Chapter 25

Drug-Induced Oral Reactions

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Additional information is available at the end of the chapter

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1. Introduction

Oral Medicine is a specialty that deals with the diagnosis and medical management of the complex medical disorders involving the oral mucosa. The success of any treatment depends on a proper and correct diagnosis. A successful diagnostician has to have qualities like knowledge, interest, intuition, curiosity, and patience. 99.9% of systemic diseases have one or more oral manifestations which are diagnosed by oral physician even before the general physician. Early recognition and diagnosis are important for early treatment, improving survival and for limiting the complications of therapy.

In present day the number of elderly people is on the rise. This is a rapidly growing population who has chronic medical conditions, take multiple medications and require routine, safe and appropriate oral and general healthcare, which may be challenging for the dental physician. The oral medicine specialists require careful assessment of each elderly person to help in the formulation of a strategy for their care, maintenance of comfort, self-respect and, effective and sympathetic dental care for them [1].

Several systemic factors are known to contribute to oral diseases or conditions, and among those are the intakes of drugs. The pathogenesis of oral adverse reactions related to intake of medications is not well-understood, and the prevalence is not known. They are, however, believed to be a relatively common phenomenon, although medication-induced oral reactions are often regarded by the health profession as trivial complaints [2].

Drug-induced side effects are a frequent occurrence. Many commonly available drugs can produce untoward consequences, even when used according to standard or recommended methods of administration. Such adverse drug reactions can involve every organ and system of the body and may be seen in all age group, and present in many different forms [3]. Regarding different parts of the oral system, these reactions can be categorized to oral mucosa and tongue, periodontal tissues, dental structures, salivary glands, cleft lip and palate,

muscular and neurological disorders, taste disturbances, drug-induced oral infection, and facial edema. The oral drug reactions are often nonspecific, but they may mimic specific disease states such as Pemphigus vulgaris, Erythema multiforme, or Lichen planus [4,5]. The knowledge about drug-induced oral adverse effects helps health professionals to better diagnose oral disease, administer drugs, improve patient compliance during drug therapy, and may influence a more rational use of drugs [6].

Oral drug-reaction patterns with associated drugs and drug classes include:

2. Aphthous stomatitis

Aphthous stomatitis (also termed recurrent aphthous stomatitis, recurring oral aphthae or recurrent aphthous ulceration) is a common condition characterized by the repeated formation of benign and non-contagious mouth ulcers (aphthae), in otherwise healthy individuals. Aphthous–like ulcerations may occur from a variety of medications, including capropril and nonsteroidal anti-inflammatory drugs (NSAIDs), Asathiopurine, Losartan, and Gold compounds. It is unclear as to the mechanism leading to this reaction pattern [7,8].

The lesions may be single or multiple. Three clinical variations have been recognized: minor, major and herpetiforme ulcers. Minor form and herpetiforme ulcers heal without scarring in 7-12 days and major form persist for 3-6 weeks [9].

For treatment used topical steroids or, in severe cases, intralesional steroid injection or systemic steroids in low dose.

3. Burning mouth syndrome

Burning mouth syndrome (BMS) is a painful, frustrating condition often described as a scalding sensation in the tongue, lips, palate, or throughout the mouth. Signs and symptoms are: burning, scalding or tingling feeling on the tongue, lips, throat or palate, no specific lesion evident, with or without any sing of inflammation and discomfort usually worse at the end of the day. This syndrome may occur due to psychogenic factors, hormonal withdrawal, folate, iron, pyridoxine deficiency, or hypersensitivity reactions to the materials utilized in dental prostheses [10,11]. The most common medications that produce this side effect are: ACE inhibitors, antibiotics, hormone replacement therapy antidepressants and cephalosporin [12,13,14]. Possible treatments may include: replacing medication, treating existing disorder or treatment is aimed at the symptoms to try to reduce the pain associated with burning mouth syndrome.

- **Glossitis-**Glossitis is inflammation of the tongue. Signs and symptoms are: swollen intensely painful tongue, red and smooth tongue. Pain may be referred to the ears and salivation, fever and enlarged lymph nodes may develop if infection is present. Various

drugs which can cause glossitis are: antibiotics, corticosteroids, methotrezole, and tricyclic antidepressants [15,16].

