

## OROFACIAL MANIFESTATIONS OF ADVERSE DRUG REACTIONS: A REVIEW STUDY

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### Abstract

**Background.** Adverse reaction to medication is common and may have a variety of clinical manifestations in the oral cavity. The present review paper aimed to describe adverse drug reactions (ADRs) which might be encountered by dental practitioners in every discipline.

**Methods.** In this narrative review article, the specialized databases such as PubMed, PubMed Central, MEDLINE, EBSCO, Science Direct, Scopus, and reference books from the years 2000-2016 were used to find relevant documents by using MeSH terms: Adverse Drug Reaction, Drug induced, Medication Related, Mouth, Oral Manifestation, Tooth, Hard Tissue, Soft Tissue.

**Results.** The data were categorized in 4 groups as follows: saliva and salivary glands involvement, soft tissue (mucosal) involvement, hard tissue involvement, and non specific conditions (taste disorders, halitosis, neuropathies, movement disturbances, and infection). Most articles were about the adverse effect of drugs on the function of salivary glands, which often cause a decrease in saliva secretion. Other reactions were less common; meanwhile, the side effect of bisphosphonate was increasing in the alveolar bone, because of its unlimited prescription.

**Conclusion.** Oral health care providers should be familiar with such events, as they will be confronted with them in their practice.

**Keywords:** adverse drug reaction, drug induced, medication related, mouth, oral manifestation, tooth, hard tissue, soft tissue

### Introduction

Different drugs that patients take to prevent or control disease expose them to the risk of developing adverse reactions [1]. An adverse drug reaction (ADR) is defined by WHO as "a response to a drug which is noxious and unintended, and which occurs at dose normally used in man for the prophylaxis, diagnosis, therapy of disease or for the modification of physiological function" [2]. ADRs have been classified into two types. Type A reactions represent about 80% of the cases. They are dose-dependent and predictable and are also associated with the pharmacology of drug. Pharmacology can be divided into

two subgroups as primary and secondary. Type A primary reactions are characterized as an abnormal reaction due to excessive action of the primary pharmacology of the drug such as oral mucosal bleeding after the use of anticoagulant agents, whereas a type A secondary reaction is a secondary pharmacology of the drug such as dysgeusia during the use of anti hypertension drugs. About 20% of ADRs are caused by an unpredictable reaction to drug which are known as type B reactions and are usually non-dose-related. Type B reactions are also divided into two subgroups, immunological and non-immunological reactions. Most of these reactions are immune-mediated side effects like hypersensitivity responses. Furthermore, recently other types of drug reactions have been described. For example, adverse effects may depend on the duration of the treatment in addition to dose (type C). Delayed adverse reactions

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of the drug are labeled as type D, and those reactions appearing after many years of treatment are defined as type E. Finally, reactions occurring after withdrawals are referred to as type F [3]. Since many patients take prescriptions and over-the-counter medications, dentists should be aware of drug-related problems in the orofacial regions [4]. The presence and severity of ADRs are related to patient and drug-dependent factors. Patients' risk factors include gender (more common in women), age (frequently in neonates and the elderly), underlying disease (more common in patients with hepatic disease and renal failure), and genetics. Drug factors include route of administration, duration, dose, and variation in metabolism [3]. Adverse drug events in the oral cavity have a variety of clinical presentation. Typically, these changes occur within weeks or months after taking the drugs and may be symptomatic or asymptomatic [1]. The aim of this study is to review the literature and highlights the more common and significant adverse oral consequences of drug therapy.

### Methods

The specialized data bases such as PubMed, PubMed Central, MEDLINE, EBSCO, Science Direct, Scopus, and reference books from the years 2000-2016 were used to find relevant documents by using of MeSH terms: Adverse Drug Reaction, Drug induced, Medication Related, Mouth, Oral Manifestation, Tooth, Hard Tissue, Soft Tissue. In this narrative review we took into consideration both medical and dental journals, including reviews, original papers, case reports, and case series.

### Results

We found approximately 100 relative articles, 39 were excluded due to lack of full texts or being written in languages other than English. Finally, 1 textbooks and 60 papers were selected, including 34 reviews, 15 case reports or case series, and 11 original articles.

Then, for better understanding, in the present paper, oral manifestations of ADRs were categorized into 4 main groups as follows:

#### 1. Saliva and salivary glands involvement:

*Xerostomia, Ptyalism, Salivary gland enlargement, Salivary gland pain, Discoloration of saliva*

#### 2. Soft tissue (mucosal) involvement:

*Lichenoid reaction, Erythema multiform, Pemphigoid, Lupus erythematosus, Fixed drug eruption, Angioedema, Mucous membrane pigmentation, Drug induced gingival enlargement*

#### 3. Hard tissue involvement

*Drug-related osteonecrosis of the jaw, Dental caries, Dry socket, Tooth discoloration*

#### 4. Non specific conditions

*Taste disorders, Halitosis (malodor), Neuropathies, Movement disturbance, Infection*

### Literature review

#### Saliva and salivary glands involvement

##### Xerostomia

Xerostomia, the most common adverse drug reaction affecting the oral cavity, is associated with over 500 drugs [1,3,5,6]. In a systematic review in USA, xerostomia was found as a secondary effect in 80-100% of prescribed drugs [7].

