Adverse Oral and Dental Effects of Medications

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Learning Objectives:

1. Discuss the various categories of adverse dental and oral effects of medications.
2. Provide specific examples of drugs that are associated with corresponding oral and dental side effects.
3. Describe the mechanisms by which drug-induced adverse dental and oral effects arise.
4. Discuss the role of the pharmacist in limiting the incidence and/or severity of adverse dental and oral effects of medication.

INTRODUCTION

Numerous drugs can adversely affect the oral cavity and dentition. Patients who develop oral problems will seek help and treatment from their dentist, pharmacist, or prescribing physician. These clinicians must work in collaboration in order to reverse or resolve the patient's condition. It may be necessary to discontinue an agent if the oral effects are severe enough. While adverse effects to medications can affect anyone, it is important to recognize that elderly patients, or those with nutritional deficiencies, may be at increased risk for developing iatrogenic oral problems. Patients older than sixty-five years of age, are often on multiple chronic medications in order to manage a number of medical conditions, such as diabetes mellitus, arthritis, congestive heart failure, and hypertension.

In order for the physician, pharmacist or dentist to properly assess and manage a patient, a complete medication history must be conducted. It is imperative inquires be made not only about prescription medications, but also over-the-counter (OTC) and herbal medication use. Drugs have the potential to affect the oral cavity in a number of ways and this continuing education lesson will specifically reflect on eight conditions. The conditions addressed herein include: xerostomia, intraoral hemorrhage, candidia albicans (oral thrush), gingival hyperplasia, taste changes, tooth discoloration, stomatitis, and ulceration or necrosis. Table 1 provides an overview of common medications and the associated dental or oral side effect. It is important that healthcare professionals

understand the impact and severity that medications can have on the oral health of their patients.

Xerostomia (dry mouth)

Dryness of the mouth, or xerostomia, results from diminished secretions of saliva. More than two 250 medications claim xerostomia as a side effect. Drugs that produce xerostomia as a side effect include anticholinergics, antidepressants, anti-Parkinson's drugs, antihistamines/decongestants, urinary antispastics, antipsychotics, diuretics, hypnotics, systemic bronchodilators, muscle relaxants, reserpine, methyldopa, laxatives, beta-blockers, narcotics, guanabenz, and clonidine. A more comprehensive listing of drugs associated with dry mouth is shown in Table 2. Medications that produce xerostomia, also may increase the incidence of root surface caries (cavities). Medications with significant anticholinergic activity, such as oxybutynin, hyoscyamine, and scopolamine (Table 2), have the potential to cause xerostomia.

Xerostomia is a common complaint of numerous dental patients, especially the elderly patients who take some of these medications on a regular basis for a prolonged period of time. In the absence of medication use in a patient with xerostomia, the dentist is also positioned to screen for medical disorders associated with dry mouth, such as diabetes mellitus. An in-depth review of the patient's medication history should be conducted. Furthermore, a complete history and physical exam, and lab testing may be necessary to properly diagnosis and treat xerostomia. Upon examination patients with

xerostomia may complain of generalized mouth soreness, dry mouth, painful or burning tongue, reduced denture retention, taste changes, difficulty in chewing, and problems with talking and swallowing. Clinical presentation of xerostomia includes oral fissuring, ulceration, and epithelial atrophy. Xerostomia is managed symptomatically by increasing the patient's water intake, using saliva substitutes, and oral lubricants. Saliva stimulation is a way to manage xerostomia. The patient can be instructed to suck on grape or lemon sugarless gum or candies in order to increase saliva. It is known that the flow of saliva occurs during eating, so another way to increase saliva stimulation is by increasing the frequency of eating more small meals. Finally, agents such as citric acid, neostigmine, and cholinergic agents such as pilocarpine and bethanecol can also be used to stimulate the flow of saliva.

