn, decreasing one's sense of taste. Olfaction may also be altered by head injuries and with aging. Xerostomia affects taste. Alteration in the taste buds by local irritation (e.g., burns) or nutritional deficiencies (e.g., zinc) may result in taste perception abnormalities. Drugs

**Table 9.** Disorders altering taste

Local disorders
Foods
Nasal disease
Oral infection
Xerostomia
Taste bud disorders
Cytostatic drugs
Irritation or burn
Nutritional deficiencies (e.g., zinc)
Cranial nerve disorders
Bell's palsy
Chorda tympani damage
Facial nerve injury (intracranial)
Lingual nerve damage
Cerebral disorders
Frontal lobe damage/tumors
Psychogenic disorders
Smoking
Cirrhosis
Old age
Gastric regurgitation
Drugs (see Table 10)

**Table 10.** Drugs altering taste

Acetazolamide	Iron
Benzodiazepines	Imipramine
Clofibrate	Isotretinoin
Cyclosporine	Levodopa
Diltiazem	Lithium
Dimethylsulfoxide	Methamphetamine
Gallium nitrate	Metronidazole
Gold salts	Nifedipine
Griseofulvin	Penicillamine
Guanethidine	Terbinafine
Idoxuridine	Verapamil

can also distort taste (Table 10). Calcium channel blockers, ACE inhibitors, iron, isotretinoin, terbinafine, and griseofulvin have been reported to alter taste. It may take months for the taste perception to normalize.

### Halitosis

Halitosis, or bad breath, may have many different etiologies (Table 11). It may be associated with an abnormal taste in the mouth. This association is commonly seen with smoking, various foods, alcohol, periodontal disease or other oral infections, and xerostomia. A number of systemic diseases can cause halitosis, especially cirrhosis and renal failure. In diabetic ketoacidosis, patients' breath may smell of acetone. Drugs are not frequently implicated, but disulfiram, isosorbide dinitrate, and dimethylsulfoxide have been associated with halitosis.

**Table 11.** Causes of halitosis

Alcohol
Drugs
DMSO
Disulfiram
Isosorbide dinitrate
Foods
Nasal foreign bodies
Oral infections
Oro-antral fistula
Respiratory tract infections
Smoking
Systemic disease
Diabetic ketoacidosis
Cirrhosis
Renal failure
Gastrointestinal disease
Xerostomia

## Stomatotoxic medications

Numerous topical and systemic medications are capable of causing adverse oral drug reactions. In the following section we will concentrate on common culprits within broad pharmacologic classes. Specific therapy, if applicable, will be indicated.

### Chemotherapeutic agents

Chemotherapeutic agents are the most common cause of nonspecific stomatitis (13). Although many reactions are possible (Table 12), the most common are xerostomia, ulceration, and infection (27). The reactions are typically dose related and may develop from either direct or indirect effects on the oral mucosa.

Direct reactions of chemotherapeutic agents are related to their cytotoxicity on the rapidly dividing cells of the oral mucosa. Initially patients may have an atrophic oral epithelium (28). Histologically one will see epithelial hypoplasia or atrophy, collagen degradation, glandular degeneration, and dysplasia (29). The agents most commonly associated with direct stomatotoxicity are listed in Table 13. Many of these agents are used in combination to enhance their cytotoxicity, so the potential increases for direct and indirect oral reactions.

Indirect oral reactions have several clinical presentations (Table 12). Most result from myelosuppression which is most pronounced 2 weeks after administration of the chemotherapeutic

**Table 12.** Oral reactions caused by chemotherapeutic agents

Direct reactions
Erythema multiforme
Lichenoid stomatitis
Ulcerative stomatitis
Indirect reactions
Hemorrhage (thrombocytopenic)
Hematoma
Petechiae, purpura
Bleeding
Infections (neutropenic)
Candidiasis
Herpes simplex
Gram-negative bacilli
Oral pain (neurotoxicity)
Pallor (anemia)
Xerostomia

**Table 13.** Stomatotoxic chemotherapeutic agents

Antimetabolites
Azathioprine
Cytosine arabinoside <sup>a</sup>
5-fluorouracil <sup>a</sup>
6-mercaptopurine
Methotrexate <sup>a</sup>
Antibiotics
Actinomycin D <sup>a</sup>
Adriamycin <sup>a</sup>
Bleomycin <sup>a</sup>
Daunorubicin <sup>a</sup>
Mitomycin C
Plant alkaloids
Vinblastine
Vincristine
Alkylating agents
Busulfan
Chlorambucil <sup>a</sup>
Cyclophosphamide <sup>a</sup>

<sup>a</sup>Causes direct stomatotoxicity.

agent (30). Neutropenia, thrombocytopenia, and anemia predispose patients to certain oral complications. Vincristine-induced neurotoxicity may present with oral pain, paresthesia, or facial weakness (12).

