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Review Article

DRUG INDUCED ORAL ADVERSE REACTIONS: A REVIEW

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A B S T R A C T

The incidence of drug-related adverse drug reactions in the mouth is frequent, which is often underestimated and unreported. It makes significant health concern because it represents the fourth-sixth leading cause of death in the world. Most of the drug has the potential to cause deleterious effects which affect any region of the oral route. It may lower the quality of life and predispose patients to serious clinical disorders. Various clinical patterns of drug-induced oral complications include Xerostomia, pigmentation, gingival enlargement, dysgeusia, angioedema and so on. It is critical to establish the possible cause is due to drug exposure or other crucial factors such as patients underlying disease, age factor, lifestyle modification or hereditary disorder. This review focuses on undesirable effects caused by drugs in the oral region and highlights the preventive and treatment options available for these disorders.

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INTRODUCTION

Medicine is the diverse field of science, encompasses the diagnosis and treatment of any ill manifestations. The success of any treatment requires an early and proper diagnostic procedure which helps to reduce the discomfort of the patients. Thus it is essential to reduce the further complications of the disease, and also to improve the survival rate of the individual. Drug administration is an important factor in medicine. It is not only a must to prevent predicted disease, but also to treat the apparent diseases. Multiple medications are common which gives to a wide range of adverse drug reactions; even it is used according to the standard method of administration. It is estimated that 2-4% of hospital admission are mainly due to drug-induced adverse effects. Patients, who explicate various unwanted drug issues, will get the help and treatment from a physician, dentists, and mid-level practitioners. They work to reverse or resolve the patient's status and it is crucial to discontinue the causative agent if the event is severe enough. Children, elderly persons, nutritional and immunodeficient individuals are at high risk to develop iatrogenic diseases. Attention must be given to age, sex, health status and prior medications of an individual.

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Widespread use of prescription, over the counter (OTC) drugs, herbal medicine, folklore remedies increase the chance of drug ill effects. Thus, health care professionals should be aware and ready to encounter these notorious effects which have a broad range of clinical manifestations resembles normal diseased state.

Adverse Drug Reactions

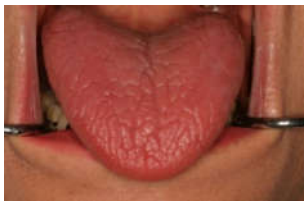
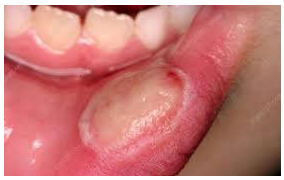
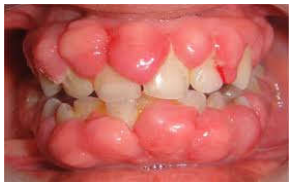
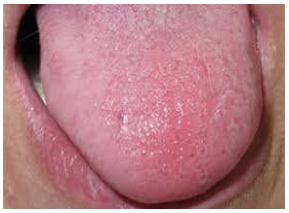
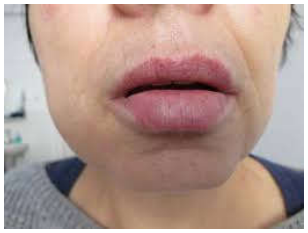
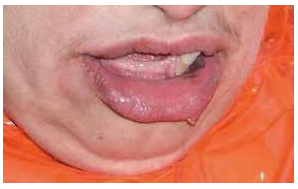
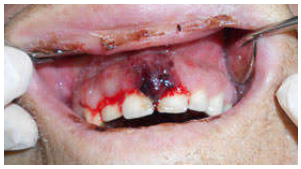
World Health Organization (WHO) states Adverse Drug Reaction (ADR) as a drug response that is noxious and unintended, which occurs even at doses normally used in humans for prophylaxis, diagnosis or therapy of a disease or the restoration, correction or modification of a physiological function (Femiano 2008). Two types of effects can be seen after the drug administration to the patient. The first type of effect is the intended effect, the reason why the drug was given to the patient. This type of effect is common, augmented, dose-related and based on the pharmacological property of the drug. The second type of effect is unwanted which is unpredictable, non-dose-related and based on the patient's immune response towards the drug. Approximately 15-20% of the adverse effect caused by an unpredictable reaction (Femiano 2008).