Intraoral Hemorrhage

Intraoral hemorrhage is another condition which can be drug-induced. Intraoral hemorrhage can be associated with numerous factors such as thrombocytopenia, defective vascular integrity, or alterations in coagulation. A majority of bleeding episodes occur as a result of a decrease in the number of platelets or thrombocytopenia. Numerous agents have been implicated to cause thrombocytopenia including sulfonamides, quinine, quinidine, thiazide diuretics, allopurinol, methyldopa, antineoplastic agents, digitalis, heparin, phenytoin, coumadin, and gold salts. Numerous antibiotics such as cephalosporins, penicillin, and tetracyclines have also been associated with intraoral hemorrhage.

Certain patients are at increased risk for developing intraoral hemorrhage. Patients who have cardiovascular disease and are on long term aspirin therapy should be anticipated to have a reduction in platelet aggregation. Also patients who are on long term antibiotic therapy may have a reduction in synthesized vitamin K. Vitamin K is necessary for the production of clotting factors II, VII, IX, and X. Antibiotics reduce the intestinal flora's ability to synthesize vitamin K, which could cause potential oral hemorrhage problems with prolonged use. Alcohol also has the propensity to reduce platelet lifespan, which can lead to bleeding problems. Many patients may be stabilized on warfarin prophylaxis or for treatment of venous thrombosis, pulmonary embolism, and thromboembolic disorders. Since warfarin interferes with hepatic synthesis of vitamin K dependent clotting factors, the international normalized ratio (INR) and prothrombin time time (PT) must be closely monitored, especially in patients with perioral hemorrhage.

Thrombocytopenia clinically may present as petechiae, which are small round flat dark-red spots caused by bleeding beneath the mucous membranes. The petichiae in the mouth are most commonly found as very tiny bleeding points in the palatel mucosa. In order to diagnosis drug induced thrombocytopenia, a platelet count, and medication history need to be conducted. To resolve the thrombocytopenia the dentist or pharmacist may need to contact the prescribing physician in order to discontinue the offending medication.

Dysguesia (taste changes)

Individuals taking any variety of medications may present with subjective complaints of taste changes. Patients may have complaints of a bitter, metallic, unpleasant or altered taste, “medication” taste, complete loss of taste, and decreased taste sensation. There are more than 200 drugs in the that have the potential to cause changes in taste sensations. Numerous drugs can cause taste changes including clarithromycin, captopril, enalapril, griseofulvin, penicillamine, metronidazole, carbenicillin, chlorhexidine, diltiazem, chloral hydrate, gold salts, flecanide, lithium, vitamin D, and sulfasalazine. The most common complaint by patients taking medications is a sense of altered taste.

The mechanisms by which drugs affect the taste sensations vary. Researchers propose three mechanisms involved in medication taste disorders. First, there is the influence of saliva on taste, i.e. the drug itself may be secreted into the saliva, producing dyguesia. Another potential mechanism is the effect of drug metabolite which could possibly interact with taste buds or saliva. Finally, drugs may directly damage the taste buds. There may be age-related effects on taste that can enhance medication taste disorders. The dentist will likely do a complete medication history in patients that present with complaints of taste changes. Once the offending agent has been identified, patients are usually relieved just to know that the medication is the cause of the alteration in taste perception. Fortunately, many medications that cause taste disturbances, such as antibiotics, are only prescribed for a limited time period. However, some individuals may present with severe symptoms and may require a change in their chronic drug therapy (e.g. captopril).

Oral Candidiasis (thrush)

Candidiasis is the most common oral opportunistic infection seen in dental practices. Patients usually present with creamy, white plaques on the tongue and buccal mucosa. When scraped the lesions leave a red, painful ulcerated surface exposed. Immunocompromised patients such as AIDS and cancer patients may be more susceptible to oral infections since they have defects in cell-mediated immunity. Immunosuppressed patients are more likely to develop complications from candidiasis, such as infection in the esophagus, ulcerations, mucosa perforation and invasive disease. Therefore, candidiasis has the capability to become life threatening in some immunocompromised patients.

Drugs either act locally or systemically to predispose patients to superinfection with *Candida albicans*. Broad spectrum antibiotics, antineoplastic agents (cancer chemotherapy), corticosteroids (including metered-dose inhalers), and immunosuppressive agents used to prevent rejection of transplant organs are all drugs which have the potential to produce oral candidiasis.

