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The Effect of Drugs in the Oral Cavity - A Review

Trophimus Gnanabagyan Jayakaran

Saveetha Dental College and Hospitals,
Saveetha University,
Chennai, India

Abstract:

It is estimated that more than 2-4% of hospital admissions are related to drug induced reactions. There is an ever expanding list of medications linked to pathologic reactions in the oral and perioral region. Several patterns of diseases have been identified, and these can assist the clinician in determining a possible cause and effect relationship with a particular or a group of drugs. The mechanism of drug induced reaction is not always known or not always predictable since aspects other than pharmacodynamics and/or pharmacokinetics, as well as various interacting variables contribute to the final outcome. Drug induced oral reactions clinically present as Xerostomia, Swelling, Dysguesia, Nonspecific Ulceration, Vesiculobullous or ulcerative mucositis, pigmentation of mucosa, Gingival enlargement, oral malodor, taste alterations, discoloration of teeth. This review gives an update of the various drug induced oral reactions, so that Dentists and oral health professionals increase their knowledge for a better diagnosis and therapy.

Key Words: Adverse drug reactions, Oral reactions, Oral manifestations, Mucosal lesions, Drug pharmacodyanamics,

INTRODUCTION:

Several systemic factors are known to contribute to oral diseases or conditions and among those are the intake of drugs. An adverse drug reaction is defined by WHO as 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, therapy of diseases or for the modification of physiological function'. [1]. Fortunately several patterns of diseases have been identified and these can assist the clinician in determining a possible cause and effect relationship with a particular medication or a group of medications. The clinical patterns of drug induced oral reactions include. Considering the ageing of the population and widespread and increased use of presciptions, over the counter drugs and herbal remedies, dentists can expect to encounter oral side effects among their patients due to the usage of these medications. Since many patients take prescriptions and nonprescription medications, dentists should take a thorough medical history and be aware of medication related problems and their potential effects on diagnosis and treatment planning [2-4].

SALIVARY GLAND DISORDERS:

Salivary gland function can be affected by a variety of drugs that can produce xerostomia, ptyalism, Salivary gland pain and discolouration of saliva.

A] XEROSTOMIA:

Dryness of mouth or Xerostomia, results from diminished secretions of saliva and a decrease in salivary calcium phosphate concentration. More than 250 medications claim xerostomia as a side effect. Few of the drugs are, anticholinergics, antidepressants, anti-Parkinson's drugs, antihistamines, antipsychotics, diuretics, hypnotics, systemic bronchodilators, muscle relaxants, methyldopa, laxatives, betablockers, narcotics, guanabenz, and clonidine. Furthermore the possibility of an underlying autoimmune etiology(eg. Sjogren Syndrome) should also be considered in Xerostomic patients, especially those who also present with Xerophthalmia or evidence of parotid gland swelling. Common oral manifestations resulting from decreased salivary flow include increased dental caries, fungal infections, bacterial infections, aphthous lesions, and dysphagia. Pilocarpine and Bethanechol have been suggested to be of potential use in the management of drug induced Xerostomia [5]. Drugs with potential to cause xerostomia are shown in Table 1.

B] PTYALISM:

Ptyalism or sialorrhoea , is the condition of increased salivary flow, and it is uncommon. Salivary hypersecretion is usually caused by physiological factors such as menstruation or early pregnancy, local factors such as teething, oral inflammatory lesions, food, medication, or by nasogastric intubation.[6]. Sialorrhoea is also caused by certain heavy metal toxins (mercury and thallium),from exposure to irreversible acetylcholinesterase inhibitors (insecticides and nerve agents) and by a few other drugs such as yohimbine, mucosa irritanting antibiotics.[7]. Drugs causing ptyalism are listed in Table 2.

C] SALIVARY GLAND PAIN:

Antihypertensives, anti-thyroid agents, chlorhexidine, cytotoxics, ganglion-blocking agents, iodides, phenothiazines, and sulphonamides may cause salivary gland pain, as may drugs causing dry mouth.[8]. Salivary gland pain is rarely associated with guanethidine or guanacline. Drugs causing salivary gland pain and swelling are listed in Table 3

Table 1: Drugs Causing Xerostomia. [30,34,43-45].