Patterns of Drug Induced Oral Adverse Effects

Adverse drug reaction caused by drugs is vast and well recognized. The oral route is the important target organ for a

variety of abnormalities that results from drug intake. Some of the conditions discussed herein include Xerostomia, pigmentation, oral ulceration, aphthous stomatitis, taste disturbances, gingival enlargement, oral thrush, gingival bleeding, angioedema, halitosis. Health care professionals should aware of the major patterns of drug-induced oral effects which help them to understand the severity and impact on the oral health of the patients.

Table 1 List of Drugs that causes adverse reactions in oral route

Drug Induced Oral Complications	Causative drugs
 Xerostomia	Antidepressants,antipsycotics,antihypertensives,antiretrovirals, bronchodialators, skeletal muscle relaxants, appetite suppressants, decongestants, multivitamins and supplements, Non-steroidal anti-inflammatory drugs(NSAIDs), steroid inhalers, antithyroid drugs, trospium chloride, elloptinium, tramadol, chlorhexidine, cytotoxics, ganglion blocking agents, iodides, phenothiazines, sulfonamides,New generation Anti Histamines.
 Apthous Stomatitis	NSAIDs, alendronate, azathiopurine, gold compounds, cyclosporine,sulfonamides,Losartan,Nicorandil,docetaxel, fluoxetine,Beta blockers, captopril, indinavir, interferons, penicillamine.
 Gingival Hyperplasia	Anticonvulsants/antiseizures (such as Phenytoin, carbamazepine, valproic acid), Calcium channel blockers(CCB such as amlodipine, Nifedipine, nitrendipine, verapamil, diltiazem, felodipine) Calcineurin inhibitors such as Cyclosporine , tacrolimus , Mycophenolate mofetil,) Oral Contraceptives(OCP), and some antimicrobial agents such as Ketaconazole, Erythromycin.
 Taste Disorders	Captopril, enalapril, metronidazole, penicillaines,vitamin D, sulfasalazine, diltiazem, gold salts, clarithromycin, Lithium, tripotassium dicitrato bismuthate chelate, anti-HIV protease inhibitor, terbinafine, chlorhexidine, flecanide, carbenicillin, intravenous pentamide, Isotretinoin, Aspirin, diclofenac, propranalol, sulphonamide.
 Angioedema	ACE Inhibitors NSAIDs(Aspirin,Indomethacin),angiotensin teceptor blockers(ARB),barbiturates,calcum channel blockers, hydrochlorothiazides, antiplatelet agents such as thienopyridine and clopidogrel, statin drugs such as simvastatin, fluvastatin,atorvastatin and pravastatin.
 Angular Cheilitis	Hydralazine, oral contraceptive, D-penicillamine para- aminosalicylic acid, colestipol, cholestyramine, Methotrexate, triamterene, phenobarbital, primidone, clofazimine, psoralens, statins, protease inhibitors, busulfan, tetrcycline, isotetrinoin.
 Halitosis	Dimethyl sulphoxide or disulfiram, isosorbide dinitrate,chloral hydrate,succimer,cytotoxic drugs.
 Oral Pigmentation	Minocycline, doxycycline,co-amoxiclav,linezolid, bismuth subsalicylate, chlorhexidine, cetylpyridium, cocaine, Clofazimine, cyclophosphamide, estrogen, amiodarone, tetracycline, zidovudine, anti-inflammatory drugs and anti-malarial agents such as quinine hydrochloride, chloroquine, hydroxyl chloroquine and amodiaquine, Oral contraceptives, phenothiazines such as chlorpromazine, Tetracycline, oxytetracycline, chlortetracycline, Minocycline, Ciprofloxacin, chlorhexidine, penicillin, erythromycin, doxycycline, neomycin, aureomycin, corticosteroids, sulfonamides, methyldopa.
 Sialorrhoea	Acetyl cholinesterase inhibitors, yohimbine, nifedepine, rivastigmin, lithium, dimercaptol, mucosa irritating drugs.
 Gingival Hemorrhage	Thiazide diuretics,allopurinol, methyldopa, digitalis,cepalosporins,quinine,quinidine,antineoplastic agents, coumarin, gold salts, heparin, phenytoin, penicillin, tetracycline.