In the study by Villa, xerostomia was almost 3 times more in adults undergoing medication than those who didn't take any medication. Furthermore, the patients who took one or more drugs were two times more at the risk of xerostomia than those who didn't take any medication [8].

Many middle-aged and older patients are on multiple medications (poly pharmacy) that induce dry mouth because of synergic effects of these drugs (even with low anticholinergic effects) [1].

Xerostomia is also the most common side effect of salivary gland radiotherapy, chemotherapy, graft versus host disease (GVHD) and some disease like Sjogren syndrome, diabetes and AIDS [5,6]. Smoking, alcohol and caffeine consumption decreases in salivary flow rate [3].

Different mechanisms exist for drug induced xerostomia. Some drugs such as cytotoxic agents cause dry mouth by direct damage to salivary gland, diuretics by excreting body liquids and dehydration [2,6]. But this side effect of most drugs is due to their anticholinergic or sympathomimetic effect [3,9,10,11].

Some drugs can decrease salivary flow by causing vasoconstriction in the salivary glands [10].

A wide range of drugs may give rise to xerostomia, but the most important ones are:

Anti-cholinergics, anti-depressants, anti-histamines, anti-hypertensive agents, anti-parkinsonian drugs, anti-migraines, anti-neoplastic drugs, anti-psychotics, anti-seizures, cytotoxic agents, diuretics, muscle relaxants, sedatives and anxiolytics [1,6,10,12]. Appetite suppressants, supplements, non steroid anti inflammatory drugs (NSAIDs), systemic retinoids, anti-retoviral drugs, and medications like cytokines (interferon a, interleukin 2) can cause xerostomia as well [1,12-15].

Complications of xerostomia are taste alternations, dysphagia, speech disturbance, dental caries, susceptibility to infections (e.g. candidiasis and sialadenitis) [5,6].

Drug induced xerostomia is a reversible phenomenon and drug-cessation can lead to normal function of salivary glands [3]. Pilocarpine, cevimeline, bethanechol, and saliva substitute are used for management of this complication [6].

##### Ptyalism

Ptyalism or sialorrhoea is an uncommon condition that increases saliva amount or flow rate and can occur during menstruation, beginning of pregnancy, tooth eruption, inflammation, gastroesophageal reflux disease, heavy metal toxicity (like thallium, lead, arsenic, mercury) and neurologic disease (Down syndrome, Parkinson, autism,

cerebral palsy) [4,5].

Ptyalism may result from local irritation such as ill-fitting denture. The most important drugs that can induce hypersalivation are para-symphathomimetic drugs such as physostigmin, neostigmine, rivastigmine, cholinergic drugs (bethanechol, pilocarpine, cevimeline), lithium, clozapine, alprazolam, digoxin, and haloperidol [9,10,16,17].

Mefenamic acid, theophylline, captopril, nifedipin and some antibiotic agents like gentamycin, tobramycin, imipenem and kanamycin can increase the salivary flow as well [5,9].

Treatment of drug induced drooling, induced by drugs, is often symptomatic. Attempts are made to reduce the amount of saliva so that the patient can swallow it. It has been recommended that anticholinergic agents like benztropine, glycopyrrolate and scopolamine could be useful for management of drooling. Scopolamine skin patches for transdermal administration and applying Itratropium spray or increasing adrenergic ton, such as Clonidine patches, can also be employed alternatively. Botulinum injection into parotid gland in resistant cases has been successfully applied [16,18].

#### **Salivary gland enlargement**

Salivary gland enlargement has been reported as an adverse drug reaction. The most common drugs associated with parotid enlargement are iodine containing drugs such as those used as imaging contrast media [5]. Radioiodine is an important therapeutic agent used to treat thyroid cancer; one of its most common side effects is salivary gland swelling [10].

Other agents known to cause salivary gland enlargement include Insulin, methyl dopa, phenylbutazone, oxyphenbutazone, potassium chloride, sulfonamide, sodium warfarin, naproxen, guanidine, nitrofurantoin, clonidine, terbinafine, chlorhexidine, and doxycycline. Diazepam can also induce bilateral salivary glands enlargement associated with sialorrhoea [4,19].

In a review study, clonazepam, L-asparaginases and phenylbutazone have been found to induce parotiditis and parotid gland enlargement [20]. In Vinayak study a patient with malignant hypertension who was treated with enalapril developed bilateral parotid swelling 5 minutes after injection of the drug. On the basis of many studies, the salivary gland enlargement subsides after cessation of the drugs with or without corticosteroid therapy [10].

#### **Salivary gland pain**

Anti-hypertensive agents, cytotoxic drugs, anti-thyroids, chlorhexidine, ganglion blocker agents, iodides, phenothiazines, sulfonamides, and drugs that induce dry mouth can also cause salivary gland pain [4,9].