- Alizapride
- Ambroxol
- Amphetamines
- Antihistamines
- Antimigrain agents
- Antineoplastics
- Antiparkinson drugs
- Atropine
- Benzodiazepines
- Beta blockers
- Bladonna alkaloids
- Botulinum toxin-A
- Bupropion
- Cadmium
- Calcium channel blockers
- Ciprofloxacin
- Clidinium
- Clozapine
- Cyclobezaprine
- Cyclopentolate
- Cyclosporine
- Cytokines
- Dexmedetomidine
- Ephedrine
- Fenfluramine
- Gentamycin
- Glycopyrolate
- Guanabenz
- Guanfacine
- Hyoscine
- Insulin
- Ipratropium
- Isotretinoin
- Ketanserin
- Ketotifen
- L-dopa
- Lead
- Lithium
- Lubiprostone
- Mazindol
- Methdilazine
- Modafinil
- Molindone
- Nabilone
- Nefazodone
- Nefopam
- Nicotine
- Nitric oxide inhibitors
- Ofloxacin
- Olanzapine
- Ondansetron
- Opioids
- Orphenadrine
- Oxybutynin
- Paricalcitol
- Phenothiazines
- Phenylpropanolamine
- Posaconazole
- Pregabalin
- Propantheline
- Proton pump inhibitors
- Radioiodine
- Reboxetine
- Selegiline
- Sertraline
- Sibutramine
- Solifenacin
- Sotalol
- Spiramycin
- Sucralfate
- Tadalafil
- Tamsulosin
- Tadalafil
- Terazosin
- Terodiline
- Thiabendazole
- Thioridazine
- Tiamenidine
- Tiapride
- Tiotropium
- Tizamidine
- Tolterodine
- Tramadol
- Tranylcypromine
- Trazodone
- Trepium chloride
- Triamterene
- Trimipramine
- Tropicamide
- Trospium
- Venlafaxine
- Viloxazine
- Vigabatrin
- Zuclopenthixol
- Zopiclone

Table 2: Drugs Causing Ptyalism.[30,34,43-45].

- Alprazolam
- Ambroxol
- Amiodarone
- Bethanechol
- Buprenorphine
- Buspirone
- Clozapine
- Desfluorane
- Diazoxide
- Digoxin
- Ethoinamide
- Edrophonium
- Galantamine
- Gentamycin
- Guanethidine
- Haloperidol
- Imipenem/cilastatin
- Iodides
- Kanamycin
- Ketamine
- Lamotrigine
- Levodopa
- Mefenamic acid
- Mercurial salts
- Modafinil
- Neostigmine
- Nicardipine
- Niridazole
- Nitrazepam
- Ofanzapine
- Organophosphates
- Pentoxifylline
- Physostigmine
- Pilocarpine
- Remoxipride
- Risperidone
- Rivestigmine
- Sildenafil
- Succinylchloride
- Tacrine
- Theophylline
- Tobramycin
- Venlafaxine
- Zaleplon
- Zonisamide

Table 3: Drugs Causing Salivary Gland Swelling and Pain.[30,34,43-45].

- Bethanidine
- Bretylium
- Catecholamine inhalation
- Cimetidine
- Clonidine
- Clozapine
- Deoxycycline
- Famotidine
- Guanethidine
- Iodine
- Insulin
- Interferon
- Isoprenaline
- Methyldopa
- Naproxen
- Nifedipine
- Nitrofurantoin
- Oxyphenylbutazone
- Phenylbutazone
- Phenytoin
- Ranitidine
- Ritodrine
- Sulofonamides
- Trimepramine
- Warfarin

D] DISCOLORATION OF SALIVA:

Discoloration of saliva and other body fluids into red or orange colour may be seen in patients treated with clofazimine, levodopa, rifampicin, and rifabutin therapy.[9].

ORAL ULCERATION:

Ulceration is a breach in the oral epithelium, which typically exposes nerve endings in the underlying lamina propria, resulting in pain or soreness especially when eating spicy foods or citrus fruits. Oral Ulcers are Inflammatory lesions of the oral mucosa that affect approximately 20% of the

population.[10]. Numerous causes of these ulcers include, immunological alterations, infections, nutritional deficiencies, repetitive trauma to the mucosa, food and contact allergies, autoimmune diseases and neoplasms, as well as psychosomatic, genetic and environmental factors.[11]. Drugs with potential to cause oral ulceration are shown in Table 4.

