ORIGINAL RESEARCH PAPER

Oral Medicine & Radiology

DRUG INDUCED ORAL LESIONS AND PIGMENTATIONS; A Review

KEY WORDS:

Dr. Ranjith Kumar K S Undergraduate student, Department of Oral medicine and Radiology, Adhiparasakthi Dental College and Hospital, Melmaruvathur, Tamil Nadu 603319

Dr. Mukundh Chaithanya Senior lecturer, Department of Oral medicine and Radiology, Adhiparasakthi Dental College and Hospital, Melmaruvathur, Tamil Nadu 603319

Dr. Deivanayagi Professor, Department of Oral medicine and Radiology, Adhiparasakthi Dental College and Hospital, Melmaruvathur, Tamil Nadu 603319

ABSTRACT

Background Every organ and system in the body can have adverse medication reactions, which are commonly misdiagnosed as symptoms of underlying diseases. Similarly, a variety of medications or chemicals can have an impact on the mouth and related structures. The term "drug allergy" only refers to an IgE-mediated reaction. An allergic reaction to a substance is one that is immunologically mediated and that manifests specificity and recurrence with re-exposure to the offending drug. Clinically, there are two forms of typical drug-induced mouth ulcers. The first is severe mucositis and ulceration, such features are seen like Aphthous stomatitis, Burning mouth syndrome, Vesiculo–bullous Lesions, Effects of Drugs on Oral Mucosa and Tongue, Color Changes of Oral Mucosa and Teeth, Etc., **Management** The seriousness of a potential adverse medication reaction, such as anaphylactic shock, might often make quick intervention crucial. **Conclusion** Many oral lesions and drug reaction symptoms can mimic systemic disorders and can be treated locally or occasionally systemically. An issue emerges when a patient is declared allergic to a drug and is consequently prohibited from receiving that drug or that set of pharmaceuticals in the future

INTRODUCTION

Compared to adverse medication responses that affect the skin, oral reactions are less frequent. Since these reactions might mirror other disease states like erythema multiforme or xerostomia, the diagnosis of these reactions occasionally calls for a high index of suspicion.(1). Even when used as directed and in the prescribed manner, all medications have the potential to have negative side effects. Adverse effects from drugs taken either locally or systemically might have an impact on every area of the mouth mucosa. Since oral adverse medication events are uncommon, they can occasionally be difficult to identify. (2). Patients are exposed to the danger of experiencing drug reactions due to the wide range of medications they take to treat their illnesses. An example of an "adverse drug reaction," as defined by Edwards and Aronson in 2000, is "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts risk from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."(3). Regardless of their aetiology, drug responses include all unfavourable occurrences connected to the administration of drugs.

Drug hypersensitivity is an immune-mediated reaction to a drug in a patient who has already been exposed to it. The term "drug allergy" only refers to an IgE-mediated reaction. An allergic reaction to a substance is one that is immunologically mediated and that manifests specificity and recurrence with re-exposure to the offending drug. (4). every organ and system in the body may experience negative medication reactions, which are frequently misdiagnosed as symptoms of a disease. Many medications or chemicals can have negative effects on the mouth and related structures. Salivary function and good mouth health are crucial for overall body wellness. (5). The pathogenetic mechanism appears to be very complex and includes two different types of reaction: type A, which are dose-dependent and based on the pharmacology of the drug, and type B, immunologic (antibody or T-cell mediated) and non-immunologic, such as direct mucosal/submucosal toxicity as seen in oral ulcer induced by nicorandil or by conventional and targeted anticancer therapy. (7). Both Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous reactions characterised by widespread apoptosis and detachment of the skin's and mucous membranes' epithelium. (8).

Clinical Features

Clinically, there are two forms of typical drug-induced mouth ulcers. The first is severe mucositis and ulceration, primarily brought on by cytotoxic medications used in chemotherapy for cancer treatment. Within days of starting therapy, severe sloughing and ulceration appear, and the resulting discomfort frequently necessitates opioid medication as well as a change in or discontinuation of chemotherapy. These cytotoxic medications include cisplatin, methotrexate, bleomycin, and 5-fluorouracil. Oral ulcers can also be brought on by immunosuppressive medications through opportunistic secondary infections including germs like gram-negative bacteria and fungi. (20).