#### **Discoloration of saliva**

Clofazimine, levodopa, rifampin, and rifabutins can cause saliva and other body liquids discoloration (orange to red color) [4,9,10,14].

### **Soft tissue (mucosal) involvement**

#### **Lichenoid reaction**

Many systemic medications can cause oral lichenoid reactions although the pathogenesis is still unclear. Etiology of lichenoid reactions is related to the contact with specific agents such as drugs and metallic restorative material. Drug induced lichenoid reaction (LR) is similar to Lichen Planus clinically and histopathologically, except that LR is predominantly unilateral and present with an ulcerative reaction pattern [2,5]. Healing of LR after some weeks of the drug cessation is the most important mean for proper diagnosis. Time interval between starting the medication and beginning of lichenoid lesion varies from weeks to months with an average of 2 to 3 months [4,21].

Drugs that commonly induce LR are: NSAIDs, anti-hypertensive (especially B-blockers, angiotensin converting enzyme inhibitors (ACEIs) and anti-retrovirals. Gold is probably one of the most common agents that results in lichenoid lesions. Gold salt (for treatment of rheumatoid arthritis) induces a range of mucocutaneous lesions; with oral lichenoid lesions being the first manifestation [3].

Penicillins, tetracycline, anti-diabetics (tolbutamide, glipizide), sulfonamides, HIV protease inhibitors, anti-malarials, mercury, phenothiazine, anti-leptics (phenytoin, carbamazepine), penicillamine, ketoconazole, cyclosporine, prednisolone, indomethacin, pyridoxine, barbiturates, BCG vaccine, anti-lipid medications (simvastatin, clofibrate), tyrosine kinase inhibitors (imatinib) and alendronate can induce these lesions in the oral cavity [1,3,9,5,22-24].

Biological agents as prescribed for rheumatoid arthritis and oncology treatment, such as obinutuzumab (anti-CD20 monoclonal antibody) and infliximab (TNF- $\alpha$  inhibitors) can induce lichenoid reaction [25].

Nowadays it is unknown whether lesions in patients with thyroid disease are due to anti-thyroid agents or are just associated with thyroid disorders [1].

#### **Erythema multiform**

Erythema multiform (EM) is a hypersensitive reaction that can affect both skin and mucous membranes. It can be manifested as papule, macule, vesicle, erosion or ulceration. The lesions can affect any site of oral mucosa with a little tendency to gingiva, but extensive lip involvement with ulcer and crust can be especially predominant [1,5]. The most common cause of EM is infection especially herpes simplex virus (HSV) and less commonly Mycoplasma Pneumonia [4,5]. In 18-25% of cases, drugs such as NSAIDs and anti-leptic agents induce this reaction. It is also resulted from sulfonamides, sulfonyl urea and barbiturates [1,26].

Antibiotics (like penicillin, cephalosporin, tetracycline, clindamycin and rifampin), estrogen, progesterone, protease inhibitors and homeopathy medicine can induce EM [2,3,27]. EM is also reported to result from administration of infliximab and adalimumabs [1,28].

### ***Pemphigus***

Pemphigus is a group of life threatening autoimmune disorders that affect skin and mucous membranes. In 60% of cases oral lesions represent the first symptom of the disease and they appear as a bullae that is rapidly disrupted and leave irregular shallow ulceration.

Some drugs can induce oral lesions similar to pemphigus clinically, histopathologically and in immunofluorescent aspects [5,29]. These drugs produce antibodies leading to acantholysis and show symptoms similar to pemphigus vulgaris pathogenesis. Drugs capable of inducing pemphigus are divided into 2 groups:

Thiol agents (containing sulfidryle) and Non- thiol agents that often have active amid groups [3].

Thiol drugs such as penicillamine, ACEIs (captopril, enalapril) are the most common cause of pemphigus like lesions [3,4].

NSAIDs (diclofenac, ibuprofen and piroxicam), rifampin, phenobarbital, phenylbutazon, propranolol and heroin can also induce pemphigus-like lesions [4,9,29,30].

### ***Pemphigoid***

Drug induced pemphigoid often involves oral mucosa and can also appear as cutaneous lesions. The patients suffering from drug-induced pemphigoid are younger than those with autoimmune pemphigoid. Eliminating the special drug will make the lesions heal [31].

Drugs containing thiol and sulfonamide components are the most common drugs known to induce pemphigoid [4,9].

Anti-arrhythmics, anti-hypertensives (calcium channel blockers, ACEIs, beta blockers), anti-diabetics (tulbutamide), diuretics (furosemide, spironolactone), antibiotics (penicillin, cephalixin, ciprofloxacin), anti-rheumatic agents (D-penicillamine), anti-TNF a (adalimumab, etanercept), anti-psychotics and NSAIDs can induce pemphigoid reaction [1,9,32].

