Current Opinion on Drug-induced Oral Reactions: A Comprehensive Review

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Abstract

Aim: The aim of this comprehensive review is to present an update to our previous review about drug-induced oral reactions. All drugs that may cause adverse effects in the mouth and related structures are reviewed.

Background: 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. The mouth and associated structures can also be affected by many drugs or chemicals. Good oral health including salivary function is very important in maintaining whole body health. Drug reactions can be categorized as to the parts of the oral complex such as the oral mucosa and tongue, periodontal tissues, dental structures, salivary glands, cleft lip and palate, muscles, and nerves.

Review Results: This review suggests the number of drugs and chemicals that can produce adverse or toxic reactions in the oral cavity are on the rise. An updated listing of offending drugs is provided along with current strategies for dealing with adverse reactions.

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Conclusion: Clinicians must 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.

Clinical Significance: Dentists and specialists of oral diseases should be aware of adverse drug oral reactions for better diagnosis of oral diseases, administration of drugs, and patient compliance during drug therapy.

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

Citation: Abdollahi M, Rahimi R, Radfar M. Current Opinion on Drug-induced Oral Reactions: A Comprehensive Review. J Contemp Dent Pract 2008 March; (9)3:001-015.

Introduction

The oral cavity may be the target organ for a number of diverse abnormalities that develop from side effects of medications. In theory, all drugs are capable of inducing adverse side effects, the most serious of which include blood dyscrasias, altered immune responses, immediate or delayed hypersensitivity reactions, and predisposition to oncogenic changes. Any of these effects can present oral manifestations, and mucositis can occur as either a direct or secondary effect of drug use.

Considering the aging of the population along with widespread and increased use of prescription, over-the-counter, and herbal remedies, dentists can expect to encounter oral side effects from medication use among their patients. A survey of 3302 patients visiting the Stomatology Center at Baylor College of Dentistry revealed 66% were taking prescription drugs and 42% were taking two or more prescription medications daily. Since many patients regularly take prescription and nonprescription medications, dentists always should take thorough medical histories and be aware of medication-related problems and their potential effects on diagnosis and treatment planning.¹⁻³

The three most frequent oral side-effects encountered with the 200 most frequently prescribed drugs for 1992 were xerostomia, dysgeusia, and stomatitis with prevalence rates of 80.5%, 47.5%, and 33.9%, respectively.⁴

The 2003 review of drug-induced oral reactions published by Abdollahi and Radfar⁵ included the subjects shown in Table 1. (page 15)

The present review re-evaluated the literature since 2003 to provide an update of drug-related data on drug-induced oral reactions. Sections on oral mucositis, fluorosis, osteonecrosis of jaws, and a review of diagnosis and management strategies for each of these reactions have been added.

Oral Allergic Reactions

Recent evidence suggests the incidence of allergic responses within the oral cavity is rapidly increasing.³

Systemic medications can cause allergic reactions in the mouth as a fixed drug eruption called stomatitis medicamentosa. Fixed drug eruptions are localized hypersensitivity reactions that recur in the same site each time the causative drug is ingested. They feature erythematous eruptions on the skin and mucous membranes and often heal with residual hyperpigmentation. Oral lesions can also be erosive and ulcerated. They may occur on the gingiva and palate, although the buccal mucosa, lips, and tongue are more frequently involved. Lesions associated with fixed drug eruption usually appear within 24 hours post-ingestion of the drug. Delayed reaction (up to two weeks) has

been noted after use of ampicillin for example. Withdrawal of the causative drug results in resolution of the lesions. Drugs with potential to cause fixed drug eruptions are shown in Table 2.

Oral contact allergic reactions or stomatitis venennata has increased in recent years because of the increased use of oral hygiene products, esthetics related products, dental restorative materials, and the establishment of infection control procedures that mandate the wearing of latex gloves for dental treatment procedures. The reaction may develop from days to years post-exposure to the causative agent. There are various types of oral contact allergic reactions. Allergic gingivo-stomatitis features intense hyperemic inflammation of the gingiva, with or without involvement of the buccal and labial mucosa. On occasion angular cheilitis and glossitis are present and involvement of the vermilion border of the lips and perioral skin has been described. The condition was first reported in the 1960s and proved to represent a contact allergic reaction to an ingredient in chewing gum, toothpaste, or mints. Subsequently, candies, cough drops, dentifrices, mouthrinses, topical fluorides, other therapeutic agents, and a variety of food products have been implicated. Dentifrice hypersensitivity reactions appear to be more common since the advent of tartar-control toothpastes.^{3,4} The gingiva is often the only site of reaction or the most severely involved, perhaps because the antigen is in intimate contact with the gingiva during toothbrushing. In most instances the reactions appear to be induced by the flavoring agents in the dentifrices, often cinnamic aldehyde, a common allergen.^{3,5} Compounds with potential to cause oral contact allergic reactions are shown in Table 3.

Aphthous-Like Ulcers

Ulcers resembling recurrent aphthous stomatitis but have systemic causes are often termed aphthous-like ulcers. Examples include Behçet's syndrome, gastrointestinal diseases such as gluten-sensitive enteropathy or inflammatory bowel disease, immunodeficiency syndromes such as infection with the human immunodeficiency virus (HIV), cyclic neutropenia, and adverse reactions to medications. Recurrent aphthous stomatitis (also referred to as aphthae or canker sores) is one of the most common

oral ailments. It is a common condition which is characterized by multiple recurrent small, round, or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors. The term "recurrent aphthous stomatitis" should be reserved for recurrent ulcers confined to the mouth and seen in the absence of any systemic cause.⁹⁻¹¹

Drugs with potential to cause aphthous-like ulcers are shown in Table 4.

The diagnosis of aphthous ulcers is invariably based upon the history and clinical findings. The proper treatment of aphthous ulcers depends on the frequency, size, and number of the ulcers. Patients who experience minor aphthous ulcers experience significant relief with appropriate topical therapy such as tannic acid (zilactin), orabase, diclofenac, or amlexanox paste. In patients with more severe disease, use of a topical glucocorticoid is an effective therapy to decrease both the size and healing time of the ulcers, especially when the medication is used early in the developing stage of the lesion.¹⁶

Burning Mouth Syndrome

Burning mouth syndrome (BMS) is synonymous with stomatodynia, oral dysaesthesia, glossodynia, glossopyrosis, and stomatopyrosis characterized by oral mucosa pain, with or without inflammatory signs, and without a specific lesion. The pain feels like a moderate to severe burning sensation occurring more frequently on the tongue but can also occur on the gingiva, lips, and jugal (malar) mucosa. It can worsen during the day as a result of stress and fatigue, excessive speaking, or by ingesting spicy/hot foods. The burning can be diminished with cold food and leisure. This syndrome may occur due to xerostomia or radiotherapy; endocrine disease such as diabetes mellitus, hypothyroidism, and menopause; medication; nutritional deficiencies including iron, vitamin B complex, folic acid and zinc; neuralgia; dental prostheses; allergy; infection; and psychiatric disorders such as depression and anxiety.¹⁷⁻¹⁹

Angiotensin converting enzyme inhibitors (ACEIs) are a class of medications that can cause BMS. ACEI-induced burning sensation of the tongue, throat, and palate has been described as being

similar to the scalding caused by hot coffee or pizza and so called scalded mouth syndrome.²⁰ Cases of “scalded mouth” caused by ACEIs such as captopril, lisinopril, and enalapril have been described.²¹⁻²³ The mechanism of ACEI “scalded mouth” is uncertain, but it may be a subclinical manifestation of lichen planus. A list of drugs that can induce BMS is shown in Table 5.

The diagnosis of BMS is based upon the history, clinical findings, and physical examination. Usually, the classic BMS patient presents with a chief complaint of a burning, scalding, or tingling feeling in the mouth and may complain of a persistent bad or uncommon taste or altered taste perception. It is important to note pain/burning sensations usually increase in intensity at the end of the day but very rarely interfere with sleep. In the past two decades a variety of different therapies for BMS have been proposed, including the use of benzodiazepines, tricyclic antidepressants, gabapentin, trazodone, selective serotonin reuptake inhibitors, amisulpride, topical capsaicin, alpha-lipoic acid, and cognitive behavioral therapy. Variable, unpredictable, and often discouraging outcomes have been reported, leading to the impression BMS therapy is always difficult and often unsuccessful. Treatments proven to be effective in controlled double-blind studies are cognitive behavior therapy, topical or systemic clonazepam, and alpha lipoic acid.^{19,27}

Glossitis

Glossitis is inflammation of the tongue characterized by swelling and intense pain that may be referred to the ears. Salivation, fever, and enlarged regional lymph nodes may develop during an infectious disease, after a burn, or other injury.²⁸ Drugs having the potential to cause glossitis are shown in Table 6.