Drug Induced Xerostomia

Xerostomia or dryness of mouth is the most frequent adverse effect in the oral cavity. It may be due to diminished salivary secretions and decreased salivary calcium and phosphate concentration (Abdollahi 2008). The principal action behind the drug-induced xerostomia is anticholinergic or sympathomimetic action (Femiano 2008)**.** More than 500medications causes dry mouth. Chronic use of drugs, the synergistic effect of the combination therapy in elderly patients, anxiety, diabetes mellitus, smoking, alcohol consumption are some of the factors responsible for oral dryness. Consequences of this condition may lead to mouth soreness, painful or burning sensation of the tongue, altered taste perception, difficulty in chewing, swallowing and speaking, reduced denture retention(Darrell 2005), dental caries, oral bacterial and fungal infections, halitosis, aphthous lesions**(**Abdollahi 2008, Darrell 2005). Most frequently reported drugs results in hyposalivation are antidepressants, antipsychotics, antihypertensives, antiretrovirals, bronchodilators, skeletal muscle relaxants, appetite suppressants, decongestants, multivitamins and supplements, Non-steroidal anti-inflammatory drugs(NSAIDs), steroid inhalers(AnnaYuan 2015), antithyroid drugs, trospium chloride, elloptinium, tramadol, chlorhexidine, cytotoxics, ganglion blocking agents, iodides, phenothiazines, sulfonamides, New generation Anti Histamines(Femiano 2008). Pilocarpine and bethanechol have been suggested to be

of potential use in the management of drug-induced Xerostomia (Trophimus 2014). Other ways to activate saliva secretions such as the use of saliva substitutes, oral lubricants, and citric acid can be used. Drug hyposalivation is a reversible phenomenon thus to reduce the severity of the condition, the causative agent can be discontinued to get the normal salivary action (Femiano 2008)

Drug Induced Apthous Stomatitis

Aphthous Stomatitis (also known as canker sores, recurring oral aphthae, recurrent aphthous stomatitis) is a common dental adverse effect seen after drug therapy (Beguerie 2015), affecting 5-25% of the population (Ship 2000)predominantly seen in developing countries. It is a painful inflammatory mucosal disorder that occurs as single or multiple lesions. Exact mechanism remains unclear and believed to be multifactorial such as stress, anxiety, chemical agents, tobacco, local trauma, genetic factors, toothpaste, microbial agents, and various well defined diseases such as Behcet's syndrome, gluten-sensitive enteropathy, cyclic neutropenia, infection with HIV and medications induced complications (Belenguer 2014, Jurge 2006). Agents that cause aphthous stomatitis includes NSAIDs, alendronate, azathioprine, gold compounds, cyclosporine, sulfonamides, Losartan, Nicorandil, docetaxel, fluoxetine, Beta-blockers, captopril, indinavir, interferons, penicillamine. Based on the intensity of the ulcers topical steroids, immunomodulatory agents, topical analgesics/anti-inflammatory agents can be used to manage the condition (Preeti 2011**)**. An intralesional steroid injection or systemic steroids in low doses can be used to treat in severe cases (Ana Pejcic 2015).

Drug Induced Gingival Hyperplasia

One of the most familiar oral adverse effects due to the manifestation of systemic drug use is gingival hyperplasia (also known as gum hypertrophy, gingival enlargement). It is a disfiguring effect occurs in patients taking medicaments like anticonvulsants/anti seizures (such as Phenytoin, carbamazepine, valproic acid), Calcium channel blockers(CCB such as amlodipine, Nifedipine, nitrendipine, verapamil, diltiazem, felodipine) Calcineurin inhibitors such as Cyclosporine, tacrolimus, Mycophenolate mofetil) Oral Contraceptives(OCP), and some antimicrobial agents such as Ketoconazole, Erythromycin. incidence of overgrowth by Phenytoin, Nifedipine, and Cyclosporine present as 10-83%,7-80%,25% respectively(Brown 2015).Other correlated factors like gingival irritants, mouth breathers, dental calculus, and impaired dental restorations induce this drug-induced state.