### ***Lupus erythematous***

Oral lesions of lupus erythematous (LE) may be similar to lichen planus with irregular areas of erythema or ulceration bordered by radiating keratotic striae. These lesions usually involve palate, buccal, gingiva or alveolar mucosa [5]. Considering that palate involvement is rare in lichen planus is helpful in differentiating from drug induced LE [3].

Drug induced LE is a variant of LE that improves within days to months after withdrawal of drug. Nowadays up to 70 types of drugs are known can induce LE. The most important drugs that cause systemic lupus erythematous is hydralazine and procainamide (20%) [3,5,33]. The other drugs with the potential to cause LE are:

All of anti-leptic groups, beta-blockers, sulfonamide, isoniazid, chlorpromazine, methyl dopa, penicillamine, quinidine, and biologic agents such as anti-TNF inhibitors [1,4,9,5,34].

### ***Fixed drug eruption***

The only cause of fixed drug eruption (FDE) is medications. Clinically it appears as non-specific diffuse erythema to vesicle and ulceration. Symptoms vary from tingling and burning sensation to severe pain of oral mucosa. The labial mucosa is most commonly involved [3,5,9]. It recurs at the same site after drug use [3]. FDE is a form of delayed hypersensitivity mediated by CD8 Tcell [5].

In the Ozkara study, naproxen and co-trimoxazole were the main inducers of FDE [35].

Barbiturates, dapsone, indomethacin, oxyphenbutazone, meprobamate, salicylates, sulfonamides, tetracycline, ibuprofen, clarithromycin and gabapentin can also induce fixed drug eruption [4,36,37].

### ***Angioedema***

Angioedema is a common clinical manifestation that comes along rapid painless swelling of lips, tongue, around the eye and adjacent area due to contact with an allergen or specific drug in susceptible patients. If angioedema involves the oropharynx, it may be life threatening. Swelling continues for 24- 48 hours, after the contact with allergen [3,5].

Some medications act directly on the mast cells and result in their degranulation and release of inflammatory cytokines such as serotonin, histamine, and kinins these medications can cause angioedema [3].

ACE inhibitors are the most common drugs that induce this situation [1]. Other drugs include: penicillins, cephalosporins, local anesthetic agents, aspirin, barbiturates, NSAIDs, anti-hypertensive agents (angiotensin receptor blockers, hydrochlorothiazide, isotretinoin, calcium channel blockers), anti- platelet drugs (clopidogrel) and anti-hyperlipidemia (simvastatin, atorvastatin, fluvastatin) [1,3,14,38-40].

### ***Mucous membrane pigmentation***

Acquired melanocytic pigmentations are drug induced in 10 to 20% of cases. This pigmentation can be localized, diffuse or multifocal in oral mucosa and is often seen on the palate. The lesions are flat, without any swelling and nodularity. In most cases discoloration dissolves a few months after drug withdrawal; however, pigmentation associated with hormonal drugs may be everlasting. Exact mechanism is unknown but drugs or metabolites can induce melanogenesis [4,5].

Temporary discoloration (yellow to brown) usually appears on dorsum of the tongue and oral mucosa through consumption of some foods and drinks (tea, coffee), or specific habits (smoking, betel, cocaine and crack use), some medications (iron, bismuth, chlorhexidine and antibiotics) and psychotropic agents that induce xerostomia [1,4]. The most important drugs that give rise to melanosis are:

Anti-malarias (chloroquine, hydroxychloroquine, mepacrine, quinacrine), oral contraceptive (OCP), chlorpromazine, cytotoxic drugs such as cyclophosphamide

and busulfan [5,9].

OCP induce oral pigmentation by stimulating melanocyte activity [3].

HIV- patients who are treated with clofazimine, zidovudine or ketoconazole may suffer from melanin induced pigmentation. In addition, heavy metal drugs such as silver, mercury, bismuth and gold may induce gingival pigmentation [4]. In 66% of cases anti-malaria drugs lead to gray-brown to black or yellowish discoloration on the palate. Also, clofazimine may lead to red color in the mucocutaneous mucosa [3].

Some drug metabolites such as minocycline, tetracycline, anti-malaria drugs and clofazimine may deposit in the oral mucosa. These metabolites chelate with iron and melanin.

Some drugs affect specific sites. For instance, zidovudine affects the tongue, OCPs involve the maxilla, mandibular gingiva, and chemotherapeutic agents (cyclophosphamide, doxorubicin, docetaxel) influence the dorsum of tongue and buccal mucosa [1].

There are many reports about blue, blue-gray or brown discoloration of gingiva by minocycline due to drug interaction with bone, during its formation. However, many of these discolorations may reflect the pigmentation of underlying bone and tooth roots [4,9].

#### ***Drug induced gingival enlargement***

Gingival enlargement is represented by the over growth of connective and epithelial tissues that develop between 1 to 3 months after treatment with some specific medications. Typically it affects interdental papilla and may cover a part or whole of the tooth. Usually it is generalized and involves anterior teeth. Commonly it is painless, but may be traumatized and tender during function. Severity of enlargement is related to drug intake duration, dose and patients' oral hygiene [1,3,9].