Erythema Multiforme

Erythema multiforme (EM) is an acute reactive mucocutaneous inflammatory and hypersensitivity reaction characterized by a skin eruption, with symmetrical erythematous edematous or bullous lesions of the skin or mucous membranes. EM is a disorder with variations ranging from self-limited, mild, exanthematous, cutaneous lesions with minimal oral involvement to a progressive, fulminating, severe disease with extensive mucocutaneous epithelial necrosis (Stevens-Johnson syndrome and toxic epidermal

necrosis). More than half the cases have no known cause, while half are caused by medications, infections, immunotherapy, or illnesses.³⁰⁻³² Only 4% of EM reactions are caused by drugs, however, 80% of cases are found with Stevens-Johnson syndrome. The oral lesions disappear within 14 days of drug withdrawal.⁵ Drugs with potential to cause EM are shown in Table 7.

There are no specific diagnostic tests for EM. Therefore, the diagnosis is mainly clinical, and it can be difficult to differentiate between it and viral stomatitis, pemphigus, toxic epidermal necrolysis, and sub-epithelial immune blistering disorders. Spontaneous healing can be slow. Up to two or three weeks of healing time is typical for minor EM and up to six weeks for major EM cases. Treatment is indicated but controversial, and care by a specialist should be sought. Supportive care is important. A liquid diet and even intravenous fluid therapy may be necessary. Oral hygiene should be improved with 0.2% aqueous chlorhexidine oral rinses. The use of corticosteroids is controversial but minor EM may respond to topical corticosteroids. Patients with major EM such as the Stevens-Johnson syndrome may need to be admitted for hospital care. Major EM patients should be referred for treatment with systemic corticosteroids or other immunomodulatory drugs.^{30,33}

Oral Ulceration

Ulceration is a breach in the oral epithelium, which typically exposes nerve endings in the underlying lamina propria, resulting in pain or soreness, especially when eating spicy foods or citrus fruits. Patients vary in the degree to which they suffer of soreness in relation to an

oral ulceration. Ulcers and erosions can also be a final common manifestation of a spectrum of conditions. These conditions include the following:³⁷

- Epithelial damage resulting from trauma
- An immunological attack as in lichen planus
- Pemphigoid or pemphigus
- Damage due to an immune defect as in HIV disease and leukemia
- Infections such as herpes viruses
- Tuberculosis and syphilis
- Cancer
- Nutritional defects such as vitamin deficiencies
- Some gastrointestinal diseases
- Medications

The number, persistence, shape, character of the edge of the ulcer, and the appearance of the ulcer base should be noted for diagnosis. Treatment includes prescribing a chlorhexidine 0.2% mouthwash, maintaining good oral hygiene, a benzydamine mouthwash or spray, application of a topical lidocaine solution or carboxymethylcellulose paste or powder may reduce pain from these ulcers.³³

Drugs and chemicals that may cause local irritation and ulceration of the mouth include those listed in Tables 8 and 9.

Vesiculo–Bullous Lesions

The exact mechanism of this tissue reaction is unclear, but it appears to be the consequence of a direct irritant. Patients using steroid inhalers for more than five years are more prone to the development of oral blistering. This type of reaction has also been reported for naproxen and penicillamine.⁵ The keys to diagnosis are the presence of other mucosal or cutaneous lesions, the histological examination, and the finding of perilesional antibodies on the mucosa. The symptomatic treatment of oral bullous lesions includes the adherence to a specific diet, use of analgesics, and the prevention or treatment of a superimposed infection.⁴²

Oral Lichenoid Reactions

Lichen planus is a chronic systemic disease of established immune-mediated pathogenesis. It commonly involves the mucosa of the oral cavity but can involve other sites, such as the skin, vulvar and vaginal mucosa, the glans penis, the

scalp, and the nails. Oral lichen planus is usually a persistent disorder and may persist for many years despite several treatment strategies. Some drugs can induce oral disorders resembling lichen planus and are said to be oral lichenoid drug reactions. Oral lichenoid drug reactions are uncommon.^{30,43,44} Unlike true oral lichen planus, drug-induced oral 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 drugs causing lichenoid reactions only uncover the latent disease of lichen planus or amplify a previous disorder rather than inducing the disease *de novo*.⁵ Such drugs are listed in Table 10.

Clinical presentation and histopathological investigation may help with the diagnosis. Management of drug-induced oral lichenoid eruptions involves withdrawal or replacement of the offending medication. If this approach is not possible, then the corticosteroids, tacrolimus, and psoralens are used to treat this disorder.⁴⁵

Color Changes of the Oral Mucosa and Teeth

Mucosal Pigmentation

Oral discoloration may be superficial due to extrinsic or deep due to intrinsic (in or beneath mucosa) causes.

Extrinsic discoloration is rarely of consequence and is usually caused by habits that include the following:

- Use of tobacco or betel nut.
- Consumption of colored foods or beverages (such as liquorice, beet root, red wine, coffee, and tea).
- Use of drugs (such as chlorhexidine, iron salts, crack, cocaine, minocycline, bismuth subsalicylate, and lansoprazole).

The primary causes of intrinsic mucosal hyperpigmentation include:⁴⁷

- Amalgam or other tattoo
- Nevus
- Melanotic macule
- Neoplasms (e.g., malignant melanoma or Kaposi's)
- Pigmentary incontinence
- Peutz-Jegher's syndrome
- Racial pigmentation
- Localized irritation such as the use of tobacco or betel
- Drugs such as antimalarials and oral contraceptives
- Pregnancy
- Addison's disease

The exact mechanism of tissue discoloration by many drugs is uncertain but generally resolves within weeks to months when the offending drug is withdrawn. However, sometimes the discoloration is permanent.

For antimalarial drugs like chloroquine and mepacrine (quinolones), the deposit of melanin or iron in mucosal tissues has been suggested. Long-term use of phenothiazines, especially chlorpromazine, produces widespread mucosal pigmentation which is caused by the accumulation of a drug metabolite in the tissue. 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 which contributes to the decrease of a portion of plasma free cortisol and as a result produces a hypersecretion of ACTH and β -melanocyte-stimulating hormone. The later may cause the increased oral pigmentation.⁵ Minocycline-induced oral pigmentation consequent to the interaction of the drug with bone during its formation is common. Almost all cases of intraoral pigmentation represent minocycline staining of the underlying bones without involvement of the overlying oral mucosa surfaces.

Pigmented lesions of the tongue (dark macular patches) are reported to occur in heroin addicts who inhale the smoke.⁴⁸ Drugs and chemicals with potential to cause oral pigmentation are listed in Table 11.

Dental Discoloration

Numerous drugs are known to have the capability of causing either extrinsic or intrinsic tooth discoloration. Extrinsic stains are located on the surface of the tooth and are most easily removed by external cleaning. Drugs that are well-recognized as causing extrinsic discoloration include chlorhexidine, oral iron salts in liquid form, essential oils, and co-amoxiclav. Intrinsic stains are located within the tooth structure and are accessible only by bleaching. Some extrinsic stains that remain on the tooth for a long time can become intrinsic. By recognizing the likely cause of the stain, the dentist can better inform a patient about the rate at which the teeth may lighten in color and the limitations of improvement to be expected following treatment.

Tetracycline can cause the most common distracting, generalized type of intrinsic discoloration. It is hypothesized to occur by the joining of the tetracycline molecule with calcium through a chelation process and a subsequent incorporation into the hydroxyl apatite crystal of the tooth during the mineralization stage of development.⁵⁰⁻⁵² Drugs and chemicals with potential to cause tooth discoloration are listed in Table 12.