It is an abnormal overgrowth of fibrous gingival tissue characterized by an accumulation of extracellular matrix within the gingival connective tissue particularly the collageneous component with various degrees of chronic inflammation (Abdollahi 2008). Discomforts such as difficulty in speaking and chewing, change in facial appearances, bleeding, teeth eruption, and occlusion teeth problems influence the risk of infections, caries, and periodontal diseases **(**Stephen 1998, Ciavarella D 2007, Anushi 2017**)**. Tissue enlargements develop within 2-3 months of commencement of drug therapy (Abdollahi 2008, Femiano 2008). Various factors have been reported such as inflammation, oral hygiene, age, hereditary, drugs, and systemic causes of gum hypertrophy. The growth starts as painless, bead-like papillary or velvety bright red lingual gingival margin that bleeds easily. Anterior segments are more frequently involved than posterior areas (Femiano 2008).

A common hypothesis has been reported which begins with the inhibition of cation influx, decreases the cellular folic acid uptake within the gingival fibroblasts, in turn, decreases the activity of matrix metalloproteinases results in failure to activate collagenase (Anna yuan 2015). Insufficient availability of activated collagenase leads to less degradation of accumulated connective tissue which outcomes as drug-induced gingival overgrowth (Brown 2015). Phenytoin, an antiepileptic agent increases the gene expression for Platelet-derived growth factor B (PDGF-B). When the gingival macrophages exposed to phenytoin, increase the PDGF-B, and in turn increase, the proliferation of gingival and alveolar bone cells results in hypertrophy (Darrell 2005).

Nifedipine, the most commonly used calcium channel blocker used for the treatment of cardiovascular diseases such as angina pectoris and hypertension. It is also used in combination with Cyclosporine to reduce the immunosuppressant activity during organ transplantation. It alters the intracellular calcium and enhances the action of inflammatory cells by replacing the collagen connective tissue in the fibroblasts, thus activated well to elicit the epithelial growth in the gingival region (Abdollahi 2008). Evidence shows that nifedipine inhibits the adherence of fibroblast their lipopolysaccharide-stimulated, macrophage induced death (Femiano 2008).

Cyclosporine, an immunosuppressant agent able to alters gingival fibroblasts metabolism, thus decrease the collagenase activity by increase the fibroblast production of collagen and matrix. This activity will further exaggerate by the presence of dental plaque and bacterial toxins (Brown 2015).

Chronic use of Oral Contraceptives (OCP) increases the gum overgrowth as the occurrence of sex hormones metabolites is more in the gingiva, induces tissue destruction by activating the matrix metalloproteinase (Robert 1988). Other agents like ketoconazole, an antifungal agent and Erythromycin, an antibacterial agent involves in potentiates the action of gingival fibroblasts (Anushi 2017).

The treatment option for this oral ill effect is based on the intensity of the particular case. Good oral hygiene before and during the therapy, stoppage or alternate drug selection, gingivectomy can be done.

Drug Induced Taste Disorders

Various causes prevail to reduce taste perception or causing taste changes. Many drugs induce these abnormalities in individuals taking multiple medications. Subjective complaints of taste disturbances may be simply a blunt loss of taste perception (Hypoguesia), or a distortion in perception of correct taste of disturbances, for eg sweet or sour (dysgeusia)(Ana Pejcic 2015) or complete loss of taste sensation(ageusia). Manifestations of taste disorders like bitter, metallic taste, altered taste or unpleasant taste for food may occur. The mechanism by which the taste disturbances occur may vary and due to dose-related (Abdollahi 2008). Researchers propose three different mechanisms.