Most common drugs causing gingival enlargement are as follows [4,41],

Calcium channel blockers (diltiazem, nifedipine, amlodipine, felodipine, nisoldipine, verapamil) anti-convulsant drugs (phenytoin, sodium valproate, phenobarbitone, vigabatrin, primidone, ethosuximide), and immunosuppressants (tacrolimus, sirolimus, cyclosporine).

These groups have similar mechanism of action at intracellular level. They inhibit intracellular calcium ion infusion.

Gingival enlargement has been reported in 16 to 94% of patients who take phenytoin. On the other hand, other anti-leptic drugs such as valproic acid make less gingival enlargement [40].

Gingival enlargement was reported as a disease affect in 8% of the cases taking cyclosporine and in 100% of the patients taking cyclosporine and having kidney transplant as well [41].

Gingival hyperplasia due to calcium channel blockers is diffuse, generalized and often nodular with

fibrotic consistency [1].

Mostly, Calcineurin inhibitors (cyclosporine) induce gingival hyperplasia. However, tacrolimus can also lead to fibrovascular gingival hyperplasia less frequently. Fibrovascular hyperplasia manifests as a localized polypoid fibrous tumor involving tongue and buccal mucosa rather than gingiva [1]. Clinically, the Gingival enlargement due to cyclosporine has higher signs of inflammation and is less fibrotic; however, nifedipine and phenytoin are more fibrotic [5,42].

Oral contraceptives (OCP) can cause gingival enlargement as well [41].

#### **Hard tissue involvement**

##### ***Drug-related osteonecrosis of the jaw***

Osteonecrosis is a result of temporary or permanent loss of blood supply to the bone. This is a serious oral complication from taking bisphosphonates (BPs), anti-resorptive (denosumab), anti-angiogenic, and immunomodulatory medication [1,3,43].

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) was first described by Marx in 2003, and commonly result from zoledronic acid usage [44].

Osteonecrosis was reported not only for BPs but also for anti-angiogenic agents and the distinctive ulcer, caused by mammalian targets of rapamycin inhibitors [1]. Thus the term "medication-related osteonecrosis of the jaw" (MRONJ) is more accurate than BRONJ.

Bisphosphonates are non-metabolized analogs of pyrophosphate that are located in the bone and prevent or reduce skeletal complications [3].

BPs reduce turnover rate of the bone by inhibiting osteoclast activities. They are used in osteoporosis, bone metastatic disease, hypercalcemia due to malignancy, and bone lesions (such as multiple myeloma, osteopenia, osteogenesis imperfecta and Paget disease [19,45].

MRONJ is more common in patients with cancers treated with intravenous BPs, and it is uncommon in patients on oral administration (0.1- 0.4% in orally taking versus 0.8- 12% in IV injection).

MRONJ risk is noted to be higher in patients suffering from cancer, since they get the intravenous form of Bisphosphonates. Intravenous Bisphosphonates are prescribed to treat cancers and bone problems induced by bone metastases, solid tumors, and lytic bone lesions such as Multiple Myeloma. On the other hand, the oral form of Bisphosphonates are prescribed to treat osteoporosis, osteopenia, and less common cases in Paget's disease or osteogenesis imperfecta. MRONJ risk is said to be dependent on time in a way that taking intravenous Bisphosphonates for an average period of 33 months (in patients suffering from cancer) and 48 months of the oral form in patients with osteoporosis. Tooth extraction, as initiator factor, is considered to be of high importance. In the oral form, the risk is 5% and in the intravenous one, it ranges from 1.6% to about 14%. In patients suffering from cancer, all oral

cavity mucosa and teeth should be examined before any intra venous treatment. Then, any source of infection, pathology and infection risk factors should be removed. In the following, any teeth with poor prognosis should be extracted, and endodontic and prosthodontic treatment should be performed for the teeth with good prognosis. Teeth with three grade mobility should be extracted as well. After starting the treatment with Bisphosphonates, the patients have to visit the dentists every four or six months and panoramic radiography should be done every six to 12 months in order to diagnose osteosclerosis, or lytic bone, forca involment, and periodontal ligament widening. For tooth extraction, antibiotic prescription is essential and teeth should be extracted with minimal trauma. In cases of patients with osteoporosis who are willing to take the oral form, it is necessary to be informed about MRONJ problems and symptoms and that taking them for more than four years predisposes them to this situation [45,46].

Some risk factors that are related to MRONJ included: history of dento alveolar trauma, duration of taking BPs and its type. Patients with history of dental inflammatory disease are at risk of MRONJ, seven times more than others [47].

Yarom stated that patients who took 70 mg alendronate in 1 week (for more than 3 years) or 35 mg in 1 week (for more than 5 years) are susceptible for BRONJ [48].

BPs consist of alendronate (fosamax), pamidronate (aredia), ibandronate (bonvia), residronate (actonel) and zolendronate (reclost, zometa) [3].

If tooth extraction is necessary for these patients, they must stop taking drugs 3 months before and start the medication 3 months later (after complete healing of tooth socket [43].