The majority of chemotherapeutic-related effects, whether direct or indirect, will subside within 3 weeks of removing the offending agent. Prophylactic measures are very important in patients receiving chemotherapy. Close monitoring of peripheral blood cell counts, avoidance of invasive and manipulative techniques, and frequent changes of peripheral venous access catheters will reduce the number of infections (31). If procedures cannot be avoided, prophylactic, broad-spectrum antibiotics may be used to decrease the incidence of infection (31). Meticulous hand washing by hospital personnel, appropriate cleansing of the patient's living area and instrumentation, and avoidance of raw foods and flowers can all reduce pathogenic exposure. Other measures such as nystatin swish and swallow, fluoride rinses, artificial saliva, and a soft, bland diet may help reduce the risk of oral complications (30).

### Antibiotics

Antibiotics are capable of causing a number of different oral drug reactions. Unlike the antineoplastic drugs, antibiotics do not have a direct toxic effect on the oral mucosa. Instead, most of the

reactions are related to allergic, ecologic, and indirect mechanisms. Table 14 lists antibiotic-induced oral drug reactions based on suspected mechanisms. The separate classes of antibiotics and their common oral complications are discussed in the following sections.

*Cephalosporins.* These  $\beta$ -lactam compounds can elicit cross-sensitivity in patients allergic to penicillin (20). Most patients allergic to penicillin tolerate cephalosporins; however, they are contraindicated in those with type I hypersensitivity (e.g., urticaria, angioedema, bronchospasm, anaphylaxis) to penicillin (20).

Hemorrhage or purpura may occur in individuals taking broad-spectrum cephalosporins. This complication results from alterations in normal gut flora, resulting in a decreased production of vitamin K, thereby affecting the ability to produce clotting factors (20).

*Penicillins.* Penicillins are bactericidal antibiotics that are generally safe and effective. These drugs are known to cause type I sensitivity reactions, however. The estimated incidence of hypersensitivity to penicillin is 1–5% with 5–10% of these patients sensitive to cephalosporins (20). Patients may be tested for hypersensitivity with prick tests. If the prick tests are negative, then intradermal testing should be performed with each agent to achieve 95% predictability of penicillin IgE-

mediated hypersensitivity (20). The treatment for a reaction is subcutaneous epinephrine. Erythema multiforme or Stevens–Johnson syndrome is another relatively common allergic reaction that can occur with penicillins.

The penicillins, as well as many other broad-spectrum antibiotics, may cause black hairy tongue. This condition results from an overgrowth of pigment-producing bacteria after suppression of normal oral bacteria by the antibiotic. The discoloration disappears 2–3 weeks after discontinuation of the antibiotic. Alternatively the tongue may be brushed with 1% hydrogen peroxide.

*Sulfonamides.* The sulfonamides competitively inhibit bacterial synthesis of folic acid. These medications can cause hypersensitivity reactions involving the skin and mucous membranes, particularly EM and SJS. The long-acting sulfonamides are more commonly associated with SJS (32). There have been case reports of topical sulfonamides causing SJS (33). Sulfonamides can also cause thrombocytopenia and granulocytopenia. Patients on prolonged courses of these medications should be followed and monitored for blood dyscrasias.

*Tetracyclines.* Tetracyclines are bacteriostatic agents that interfere with bacterial protein synthesis. Perhaps the most commonly recognized