1. Secretion of drug or its metabolites into the saliva, thus affecting the chemical composition or flow of the saliva, 2. Taste receptor function or signal transduction gets affected by

the drug, 3. The direct action of the drugs on the taste buds. sulfhydryl compounds are considered to be a common cause of taste abnormalities(Femiano 2008). There are around 200 drugs that can cause taste disorders(Darrell 2005). Numerous drugs cause taste alterations such as captopril, enalapril, metronidazole, penicillamine, vitamin D, sulfasalazine, diltiazem, gold salts, clarithromycin, tripotassium dicitratobismuthate chelate, anti-HIV protease inhibitors, terbinafine, chlorhexidine, flecainide, carbenicillin, intravenous pentamidine, Isotretinoin, Lithium, Aspirin, diclofenac, propranolol, sulphonamide(Ana pejcic 2015, Darrell 2005, Abdolahi 2008). Factors like polypharmacy/ polyherbacy, salivary gland disorders, hyposalivation may enhance medication taste disorders. Termination of chronic drug therapy or the use of an alternate drug may help to alleviate symptoms.

Drug Induced Oral Candidiasis

Alterations of oral microflora after drug administration induce opportunistic infections. The yeast, Candida albicans is the common oral flora that sometimes acts as opportunistic pathogen thus causing superinfections in the mouth. Clinical signs and symptoms are creamy-white plaques that resemble cottony appearance on the tongue and buccal mucosa, redness and painfully ulcerated surface-exposed scraped, loss of taste, difficulty swallowing (Darrell 2005). Predisposing factors such as immunosuppressive agents, HIV infections, Cancer, steroid therapy, xerostomia, poor oral hygiene, antibiotics, a denture may develop the infection in the oral cavity (Ana pejcic 2015). Drugs like Broad-spectrum antibiotics, anticancer agents, corticosteroids, Oralcontraceptives(OCP), Clarithromycin, Atavoquone, conivaptan, arformoterol, (Abdollahi 2008, AnaPejcic 2015). Drug-induced oral thrush present in various forms includes acute atrophic candidiasis (antibiotic sore mouth), chronic atrophic candidiasis(dentures sore mouth) and acute pseudomembranous candidiasis (thrush). Nystatin suspension, clotrimazole troches are effective in treating oral candidiasis (Darrell 2005).

Drug Induced Angioedema

Angioedema is the common iatrogenic disorder characterized by the sudden occurrence of subcutaneous or submucosal swelling, rarely isolated Ulva swelling (Allan 2008). Angioedema may lead to life-threatening airway obstruction. The swelling is acute and transient, typically lasts for several hours, but may last for several days. Angioedema caused by the release of histamine or bradykinins with the contributions of other vasoactive substances (Allan 2008).The swellings occur in two forms: Allergic and Non-allergic. Drugs such as Penicillin, sulfa drugs, NSAIDs can cause allergic swelling due to the release of IgE mediated hypersensitivity reactions (Femiano 2008). Non-allergic swelling may occur after the intake of Angiotensin-Converting Enzyme (ACE) inhibitors, NSAID which is non-immune-mediated. 30% of the swelling is due to the ACE inhibitors prescriptions (Bernstein 2017).ACE also called Kinases II, is the primary activator of bradykinins, a potent vasodilator, and mediator of capillary leakage(Femiano 2008). Bradykinins are an inflammatory mediator. It activates nociception mediates the angioedema associated with an ACE inhibitor that prevents bradykinin destruction, thus the level increases (Allan 2017). ACE inhibitor-induced angioedema is prevalent in females, black individuals and patients >40 years of age (Bernstein 2017).other drugs such as NSAIDs (Aspirin, Indomethacin), angiotensin receptor blockers(ARB), barbiturates, calcium channel blockers, hydrochlorothiazides, antiplatelet agents such as thienopyridine and clopidogrel, statin drugs such as simvastatin, fluvastatin, atorvastatin and pravastatin associated with this side effects(Anna yuan 2015,Ana Pejcic 2015, Bernstein 2017). Antihistamines, glucocorticoids,C1-esterase inhibitor(C1-INH) concentrate is the drug of choice in some forms of angioedema, (Abdollahi 2008)

Drug Induced Angular Cheilitis

Angular Cheilitis is an erosive inflammatory disorder, affecting one or both angles of the mouth. It is characterized by dry lips, soreness, maceration, cracks, and ulceration. Causative factors are an oral infection and on infectious causes such as age factor, nutritional deficiency (iron, folic acid, Vitamin B complex), dental materials, cosmetic and hygiene products, excessive carbohydrate intake(Nirima 2017, Mahmoud 2018), drug-induced side effects may produce Cheilitis. It may also be associated with various mechanisms with xerostomia, perioral eczema, contact hypersensitivity reaction, primary hypervitaminosis (ColletE 2013, Ana pejcic 2015).