### **Dental caries**

Poor oral hygiene, dietary habits and dry mouth are risk factors for dental caries. Syrups contain sucrose that are used for children reduce PH and lead to dental caries. Antifungal (nystatin oral tablet) and antibacterial agents have sucrose up to 60g% [49] and increase the risk of dental caries.

Furthermore, anti-leptic agents, psychotropic substances such as heroin, cocaine, methamphetamine and cannabis can induce dental caries as well [41,49].

### **Dry socket**

Dry socket or alveolar osteitis is a very painful condition that develops between 1 to 3 days after tooth extraction and is one of the common complications after the removal of third molars. It occurs due to removal of the clot within the socket. The prevalence of this phenomenon ranges from 0.5 to 5% of cases. OCPs can increase the incidence of dry socket. It may be related to OCP fibrinolytic effect that interferes with coagulation. Vasoconstrictor in local anesthetics may contribute to the formation of dry socket [14,50,51]. Trauma, smoking, radiotherapy, and microorganisms increase the risk of dry socket, too [50].

### **Tooth discoloration**

Tooth discoloration is classified to extrinsic and intrinsic. Extrinsic types are stains of the outer surface of the tooth that can be removed by polishing. Poor oral hygiene, mouth rinses such as chlorhexidine, excessive use of tea, coffee, tobacco, and smoking can induce tooth extrinsic discoloration. Systemic disease (like Porphyria (red), jaundice (brown), erythroblastosis fetalis (gray-brown), and fluorosis (yellow- brown)) can cause intrinsic discoloration due to their effect in the developing stage of tooth [5].

But some drugs such as antibiotics (minocycline, penicillin, ciprofloxacin, co-amoxiclave, clarithromycin, metronidazole) can effect tooth color as well [9,52].

Internal discoloration due to taking tetracycline is prominent when it is used for children under 12. Among tetracyclines, chlortetracycline makes sever discoloration with gray-brown hue [3]. Tetracycline, oxytetracycline, and methyl- chlortetracycline create a lower degree of color changes (like yellow hue). Also, minocycline can affect tooth color and make gray-black hue, but in contrast to tetracycline, it can involve erupted and fully developed tooth [4]. Other drugs which are related to tooth discoloration are as follows, [4,5,52].

Enalapril, Etidronate, Fosinopril, Pentamidine, Perindopril, Propaferone, Quinapril, Ramipril, Terbinafine, Trandolpril, Zopiclone.

### **Non specific conditions**

#### **Taste disorders**

Many drugs are associated with taste abnormalities which manifest as loss of taste acuity (hypogusia), loss of taste sense (agusia), distortion of taste (dysgusia) and bad taste (paragusia) [4]. Sometimes, taste disturbance appears in the form of uncommon, bitter or metal taste in the mouth. The exact mechanism is still unknown, but one of the mechanisms is known to be excretion of drugs or their metabolites into saliva. Another mechanism is related to direct effect of drugs on taste receptors or secondary to hypo salivation. It can affect on physical and psychological health or patient's life style [3].

The most common drugs that induce taste disturbance are: ACEI inhibitors ,anti- thyroids, beta lactam, anti-diabetic agents (metformin), chlorhexidine, opiates and protease inhibitors, calcium channel blockers (nifedipin, diltiazem), antimicrobial drugs (metronidazole, grizofulvine, carbicillin, lincomycin), aspirin, penicillamin, rifampin, lithium and imipramine. Also some drugs like anti-HIV, clarithromycin, lansoprazole, terbinafine and isotretinoiin can cause hypogusia or dysgusia [3,4].

In the Deco Camila study, the most important oral side effect of anti-diabetic and anti-hypertensive agents were taste alternation found in 19% of the patients [53].

Taking heavy metal drugs cause metal-tasting. Some investigation showed that a lipoic acid can heal taste disturbance relatively. But the most effective way to correct

this situation is the elimination or completely discontinuing such drugs [2,3,53,54]. This state heals 4 months after medicine withdrawal [5].

#### ***Halitosis (malodor)***

Malodor is the third most frequent reason for people to refer to dental care centers, after tooth decay and gum disease [55]. Poor oral hygiene, dental caries, oral infection, periodontal disease, systemic disease like renal, hepatic, gastrointestinal disease and upper airway infection, some foods or smoking can lead to malodor. Halitosis can be related to indirect effect of drugs which result in dry mouth, but other drugs like Isosorbide Dinitrate, cytotoxic agents, D-methyl sulfoxide, amyl-nitrate, Disulfiram, Paraldehyde, Chloral hydrate are directly the cause for halitosis. Using some vitamins such as B6, can also induce halitosis. Tetracycline causes malodor and hairy tongue [4]. Some drugs that cause phantom or real halitosis are lithium mineral, penicillin, griseofulvin and drugs containing iodine and bismuth [56].

#### ***Neuropathies***

Neuropathy is one of the neurological complications of chemotherapy. Often peripheral neuropathy is accompanied by taking taxanes, platinum compound, thalidomide, bortezomib and herbal alkaloids (vincristine, vinblastine) [1].