The goal of treatment is to reduce inflammation. Good oral hygiene is necessary, including thorough tooth brushing at least twice a day.

- **Oral ulcerations (nonspecific ulceration and mucositis)**

Oral ulcerations may occur in a different setting, including local irritation, chemotherapy, opportunistic infections and fixed drug reactions. Epithelial necrosis and ulceration may result from direct application of over-the-counter medications such as aspirin, hydrogen peroxide, potassium tablets, and phenol-containing compounds to the mucosa. [17]. Aspirin is often used by patients seeking relief from dental pain. The affected mucosa appears whitish and corrugated, with erosion and ulceration of the more severely damaged areas. The associated discomfort can be severe enough to require treatment. Oral drug reaction may be as small round /oval lesions/ with yellow or grey floor and may lead to difficulties in speck. Drugs including anti-neoplastics (methotrexate, 5-fluorouracil), barbiturates, dapsone, tetracyclines, nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, indomethacin, salicylates, gold salts, naproxen), meprobamate, methyldopa, penicillamine, propranolol, spironolactone, thiazides, tolbutamide, alendronate, captopril, phenytoin, and (by direct contact) compounds containing aspirin can cause oral ulcerations. [18,19].

They are clinically diverse, but usually appear as a single, painful ulcer with a smooth red or whitish-yellow surface and a thin erythematous haloo. For treatment used removal of factors and topical steroids for a short time.

4. Vesico-bullous lesions

Oral drug reactions that bear striking clinical, histopathologic, and even immunopathologic resemblance to idiopathic Lichen planus, Erythema multiforme (EM), Pemphigoid, Pemphigus vulgaris, and Lupus erythematosus (LE) are well recognized, and the list of reactions in each category is constantly expanding. Clinically, any oral site can be affected; however, the posterior buccal mucosa (cheeks), the lateral borders of the tongue, and the alveolar mucosa are most commonly involved. Lesions may be isolated, although bilaterally symmetric involvement is not uncommon [20,21].

- Lichen planus – Lichen planus is a relatively common papulosquamous disorder involving the skin and mucous membranes. Often these lesions are asymptomatic. Lichen planus–like or lichenoid drug reactions are a heterogeneous group of lesions of the oral mucosa that show clinical and histopathological similarities to lichen planus. Lichenoid reactions have subsequently been reported in association with many agents (amalgam, composite resins, and dental restorative materials). A number of drugs have been implicated in lichen planus-like eruptions. The most common agents are nonsteroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors.

Although drug-induced lichenoid reactions tend to be erosive and unilateral compared with the typical bilateral presentation in idiopathic lichen planus, these associations are not consistently observed. Middle aged individuals are more commonly affected. The predilection sites are the buccal mucosa, tongue, and gingiva. The pathogenic mechanism by which drugs cause LP-like drug eruptions is not clear, T cell-mediated autoimmune phenomena are involved in the pathogenesis of Lichen planus [22,23,24,25].

Clinical characteristic oral lesions of the disease are white papules that usually coalesce, forming a net-work of lines (Wickham's striae). Six forms of the disease are recognized in the oral mucosa. The common forms are reticular and erosive, the less common are atrophic and hypertrophic, and the rare ere bullous and pigmented.

The disease can usually be diagnosed on clinical grounds alone. Histopathological examination is very helpful.

In treatment, topical steroids may be helpful, and intralesional injection. Systemic steroids in low doses can be used in severe and extensive cases.