**Table 14.** Antibiotic-induced oral drug reactions

Mechanism	Reaction	Medication
Allergic	Stomatitis/ulcerative	Clindamycin, isoniazid, penicillin, rifampin, sulfonamides, tetracycline Chlorpromazine, clindamycin, hydralazine, isoniazid, nitrofurantoin, rifampin, procainamide, sulfonamides, tetracycline Streptomycin, tetracycline Sulfonamides, tetracycline Colistin, isoniazid, nitrofurantoin, polymyxin B, streptomycin
	Erythema multiforme	
	Lupus erythematosus	
	Lichenoid	
Ecologic	Fixed drug	Broad-spectrum antibiotics
	Neuropathy	Broad-spectrum antibiotics
Indirect	Hemorrhage, purpura (thrombocytopenia)	Chloramphenicol, penicillins, streptomycin, sulfonamides
	Infection (neutropenia)	Tetracycline, vancomycin
	Stomatitis (vitamin B deficiency)	Chloramphenicol, tetracycline
Other	Hemorrhage (decreased vitamin K)	Cephalosporins, broad-spectrum antibiotics
	Discoloration of teeth	Minocycline, tetracycline
	Taste disturbances	Griseofulvin, metronidazole

complication of tetracycline is its ability to bind with calcium and disrupt osseous tissue (20). Clinically both deciduous and permanent teeth are affected, resulting in dysgenesis and discoloration (20). The tetracyclines should be avoided in pregnant women and children less than 8 years of age. Minocycline probably causes tooth discoloration by a different mechanism, as it complexes poorly with calcium but chelates iron to form insoluble complexes. Minocycline tooth discoloration forms in the incisal aspect of the tooth, whereas tetracycline discoloration forms near the gingival aspect (21). Minocycline has also been noted to cause discoloration of the skin, sclerae, conjunctivae, gingivae, and nails.

Tetracyclines are common causes of fixed drug reactions. These eruptions most commonly occur on the palms, soles, glans penis, and lips (Fig. 3). Cases have rarely been reported intraorally (34). Other oral reactions include xerostomia, black hairy tongue, and stomatitis related to vitamin B deficiency.

### Antiarthritic agents

The drugs in this group are responsible for a variety of oral drug reactions (Table 15). Some of the most significant reactions will be discussed, including oral ulcerations. It is important to realize that approximately 20% of patients with rheumatoid arthritis will develop oral ulcerations as a part of the disease.

*Aspirin.* Aspirin can cause significant local tissue irritation, even necrosis (Fig. 1). Typically the patient applies crushed or whole aspirin alongside an aching tooth for pain relief. The irritation is usually confined to a small area, but may be diffuse, especially if the aspirin is in the form of a chewing gum. Phenylbutazone and indomethacin may cause similar reactions (13).

*Gold.* Chrysotherapy can induce stomatitis and ulceration. The ulcers are typically along the buccal mucosa and inferior aspect of the tongue. The mechanism is thought to be allergic. Acute hypersensitivities to gold dental materials and jewelry have been reported in patients with gold stomatitis (35). In addition, gold stomatitis may resemble LP, which has been reported to occur only after prolonged systemic use of the drug (Fig. 6) (36).

**Table 15.** Adverse oral drug reactions caused by antiarthritic agents

Medications	Reactions
Salicylates	Erythema multiforme Hemorrhage Hypersensitivity Lichen planus-like eruption Taste disturbances Ulcerative stomatitis
NSAIDs	Erythema multiforme Hemorrhage Lichen planus-like stomatitis Lupus erythematosus-like stomatitis Salivary gland swelling Ulcerative stomatitis
Gold	Dyspigmentation Glossitis Hemorrhage Lichen planus-like stomatitis Lupus erythematosus-like stomatitis Taste disturbances Ulcerative stomatitis
D-penicillamine	Hemorrhage Lichen planus-like stomatitis Lupus erythematosus-like stomatitis Pemphigus-like stomatitis Taste disturbances Ulcerative stomatitis

*NSAIDs.* Nonsteroidal anti-inflammatory drugs are implicated in many types of oral drug reactions, particularly ulcerative stomatitis, which may be caused by local vasoconstriction (37). The malnourished oral mucosa may then ulcerate spontaneously or in response to local trauma (38).

*D-penicillamine.* Like other agents with an active sulfhydryl group (e.g., captopril), there are numerous well-documented adverse reactions to D-penicillamine, including taste disturbances, stomatitis, and oral ulcerations (39,40). Gustatory change occurs without olfactory alteration and may persist despite discontinuation of the drug. Zinc supplementation seems to hasten the return of normal taste. Severe stomatitis is rare except in those patients with primary biliary cirrhosis (41–43).

The most common clinical presentation is of pemphigus (44). Features of pemphigus vulgaris, foliaceus, and erythematosus, as well as bullous pemphigoid, have been noted (44–47). D-penicillamine-induced pemphigus tends to spare the oral mucosa, however.