Patients who present with an early *Candida* infection usually have mild symptoms. The diagnosis of candidiasis is based upon history and clinical exam findings, but is confirmed by the presence of yeast forms or pseudohyphae. Oral candidiasis related to drug therapy can present in various forms. The forms include acute atropic candidiasis (antibiotic sore mouth), chronic atropic candidiasis (denture sore mouth), or acute pseudomembranous candidiasis

(thrush). Nystatin suspensions or clotrimazole troches are extremely effective in treating oral candidiasis.

It is known that in chronic asthma patients, inhaled corticosteroids are efficacious in controlling symptoms and reducing oral corticosteroid dependency. In order to achieve these outcomes inhaled corticosteroids may need to be used at very high doses. With high doses of inhaled corticosteroids also comes the increased risk of developing oral thrush via local deposition of glucocorticoid. This complication can lead to poor compliance with asthma medications. The use of a metered-dose inhaler (MDI) plus a spacer device, such as an Aerochamber will decrease the incidence of oral-pharnygeal *Candida* superinfections and reduces fungal colonization. It is imperative for the pharmacist, prescribing physician, or dentist to prevent the development of thrush secondary to inhaled steroid use. The use of a MDI plus a spacer device is an easy way to decrease the incidence of oral candidiasis infections in asthma patients. It is also recommended that patients adequately rinse their mouth or brush their teeth following the administration of corticosteroid inhalers.

Gingival Hyperplasia (enlarged gums)

Patients may present to the dentist with gingival enlargement if they have been taking agents such as phenytoin, nifedipine, or cyclosporin A (CsA). Gingival hyperplasia occurs when there is an increased production and growth of normal gingival cells. The affected area becomes larger but maintains its normal form. Gingival hyperplasia occurs in roughly 50% of patients taking phenytoin for

the chronic management of epileptic seizures. Within two or three months of taking phenytoin, gingival enlargement presents as a painless enlargement of interdental papillae. Phenytoin can produce gingival enlargement which is severe enough to completely cover the teeth. The severity of gingival hyperplasia is related to the degree of local irritation and inadequacy of oral hygiene and not generally related to the duration of therapy or dosage. The exact mechanism by which phenytoin induces hyperplasia is not completely understood. However, phenytoin may increase the expression of the gene for platelet derived growth factor B (PDGF-B). When gingival macrophages are exposed to phenytoin they secrete increased amounts of PDGF which may increase the proliferation of gingival cells and alveolar bone cells. Patients who are started on a strict program of oral hygiene within ten days of initiation of therapy may be able to minimize the occurrence of gingival enlargement. Phenytoin-induced gingival hyperplasia can also be treated surgically. Patients using phenyton are at risk for gingival hyperplasia, and should be supplemented with 1mg folic acid 1-3 times a day to decrease this side effect.

Approximately 5% of patients taking the calcium channel blocker nifedipine will present with gingival enlargement. Nifedipine induces gingival overgrowth when numerous inflammatory cells replace the collagen of connective tissues. Nifedipine produces alterations of the intracellular calcium levels in gingival cells and can produce local inflammatory factors to elicit gingival enlargement.

Cyclosporin A (CsA) has also been associated gingival enlargement. CsA is given to transplant recipients in order to prevent transplant rejection. Approximately 25% percent of patients who are treated with CsA will have some degree of gingival enlargement. Enlargement is correlated to gingival irritants, such as dental calculus, imperfections in dental restorations, dental plaques, and the effects of mouth breathing. Meticulous plaque control before initiation of therapy and during therapy is a preventive measure against gingival enlargement. Plaque control can be enforced and followed by the dental clinician.