- Erythema multiforme (EM) – like – Erythema multiforme is a syndrome consisting of symmetrical mucocutaneus lesions that have a predilection for the oral mucosa, hand, and feet. Initial bullae may rupture, giving rise to widespread superficial ulceration [26]. A spectrum of disease can be seen ranging from a benign cutaneus eruption to a severe mucocutaneous eruption. Steven-Johnson syndrome represents a severe manifestation of EM. Syndrome characterized by various clinical types of lesions. The lips are swollen, crusted, and bleeding. Drugs with potential to cause Erythema multiforme are: antibiotics (antimalarial, penicillin, sulfonamide, and tetracycline), allopurinol, barbiturates, protease inhibitors, and NSAIDs. Drug-induced EM represents approximately 25% of all reported cases. Drug-induced EM is frequently linked to agents such as sulfonamides, sulfonylureas, and barbiturates, among others [27,28,29].
- Pemphigoid – like – Drug-induced Pemphigoid can occur in the setting of a number of drugs. Antirheumatics (penicillamine, ibuprofen, phenacetin), cardiovascular drugs (furosemide, captopril, clonidine), antibiotics (penicillin's, sulfonamides), antimicrobials, thiol-containing drugs, and sulfonamide derivatives. Pemphigoid-like reactions can be limited to the oral mucosa, or they can affect other mucosal or cutaneous sites. Clinically, lesions appear as relatively sturdy vesicles or bullae that break down into shallow ulcerations. Generalized or multifocal involvement of the gingival tissues may be observed, with marked erythema and erosion of the superficial gingiva, a pattern that has been called Desquamative gingivitis. Thiol-containing drugs and sulfonamide derivatives are among the most commonly involved medications, as are the therapeutic classes of NSAIDs, cardiovascular agents, antimicrobials, and antirheumatics. Drug-induced pemphigoid patients may be younger and have more frequent oral involvement [30]. For treatment used steroids and, rarely, immunosuppressive drugs.
- Pemphigus – like – drug reactions have been reported to have similar clinical, histologic, and immunofluorescent patterns as Pemphigus vulgaris. Alpha-mercaptopropionylglycine, ampicillin, captopril, cephalexin, ethambutol, glibenclamide, gold, heroin, ibuprofen,

penicillamine, phenobarbital, phenylbutazone, piroxicam, practolol, propranolol, pyritinol chlorohydrate, rifampin, and theobromine. Pemphigus-like reactions can have features of either pemphigus vulgaris or pemphigus foliaceous, although pemphigus foliaceous is uncommon in the oral cavity. Thiol-containing drugs are the most common cause of pemphigus-like reactions. In drug-induced pemphigus vulgaris, the relatively fragile vesicles are rarely observed at clinical examination, and most cases are characterized by irregular ulcerations with ragged borders that may coalesce to involve large areas of the mucosa. Patients may have circulating autoantibodies to the desmosomal components [31]. Treatment is used systemic steroides, immunosuppressive drugs and dapsone.

- Lupus erythematosus (LE) – like-Drug-induced LE is a well-recognized adverse reaction that is most commonly associated with procainamide and hydralazine, although more than 70 medications are implicated (Carbamazepine, chlorpromazine, ethosuximide, gold, griseofulvin, hydantoins, hydralazine, isoniazid, lithium, methyldopa, penicillamine, primidone, procainamide, quinidine, reserpine, streptomycin, thiouracils, and trimethadione.). Clinically, the oral lesions of drug-induced LE may simulate those of erosive lichen planus, with irregular areas of erythema or ulceration bordered by radiating keratotic striae. These lesions may affect the palate, buccal mucosa, and gingival or alveolar tissues. The rarity of lichen planus on the hard palate may be helpful in differentiating it from drug-induced LE [32]. In treatment used steroids and antimalarial drugs.

5. Color changes of oral mucosa and teeth (Pigmentation)

Pigmentation may by normal pigmentation which are a physiological finding, particularly in dark-skinned individuals because increased melanin production and deposition in the oral mucosa. No treatment is required. Abnormal oral pigmentation can result from a number of causes, including local and systemic medications (amiodarone, antimalarials, bisulfan, clofazimine, cyclophosphamide, estrogen). Discoloration can occur after direct contact with or following systemic absorption of a drug. Discoloration of the oral mucosa after drug use may be due to direct melanocytic stimulation, the deposition of pigmented drug metabolites, and erythrocyte degradation products. Local agents such as heavy metals (bismuth, lead) or dental amalgam (amalgam tattoo) may cause discoloration by traumatic implantation. Systemic medications may leave the patient with a bluish gray to yellowish-brown discoloration of the buccal mucosa, tongue, or hard palate. Typically, such pigmentation is most notable on the posterior regions of the hard palate, appears bluish-black to brown, and may be bilateral. Smoker's melanosis, or smoking-associated melanosis, is an abnormal melanin pigmentation of the oral mucosa [33].