## Cardiovascular medications

Antihypertensive, antiarrhythmic, and antianginal medications play an important role in the patient's health. These medications can cause a variety of adverse effects, however. Those with notable occurrences are listed in Table 16. The decision to discontinue a medication must carefully consider the benefits of that drug against the adverse reactions it may cause.

*Captopril.* Captopril is an ACE inhibitor that has been reported to cause oral reactions similar to those of D-penicillamine (e.g., taste disturbances, stomatitis, and oral ulcerations) (39,48). This finding is most likely explained by the presence of an active sulfhydryl in both medications. Enalapril, an ACE inhibitor which lacks an active sulfhydryl group, and captopril both cause oral paresthesia (49). Some of these adverse reactions may be avoided by decreasing the dose of medication.

*Other agents.* Drug-induced systemic lupus erythematosus (SLE) is commonly associated with the cardiovascular medicines hydralazine and procainamide. Patients who are slow acetylators of these medications tend to be more susceptible to developing drug-induced SLE. Up to 21% of patients taking these two medications may develop drug-induced SLE. It is unclear whether the drug-induced SLE is an allergic response or whether it is uncovering underlying disease.

**Table 16.** Cardiovascular medications associated with oral drug reactions

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Antihypertensives
Captopril
Clonidine
Guanethidine
Hydralazine
Labetolol
Methyldopa
Pindolol
Propranolol
Spironolactone
Thiazides
Antiarrhythmics
Digitalis
Procainamide
Quinidine
Antianginal
Isosorbide dinitrate
Nifedipine

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Nonetheless, patients with drug-induced SLE may be indistinguishable from those with spontaneous disease, as serologic abnormalities may be identical. Nearly 25% of patients with SLE will have oral ulcerations (12). Upon discontinuing the medications, most patients have resolution of their symptoms.

## Antidepressant medications

Four principal drug classes are employed for the treatment of affective disorders: tricyclic and tetracyclic compounds, monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors (SSRIs), and lithium. The tricyclic and tetracyclic compounds are listed in Table 17. Xerostomia is a common complication of these medications and is related to anticholinergic activity. As noted earlier, dental caries, ulceration, and opportunistic infections may all develop secondary to xerostomia. A toxic neuropathy with resulting paresthesia can develop with these medications (12).

MAO inhibitors rarely cause oral complications (20). Xerostomia rarely occurs. The SSRIs generally have a lower risk for anticholinergic side effects, including xerostomia, than do heterocyclic compounds and MAO inhibitors.

Lithium may cause a variety of drug reactions. Nonspecific lichenoid and stomatitis reactions have been reported (50,51). Sialorrhea with painless parotid enlargement has also been reported (52).

The adverse oral reactions caused by antidepressants tend to be mild and may resolve spontaneously or with decreasing doses or discontinuation of the drug.

## Anticonvulsant medications

The anticonvulsants are comprised of several heterogeneous chemical classes. Many of these drugs can elicit a skin hypersensitivity reaction that is apparent 2 weeks after therapy initiation (20). Drug-induced SLE, EM, and SJS may all develop. Blood dyscrasias, which are most commonly associated with phenacemide and mephenytoin, may present as intraoral hemorrhage or infection (53).

*Phenytoins.* Gingival hyperplasia is probably the most recognized oral reaction associated with phenytoin therapy (Fig. 10). It is characterized by a firm, painless overgrowth of fibrous tissue as opposed to the inflammatory gingival enlargement seen in pregnant patients and those taking

**Table 17.** Antidepressants that cause adverse oral drug reactions

Tricyclic antidepressants	
Dibenzazepines	
Desipramine <sup>a</sup>	
Imipramine <sup>b</sup>	
Trimipramine <sup>b</sup>	
Dibenzocycloheptdienes	
Amitriptyline <sup>c</sup>	
Nortriptyline <sup>a</sup>	
Protriptyline <sup>b</sup>	
Dibenzoxepin	
Doxepin <sup>c</sup>	
Dibenzoxazepine	
Amoxapine <sup>a</sup>	
Tetracyclic antidepressants	
Maprotiline <sup>b</sup>	
SSRIs	
Citalopram	
Fluoxetine <sup>a</sup>	
Fluvoxamine <sup>a</sup>	
Paroxetine <sup>a</sup>	
Sertraline <sup>a</sup>	
Monamine oxidase inhibitors	
Hydralazines	
Isocarboxazid	
Phenelzine	
Nonhydralazines	
Tranlycypromine	
Mood stabilizer	
Lithium	