Besides, neuropathies are seen in taking acetazolamide, tricyclic anti-depressants, chlorpropamide, isoniazid, nalidoxic acid, nitrofurantoin, polymixin-B, streptomycin, ergotamine, hydralazine, monoamino oxidase inhibitors (MAOIs), nicotinic acid, tulbutamide and local anesthetics (like articaine and prilocaine) [57-59].

#### ***Movement disturbance***

Movement disturbance is divided into 3 main groups by symptoms onset: acute, subacute, and tardive. Acute movement disturbance occurs from hours to days after exposure; subacute one occurs within weeks and tardive one occurs from months to years after medication exposure. Tardive dyskinesia, dystonia, and Parkinson are included in this group of disorders [59].

Tardive dyskinesia (TD) is an involuntary, repetitive, purposeless movement in the body, extremities and orofacial region such as tongue, it happens in the form of tongue protrusion, lip smacking, chewing movement, grimacing and puckering. This condition is not painful;

however, it is socially unpleasant and makes swallowing, chewing and speaking difficult. They are seen repeatedly in patients who take dopaminergic antagonists for a long time [3].

The most common drugs that induce movement disorder are dopamine receptor antagonists (Chlorpromazine, Haloperidol) and anti-emetics (Chlorpromazine, Prochlorperazine). Anti-depressants, anti-psychotics (Phenothiazine), anxiolytics, OCP and Metoclopramide HCL can also result TD [3,14].

Phenothiazines may induce involuntary movements in the facial muscles 4 days after consumption (grimacing syndrome). It is accompanied by spasm of facial muscles, neck, tongue, abdomen, tetanus like with movement disorder [59].

Benzodiazepines, dopamine agonists and adrenergic agonists are helpful in the treatment [3].

#### ***Infection***

Some drugs which are used locally or systemically may alter the normal flora of the mouth and increase susceptibility to infections. Antibiotics, especially the wide spectrum ones, cause secondary infection. The drugs that are capable of inducing infection include Cephalosporin, Penicillin, Ciprofloxacin and Griseofulvin. Corticosteroids also can increase infection susceptibility. Cytotoxic drugs cause bone marrow suppression and increase bacterial, viral, fungal and childhood viral infections (like measles and chickenpox) [4,9,14,60].

Long term use of immunosuppressive and anti-rheumatic agents such as methotrexate, abatacept, alefacept increase herpes virus infection, deep fungal infections and pseudomembrane candidiasis [1]. Anti-TNF antibody therapy (infliximab, adalimumab) increases the risk of serious infections [60,61]. Likewise, drugs with the potential of inducing dry mouth increase the chance of oral infection.

We show the orofacial related side effects of medication in the Table I.

We found that most studies were about the adverse effects of drugs on the function of salivary glands, which often cause a decrease in saliva secretion. Other reactions were less common; meanwhile, the side effect of bisphosphonate was increasing in the alveolar bone, because it has being over prescribed.

**Table I.** Orofacial related side effects of medication; Saliva and Salivary gland involvement, Soft tissue (mucosal) involvement, Hard tissue involvement, Non specific conditions.