Table 4: Drugs Causing Oral ulceration. [17,37,46].

• Anti HIV drugs	• Imipramine
• Antineoplastics	• Indomethacin
• Alendronate	• Interferons
• Allopurinol	• Interleukin-2
• Alprazolam	• Isoprenaline
• Asprin	• Ketorolac
• Atrovastatin	• Lamotrigine
• Aurothiomalate	• Levamisole
• Azathiopurine	• Lithium
• Aztreonam	• Losartan
• Barbiturates	• Mesalamine
• Captopril	• Methimazole
• Carbamazepine	• Methotrexate
• Chlorambucil	• Metronidazole
• Chloramphenicol	• Mitomycin
• Choloroquine	• Naproxen
• Chlorpromazine	• Nicorandil
• Clarithromycin	• NSAIDs
• Clofibrate	• Olanzapines
• Clonazepam	• Pancreatin
• Codeine	• Penicillamine
• Cyclosporine	• Penicillins
• Diclofenac	• Phenylbutazone
• Dideoxycytidine	• Phenytoin
• Emepromium	• Potassium chloride
• Enalapril	• Proguanil
• Erythromycin	• Promethazine
• Fluconazole	• Propranolol
• Fluoxetine	• Quinidine
• Ganciclovir	• Streptomycin
• Gefitinib	• Sulindac
• Gold Compounds	• Terbutaline
• Hydralazine	• Tetracycline
• Hydroxyurea	• Vancomycin
• Ibuprofen	• Venlafaxine
• Imatinib	• Warfarin

A].NONSPECIFIC ULCERATION:

Oral Ulceration may be caused as a result of direct application of over the counter drugs like asprin, hydrogen peroxide, potassium tablets, and phenol containing compounds. The affected mucosa appears whitish and corrugated, with erosion and ulceration of the more severely damaged areas.[12].

B]. APHTHOUS ULCERATION:

Ulcers resembling recurrent aphthous stomatitis but have systemic causes are often termed Aphthous like ulcers. Examples include Behcet's syndrome, gastrointestinal diseases, such as gluten-sensitive enteropathy or inflammatory bowel disease, immunodeficiency syndromes such as infection with HIV, cyclic neutropenia and adverse reactions to medications.[13-15]. A number of drug are implicated in the development of nonspecific ulceration and oral mucositis, and the lesions are often associated with an equally nonspecific histologic appearance at biopsy. These include barbiturates, beta-blockers, dapsone, NSAIDs, phenazone derivatives, thiazide derivatives, phenolphthalein, sulfonamides, tetracyclines, and sirolimus.[16]. Ulceration of the mucosa is a common adverse effect of a wide variety of antineoplastic agents, including methotrexate, 5-fluoroucil, doxorubicin and melphalan.

C].FIXED DRUG ERUPTIONS:

Fixed drug eruptions in the oral cavity often initially appear as areas of edema and erythema that lead to the localized, nonspecific ulceration. The labial mucosa is most commonly involved, and a clinical course of recurrence at the same site after drug use is diagnostically helpful, but this relationship is not always easy to establish. A number of drugs are implicated in the development of nonspecific ulceration and oral mucositis, and the lesions are often associated with an equally nonspecific histologic appearance at biopsy. These include barbiturates, beta-blockers, dapsone, NSAIDs, phenazone derivatives, thiazide derivatives, phenolphthalein, sulfonamides, and tetracyclines.[17].

D]. MUCOSITIS:

Chemotherapy regimens play a vital role in Oral mucositis and ulceration, particularly those involving methotrexate, 5-fluorouracil, doxorubicine, melphelan, mercaptopurine, or bleomycin.[18]. Widespread sloughing and ulceration arise within days of commencement of therapy, the associated pain often requiring opioid therapy and/or alteration or cessation of chemotherapy. The ulceration may be a portal of entry for infection and hence a potential cause of septicemia.