Black Hairy Tongue (Lingua villosa nigra)

In this condition there is an elongation of the filiform papillae of the tongue to form hair-like overgrowth which becomes stained brown or black due to the proliferation of chromogenic microorganisms. Black hairy tongue can be seen with the administration of oral antibiotics, poor dental hygiene, and excessive smoking in adults.⁵ Drugs and chemicals with potential to cause black tongue include those listed in Table 13.

Therapeutic options of modest benefit include increasing hydration and salivation, brushing the tongue with a soft toothbrush enhanced by previous application of 40% urea solution, applying topical retinoids or salicylic acid, or undergoing surgical excision.⁵⁴

Postmortem Pink-red Coloration

Tooth coloration of this nature is due to hemolysis and exudation of hemoglobin to the dental pulp which 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, dichloralphenazon, and carbon monoxide also demonstrate similar findings.²⁹

Oral Mucositis

Oral mucositis is a common toxicity associated with both head and neck radiation and chemotherapy used for the treatment of cancer. Mucositis can present different levels of severity, ranging from a minor erythema, edema, or a burning sensation to the development of large and painful ulcers that limit basic oral functions such as eating, swallowing, and talking. The more severe cases can even interrupt the oncological treatment. The early clinical sign of chemotherapy-induced mucositis is erythema presenting at about four to five days following chemotherapy infusion. Patients also often complain of burning and intolerance of spicy foods at this stage. Seven to ten days after chemotherapy ulcers may develop with marked discomfort often requiring opioid intervention and, in many cases, causing patients to alter their diet. Lesions are seen mostly on the movable tissues of the buccal mucosa and the lateral and ventral surfaces of the tongue. The hard palate and gingiva appear not to be susceptible to chemotherapy-induced mucositis.

Chemotherapy-induced mucositis lasts approximately one week and generally heals spontaneously by 21 days after infusion. The prevalence of oral mucositis after chemotherapy is 30% to 70% and can increase to 90% in bone marrow transplant cases. Mucositis has been reported to occur in over 50% of patients being treated with fluorouracil, adriamycin, and cytoxan for nodepositive breast cancer. For patients being treated with the most common chemotherapy

regimens for colorectal cancer, the prevalence of mucositis is reportedly approximately 15–20%. The combining of different chemotherapeutic drugs further increases the possibility of mucositis from 40% of patients treated with standard chemotherapy regimens to 70% of patients treated with a combination of chemotherapeutic drugs. In patients receiving cancer chemotherapy the frequency and severity of mucositis is mainly dependent on the type(s) and dose of cancer chemotherapeutic agents used but also patient characteristics such as age, nutritional, buccodental, and hematological status play a role. Cisplatin, 5-fluorouracil (5-FU), etoposide, and melphalan are particularly stomatotoxic. Mucositis is common with doxorubicin, vinblastine, taxanes, and methotrexate but uncommon with sparaginase and carmustine. A healthy gingival status as well as good oral hygiene during chemotherapy is associated with a lower incidence and severity of mucositis.⁵⁶⁻⁵⁸

The diagnosis of mucositis is clinical and based on the use of known stomatotoxic therapy, and the appearance, timing, and location of oral lesions. Chemotherapy-induced mucositis occurs on the movable mucosa and rarely affects the dorsum of the tongue, the hard palate, or the gingiva. Methods have been developed to reduce exposure of the mucosa to chemotherapeutic drugs. The use of ice chips (cryotherapy) to produce mucosal cooling and subsequent blood vessel constriction is thought to result in the reduction of exposure of mucosal tissues to the chemotherapy agent.

Propantheline is another agent that might reduce the topical exposure of the oral mucosa to chemotherapeutic drugs excreted in saliva

by altering salivation. Use of antifungal agents such as fluconazole also seems to be effective in prevention of chemotherapy-induced mucositis. Palifermin has also been approved for the treatment of chemotherapy-induced mucositis. Benzydamine and povidone may have a place in a treatment regimen. None of the other available interventions for the management of mucositis, including low energy laser therapy, has been shown to be reliably effective in clinical trials.⁵⁶

Gingival Hyperplasia

Gingival hyperplasia or gingival overgrowth is characterized by an accumulation of extracellular matrix within the gingival connective tissue, particularly the collagenous component, with various degrees of chronic inflammation. Phenytoin, cyclosporine-A, calcium channel blockers, and oral contraceptives are main causative agents of drug-induced gingival hyperplasia. The prevalence rate of this disorder has been reported to vary: 10% to 50% for phenytoin; 8% to 70% for cyclosporine-A; and 0.5% to 83% for nifedipine.⁵⁹

The growth starts as a painless, beadlike enlargement of the interdental papilla and extends to the facial and lingual gingival margins. The enlargement is usually generalized throughout the mouth but is more severe in the maxillary and mandibular anterior regions. Plaque removal and maintaining good oral hygiene may provide benefits in terms of rapid recovery and limitation of the severity of the lesion but the lesion does not completely resolve. It is hypothesized fibroblasts in non-inflamed gingiva are less active, or even quiescent, and do not respond to circulating systemic drugs. In contrast, fibroblasts within inflamed tissue are in an active state and responsive to drug therapy as a result of inflammatory mediators and the endogenous growth factors. It is known causative drugs inhibit Ca^{2+} uptake by gingival fibroblasts which correlates with the rate of fibroblast proliferation. Drug variables, plaque-induced inflammatory changes in the gingival tissues, and genetic factors should be considered. The latter determines the heterogeneity of the gingival fibroblast and could also influence drug pharmacokinetics and pharmacodynamics.⁵

Several mechanisms have been suggested for the etiology of drug-induced gingival hyperplasia.

Cyclosporine-A has been shown to increase the fibroblast production of collagen and protein. This leads to extracellular collagen and matrix formation and a decrease in 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.⁶⁰ The keratinocyte growth factor receptor has been reported to be up-regulated by cyclosporine-A,⁶¹ and there is evidence cyclosporine-A regulates cytokine expression in gingival tissue.⁶²

There is evidence mast-cell mediated androgen action in the gingiva in response to phenytoin could contribute to gingival overgrowth.⁶³ The incidence of phenytoin-induced gingival overgrowth is approximately 50%, but it is higher in both teenagers and institutionalized epileptics.⁶⁴ Gingival overgrowth usually becomes apparent during the first three months after starting phenytoin and is more rapid in the first year. Unlike phenytoin, cyclosporine-induced hyperplasia is reversible following cessation of drug use.⁶⁴

Nifedipine, the most commonly used calcium channel blocker, induces gingival enlargement in 20% of the cases.⁶⁵ 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.⁶⁵ It has been shown nifedipine-induced gingival hyperplasia accompanies submandibular gland dysfunction evidenced by the reduction of salivary flow rate and concentrations of EGF, calcium, and total protein.⁶⁶ There is also evidence nifedipine inhibits both the adherence- and lipopolysaccharide-stimulated macrophage-induced death of fibroblasts which results in gingival overgrowth.⁶⁷ 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.⁶⁸

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.⁵ Other drugs with potential to cause gingival hyperplasia are listed in Table 14.

The treatment options for drug-induced gingival enlargement should be based on the medication being used and the clinical presentation of each particular case. Consideration should be given first to the possibility of discontinuing the drug or of changing medication. It has been shown cyclosporin-induced gingival enlargement can spontaneously resolve if the drug is substituted by tacrolimus.

Drug substitution is a second alternative. There is also preliminary evidence the antibiotic azithromycin may aid in decreasing the severity of cyclosporin-induced gingival enlargement. If any drug substitution is attempted, it is important to allow six-12 months to elapse between discontinuation of the offending drug and the possible resolution of gingival enlargement before a decision to implement surgical treatment is made.