Relative anticholinergic effects: <sup>a</sup>minimal, <sup>b</sup>intermediate, <sup>c</sup>maximal.

oral contraceptives. The incidence approaches 50% of the patients taking phenytoin and occurs within 3 months of starting the medication (13). Local irritation and poor dental hygiene are thought to be related to the severity of the hyperplasia. Therefore good oral hygiene is a mainstay of therapy. Phenytoin induces folic acid deficiency. Correction of this deficiency with up to 1 mg of folate three times a day may help reduce the enlargement in some patients (13). Gingivectomy may be used with good success in those severely affected.

### Topical medications

Adverse oral reactions to topical medications are divided into contact stomatitis and primary irritant stomatitis. These have previously been discussed. Table 18 lists some common agents that cause these reactions. The only specific therapy is to remove the offending agent.

## General clinical management and therapies

Discontinuation of the offending agent is the definitive treatment of oral drug reactions; however, the patient may have significant discomfort prior to the resolution of the reaction that requires palliative measures. Four of the most common oral drug reactions and supportive care techniques are outlined in Table 19. These regimens will mitigate symptoms until the reaction resolves. Also, these techniques may reduce the symptoms enough to resume the medications if necessary. General prophylactic measures, such as meticulous daily dental hygiene and regular dental visits may be helpful.

## Conclusion

Drug-induced oral disorders present a variable clinical picture and are produced by numerous medications. These reactions may result from both systemic and topical medications. Stomatitis medicamentosa may result from immunologically mediated or toxic mechanisms. Contact stomatitis reactions result from delayed-type hypersensitivity or primary irritation reactions. The diagnosis of an oral drug reaction depends upon history, examination, and index of suspicion. The possibility of an oral drug disorder should be considered when the etiology is not apparent. The clinical appearance of an oral drug reaction

**Table 18.** Local agents that cause oral reactions

Allergic contact stomatitis	
Anesthetics: topical and local	
Antibiotic lozenges	
Chewing gums	
Cough drops	
Dental adhesives	
Flavorings: mint and cinnamon	
Lipstick: perfumed	
Mouthwashes	
Pipe stems, cigarette holders	
Toothpastes	
Primary irritant reactions	
Aspirin	
Chlorhexidine mouthwash	
Gentian violet	
Nitric acid	
Silver nitrate	
Sodium lauryl sulfate	

**Table 19.** Supportive care for four common oral drug reactions

Reaction or symptom	Supportive care
Xerostomia	Ice chips, ↑ sips of water ↓ Dry foods (bread) ↓ Alcohol and smoking Sugarless gum or hard candies Artificial saliva Lemon and glycerine mouthwash: Citric acid 12.5 g Lemon spirit 20 ml Glycerine BP to 100 ml Use (1) 5–10 ml in 100 ml of water as a moisturizer; (2) Several undiluted drops to swish in mouth as needed Biotene toothpaste <sup>a</sup> Fluoride rinses to help reduce dental caries
Oral pain	Ice chips Soft, bland diet Viscous xylocaine Benzocaine in Orabase to discrete lesions Systemic analgesia if severe
Infection	
Bacterial	Broad-spectrum systemic antibiotics; specific therapy guided by culture and sensitivities
Candidiasis	Nystatin swish and swallow Amphotericin, ketoconazole, or fluconazole for esophageal or systemic involvement Pain control as needed
Herpes labialis	Lubrication Pain control as needed Acyclovir or analogues systemically Topical antibiotics to help reduce secondary bacterial infection
Hemorrhage	Soft, bland diet Stop mechanical hygiene Remove orthodontic appliances Topical thrombin solution Platelet transfusion Vitamin K if needed Care for infection

<sup>a</sup>Biotene toothpaste with glucose oxidase, enzymes, and other ingredients to stimulate the antibacterial action of normal saliva (available from Lackede Research Laboratories, Gardena, CA).

may be nonspecific or resemble other distinct clinical entities. The clinician who is familiar with the types of oral drug reactions, medications commonly involved, and mechanisms by which these reactions occur will be well prepared to make a diagnosis and recommend treatments.

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