E]. PEMPHIGOID LIKE REACTIONS:

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 ulceration. 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.[19]. The oral mucosa is frequently affected in drug induced pemphigoid, particularly penicillamine-induced disease, and can be the only affected mucosal surface, although patients often also have cutaneous lesions.

F]. PEMPHIGUS:

Pemphigus like reactions can have features of either Pemphigus vulgaris or Pemphigus foliaceous, although

pemphigus foliaceous is uncommon in the oral cavity. Traditionally, drugs that are capable of inducing pemphigus are divided into two main groups according to their chemical structure—drugs containing a sulfhydryl radical (thiol drugs or SH drugs) and non-thiol.[20]. Pemphigus vulgaris may occasionally be associated with drugs with active thiol groups in the molecule. Drugs implicated include penicillamine, phenol drugs , rifampicin, diclofenac , and other ACE-inhibitors.[21].

G]. ERYTHEMA MULTIFORMAE:

As with idiopathic or virally induced cases(Herpes simplex virus), the disease has a rapid onset with a variable expression that can range from lesions limited to the oral mucosa with widespread mucocutaneous involvement. Drug induced EM is frequently linked to agents such as barbiturates, cephalosporins, NSAIDs, estrogens, phenothiazines, progestogens, protease inhibitors, sulphonamides, sulphonylurea derivatives, and tetracyclines—may give rise to erythema multiforme, and it may be clinically impossible to distinguish drug-induced erythema multiforme from disease due to other causes.[22]. The distinction of severe erythema multiforme from toxic epidermal necrolysis is quite unclear.

H]. LUPOID REACTIONS:

Systemic lupus erythematosus (SLE) may be induced by a wide variety of different drugs. Indeed, over 70 agents have been implicated in causing drug-induced lupus.[23]. The most commonly implicated agents of drug-induced SLE are procainamide and hydralazine, although drugs less commonly associated include chlorpromazine, isoniazid, methyldopa, penicillamine, and quinine, as well as whole groups of drugs such as anticonvulsants, beta-blockers, sulphonamides,[24]. and others.

ORAL MALODOR:

Oral Malodor or Halitosis is offensive breath resulting from poor oral hygiene, dental or oral infections, ingestion of certain foods, use of tobacco, and some systemic disease and medications. Drugs causing xerostomia, may indirectly cause or aggrave this problem, but other drugs, such as isosorbide dinitrate, dimethyl sulphoxide, or disulfiram, can be directly responsible for malodor.[17]. Drugs causing oral malodor are shown in Table 5.

Table 5: Drugs causing Oral Malodor.[37,47].

- Chloral hydrate
- Cytotoxic drugs
- Dimethyl sulphoxide
- Disulfiram
- Nitrates and nitrites
- Succimer

WHITE LESIONS:

A]. LICHENOID ERUPTIONS:

Lichen planus is a chronic systemic disease of the established immune mediated pathogenesis. Oral lichen planus is usually a persistent disorder and may persist for many years despite several treatment strategies. Some drugs can induce oral disorders resembling lichen planus and are said to be oral lichenoid drug reactions. Oral lichenoid reactions are uncommon and these reactions disappear after drug withdrawal.[25,26]. A characteristic white lace pattern may be seen. The drugs now most commonly implicated in lichenoid reactions are the non-steroidal anti-inflammatory drugs and the angiotensin-converting enzyme inhibitors. Lichenoid reactions also may follow the use of HIV protease inhibitors , antihypertensive agents, antimalarials, phenothiazines, sulphonamides, tetracyclines, thiazide diuretics,[27] and many others. Drugs with potential to cause oral lichenoid eruptions are listed in Table 6.

Table 6: Drugs Causing Oral Lichenoid Reactions. [17,37,48].