The clinician should also emphasize plaque control as the first step in the treatment of drug-induced gingival enlargement. Although the exact role played by bacterial plaque in drug-induced gingival enlargement is unclear, there is evidence good oral hygiene and frequent professional removal of plaque decreases the degree of the gingival enlargement and improves overall gingival health. If gingival enlargement persists, despite drug substitution attempts and good plaque control, it needs to be treated by periodontal surgery.⁶⁹

Salivary Glands

The most important functions of saliva are to facilitate digestion by lubricating and initiating the chemical processing of food and to protect the mucosa and teeth. Saliva is protective through a cleansing action as well as through the antimicrobial action of various salivary components such as mucin, histatins, lysozyme, and lactoferrin and through the function of specific antibodies to a range of microorganisms the host

has encountered. The composition of saliva is altered in various diseases such as inflammatory bowel disease, diabetes, periodontitis, and organophosphate poisoning making it useful as a diagnostic factor in these diseases.⁷⁰⁻⁷⁵

Salivary gland secretion from the major and minor glands is mainly under neural control influenced by the autonomic nervous system, although various hormones may also modulate its composition. In general, parasympathetic stimulation increases salivation, while sympathetic stimulation produces more viscous saliva and, therefore, appears to depress salivation.^{52,76} Salivary gland function can be affected by a variety of drugs that can produce xerostomia or ptyalism.

Xerostomia may be due to both the reduced salivary flow rate and to a decrease in salivary calcium and phosphate concentration caused by such drugs as amphetamines.⁵ Drugs recognized as causes of reduced salivation include mainly those with cytotoxic, anticholinergic, sympathomimetic, or diuretic activity.⁷⁶ An altered salivary flow rate and reduced levels of secretory proteins or enzymes may cause destructive effects on oral and dental health and the rate of wound due to lower levels of specific growth factors being present. Salivary mucins and growth factors are involved in the maintenance of mucosal integrity. Mucins have the ability to trap water thus protecting the mucosa from injury through desiccation, while growth factors may assist in tissue regeneration. Epidermal growth factor which is secreted from salivary glands has a potential role in oral wound healing.⁷⁷

Common oral manifestations resulting from decreased salivary flow include increased dental caries, fungal infections, bacterial infections, aphthous lesions, and dysphagia. Therefore, it is essential to substitute, reduce, or suppress any xerostomizing medication. Pilocarpine and bethanechol have been suggested to be of potential use in the management of drug-induced xerostomia.⁷⁸

Sialorrhoea or ptyalism, the condition of increased salivary flow, is uncommon. Salivary hypersecretion is usually caused by physiological factors such as menstruation or early pregnancy, local factors such as teething, oral inflammatory lesions, food, medications, or by nasogastric intubation.⁷⁹ Major medication groups that are clearly associated with sialorrhoea are antipsychotics, particularly clozapine, and direct and indirect cholinergic agonists that are used to treat dementia of the Alzheimer type and myasthenia gravis. Sialorrhoea is also caused by certain heavy metal toxins (mercury and thallium); from exposure to irreversible acetylcholinesterase inhibitors (insecticides and nerve agents); and by a few other drugs such as yohimbine, mucosa-irritating antibiotics. The treatment of medication-induced sialorrhoea is often only symptomatic and is designed to decrease saliva to amounts that can be swallowed. Most pharmacological approaches reduce cholinergic tone; either systemically using atropine-related oral anticholinergics or more locally using a sublingual ipratropium spray; or by increasing adrenergic tone using a clonidine patch. Recently, botulinum injections into the parotid gland have been used successfully to treat refractory cases.⁸⁰

Systemic drug therapy can also produce pain and swelling of the salivary glands.⁸¹

Table 15 lists drugs and chemicals with potential to disturb the function of salivary glands.

Effects on Dental Structure

Some drugs have the potential to cause physical damage to tooth structure. Table 16 summarizes the categories of drugs and the subsequent possible damage that can result.

Enamel fluorosis is a hypomineralization of enamel characterized by greater surface and subsurface porosity than in normal enamel as

a result of excess fluoride intake during the period of enamel formation. It has been defined as being “a dose response effect” caused by fluoride ingestion during the pre-eruptive development of teeth. This change in the enamel is characterized by altered appearance of the tooth ranging from fine white lines to pitting or staining of the enamel.¹⁰⁵ Preventive management of dental fluorosis includes de-fluoridation of drinking water in endemic areas, cautious use of fluoride supplements, and supervision of the use of fluoride toothpaste by children below five years of age. The anesthetically objectionable discoloration of fluorosed teeth can be managed by bleaching, micro-abrasion, veneering, or crowning.¹⁰⁶

There have been several reports of the effects on dental development of pre- and post-natal administration of anticonvulsants. Pre-natal exposure to anticonvulsants has been shown to cause a significant increase in mesiodistal crown dimensions of the posterior maxillary teeth—specifically, primary molars and their permanent premolar successors, as well as permanent molars. Hypodontia and disturbance in root formation were also observed following anticonvulsant administration.¹⁰⁷ Studies on drugs used for the treatment of childhood cancer have consistently shown at diagnosis and the start of treatment children younger than five years of age exhibit abnormal dental development.^{107,108} The severity of dentofacial-developmental and tooth-related abnormalities secondary to the therapy is related to the age of the child, the dosage, and the duration of treatment. Dental abnormalities include tooth agenesis, arrested tooth development, microdontia, and disturbances affecting enamel, dentin, and cementum.⁵²

Bisphosphonate-associated osteonecrosis of jaws is a serious oral complication of bisphosphonate treatment involving the exposure of necrotic maxillary or mandibular bone. The clinical presentation may closely simulate dental abscesses, toothaches, denture sore spots, and osteomyelitis. This disorder most commonly occurs in patients who received intravenously administered bisphosphonates (zoledronic acid, pamidronate) to control hypercalcemia in metastatic bone disease. However, some reports implicated oral alendronate or risedronate used to treat osteoporosis.^{109,110,111} The prevalence of

osteonecrosis of the jaws among individuals who received intravenous bisphosphonates is 0.8% to 12%.^{112,113} The clinical presentation, histopathology, and specific laboratory investigation for the levels of markers of bone turnover including N-telopeptide and C-telopeptide help with the diagnosis. The management of this disorder presents a challenge to dentists as there is no effective treatment for this condition at present. Patients with asymptomatic exposed bone may be best treated with systemic antibiotics such as penicillin or clindamycin, an oral antimicrobial rinse such as chlorhexidine, and close follow-up regimen.¹¹³

Oral Motor Disorders

Some drugs can induce oral motor hyperactivity. These medications and illegal drugs produce a motor response that is classified better as an unspecified extrapyramidal syndrome (EPS) reaction. EPS responses typically have three presentations: dystonia, akathisia, and parkinsonism. Dystonic reactions consist of involuntary, tonic contractions of skeletal muscles. Akathisia reactions occur as a subjective experience of motor restlessness. Patients may complain of an inability to sit or stand still or a compulsion to pace or cross and uncross their legs. Parkinsonian reactions manifest themselves as tremor, rigidity, and akinesia, which shows as a slowness in initiating motor tasks and fatigue when performing activities that require repetitive movements (bradykinesia). When a medication or drug induces a dystonic EPS reaction, it typically involves the muscles of the head, face, and jaw that produce spasm, grimacing, tics, or trismus. Most of the literature has focused on the more severe acute dystonic EPS reactions that occur with use of antipsychotic medications. In addition to the antipsychotics, several antiemetics with dopamine receptor–blocking properties have been associated with tardive dystonia. These include prochlorperazine, promethazine, and metoclopramide. Of course, other less severe reactions occur that vary in intensity and even wax and wane over time. The most commonly reported offending agents other than neuroleptics are the selective serotonin reuptake inhibitors (SSRIs) and the stimulant medications and illegal drugs. SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram) are reported to produce the side effect of increased clenching and bruxism.

Patients generally describe an elevated headache and tightness in their jaw, tongue, and facial structures.

Illegal drugs, such as methamphetamine cocaine and 3,4-methylenedioxymethamphetamine (Ecstasy), and legal prescription stimulants, such as methylphenidate, phentermine, pemoline, dextroamphetamine, amphetamines, and diethylpropion, have been reported to induce bruxism and dystonic extrapyramidal reactions. All stimulant drugs have the potential to cause extrapyramidal reactions. They are being used in greater numbers to treat obesity and as stimulants for children who have attention deficit hyperactivity disorder, narcolepsy, and even for severe depression. Table 17 shows a list of drugs that have potential to induce oral motor disorders.