Tooth Discoloration

Numerous drugs are noted to have the capability to produce tooth discoloration. One of the most highly profiled drugs to cause tooth discoloration in young adults is tetracycline. However, other agents such as minocycline, isoproterenol, iron salts, ciprofloxacin, chlorhexidine, and methacycline all have reportedly caused tooth discoloration. It is important for health professionals to be aware of the consequences of using these drugs and how they can affect the oral hygiene of patients. Some of these medications will cause only cosmetic problems with discoloration and others will cause permanent tooth staining. Tetracyclines are most noted for their ability to penetrate bony tissues, especially the growing dentition of young children. Tetracyclines are able to widely distribute throughout the body; therefore, they are able to deposit in the growing dentition and other bony tissues. It is disputable whether tetracycline is specifically incorporated into the dentin or the enamel to produce its characteristic yellow-

brownish discoloration. Females who are exposed to tetracycline during the second or third trimester of pregnancy, may give birth to a child who will develop tooth staining. The teeth will become bright yellow upon development and the stains will eventually turn to gray or brown over time. These effects can also occur in the permanent teeth of children between the ages of two and eight years old who have received tetracycline. In pediatric patients who have received tetracyclines, one-third of them have reports of tooth staining. The staining that occurs in pediatric patients is a permanent tooth discoloration. Discoloration occurs with the greatest frequency when total dosage administration is over three grams or treatment exceeds ten days.

Tooth discoloration occurs when tetracyclines are deposited in calcifying areas of teeth and bone. The mechanism by which tetracycline is incorporated into the mineralizing tissues in not completely understood. However, it is theorized that a chelate of calcium and tetracycline is incorporated into the mineralized tissues. Depending on the specific tetracycline used, the type and severity of discoloration may vary. Tetracycline and oxytetracycline cause a yellow discoloration, whereas chlortetracycline produces a gray-brown discoloration. Evidence suggests that of all the tetracyclines, oxytetracycline causes the least tooth discoloration.

Other agents such as minocycline, iron, ciprofloxacin, and cholrhexidine have been documented to cause tooth discoloration. Minocycline is often given to adult patients and adolescents to control acne. Minocycline produces pigmentation changes of permanent teeth when it chelates with iron to form

insoluble complexes. Oral iron solutions can cause superficial discoloration of teeth. In this case the discoloration can be removed with proper oral hygiene. Ciprofloxacin given intravenously to infants at doses of ten to forty milligrams/kilogram/day for Klebsiella pneumonia has been associated with tooth discoloration. A greenish discoloration which could not be removed was noted when infants teeth developed. Finally, chlorhexidine tooth staining occurs in fifty percent of patients after a few days of use. The most common side effect of oral chlorhexidine mouth rinse is the formation of yellow-brown stains. Fortunately, the staining that occurs with chlorhexidine can be removed by professional cleaning.

Stomatitis

Stomatitis is an inflammation of the mucous lining of the mouth and is characterized as painful, generalized erythema. Severe cases of stomatitis can develop into ulcerations The most common cause of nonspecific stomatitis is the use of antineoplastic agents. Agents which have the potential to cause stomatitis include melphalan, thiopeta, doxarubicin, epirubicin, idarubicin, busulfan, procarbazine, dactinomycin, mitoxantrone, methotrexate, fluorouracil, cytarabine, etoposide and gemcitabine

Chemotherapeutic agents are frequently used to treat a wide array of malignant neoplasms, and oral complications due to chemotherapy are often overlooked. Oral complications due to antineoplastic agents can jeopardize the effectiveness of treatment by allowing development of a focus for infection.

Additionally, patients may not eat, or may discontinue further chemotherapy treatments due to the development of stomatitis. Oral/dental care is often overlooked in cancer patients until a problem such as stomatitis occurs. Clinicians can have a great impact on cancer patients treated with antineoplastic agents by recommending meticulous dental care prior to, during, and after treatment begins.

Antineoplastic agents do not have the ability to differentiate between rapidly growing malignant cells and normal cells. Normal cells most affected by anticancer drugs are the ones with the highest turnover rate including hair follicles, gastrointestinal mucosa, and bone marrow. Over time the antineoplastic agents cause the oral mucosa to become thin. The atropic mucosa is more susceptible to stomatitis and ulceration due to the rubbing of the mucosal surfaces on one another, or on adjacent teeth. Mild forms of stomatitis can be managed by cleansing the oral cavity with a soft tooth brush and rinsing with a saline solution. Mouth rinses such as Kaopectate® have been successful in decreasing the patient's discomfort.