- ACE inhibitors
- Allopurinol
- Amiphenazole
- Angiotensin converting enzyme inhibitors
- Antimalarials
- Arsenical compounds
- Barbiturates
- BCG vaccine
- Carbamazepine
- Carbimazole
- Chloroquine
- Chlorpropamide
- Cholera vaccine
- Clofibrate
- Colchicine
- Dapsone
- Dipyridamole
- Ethionamide
- Flunarizine
- Gaunoclor
- Gold compounds
- Griseofulvin
- Hepatitis B vaccine
- Hydroxychloroquine
- Ketoconazole
- Lithium carbonate
- Lorazepam
- Mepacrine
- Mercury (Amalgam)
- Metformin
- Methyldopa
- Metronidazole
- NSAIDs
- Penicillins
- Phenytoin
- Piroxicam
- Propranolol
- Quinidine
- Rifampicin
- Streptomycin
- Sulphonamides
- Tetracyclines
- Thalidomide
- Thiazides
- Tolbutamide
- Triprolidine

B].ORAL CANDIDIASIS:

Candidiasis is the most common opportunistic infection seen in dental practices. Patients usually present with creamy, white plaques on the tongue and buccal mucosa, it when scraped leave a red, painful ulcerated surface exposed. Pseudomembranous candidosis arises secondary to therapy with broad-spectrum antibiotics, corticosteroids - systemic and inhaler preparations, and other immunosuppressive regimens (e.g., ciclosporin) and cytotoxic therapy.[28].

C]. BLACK HAIRY TONGUE (Lingua villosa nigra)

This condition is presented with an elongation of the filliform papillae of the tongue to form hair like over growth which becomes stained brown or black due to the proliferation of

chromogenic microorganisms. Black hairy tongue can be seen with the administration of oral antibiotics, poor oral hygiene and excessive smoking in adults.[17]. Drugs causing black hairy tongue are listed in Table 7.

Table 7: Drugs and Chemicals Causing Black Hairy Tongue. [17,37,49].

• Amitriptyline	• Maprotilline
• Benztropine	• Nortriptyline
• Cephalosporines	• Olanzapine
• Chloramphenicol	• Penicillins
• Clarithromycin	• Sodium perborate
• Clomipramine	• Sodium peroxide
• Clonazepam	• Streptomycin
• Corticosteroids	• Sulfonamides
• Desipramine	• Tobacco
• Fluoxetine	• Tetracycline
• Griseofulvin	• Thiothixene
• Imipramine	• Tranylcypromine
• Lansoprazole	• Vegetable dyes
• Methyldopa	

Table 8: Drugs Causing Gingival Hyperplasia. [4,17,37].

• Amlodipine	• Lithium
• Bepridil	• Mephenytoin
• Cannabis	• Nifedipine
• Cotrimoxazole	• Nitrendipine
• Cyclosporine	• Oral contraceptives
• Diltiazem	• Phenytoin
• Erythromycin	• Phenobarbitone
• Ethosuximide	• Primidone
• Ethotoin	• Sertraline
• Felodipine	• Sodium valproate
• Flunarizine	• Topiramate
• Interferon alpha	• Verapamil
• Ketoconazole	• Vigabatrin
• Lamotrigene	

TASTE ALTERATIONS:

Individuals taking any variety of medications may present with subjective complaints of taste changes. Many classes of drus are associated with taste alteration, which manifests as hypoguesia (decreased taste), dysguesia (distortion of the correct taste), paraguesia (bad taste), aguesia (no taste).[29].

ACE inhibitors, anti-thyroids, beta-lactam antibiotics, biguanides, chlorhexidine, opiates, and protease inhibitors are particularly implicated. Up to 4% of patients treated with ACE inhibitors may have dysgeusia, although this adverse effect is self-limiting and reversible within a few months, even with continued therapy. Newer therapies—such as the anti-HIV protease inhibitors, therapy with tripotassium dicitrato bismuthate chelate, clarithromycin, and lansoprazole therapy for H. pylori infection, terbinafine, intravenous pentamidine , and isotretinoin.[30]. Reduction of the offending drug can improve the taste. Drugs with potential to cause aguesia and dysguesia are listed in Table 9 and 10.

Table 9: Drugs Causing Ageusia. [17,37,50,51].

• Acarbose	• Fluvoxamine
• Acetazolamide	• Indomethacin
• Amitriptyline	• isotretinoin
• Angiotensin II receptor antagonist	• Levodopa
• Asprin	• Methimazole
• Atrovastatin	• Penicilliamine
• Captopril	• Pentamidine
• Ceftirizine	• Phenytoin
• Cisplatin	• Propantheline
• Clidinium	• Propylthiouracil
• Clopidogrel	• Rifabutin
• Cocaine	• Ritonavir
• Diazoxide	• Rivastigmine
• Dicyclomine	• Spironolactone
• Enalapril	• Sulfadoxine
• Etridonate	• Terbinafine topiramate
• fluoxetine	• Venlafaxine

Table 10: Drugs Causing Dysgeusia. [17,37,52,53].