With the exception of bruxism, all of the other motor disorders require a neurologic consultation to achieve a definitive diagnosis. Although the dentist will not perform this examination, it is necessary to identify whether a patient has had an accurate assessment before participating in the management of the patient.¹¹⁴

The general rule for treatment is to withdraw the offending medication in the hope the dyskinesia or dystonic reaction goes away. Fortunately, acute dystonic reactions secondary to drugs disappear upon discontinuation of the medication. However, this may take days to months, depending upon the drug, its dose, and the patient. If the suspected medication cannot be stopped or if the motor hyperactivity is severe, diphenhydramine or benztropine are administered intravenously or intramuscularly to treat the motor hyperactivity. It should be noted amantadine and intravenous diazepam have been shown to be effective for recurrent neuroleptic-induced dystonic reactions.¹¹⁴

Taste Disorders

Many drugs induce abnormalities of taste by mechanisms not yet fully understood. The alternation 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 with the chemical composition of saliva, the flow of saliva, or by affecting either taste receptor function or signal transduction. Sulfhydryl compounds are a common cause of taste disturbance.⁹⁸ Drugs with the potential for affecting taste are listed in Tables 18 and 19.

Penicillamine causes partial or total loss of taste in many patients. There appears to be 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, the frequency is much lower. Loss of taste has been found to be dose related. Taste disturbance is reversible within a period of eight to ten weeks, whether or not penicillamine is discontinued.¹¹⁹

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

Systemic griseofulvin can render certain foods profoundly tasteless, with 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. Other drugs, especially those used for gastrointestinal disorders such as tripotassium dicitrato bismuthate chelate, clarithromycin, lansoprazole, anti-HIV protease inhibitors, terbinafine, intravenous pentamidine, and isotretinoin may cause some degree of loss of taste or altered taste.⁹⁸

History taking should always include the assessment of the current and former medication history. Conditions that interfere with access of a tastant to the taste bud are differentiated from conditions that either injure the receptor cell or damage the gustatory afferent nerves and the central pathways. Psychophysical taste evaluation includes identification of taste quality using sprays or taste strips and testing of the intensity of taste perception by measuring the taste threshold using the 3-drop technique. Moreover, measurement of taste in localized areas can be performed

either with conventional chemicals or using an electrogustometer.¹²⁰

Termination of drug therapy is commonly associated with termination of taste/smell dysfunction, but occasionally effects persist and require specific therapy to alleviate symptoms. According to Henkin,¹²¹ treatment that inhibits sensory distortions requires reactivation of biochemical inhibition at the receptor or inactivation of an inappropriate stimulus receptor binding and/or correction of other steps initiating the causal pathology. These agents include dopaminergic antagonists, gamma-aminobutyric acid (GABA)-ergic agonists, calcium channel blockers, some orally active local anaesthetics, and antiarrhythmic drugs.

Halitosis

Halitosis or oral malodor is offensive breath resulting from poor oral hygiene, dental or oral infections, ingestion of certain foods, use of tobacco, and some systemic diseases and medications.⁵ Table 20 shows a list of drugs that can cause halitosis. Drugs causing xerostomia, which was discussed earlier, may indirectly cause or aggravate this problem.

Assessment of oral malodor is usually subjective by simply smelling exhaled air (organoleptic method) coming from the mouth and nose and comparing the two. Odor originating in the mouth but not detectable from the nose is likely to be either oral or pharyngeal in origin. Odor originating in the nose may come from the sinuses or nasal passages.¹²²

Oral Infections

Many types of systemic drug therapy can alter oral flora and, therefore, predispose the mouth

to bacterial or fungal infection. Drugs causing xerostomia may also potentiate the initiation of oral infections.¹⁵ Table 21 lists drugs with potential to cause oral candidiasis.

Superficial candida infections usually have a characteristic clinical appearance, and diagnosis is often based on clinical findings. Subjective complaints of localized oral burning are sometimes empirically treated for candidiasis. Objective assays in the diagnosis of oral candidiasis include exfoliative cytology, imprint culture, swab culture, salivary assays, and mucosal biopsy. Topical and systemic antifungal agents are used more frequently by dentists to treat oral fungal infections.¹²³

Alveolar Osteitis

Alveolar osteitis, commonly referred to as “dry socket”, is by far the most common complication following dental extraction and has been defined as an inflammation of the alveolus.^{124,125} The use of oral contraceptives has been associated with a significant increase in the frequency of dry sockets after removal of impacted lower third molars. The probability of dry sockets increases with the estrogen dose in the oral contraceptive.⁵ Estrogens and other drugs activate the fibrinolytic system in an indirect way (increasing the factors II, VII, VIII, X, and the plasminogen), contributing to the premature destruction of the clot and the development of dry socket.¹²⁵ Dry sockets can be minimized by performing extractions during days 23-28 of the contraceptive tablet cycle.

Dry socket is clinically recognizable by the existence of a naked alveolus without the presence of a sanguine clot revealing the exposed bony walls and separation of gingival borders. Although suppuration is not evident, a very profound sharp pain persists for days and increases with mastication and sucking forces in the mouth. Dry socket typically appears on the second or third day following an extraction and usually lasts about ten or 15 days regardless of whether it is treated or not. The patient experiences a slight initial uneasiness followed by a slight improvement and then a sudden worsening in the form of profound pain that is difficult to control even with strong analgesics. The goal of treatment is to control the pain during the ten to 15 day period. Even though healing occurs within this time period, with or without

the use of medication, the global tendency is to carry out analgesic symptomatic treatment, accompanied by antiinflammatory treatment and antibiotics. Some authors advise the placement of antiseptic intra-alveolar pastes. These pastes, according to their active ingredients, can be classified into antimicrobial dressings, soothing dressings, or dressings with local anesthetics.¹²⁵

Angioedema

Angioedema is a sudden occurrence of subcutaneous or submucosal swelling. It is well known and in cases where the pharynx or larynx are involved it can be a potentially life-threatening condition. These swellings occur under different conditions and often remain unrecognized.

The majority of cases of angioedema are due to allergic reactions. Some drugs like penicillin and sulfa drugs can cause allergic angioedema. Beside the well-known forms of allergic angioedema, many forms of non-allergic angioedema are known.¹²⁶

Some drugs have the potential to induce non-allergic angioedema; among them the ACEIs are the most important. Angioedema is an established and potentially life threatening side effect of ACEIs. Occurrence of angioedema following the onset of ACEI treatment ranges from one day to eight years with a median of six months and reverses within hours of terminating the use of the drug. The incidence of ACEI-induced angioedema is 0.4–0.7%. The mortality worldwide is 0.1% of these cases. Black people may have an increased risk of developing angioedema. It seems ACEI-induced angioedema arises as a consequence of an alternation in bradykinin metabolism in susceptible patients. Inhibitors of angiotensin converting enzyme (ACE) inevitably account for increased bradykinin plasma levels.

Bradykinin is a mediator of inflammation, activates nociceptors, increases vascular permeability, and causes endothelium-dependent vasodilatation. High levels of bradykinin have been demonstrated in plasma during an acute episode of angioedema.^{126,127}

A variety of non-steroidal anti-inflammatory drugs (NSAIDs) can cause angioedema. Aspirin is the most common and the reaction is called pseudoallergic angioedema. Only cyclooxygenase (COX)-1 inhibitors cause pseudoallergic angioedema, while COX-2 inhibitors are thought to be inactive. Acetaminophen is generally tolerated even by patients sensitive to aspirin, most likely because of very weak COX-1 inhibition.¹²⁸ Table 22 lists drugs that can cause angioedema.

One of the most important steps in the diagnosis of edema is to separate allergic from non-allergic angioedema and then exclude other pathologies such as infection, inflammation, tumors, and diseases of large salivary glands. A physical examination (preferably laryngoscopy), blood studies (C1-esterase inhibitor and markers of inflammation, e.g., C-reactive protein and the leucocyte count), some imaging procedures, family history, and a review of current medications may help with the diagnosis of angioedema.