Classification	Adverse effect	Mechanism	Clinical findings	Related medication
<b>Saliva and Salivary gland involvement</b>	Xerostomia	Sympathomimetic effect (Anti-cholinergic) Damage to salivary gland Excreting body liquids (dehydration) Vasoconstriction in salivary glands	Stomatitis, Difficulties in eating, speaking, tasting, swallowing and retention of removable denture Dysgeusia, Burning sensation	Anti- cholinergics, Anti- histamine, Antihypertensive, Anti-depressant, Diuretics
	Sialorrhoea	Parasympathomimetic effect (cholinergic action)	Drooling, Choking sensation, May aspirate saliva at night	Sympathomimetic drugs (pilocarpine, cevimilline), Physostigmine, Heavy metals
	Salivary gland Enlargement	Hyper sensitivity reaction Oedema (spasm of smooth muscles)	Swelling of salivary glands	Radioiodine, Chlorhexidin, Clozapine
<b>Soft tissue (mucosal) involvement:</b>	Lichenoid reaction	Delay hypersensitivity reaction	Similar as lichen planus specially ulcerative form	Anti- hypertensive (B blockers, ACE *inhibitors) Anti- hyperglycemic, Anti- leptic, Anti- malaria, NSAIDS**, Gold sulfonamides
	Erythema multiform	Hyper sensitivity reaction (immune complex)	Mild erythema to painful ulceration, Crusting and bleeding specially on the lips	NSAIDS, Antibiotics, Sulfanamides
	pemphigus	Auto immune (Auto antibody versus spinosom layer)	Shallow irregular erosions and ulcers	Penicillamine, ACEIS (captopril, enalapril)
	Pemphigoid	Auto immune (Auto antibody versus basal layer)	-Desquamative gingivitis - Similar as lichen planus specially ulcerative form	Sulfonamides, Penicillin, Foresnide, Captopril, Penicillamine, NSADIS
	Lupus erythematosus	Auto immune (by Involving immune complex)	-Same as lichen planus -Irregular areas of erythema or ulceration bordered by radiating keratotic stria	Hydralazine, Procainamide
	Fixed drug eruption	Delayed type of hypersensitivity	-Diffuse erythema to vesicle and ulceration -Burning sensation to sever pain in oral mucosa	Naproxen, Co- trimoxazole, Barbiturates, Indomethacin, Salicylates, Sulfonamids
	Angioedema	Allergy and hypersensitivity reaction(is mediated by inflammatory cytokines such as serotonin, histamine and kinins)	Painless swelling of lips and orofacial regions	ACEIS, Penicilline, Barbiturates, Anti- hypertensive agents
	Mucous membrane pigmentation	Stimulatory melanocyte activity, Deposition of drug metabolites in mucosa	Focal, multifocal or diffuse discoloration specially on hard palate	Anti- malarials, Cytotoxic agents, (cyclophosphamide, busulfan), Chlorpromazine Clofazimine, OCP***
	Gingival enlargement	Decrease activity of matrix metalloproteinase and failure to activate collagenase, Dysregulation of cytokines and growth factor	Over growth of gingiva specially inter dental papilla of anterior region	Calcium channel blockers, Anti- convulsant, Immune suppressant ( cyclosporine) ,OCP
<b>Hard tissue involvement</b>	Drug related osteonecrosis	Loss of blood supply to bone, Reduce the rate of bone turn over by inhibiting osteoclast activity	Necrosis of bone, Pain, fistula	Bisphosphonate, Anti- angiogenic agents
	Dental caries	Reduce PH	Caries especially in the cervical tooth	Antifungal, Antibacterial Anti-leptic agents, Psychotropic substances
	Dry socket	Vasoconstriction, Interferes with fibrinolytic effect of coagulation	very painful condition	Smoking, OCP
	Tooth discoloration	Intrinsic: effect in the developing stage of tooth Extrinsic: deposition of stains on the outer surface of tooth	Different tooth colors, yellow- brown, gray- brown, black, brown	Intrinsic: antibiotics especially; Tetracycline Extrinsic :mouth rinses such as chlorhexidine, excessive use of tea, coffee, tobacco, and smoking
<b>Non specific conditions</b>	Taste disorder	Direct effect to taste receptors, Exertion of drugs or its metabolites into saliva, Secondary to hyposalivation	Loss of taste acuity, Loss of taste sense, Bad taste, Metallic taste	Anti- diabetics, Anti- hypertensive, Anti- thyroids, Chlorhexidine, Anti- microbial, Opiats
	Halitosis (malodor)	Dry mouth,metabolits	Bad breath in the exhale	Isosorbide Dinitrate, cytotoxic agents, D- methyl sulfoxide, Amyl- nitrate, Disulfiram, Paraldehyde, Chloral hydrate
	Movement disturbance		Purposeless movement of the tongue, difficulty in the swallowing, chewing and speaking	Dopaminergic antagonists, Anti- emetics, Anti- depressant, anti- psychotics (Phenothiazine), anxiolytics, OCP, Metoclopramide HCL
	Infection	Changes in the normal oral flora	Susceptibility to infection such as candidiasis, herpetic lesion	Antibiotics, Corticosteroids, Cytotoxic drugs, Immunosuppressive, Anti- rheumatic agents

\* Angiotensin Converting Enzyme Inhibitor \*\* Non Steroid Anti Inflammatory Drugs \*\*\* Oral Contraceptives

## Discussion

Hyposalivation or dry mouth is by far the most common side effect of medications especially after consumption of anticholinergics, antihypertensives, and cardiovascular drugs [1,3,5-7].

On the other hand, involvement of the oral mucosa following medication is mainly encountered in the form of white lesions or ulcerations through hypersensitivity or autoimmune mechanisms [1,3,9,5,22-25].

Nowadays increasing prescription of bisphosphonates subjects the patients to oral hard tissue involvement such as jawbone lesions [43-48]. There are some non specific side effects due to drug consumption such as taste disorders and bad breath resulting from salivary hypofunction [3,4,53]. Antihypertensive drugs and medications used for the treatment of metabolic diseases like thyroid disorders or diabetes can cause changes in taste perception [53]. Moreover, any alterations in salivary secretion or composition may lead to imbalance of microflora which in turn results in fungal infections. Consumption of antibiotics, non steroidal anti-inflammatory drugs (NSAIDs), and immunosuppressors are the most frequent drugs that cause infection in oral cavity as a drug adverse effect [1,4,9,14,60].

Increasing life expectancy worldwide, with more elder population needing medications in different communities makes it mandatory for dental practitioners to be closely familiar with oral side effects of drugs.

## Conclusion

Although drug reactions sometimes occur in the mouth, they are not usually diagnosed properly. Dentists need to be aware of drug side effects in the oral cavity or refer to specialist in time. An effective cooperation between dentists and medical teams is necessary and helpful.

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