Clinically, it appears as multiple brown pigmented areas, usually located on the anterior labial gingiva of the mandible. Teeth discoloration may be intrinsic or extrinsic. Intrinsic stains are caused by drugs (tetracycline) taken during development of tooth [34]. Extrinsic stains are taken up by tooth after development of tooth (tea, coffee, chlorhexidine) [35,36,37].

6. Black hairy tongue (Lingua villosa, Lingua nigra)

Hairy changes are on the upper side of the tongue (never on under side).Hairy tongue is a relatively common disorder that is due to marked accumulation of keratin on the filiforme papillae of the tongue. Lingua is black but may also be brown, white, green or pink. Normally asymptomatic and may develop secondary fungal infection (Candidosis). Hairy tongue may appear as a result of the growth of pigment-producing bacteria that colonize the elongate filiforme papillae. The black tongue may also be due to staining from food and tobacco. Black hairy tongue can be seen with the administration of oral antibiotics, corticosteroides, aldomet, sulfonamides and excessive smoking in adult's [38]. Treatment is elimination of predisposing factors, brushing of the tongue and local use of keratolytic agents.

7. Drug induced gingival enlargement

Gingival enlargement is seen in periodontitis, system disorders, and drug-induced states. The enlargement is usually generalized throughout the mouth but is more severe in maxillary and mandibular anterior regions. Drug-induced gingival overgrowth is a relatively common disorder of the gingiva due to several drugs. The drugs most commonly implicated are: Calcium channel blockers (amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, oxidipine, and verapamil), other dihydropyridines (bleomycin), cyclosporine, phenytoin, and sodium valproate. Diffuse, non-neoplastic enlargement or overgrowth of the gingival tissues was initially recognized in patients who were using phenytoin. More recently, calcium channel blockers (members of the dihydropyridine class of medications), cyclosporine, and the antiepileptic drug sodium valproate have been associated with this reaction. Within the calcium channel blocker family, nifedipine, diltiazem, verapamil, and amlodipine are among the most commonly reported causative agents [39,40,41]. The gingival overgrowth is usually related to the dose of the drugs, the duration of therapy, the serum concentration, and the presence of dental plaque [42,43]. Clinically, both marginal gingiva and interdental papilla appear enlarged and firm, with a surface that may be smooth, stippled, or lobulated.

Treatment is discontinuation of the offending drug, improvement of oral hygiene and gingivectomy.

8. Xerostomia

Xerostomia, or dry mouth, is the most common adverse drug-related effect in the oral cavity. There are many causes of xerostomia. Pharmacologic therapy is a common cause. Xerostomia has been associated with more than 500 medications (antidepressants and antipsychotics, antihypertensives, antihistamines, anticholinergics, and decongestants). The synergistic effects of medications have been recognized and are increasingly common in elderly patients

taking multiple medications (polypharmacy). In addition, habits such as smoking, alcohol consumption, and even long-term use of caffeinated drinks may contribute to oral dryness or the perception of dryness. Clinical signs and symptoms are: difficulty eating and swallowing, difficulty speaking and little saliva present in the mouth or may be thick stringy saliva [44,45].

9. Swelling

Several drugs can induce type I hypersensitivity reactions, or disease mediated by immunoglobulin E mast cells, that can range from isolated swelling of the oral tissues to full-blown anaphylaxis. Around the mouth, the lips are the most frequently involved site, followed by the tongue. The swelling is acute and is often transient. Lesions typically last for only several hours, but may last for days. Among the most common offending agents are ACE inhibitors, penicillin and penicillin derivatives, cephalosporins, barbiturates, and aspirin and other NSAIDs. Affected mucosa typically appears edematous and erythematous within minutes or hours after exposure to the offending drug. Similar contact reactions to latex had become increasingly problematic in oral health care settings until the recent shift towards non-latex replacement materials such as vinyl or nitrile rubber [46,47].