Angioedema is usually treated by a conservative clinical approach using artificial ventilation, glucocorticoids, and antihistamines. Today, a plasma pool C1-esterase inhibitor (C1-INH) concentrate is the therapy of choice in some forms of angioedema. The current pharmacotherapy of non-allergic angioedema is unsatisfactory, thus, requiring the identification of effective agents in clinical trials. Recently, several new drugs such as a recombinant C1-INH, a kallikrein inhibitor (ecallantide), and a specific bradykinin-B2-receptor antagonist (icatibant) have been developed.¹²⁶ According to currently available reports, these drugs may improve the treatment of kinin-induced angioedema. Following basic emergency treatment as described above, it is important to break off any drug therapy known to induce angioedema.¹²⁷

Cheilitis

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

the skin. This is usually associated with fungal infections and frequently occurs with drug-induced xerostomia.⁵ Table 23 lists drugs with the potential to cause cheilitis.

Conclusion

Since most drug reactions occur within one to two weeks following initiation of therapy, reactions seen after two 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. Re-administration of the offending drug helps to establish whether the oral eruption is drug-induced. Reactions after such a re-challenge may be more severe and, therefore, a re-challenge should not be performed without medical supervision.

Since many patients take multiple medications, dentists must be aware of the issues related to drug use including indications, interactions, and adverse side effects. The ability to evaluate these issues is necessary to accurately assess patient status and prevent situations that compromise client safety. Oral side effects interfere with patient 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.¹³⁰

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.^{4,131}

Table 1. List of subjects reviewed in 2003 by Abdollahi and Radfar.⁵

<ul style="list-style-type: none"> • Alveolar osteitis • Angioedema • Aphthous stomatitis • Black hairy tongue • Burning mouth syndrome • Changes in dental structure • Cheilitis • Discoloration of oral mucosa and teeth 	<ul style="list-style-type: none"> • Erythema multiforme • Gingival hyperplasia • Glossitis • Halitosis • Lichenoid eruptions • Muscular and neurological disorders • Oral allergic reactions 	<ul style="list-style-type: none"> • Oral infections • Oral ulceration • Postmortem pink-red coloration • Side effects in salivary glands • Stomatodynia • Taste disturbance • Vesiculo-bullous lesions
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Table 2. Drugs with potential to cause fixed drug eruption.^{3,5-7}

<ul style="list-style-type: none"> • Ampicillin • Barbiturates • Chlorhexidine • Dapson • Gold • Ibuprofen • Indomethacin 	<ul style="list-style-type: none"> • Lidocaine • NSAIDs • Penicillamine • Salicylates • Sulphonamides • Tetracyclines
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Table 3. Compounds with potential to cause oral contact allergic reactions.^{3,5,8}

<ul style="list-style-type: none"> • Alendronate • Antibiotics • Antiseptic lozenges • Chewing gum • Cosmetics • Dental materials (amalgam, steel wires, beryllium, palladium, platinum, acrylic components) 	<ul style="list-style-type: none"> • Food additives • Iodine • Mouthwashes • Toothpastes (especially those containing cinnamonaldehyde, formalin and herbal components) • Topical anesthetics • Topical steroids
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Table 4. Drugs with potential to cause aphthous-like ulcers.^{5,10,12-15}

<ul style="list-style-type: none"> • Alendronate • Azathiopurine • Beta-blockers • Captopril • Cyclosporine • Docetaxel • Fluoxetine 	<ul style="list-style-type: none"> • Gold compounds • Imiquimod • Indinavir • Interferons • Losartan • Nicorandil 	<ul style="list-style-type: none"> • NSAIDs • Olanzapine • Penicillamine • Sertraline • Sulfonamides • Tiotropium bromide
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Table 5. Drugs with potential to cause burning mouth syndrome.^{17,20,24-26}

<ul style="list-style-type: none"> • ACEIs • Antiretroviral drugs • Cephalosporines • Chloramphenicol 	<ul style="list-style-type: none"> • Clonazepam • Gabapentin • Hormone replacement therapy (estradiol, didrogestosterone) • Penicillin • Tricyclic antidepressants
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Table 6. Drugs that have potential to cause glossitis.²⁹

<ul style="list-style-type: none"> • Alkylating agents • Atrovastatin • Benzodiazepines • Bleomycin • Captopril • Carbamazepine • Cephalosporines • Chloramphenicol • Chlorhexidine • Clarithromycin • Clomipramine • Corticosteroids • Cyclosporine • Doxepin 	<ul style="list-style-type: none"> • Enalapril • Etidronate • Fluoxetine • Fluvoxamine • Gabapentin • Gold compounds • Imipenem/cilastatin • Lansoprazole • Mefenamic acid • Mercaptopurine • Methotrexate • Metronidazole • Mianserin • NSAIDs 	<ul style="list-style-type: none"> • Olanzapine • Penicillamine • Penicillins • Rivastigmine • Sertraline • Sildenafil • Sulfonamides • Tacrine • Tetracyclines • Triamterene • Tricyclic antidepressants • Trihexyphenidyl • Venlafaxine • Xerostomizing medications (table 13)
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Table 7. Drugs with potential to cause erythema multiforme.^{5,29,34-36}

<ul style="list-style-type: none"> • Acarbose • Albendazole • Allopurinol • Antimalarials • Aspirin • Astemizole • Atovaquone • Barbiturates • Bupropion • Busulphan • Captopril • Carbamazepine • Carvedilol • Celecoxib • Cephalosporins • Chlorpropamide • Ciprofloxacin • Clindamycin • Clofibrate • Cocaine • Codein • Corticotropin • Cosyntropin • Cotrimoxazole • Cycloserine • Diclofenac • Diflunisal • Diltiazem • Dolcetaxel • Doxycycline • Erythromycin • Estrogens/Progestins • Etodolac • Etoposide • Ethambutol 	<ul style="list-style-type: none"> • Famciclovir • Furazolidone • Furosemide • Gabapentin • Ginseng • Glipizide • Glucagon • Gold compounds • Griseofulvin • Hetastarch • Immune globulin • Indapamide • Iodine-containing mouth washes • Itraconazole • Ketoconazole • Ketorolac • Lamotrigine Lenograstim • Loperamide • Methazolamide • Mianserin • Micafungin • Minoxidil • Nabumetone • Nefazodone • NSAIDs • Nystatin • Ofloxacin • Oxaprozin • Oxcarbazepine • Penicillamine • Penicillins • Pentamidine • Phenothiazines • Phenylbutazone • Phenytoin 	<ul style="list-style-type: none"> • Prednisolone • Propranolol • Propylthiouracil • Protease inhibitors • Proton pump inhibitors • Pyrazinamide • Pyrimethamine • Rifampin • Rifampicin • Rivasigmine • Rofecoxib • Roxatidine • Sertraline • Sulindac • Sulphonamides • Suramin • Tacrolimus • Tadalafil • Terbinafine • Tetracyclines • Thalidomide • Theophylline • Thiabendazole • Thioridazine • Tiagabine • Tiapride • Tolbutamide • Tolmetin • Trazodone • Tropicamide • Valproic acid • Vancomycin • Varicella virus vaccine • Verapamil • Zonisamide
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Table 8. Drugs with potential to cause local irritation of the mouth.^{5,29}

<ul style="list-style-type: none"> • Anticancer drugs • Aspirin • Cocaine • Ergotamine Tartrate • Hydrogen peroxide 	<ul style="list-style-type: none"> • Isoproterenol • Lithium • NSAIDs • Pancreatin • Paraquat 	<ul style="list-style-type: none"> • Potassium chloride • Selegiline • Tetracyclines • Toothache solutions (menthol, phenol, clove oil, camphor and chloroform)
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Table 9. Drugs with potential to cause oral ulceration.^{5,29,38-40}

<ul style="list-style-type: none"> • Anti HIV drugs • Antineoplastics • Alendronate • Allopurinol • Alprazolam • Aspirin • Atrovastatin • Azathiopurine • Barbiturates • Captopril • Chlorambucil • Chloramphenicol • Chloroquine • Chlorpromazine • Clofibrate 	<ul style="list-style-type: none"> • Clonazepam • Codeine • Cyclosporine • Disopyramide • Enalapril • Erythromycin • Fluconazole • Fluoxetine • Ganciclovir • Gefitinib • Gentian violet • Gold compounds • Hydralazine • Hydroxyurea 	<ul style="list-style-type: none"> • Ibuprofen • Imatinib • Imipramine • Indomethacin • Lamotrigine • Levamisole • Lithium • Mesalamine • Methimazole • Methotrexate • Metronidazole • Mitomycin • Naproxen • Olanzapine 	<ul style="list-style-type: none"> • Penicillamine • Penicillins • Phenytoin • Proguanil • Promethazine • Propranolol • Propylthiouracil • Quinidine • Streptomycin • Sulfonamides • Terbutaline • Tetracycline • Venlafaxine • Warfarin
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Table 10. Drugs with Potential to cause oral lichenoid changes.^{5,29,46}