Certain drugs such as hydralazine, oral contraceptive, D-penicillamine alters vitamin metabolism. para-aminosalicylic acid, colestipol, cholestyramine interferes with Vitamin B12 absorption. Methotrexate, triamterene, phenobarbital, primidone changes the folic acid metabolism, causes nutritional deficiencies (RobertS 1988) by drugs associated with angular cheilitis. Other drugs include clofazimine, psoralens, statins, protease inhibitors, busulfan, tetracycline, isotretinoin(Abdollohi 2008) causes AC. Diagnosis varies upon clinical findings .good oral hygiene, discontinuation of causative drugs, topical use of combined antifungals, antibacterial, steroid ointment reduces the severity of the condition. Intraoral fungal infection should be treated with appropriate therapy (Eric 2013).

Drug Induced Oral Malodor

Bad breath or halitosis is a common problem of the general population affecting an individual's quality of life. It is considered to be the third most frequent reason; peoples seek treatment from dental clinicians following tooth decay and gum diseases (Ana pejcic 2015). It is caused by bacterial putrefaction which releases the volatile sulfur compounds thus promoting offensivebreath. Etiological factors are poor oral hygiene, oral infection, intake of certain foods (onion, garlic) systematic diseases (pancreatic, hepatic, nephrotic) diseases, trimethylaminuria, upper & lower RTI infection, and drugs. Halitosis is often associated with an abnormal taste in the mouth, tobacco use, alcohol consumption. Drugs inducing xerostomia may indirectly aggravate breath malodor. Drugs such as dimethyl sulphoxide or disulfiram, isosorbide dinitrate, directly responsible for bad breath. Management includes brushing or scraping the tongue to reduce the bacterial load, proper oral hygiene, adjunctive use of antiseptic agents (Francis 2008).

Drug Induced Oral Pigmentation

Oral pigmentation is a common condition involves any portion of the oral cavity. It is due to the consequence of etiological factors such as extrinsic and intrinsic agents, hyperplasia and iatrogenic causes. Extrinsic or local factors include smoking,

betel nut, tea, coffee, beetroot, beverages, drugs (Minocycline, doxycycline, co-amoxiclav, linezolid, bismuth subsalicylate, chlorhexidine, cetylpyridium, cocaine) (Abdollahi 2008, Manuel 2010). Intrinsic or Systemic cause may be due to Peutz-Jegher's syndrome, Addison's disease, racial pigmentation, pigmentary incontinence, amalgam tattoo, drugs (Clofazimine, cyclophosphamide, estrogen, amiodarone).Dental discoloration due to neoplastic processes such as macrocytic macules, oral nevi. Iatrogenic oral pigmentation produced by melanocytes due to excessive production of melanin (e.g. Smoker melanosis) (Najjar 2016).

The exact mechanism for drug-induced discoloration is uncertain and it resolves within weeks to months, when the influencing drug is ceased (Abdollahi 2008). Drugs such as tetracycline, zidovudine, anti-inflammatory drugs and anti-malarial agents such as quinine hydrochloride, chloroquine, hydroxyl chloroquine, and amodiaquine cause direct melanocytic stimulation associated with abnormal oral pigmentation (de Andrade 2017). Drug metabolites get accumulated in the mucosal tissues cause discoloration (e.g Oral contraceptives, phenothiazines such as chlorpromazine) (Abdollahi M 2008). Dark pigmented macular lesions of the tongue seen as a result of fixed-dose drug eruption following inhalation of heroin and methaqualone (Gondak RO 2012).