10. Oral thrush — Oral candidosis

The yeast, *Candida albicans* is the most common cause of infection of the oral cavity. Drug-induced oral candidosis is usually asymptomatic, but it may have an associated erythematous, ulcerated base. It is usually by *Candida albicans*, and less frequently by other fungal species. Predisposing factors may be local (xerostomia, dentures, antibiotic, poor oral hygiene) and systemic (steroids, HIV infections, immunosuppressive drugs). Clinical sing and symptoms are: Presents of creamy-white lesions on tongue, pain, slight bleeding if the lesions are rubbed or scraped, ”cottony” feeling in the mouth, loss of taste (ageusia) and difficulty swallowing (if infection spreads to throat). This often follows the use of broad-spectrum antibiotics or the use of corticosteroid inhalers, and immunosuppressive agents such as cyclosporine, and cytotoxic therapies [48]. In treatment used topical antifungal agents and systemic.

11. Taste disturbance (Ageusia, Dysgeusia)

Numerous causes exist that can lead to a decreased ability to perceive taste or causing an unpleasant taste. The alteration in taste may be simply a blunting or decreased sensitivity in taste perception (hypogeusia), a total loss of the ability to taste (ageusia), or a distortion in perception of the correct taste of a substance, for example, sour for sweet (dysgeusia) [49].

The most common cause is due to an upper respiratory infection that affects olfaction, in turn, decreasing one’s sense of taste. Drugs can also distort taste. Clinical signs and symptoms are:

total loss of ability to taste, complaints of metallic taste, impaired salty taste, reduced appetite and weight loss. Drugs causing taste disturbance are: antibiotics, ACE inhibitors, aspirin, diclofenac, diltiazem, metronidazole, propranolol, and sulphonamides [50].

12. Stomatitis — Contact allergy

Stomatitis or oral inflammation of the mouth is a nonspecific term that describes many oral drug reactions. This is a relatively common oral mucosal reaction to continuous contact of substances. Restorative materials, mouthwashes, dentifrices, food and other substances may be responsible. The clinical symptoms may include: nonspecific generalized inflamed gums, palate, lips, tongue and buccal mucosa, bleeding, oral lesions as ulcerations and erosions, and breathing difficulties if severe allergic reaction involving tongue. Lesions occur within 24 hours of ingesting the medication. The causative medication is withdrawn. Drugs are: antibiotics, food additives, mouthwashes, toothpastes, cosmetics, dental materials and topical steroids [51]. Stomatitis refers to an inflammatory process involving the mucous membrane of the mouth that may manifest itself through a variety of signs and symptoms including erythema, vesiculation, bulla formation, desquamation, sloughing, ulceration, pseudomembranous formation, and associated discomfort.

Stomatitis may arise due to factors that may be of either local, isolated conditions or of systemic origin. For example, a solitary oral ulcer with a history of a recurrent pattern may be classified as recurrent aphthous stomatitis, a purely local phenomenon. Another clinically-similar-appearing lesion, on the other hand, may represent an oral mucosal manifestation of a more generalized disease process such as Crohn's disease. Stomatitis may involve any site in the oral cavity, including the vermillion of the lips, labial/buccal mucosa, and dorsal/ventral tongue, floor of mouth and hard/soft palate, and gingivae [52].

The diagnosis is based on the history and clinical features.

Treatment is discontinuation of any the causative medication. In severe and extended lesions, low doses of steroids for one week help the lesions to heal.

13. Angular cheilitis

Angular cheilitis (AC), or perleche, is a common disorder of the angles of the mouth. This is soreness and cracks at the corners of the mouth. Several drugs may cause AC as a side effect, by various mechanisms, such as creating drug-induced xerostomia. Medication also contributes to the onset of cheilitis. There are certain medicines that have a side effect of dry lips which is potential for cheilitis. Less commonly, angular cheilitis is associated with primary hypervitaminosis A which can occur when as a result from an excess intake of vitamin A in the form of vitamin supplements. Drugs are: Aldomet, Zocor (statins), tetracycline and vitamin A [53,54].