• ACE inhibitors	• Lignocaine
• Acetaminophen	• Maprotilline
• Alendronate	• Methocarbamol
• Allopurinol	• Metoprolol
• Alprazolam	• Minoxidil
• Amiloride	• Mupirocin
• Amiodarone	• Nedocromil
• Amlodipine	• Nitroglycerine
• Asprin	• Nylidrin
• Auranofin	• omidazole
• Baclofen	• Palifermin
• Beclomethazone	• Phenytoin
• Bleomycin	• Pilocarpine
• Busulfan	• Propafenone
• Calcitonin	• Protirelin
• Cimetidine	• Quinidine
• Ciprofloxacin	• Ranitidine
• Clomipramine	• Ribavirin
• Cotrimazole	• Risperidone
• Dantrolene	• Selegiline
• Fentanyl	• Sunitinib
• Fluvastatin	• Tacrine
• Gadobenate	• Tamoxifen
• Gancyclovir	• Tegafur
• Glyburide	• Terbinafine
• Gold compounds	• Tiagabin
• Imipramine	• Tolazamide
• Indinavir	• Tramadol
• Ketorolac	• Ursodiol
• Levodopa	• Vinblastine

MUCOSAL PIGMENTATION:

Oral discoloration may be superficial due to extrinsic or deep due to intrinsic causes.

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

- Use of tobacco or betel nut
- Consumption of colored foods or beverages
- Use of drugs (such as chlorhexidine, iron salts, cocaine, minocycline, bismuth subsalicylate and lansoprazole)

The primary causes of intrinsic mucosal hyperpigmentation include: [31]

- Amalgam or other tattoo
- Nevus
- Melanotic macule
- Peutz-jegher's syndrome
- Racial pigmentation
- Drugs such as antimalarials and oral contraceptives
- Addison's disease
- Pregnancy

Pigmented lesions of the tongue(dark macular patches) are reported to occur in heroin addicts who inhale the smoke.[32]. Drugs causing oral mucosal pigmentation along with the color and site are listed in Table 11.

Table 11: Drugs Causing Oral Mucosal Pigmentation.[17].

Drug/Chemical	Colour	Site
Amalgam	Gray	Gingiva
Aminopyrine	Brown	Tongue
Amodiaquine	Blue-gray/black	Palate
Arsenic	Brown	Tongue
Asprin	White	Mucosa
Bismuth	Blue-gray/blue-black	Gum lines/tongue
Busulfan	Brown	Mucosa
Chlorhexidine	White/brown	Tongue
Chloroquine	Blue-gray	Palate,gingiva,lip
Copper salts	Blue-green	Gum lines
Doxorubicin	Dark/Brown	Mucosa/Tongue
Gold	Purple	Gingiva
Heroin inhalation	Dark Macular Patch	Tongue
Lansoprazole	Yellow	Tongue
Lead	Blue-gray/Blue	Gum lines/Tongue
Mepacrine	Yellow	Mucosa
Mercury	Blue-gray/Blue-Black	Gum line/Mucosa
Methyldopa	Dark	Tongue
Phenolphthalein	Brown	Tongue
Phenothiazines	Blue-Gray	Mucosa
Quinacrine	Gray/Brown	Palate/Tongue
Quinidine	Blue-black	Palate
Silver salts	Gray	Gingiva
Thallium	Blue-gray	Gumlines
Tin	Dark	Mucosa
Tobacco	Hazy gray brown	Mucosa
Vanadium	Green	Tongue
Zidovudine	Dark	Soft Palate,Gingiva,lips,tongue

TEETH DISCOLORATION:

Tetracycline and minocycline are antimicrobial agents causing the teeth to stain. Systemic ingestion of tetracycline causes irreversible staining in developing teeth and bones. The cervical third is most affected and staining is directly proportional to the age at drug exposure, dosage and duration of therapy.[33].Minocycline, unlike tetracycline staining occurs after the teeth are fully developed and erupted. Minocycline penetrates easily into both soft and calcified tissues. Pigmentation is produced by incorporation of the drug from the pulp into the dentin and enamel. Oxidation from the saliva and gingival crevicular fluid produces a blue-gray staining in the middle and incisal thirds of the teeth. Minocycline staining is irreversible.[34,35]. Metals, such as lead or mercury, or drugs that contain metals, such as gold salts, produce pigmentation changes along the gingival margin. These colour changes may resolve following discontinuation of the drug, but may be permanent.[36]. Drugs causing teeth discoloration along with the color are listed in Table 12

Table 12: Drugs And Chemicals Causing Tooth Discoloration. [17,43]

Drugs/Chemicals	Color
Betel leaves (areca)	Red to black
Cadmium	Yellow ring
Cayenne	Black
Chlorhexidine	Yellow-brown
Chlortetracycline	Gray-brown
Ciprofloxacin	Green
Co-amoxiclav	Yellow or gray brown
Copper salts	Green
Doxycyclin	Yellow
Essential oils	Yellow brown
Fluoride	White brown
Iron salts (liquid)	Black
Isoproterenol	Chalky white
Minocycline	Gray black
Oxytetracycline	Yellow
Potassium permanganate	Violet to black
Silver nitrate	Gray
Tannins (coffee,Tea)	Brown
Tetracycline	Yellow
Tobacco	Yellow-brown
Tooth paste with stannous fluoride	Black or green
White wine	Black

POSTMORTEM PINK-RED COLORATION:

Tooth coloration of this type is due to hemolysis and exudation of hemoglobin to the dental pulp which is enhanced in the presence of moisture and increased venous pressure. Specific conditions of death associated with this phenomenon include drowning, aspiration, pneumonitis, and suffocation. Overdose with barbiturates, dichloralphenazon, and carbon monoxide also present with similar findings.[37].

SWELLINGS:

A] GINGIVAL HYPERPLASIA:

Gingival Hyperplasia is a known side effect associated with the anticonvulsant phenytoin, the immunosuppressant

cyclosporine, and the calcium channel blockers used for hypertension and angina. Drug induced gingival enlargement can be localized or generalized and varies with degree of severity. Enlargement typically affects the labial tissues and begins in the interdental papillae. Severity is directly proportional to the patients oral hygiene. The enlarged gingiva appears fibrotic and the patient often develops an overlying inflammation, as hyperplastic tissues can be difficult to keep clean.[38,39]. Drugs which have the potential to cause gingival hyperplasia are listed in Table 8.

B] MUCOSAL SWELLING:

Drugs are the most common cause of urticarial reactions in adults affecting approximately 15-20% of young adults. Urticaria is a vascular reaction in the superficial layers of the skin, characterized by local edema and increased capillary permeability with wheals (hives), often accompanied by severe itching. When this swelling occurs in either the subcutaneous or submucosal tissues, the condition is known as angioedema. Drugs like penicillins, local anesthetic agents, cephalosporin derivatives, angiotensin-converting enzyme inhibitors, aspirin, and barbiturates—may give rise to angio-edema.[40]. Hypersensitivity to latex is an increasing problem in oral health care and may cause rapid-onset angio-edema in susceptible patients.

Topical anaesthetic agents, dental local anaesthetics, and drugs are associated with type-I hypersensitivity reactions. This type of allergic reaction has a rapid onset, with oral lesions developing, in and around the oral cavity, with urticarial swelling or angioedema of the lips, tongue and oral mucosa.[41].

CONCLUSION:

Numerous Drugs have the capability to cause adverse effects in the oral cavity. Drugs have the potential to cause conditions such as salivary gland disease, oral ulceration, taste alterations, discoloration of teeth, mucosal pigmentation, white lesions, swellings and oral malodor. These side effects interfere with the patient function and increase risk of infection, pain and possible tooth loss. It has been reported that the most common side effects of drugs are xerostomia, Altered taste and stomatitis.[42]. It is imperative that health professionals understand the complications that medications can have on the oral health of their patients. In order to properly diagnose and treat patients, a complete medical history including prescription medications, over the counter drugs and dietary supplements must be recorded which will enable the healthcare team to identify the causative agents.

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