One of the broad-spectrum antibiotics, Tetracycline, highly profiled drug to cause tooth discoloration due to its ability to get distributed throughout the body tissues. It chelates with calcium ions in bones, teeth and subsequent incorporation into the dentin or enamel causes characteristic yellow-brownish discoloration. Tetracycline administration during the second or third trimester of pregnancy crosses the placental barrier and cause fetal tooth discoloration(Darell 2005).tetracycline and oxytetracycline produces yellow discoloration, whereas chlortetracycline cause gray-brown stains. Other agents such as Minocycline, which is a semisynthetic derivative of tetracycline used to treat acne. It binds with iron, forming insoluble complexes produces bluish-green discoloration in the oral mucosa and teeth (Stevens 2019)

Ciprofloxacin, a quinolone, given intravenously to infants to treat klebsiella infections produces green discoloration of the tooth. (Manuel 2010).Frequent use of chlorhexidine mouthwash causes yellow-brown staining of the tooth surface.
Black hairy tongue (Lingua villosa nigra) is an elongated filiform papilla on the dorsal surface of the tongue that produces black, brown, white, green, or pink discoloration. It may be due to chromogenic bacteria, foods, smoking, and drugs such as penicillin, erythromycin, doxycycline, neomycin, aureomycin, corticosteroids, sulfonamides, methyldopa associated with this condition(Gurvits 2014, Ana pejcic 2015). Treatment may be proper cleaning of the tooth surface, oral hygiene, use of keratolytic agents (Ana pejcic 2015).

Drug Induced Sialorrhoea

Ptyalism or Sialorrhea is characterized by increased saliva secretion due to parasympathetic stimulation. It is associated with neurologic disorders, emesis, menstruation, teething, oral infection and inflammation, food, nasogastric intubation, Wilson's disease, Angelman syndrome and idiopathic paroxysmal sialorrhea and medications (Abdollahi 2008, Boyce 2005). The drug induces hypersalivation includes antipsychotics, particularly clozapine, and direct and indirect anticholinergics which is used to treat dementia of the Alzheimer's disease and myasthenia gravis, heavy metal toxins, acetylcholinesterase inhibitors, yohimbine, nifedipine, rivastigmine, lithium, dimercaprol, mucosa irritating drugs(Freudrenrich 2005, Ana pejcic 2015). Behavioral modifications, speech therapy Anticholinergics (Phenothiazine, Belladonna) beta-blockers, Botox can be used to treat refractory cases (Abdollahi 2008).

Drug Induced Gingival Hemorrhage

Intraoral hemorrhage or gingival bleeding is a common drug-induced ill effect. It happens for many reasons such as traumatic injury, thrombocytopenia, rapid use of blood thinners, immunosuppression, gingival enlargement, xerostomia, alteration of oral flora and drugs. Drugs may be a direct or indirect cause to produce this condition (Ivan 2006). Use of oral antibiotics and steroids increases the number of Candida albicans which produce erythematous reaction leads to oral hemorrhage. Prolonged use of systemic antibiotics (chloramphenicol), reduces the intestinal flora's ability to synthesize vitamin K, thus cause potential gingival bleeding. Drugs such as thiazide diuretics, allopurinol, methyldopa, antineoplastic agents, coumarin, gold salts, heparin, phenytoin, penicillin, tetracycline, increases the propensity of oral bleeding. (Ivan 2006). Xerostomia, gingival enlargement increases the chance of periodontal infection cause gum bleeding. The use of immunosuppressive agents such as methotrexate causes aplastic anemia, thrombocytopenia and agranulocytosis result in oral bleeding. Intake of multiple drugs common in elderly individuals, sometimes cause gingival bleeding due to synergistic effects of drugs combined drugs (NASID & warfarin).

Treatment measures such as thorough examination for platelet count, complete drugs and medical history of the patient have to be conducted. Refer to dentist and physician should be considered to discontinue the offending drug

CONCLUSION

Adverse drug reactions of the oral cavity are common and often unnoticed which affects the patient's quality of life. Most of the drugs cause these dose-dependent reactions, causes moderate to severe reactions that can be withdrawn if the dose is minimized. Clinicians should update their knowledge on the ever-evolving field of drugs and their manifestations of adverse drug reactions encountered in their practice. Health care providers should aware of the consequences of adverse drug events, preventive and safety measures that can be implemented before patients to avoid severe and life-threatening complications.

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