The condition is characterized by erythema, maceration, fissuring, erosion, and crusting at commissures. Remissions and exacerbations are common. Diagnosis is based on the clinical findings.

Treatment is discontinuation of any the causative medication, and topical steroids.

14. Osteonecrosis

Osteonecrosis is a disease resulting from the temporary or permanent loss of blood supply to the bones. This is a serious oral complication of treatment with Bisphosphonates. Bone under teeth is exposed, usually triggered by a dental extraction. Most commonly associated with i.n. zoledronic acid. Clinical symptoms are: swelling and loosening of teeth, altered local sensation, facial pain, toothache, lose teeth, exposed bone, recurrent infection and marked oral odour [55,56].

15. Salivary glands

Salivary gland function can be affected by a variety of drugs that can by a variety of drugs that can produce xerostomia or ptyalismus. It is suggested this is due to both the reduced salivary flow rate and to a decrease in salivary calcium and phosphate concentration. Systemic drug therapy can also produce pain and swelling of the salivary glands. [57].

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 or drug related (thiouracil, sulfonamides, NSAIDs, phenothiazines) [58].

16. Sialorrhoea

Sialorrhoea, or excessive salivation is commonly associated with many systemic conditions. Clinical signs and symptoms are: increased salivary floe, drooling or dribbling and increased swallowing. Drugs causing sialorrhorea are: pilocarpine, rivastigmin, nifedipine, lithium and dimercaptol [59,60]. The treatments currently available for sialorrhoea are unsatisfactory. Systemic anticholinergic drugs are often ineffective and produce unacceptable side effects.

17. Halitosis

Halitosis is the offensive breath resulting from poor oral hygiene, dental or oral infections, ingestion of certain foods, use of tobacco, and some systemic diseases. Halitosis, or bad breath, may have many different etiologies (alcohol, drugs, and foods, smoking). It may be association

with an abnormal taste in the mouth. This association is commonly seen with smoking, various foods, alcohol, periodontal disease or other oral infection. Concern about halitosis is estimated to be the third most frequent reason for people to seek dental care, following tooth decay and gum disease) [61]. A number of systemic diseases can cause halitosis, especially cirrhosis and renal failure. In diabetic ketoacidosis, patient's breath may smell of acetone. Drugs are not frequently implicated, but disulfiram dimethylsulfoxide has been associated with halitosis. Effective treatment is not always easy to find. Gently cleaning the tongue surface twice daily is the most effective way to keep bad breath in control, than, eating a healthy breakfast with rough food and chewing gum [62].

18. Hemorrhage — Bleeding

Bleeding can occur internally, where blood leaks from blood vessels inside the body, or externally, either through a natural opening such as the mouth, nose, ear, urethra, vagina or anus, or through a break in the skin. Bleeding arises due to traumatic injury, underlying medical condition, or some drugs. Drugs such as aspirin, NSAIDS, anticoagulants which thin in the blood and drug induced thrombocytopenia as caused by chloramphenicol, penicillins, streptomycin and sulfonamides may lead to oral bleeding. Broad spectrum antibiotics such as cephalosporin's decrease Vitamin K level by altering gastrointestinal flora and may lead to bleeding disorder [63].

19. Taking care of your oral health during drug use

Some easy to prevent or reduce the adverse effects of various drug therapies are as follow:

- Use of soft bristle tooth brush
- Brush or rinse after every meal
- Use mild tooth paste
- Regular use of floss without injury in gums
- Eat dry nuts alters food that stimulate salivary flow.
- Have regular dental checkup
- Use of ice chips to decrease pain and dryness of mouth

When being prescribed a new medication, ask your doctor or pharmacist about all the possible side effects [64].

Whenever a patient comes with oral lesions ask about history of medications and if significant then either reduce to the minimum dose required or switch to alternative regimen depending upon the severity of symptoms. Sometimes active treatment of the concerned effect may also be required.

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