Oral Ulceration and Necrosis

Ulceration and necrosis of the oral mucosa occurs when patients use medications that are not intended for topical therapeutic use or they are taking medications incorrectly. The classic "aspirin burn" is a good example of what can happen when patients try to self medicate. Aspirin is one of the best-known locally toxic substances to oral mucus membranes. When a patient has a

toothache they may try to relieve the pain by placing an aspirin in the muco-buccal fold opposite the toothache. However, the tissue exposed to the aspirin will become white and depending on the severity of tissue destruction, the lesions may be scraped off. Once the lesion is scraped off, the result is a painful bleeding area. Drugs capable of producing stomatitis can potentially produce reactions that are severe and lead to ulcerations. Drugs capable of causing ulceration or mucosal necrosis include aspirin, phenylbutazone, indomethecin, silver nitrate, hydrogen peroxide, isoproterenol, phenols, acids or alkalis, and potassium chloride.

Conclusion

Hundreds of medications have the capability to cause adverse effects within the oral cavity. Drugs have the potential to cause conditions such as xerostomia, intraoral hemorrhage, oral candidiasis, gingival overgrowth, taste changes, tooth discoloration, stomatitis, ulceration and necrosis. It is imperative that health professionals understand the severe complications that medications can have on the oral health of their patients. Pharmacists can educate physicians and dentists on the adverse effects drugs have on oral health. By making health professionals aware of the drug consequences, preventative measures can often be implemented before a problem begins. In order to properly manage patients, a complete medication history including prescription medications, OTC, and dietary supplements must be conducted. A thorough medication history may enable the healthcare team to identify the offending agent.

Table 1. DRUGS THAT AFFECT THE ORAL CAVITY

Xerosomia- Anticholinergics, antidepressants, anti-Parkinson's drugs, antihistamines/decongestants, urinary antispastics, antispsychotics, diuretics, hypnotics, systemic bronchodilators, muscle relaxants, methyldopa, laxatives, beta-blockers, narcotics, and clonidine
Intraoral Hemorrhage-Sulfonamides, quinine, quinidine, thiazide diuretics, allopurinol, methyldopa, antineoplastic agents, digitalis, heparin, phenytoin, coumadin, gold, cephalosporin, penicillin, and tetracycline
Taste Changes-Captopril, enalopril, griseofulvin, D-penicillamine, metronidazole, carbenicillin, chlorhexidine, diltiazem, chloral hydrate, gold salts, flecanide, lithium, vitamin D, and sulfasalazine
Candidia albicans-Broad spectrum antibiotics, antineoplastic agents, corticosteroids including aerosol MDIs, and immunosuppressive agents
Gingival Overgrowth-phenytoin, nifedipine, cyclosporin A
Tooth Discoloration-Tetracycline, demethylchlortetracycline, oxytetracycline, chlortetracycline, minocycline, ciprofloxacin, iron, chlorhexidine
Stomatitis-Melphalan, thiopeta, doxarubicin, epirubicin, idarubicin, busulfan, procarbazine, dactinomycin, mitoxantrone, methotrexate, flurouracil, cytarabine, etoposide, and gemcitabine
Ulceration/Necrosis-Aspirin, phenylbutazone, indomethacin, silver nitrate, hydrogen peroxide, isoproterenol, phenols, acids or alkalis, and potassium chloride

Table 2. Iatrogenic Causes of Xerostomia

ANOREXIANT
- Adipex-P, Fastin, Ionamin, Zantryl (phentermine)
- Anorex SR, Adipost, Bontril PDM (phendimtrazine)
- Mazanor, Sanorex (mazindol)
- Tenuate, Tepanil, Ten-Tab (diethylpropion)

ANTIACNE
- Accutane (isotretinoin)

ANTIANXIETY
- Atarax, Vistaril (hydroxyzine)
- Ativan (lorazepam)
- Serax (oxazepam)
- Valium (diazepam)
- Xanax (alprazolam)

ANTICHOLINERIGICS
- Anaspaz (hyoscyamine)
- Atropisol, Sal-Tropine (atropine)
- Banthine (methantheline)
- Bellergal (belladonna alkaloids)
- Bentyl (dicyclomine)
- Ditropan (oxybutynin)
- Donnatal, Kinesed (hyoscyamne with atropine, phenobarbital, scopolamine)
- Pro-Banthine (propantheline)
- Transderm-Scop (scopolamine)