<ul style="list-style-type: none"> • Allopurinol • Amiphenazole • Angiotensin-converting enzyme inhibitors • Antibiotics • Antiretrovirals • Arsenical Compounds • β-blockers • Bismuth • Chloroquine • Chlorpropamide 	<ul style="list-style-type: none"> • Furosemide • Gold compounds • Hydroxychloroquine • Lithium Carbonate • Mepacrine • Mercury (Amalgam) • Methyldopa • NSAIDs • Palladium • Para-amino salicylic acid • Penicillamine 	<ul style="list-style-type: none"> • Phenothiazines • Propranolol • Quinine • Quinidine • Streptomycin • Tetracyclines • Thalidomide • Thiazides • Tolbutamide
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Table 11. Drugs and chemicals with potential to cause oral pigmentation.^{29,49}

Drug/chemical	Color	Site
Amalgam	Gray	Gingiva
Amalgam	Brown (Tattoo)	Tongue
Aminopyrine	Brown	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/Brown	Tongue
Chloroquine	Blue-gray	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	-
Lansoprazole	Yellow	Tongue
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-gray	Mucosa

Table 11 (Cont.). Drugs and chemicals with potential to cause oral pigmentation.^{29,49}

Drug/chemical	Color	Site
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, Gingiva, Lips, Tongue

Table 12. Drugs and chemicals with potential to cause tooth discoloration.^{29,52,53}

Drugs/Chemical	Color
Betel leaves (areca)	Red to black
Cadmium	Yellow ring
Cayenne	Black
Chlorhexidine	Yellow-brown
Chlortetracycline	Gray-brown
Ciprofloxacin	Green
Co-amoxiclav	Yellow or gray brown
Copper salts	Green
Doxycyclin	Yellow
Essential oils	Yellow-brown
Fluoride	White-brown
Iron salts in liquid form	Black
Isoproterenol	Chalky white

Table 12 (Cont.). Drugs and chemicals with potential to cause tooth discoloration.^{29,52,53}

Drugs/Chemical	Color
Minocycline	Gray-black
Other tetracyclines	Brown-yellow
Oxytetracycline	Yellow
Potassium permanganate	Violet to black
Silver nitrate	Gray
Tannins (coffee, tea)	Brown
Tetracycline	Yellow
Tobacco	Yellow-brown
Tooth paste containing Stannous fluoride	Black or green
White wine	Black

Table 13. Drugs and chemicals with potential to cause black hairy tongue.^{5,29,55}

<ul style="list-style-type: none"> • Amitriptyline • Benzotropine • Cephalosporines • Chloramphenicol • Chlorophyll trouches • Clarithromycin • Clomipramine • Clonazepam • Corticosteroids • Desipramine 	<ul style="list-style-type: none"> • Fluoxetine • Griseofulvin • Imipramine • Lansoprazole • Methylidopa • Maprotilline • Nortriptyline • Olanzapine • Penicillins 	<ul style="list-style-type: none"> • Sodium perborate • Sodium peroxide • Streptomycin • Sulfonamides • Tobacco • Tetracyclines • Thiothixene • Tranlycypromine • Vegetable dyes
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Table 14. Drugs with potential to cause gingival hyperplasia.^{3,5,29}

<ul style="list-style-type: none"> • Bepridil • Calcium channel blockers • Cannabis • Cotrimoxazole • Cyclosporine • Erythromycin • Ethosuximide 	<ul style="list-style-type: none"> • Ethotoin • Flunarizine • Ketoconazole • Lamotrigine • Lithium • Mephenytoin • Phenytoin 	<ul style="list-style-type: none"> • Phenobarbital • Primidone • Sertraline • Sodium valproate • Topiramate • Vigabatrin
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Table 15. Drugs with the potential to affect salivary glands.^{29,52,76,81-104}

Drugs and chemicals implicated in xerostomia		
<ul style="list-style-type: none"> • Alizapride • Alpha 1 antagonists (e.g. terazosin, prazosin, alfuzosin) • Alpha 2 antagonists (e.g. clonidine, lofexidine) • Ambroxol • Amphetamines • Antihistamines • Anti-HIV protease inhibitors • Antimigrain agents • Antineoplastics • Antiparkinson drugs • Atropine • Benzodiazepines • Beta blockers (e.g. atenolol, propranolol) • Bladonna alkaloids • Botulinum toxin type-A • Bupropion • Cadmium • Calcium channel blockers • Ciprofloxacin • Clidinium • Clozapine • Cyclobenzaprine • Cyclopentolate • Cyclosporine • Cytokines • Dexmedetomidine • Ephedrine • Fenfluramine • Gentamycin 	<ul style="list-style-type: none"> • Glycopyrolate • Guanabenz • Guanfacine • Hyoscine • Insulin • Ipratropium • Isotretinoin • Ketanserin • Ketotifen • L-dopa • Lead • Lithium • Lubiprostone • Mazindol • Methdilazine • Modafinil • Molindone • Monoamine oxidase inhibitors • Nabilone • Nefazodone • Nefopam • Nicotine • Nitric oxide inhibitors • Ofloxacin • Olanzapine • Ondansetron • Opioids • Orphenadrine • Oxybutynin • Paliperidone • Paricalcitol 	<ul style="list-style-type: none"> • Peginterferon alfa-2a • Phenothiazines • Phenylpropanolamine • posaconazole • Pregabalin • Propantheline • Proton pump inhibitors (e.g. omeprazole) • Radioliodine • Rasagiline • Risedronate • Rotigotine • Selective serotonin reuptake inhibitors • Solifenacin • Sotalol • Spiramycin • Tadalafil • Terodiline • Thiabendazole • thioridazine • Tiamenidine • Tizanidine • Trazodone • Tricyclic antidepressants • Tropicamide • Venlafaxine • Vereniciline • Vigabatrin • Vorinostat • Zuclopenthixol
Drugs that can cause sialorrhea		
<ul style="list-style-type: none"> • Alprazolam • Ambroxol • Amiodarone • Bethanechol • Buspirone • Clozapine • Desflurane • Diazoxide • Digoxin • Edrophonium • Galantamine • Gentamycin • Guanethidine • Imipenem/Cilastatin 	<ul style="list-style-type: none"> • Iodides Kanamycin • Ketamine • Lamotrigine • Levodopa • Lithium • Mianserin • Mefenamic Acid • Mercurial salts • Modafinil • Neostigmine • Nifedipine • Niridazole • Nitrazepam • Olanzapine 	<ul style="list-style-type: none"> • Organophosphates • Pentoxifylline • Physostigmine • Pilocarpine • Risperidone • Rivastigmine • Sildenafil Succinylcholine • Tacrine • Theophylline • Tobramycin • Venlafaxine • Zaleplon • Zonisamide
Drugs that have potential to cause swelling and/or pain in salivary glands		
<ul style="list-style-type: none"> • Bretylium • Catecholamine inhalation • Chlorhexidine • Cimetidine • Clonidine • Clozapine • Deoxycycline 	<ul style="list-style-type: none"> • Famotidine • Iodine • Methyldopa • Naproxen • Nifedipine • Nitrofurantoin 	<ul style="list-style-type: none"> • Phenytoin • Ranitidine • Ritodrine • Sulfonamides • Trimipramine • Warfarin

Table 16. Agents with potential to affect dental structures.

Agent	Example	Possible Damage
Sugar-containing oral (liquid) medication	Various liquid medications	Dental caries
Drugs that result in decreased salivary secretion (xerostomia)	See Table 13	Dental caries
Drugs with a pH low enough to cause tooth erosion	Aspirin, anti-asthmatic drugs	Dental erosion
Drugs that may increase susceptibility to gastro-esophageal reflux disease	Theophylline, anticholinergics, progesterone, calcium channel blockers, anti-asthmatics	Dental erosion
Drugs used for internal tooth bleaching	Hydrogen peroxide and sodium perborate	Cervical root resorption
antineoplastic drugs		Abnormal dental development
Anticonvulsants	Phenytoin	Changes in tooth size, hypodontia, disturbance in root formation
Biphosphonates	Zoledronic acid, pamidronate, alendronate, clodronate	Osteonecrosis of jaws
Amlexanox, Niacin, Silver		Dental pain
Fluoride		Dental fluorosis

Table 17. List of drugs reported to induce oral motor disorders.