ANTIDEPRESSANT
- Asendin (amoxapine)
- Elavil (amitriptyline)
- Norpramin (desipramine)
- Sinequan (doxepin)
- Tofranil (imipramine)
- Wellbutrin (bupropion)

ANTIDIARRHEAL
- Imodium AD (loperamide)
- Lomotil (diphenoxylate with atropine)

ANTIHISTAMINE
- Actifed (triprolidine with psuedoephedrine)
- Benadryl (diphenhydramine)
- Chlor-Trimeton (chlorpheniramine)
- Claritin (loratadine)

ANTIHYPERTENSIVE
- Capoten (captopril)
- Catapres (clonidine)
- Coreg (carvedilol)
- Ismelin (guanethidine)
- Minipress (prazosin)
- Serpasil (reserpine)
- Wytensin (guanabenz)

ANTIEMETIC
- Antivert (meclizine)
- Dramamine (dyphenhydramine)

Marezine (cyclizine)

ANTIPARKINSON

Akineton (biperiden)
Artane (trihexyphenidyl)
Cogentin (benztropine mesylate)
Larodopa (levodopa)
Sinemet (carbidopa with levodopa)

ANTI-PSYCHOTIC

Clozaril (clozapine)
Compazine (prochlorperazine)
Eskalith (lithium)
Haldol (haloperidol)
Mellaril (thioridazine)
Navane (thiothixene)
Orap (pimozide)
Sparine (promazine)
Stelazine (trifluoperazine)
Thorazine (chlorpromazine)

BRONCHODILATOR

Atrovent (ipratropium)
Isuprel (isoproterenol)
Proventil, Ventolin (albuterol)

DECONGESTANT

Ornade (phenylpropanolamine with hyfrochlorothiazide)
Sudafed (psuedophedrine)

DIURETIC

Diuril (chlorothiazide)
Dyazide, Maxzide (triamterene and hydrochlorothiazide)
HydroDIURIL, Esidrix (hydrochlorothiazide)
Hygroton (chlothalidone)
Laxis (furosemide)
Midamor (amiloride)

MUSCLE RELAXANT

Flexeril (cyclobenzaprine)
Lioresal (baclofen)
Norflex, Disipal (orphenadrine)

SEDATIVE

Dalmane (flurazepam)
Halcion (triazolam)
Restoril (temazepam)

Continuing Education Exam Questions

Choose the correct response for each question below

1. Which of the following drugs cause xerostomia via anticholinergic effects:
a. oxybutynin
b. reserpine
c. hydrochlorothiazide
d. pilocarpine

2. Which of the following antidepressants is most likely to cause xerostomia:
a. citalopram
b. sertraline
c. amitriptyline
d. none of the above

3. Which of the following statements is true regarding chronic, drug-induced xerostomia:
a. it can increase susceptibility to dental carries
b. phenothiazine antipsychotics (e.g. thioridazine) can cause xerostomia
c. it may be treated with either pilocarpine
d. all of the above

4. Which of the following antihypertensive drugs is associated with causing gingival hyperplasia:
a. metoprolol
b. clonidine
c. nifedipine
d. all of the above

5. Medications associated with causing gingival hyperplasia include:
a. cyclosporine
b. nifedipine
c. phenytoin
d. all of the above

6. Which of the following drugs is associated with taste disturbances?
a. captopril
b. clarithromycin
c. amlodipine
d. two of the above

7. Use of a tube spacer, such as an Aerochamber, can reduce the incidence of oral candidiasis associated with corticosteroid MDI use.
a. true
b. false

8. Which of the following can cause mucosal ulceration when applied topically to the oral cavity :
a. penicillin
b. aspirin
c. tetracycline
d. all of the above

9. The staining of teeth associated with chlorhexidine is permanent and cannot be removed by brushing the teeth :
a. true
b. false

10. The staining of teeth associated with tetracycline is permanent and cannot be removed by brushing the teeth :
a. true
b. false

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