- Amphetamine derivatives
- Antipsychotics
- Metoclopramide
- Prochlorperazine
- Promethazine
- Selective serotonin reuptake inhibitors

Table 18. Drugs with potential to cause ageusia.^{5,29,115,116}

<ul style="list-style-type: none"> • Acarbose • Acetazolamide • Amitriptyline • Angiotensin II receptor antagonists • Aspirin • Atrovastatin • Captopril • Ceftrizine • Cisplatin • Clidinium • Clomipramine • Clopidogrel 	<ul style="list-style-type: none"> • Cocaine • Diazoxide • Dicyclomine • Enalapril • Etidronate • Fluoxetine • Fluvoxamine • Indomethacin • Isotretinoin • Levodopa • Methimazole • Penicillamine 	<ul style="list-style-type: none"> • Pentamidine • Phenytoin • Propantheline • Propylthiouracil • Rifabutin • Ritonavir • Rivastigmine • Spironolactone • Sulfadoxine • Terbinafine Topiramate • Venlafaxine
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Table 19. Drugs with potential to cause dysgeusia.^{5,29,117,118}

<ul style="list-style-type: none"> • ACEIs • Acemetacin • Acetaminophen • Acetazolamide • Acyclovir • Albuterol • Alniditan • Alendronate • Allopurinol • Alprazolam • Amiloride • Amiodarone • Amitriptyline • Amlodipine • Amoxicillin • Amphetamine • Antihemophilic factor • Apomorphine • Aspirin • Atrovastatin • Atropine sulfate • Auranoftin • Aurothioglucose • Azathioprine • Azelastine • Azithromycin • Aztreonam • Baclofen • Beclofmethazone • Benztropine • Bepidil • Bevacizumab • Bleomycin 	<ul style="list-style-type: none"> • Cotrimoxazole • Cromolyn • Cyproheptadine • Cytomegalovirus immune globulin • Dacarbazine • Dantrolene • Daunorubicin citrate liposome • Desipramine • Dexfenfluramine • Dextroamphetamine • Diazoxide • Dichlorphenamide • Diclofenac • Dicyclomine • Dihydroergotamine • Diltiazem • Dimethyl sulfoxide • Dinoprostone • Dipyrldamole • Donepezil • Dorzolamide • Doxapin • Deoxycycline • Esomeprazole • Eszopiclone • Etidronate • Famotidine • Fenfluramine • Fentanyl • Filgrastim • Flecainide 	<ul style="list-style-type: none"> • Isotretinoin • Ketanserin toprofen • Ketorolac • Labetalol • Lamotrigine • Lansoprazole • Leuprolide • Levamisole • Levocarnitine • Levodopa • Lidocaine • Lithium • Loratadine • Lorcaidine • Losartan • Lovastatin • Maprotiline • Meperidine • Mesalamine • Mesna • Metformin • Methamphetamine • Methazolamide • Methimazole • Methocarbamol • Methotrexate • Metoprolol • Metronidazole • Midazolam • Minoxidil • Monoctanoin • Mupirocin • Naratriptan 	<ul style="list-style-type: none"> • Pirbuterol • Potassium iodide • Prilocaine • Procaine • Procainamide • Propafenone • Propantheline • Propranolol • Propylthiouracil • Protirelin • Pseudoephedrine • Pyrimethamine • Quinidine • Ramelteon • Ranibizumab • Ranitidine • Ribavirin • Rifabutin • Riluzole • Risperidone • Ritonavir • Rivastigmine • Saccharin • Selegiline • Serteraline • Simvastatin • Sucralfate • Sulfonamides • Sumatriptan • Sunitinib • Tacrine • Tamoxifen • Tegafur
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Table 19 (Cont.). Drugs with potential to cause dysgeusia.^{5,29,117,118}

<ul style="list-style-type: none"> • Bleomycin • Bromocriptine • Bupropion • Buspirone • Busulfan • Butorphanol • Calcitonin • Carbamazepine • Carbidopa/levodopa • Cephalosporines • Celecoxib • Chlorhexidine • Chlorfexanone • Chlorothiazide • Cholestyramine • Cimetidine • Ciprofloxacin • Citalopram • Clarithromycin • Clidinium • Clindamycin • Clofazimine • Clofibrate • Clomipramine • Clonazepam • Clonidine • Clozapine • Codeine 	<ul style="list-style-type: none"> • Flecainide • Fluconazole • Flunizolide • Fluorouracil • Fluoxetine • Flurazepam • Fluvastatin • Fluvoxamine • Gadobenate • Gallium nitrate • dimeglumine • Gadodiamide • Gancyclovir • Gemfibrozil • Glyburide • Glycopyrolate • Gold compounds • Granisetron • Grepafloxacin • Griseofulvin • Hydrochlorothiazide • Hydroxychloroquine • Imipenem/Cilastatin • Imipramine • Inamrinone • Indinavir • Interferons • Iopromide 	<ul style="list-style-type: none"> • Naratriptan • Nedocromil • Nicotine polacrilex • Nifedipine • Nitric oxide • Nitroglycerin • Norfloxacin • Nortriptyline • Nylidrin • Ofloxacin • Olanzapine • Omega-3-acid ethyl esters • Omeprazole • Ornidazole • Palifermin • Pamidronate • Penicillamine • Penicillins • Pentazocine • Pentetate calcium trisodium • Pentoxifylline • Perflexane lipid microsphere • Pergolide • Phenytoin • Phytionadione • Pilocarpine 	<ul style="list-style-type: none"> • Tegafur • Terbinafine • Terbutaline • Terfenadine • Tiagabine • Timolol • Tocainide • Tolazamide • Tolbutamide • Tolmetin • Topiramate • Tramadol • Tranylcypromine • Triamteren • Trimipramine • Ursodiol • Vancomycin • Varenicline • Venlafaxine • Veralipride • Vinblastine • Vincristine • Vorinostat • Zidovudine • Zoledronic acid
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Table 20. Drugs that can induce halitosis.^{29,122}

<ul style="list-style-type: none"> • Chloral hydrate • Cytotoxic drugs • Dimethyl sulphoxide • Disulfiram • Nitrites and nitrates • Succimer
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Table 21. Drugs with potential to cause oral candidiasis.^{5,29}

<ul style="list-style-type: none"> • Alglucosidase alfa • Antibiotics • Antineoplastics • Arformoterol • Atovaquone • Cephalosporins • Ciprofloxacin • Clarithromycin • Conivaptan 	<ul style="list-style-type: none"> • Corticosteroids • Griseofulvin • Immunosuppressives • Mesalamine • Olanzapine • Omeprazole • Oral contraceptives • Riluzole
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Table 22. Drugs that can cause angioedema.^{5,127,129}

<ul style="list-style-type: none"> • ACEIs • Adrenomimetic bronchodilators • Alteplase • Amlodipine • Angiotensin II receptor agonists • Estrogens • Fluoxetine 	<ul style="list-style-type: none"> • Intravenous clindamycin • Ketoconazole • Laronidase • Lepirudin • Mianserin • Midazolam 	<ul style="list-style-type: none"> • NSAIDs • Penicillin • Rituximab • Sulfa drugs • Tacrine • Tacrolimus
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Table 23. Drugs with potential to cause cheilitis.^{5,29}

<ul style="list-style-type: none"> • Atorvastatin • Busulfan • Clofazimine • Clomipramine • Cyanocobalamin • Gold compounds • Indinavir 	<ul style="list-style-type: none"> • Isotretinoin • Methyldopa • Panitumumab • Prochlorprazine • Psoralens • Ritonavir 	<ul style="list-style-type: none"> • Saquinavir • Simvastatin • Streptomycin • Sulfasalazine • Tetracycline • Vitamin A
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