1. Aphthous Stomatitis

Aphthous stomatitis, also known as recurrent aphthous stomatitis, recurring oral aphthae, or recurrent aphthous ulceration, is a common illness that causes persons who are otherwise healthy to repeatedly develop benign, non-contagious mouth ulcers (aphthae). Numerous medications, such as capropril, nonsteroidal anti-inflammatory drugs (NSAIDs), asathiopurine, losartan, and gold compounds can cause ulcerations that resemble aphthous. The mechanism behind this reaction pattern is not fully understood.

One or more lesions may be present. Minor, large, and herpetiforme ulcers are the three clinical variants that are known. Herpetiforme ulcers of the minor form and the main form both last for 3-6 weeks, but the minor form heals without leaving any scars. (20).

2. Burning Mouth Syndrome

A searing feeling in the tongue, lips, palate, or across the mouth is a common description of the painful, frustrating disease known as burning mouth syndrome (BMS). Burning, scorching, or tingling sensation on the tongue, lips, throat, or palate, no obvious lesion, with or without any sign of inflammation, and discomfort that is typically worse at night are signs and symptoms. Antibiotics, hormone replacement therapy, antidepressants, ACE inhibitors, and cephalosporin are the drugs that cause this side effect the most frequently.

3. Vesiculo–bullous Lesions

Oral drug reactions that remarkably resemble idiopathic Lichen planus, Erythema multiforme (EM), Pemphigoid, Pemphigus vulgaris, and Lupus erythematosus (LE) clinically, histopathologically, and even immunopathologically are well known, and the list of reactions in each category is continually growing. Clinically, any oral site can be impacted; however, the alveolar mucosa, lateral margins of the tongue, and posterior buccal mucosa (cheeks) are the most often afflicted areas. Although bilaterally symmetrical involvement is not rare, lesions can nevertheless be isolated. (77)

Skin and mucous membranes are both susceptible to the hypersensitive reaction known as erythema multiform (EM). Papule, macule, vesicle, erosion, or ulceration are some of the possible symptoms. With a slight propensity to the gingiva, the lesions can affect any area of the oral mucosa, but significant lip involvement with ulcer and crust can be particularly common. Herpes simplex virus (HSV) and less frequently Mycoplasma pneumonitis are the most frequent causes of EM. Drugs like NSAIDs and anti-leptic medications cause this reaction in 18–25% of instances. Additionally, it is a consequence of barbiturates, sulfonamides, and sulfonyl urea.

4. Effects of Drugs on Oral Mucosa and Tongue

The only site of involvement may be the mucosal membranes of the mouth, or they may be a component of a more widespread skin reaction to the offending substance. A delayed hypersensitivity reaction, which is mediated by sensitised T-lymphocytes, is the most common form to impact the oral mucosa. With systemic drug use, stomatitis medicamentosa, also known as a fixed drug eruption, and contact hypersensitivity, stomatitis venenata, manifest. In moderate situations, lesions linked to fixed drug eruption are erythematous; in severe cases, they take on an ulcerated appearance. The responses often manifest 24 hours after medication consumption. After using ampicillin, a delayed reaction (lasting up to two weeks) has been reported. Lesions vanish if the culprit medication is stopped using. (78).

5. Color Changes of Oral Mucosa and Teeth

Direct contact with a substance can cause discoloration, as can systemic drug absorption. The main causes of tissue discolouration in the past were exposure to metals like lead, mercury, zinc, copper, bismuth, silver, and gold. It is common to notice colour changes along the gingival edges, which are brought on by the production of metallic sulphides in gingival pockets as a result of interactions with plaque products.

The deposit of melanin or iron in mucosal tissues has been proposed as a mechanism of action for antimalarial medications like quinolones, including chloroquine and mepacrine. The accumulation of a drug metabolite in the tissue is what leads to widespread mucosal pigmentation in long-term users of phenothiazines, particularly chlorpromazine. Although described, smokers' melanosis is less common or noticeable than might be anticipated given the prevalence of smoking. It is characterised by increased melanin formation, particularly in the attached gingiva. (73).

6. Salivary Gland Enlargement

An adverse medication reaction has been documented as swelling of the salivary glands. Iodine-containing medications, such as those used as imaging contrast media, are the most often prescribed medications related with parotid enlargement. One of the most frequent side effects of radioiodine, a significant therapeutic substance used to treat thyroid cancer, is swelling of the salivary glands (37).

Insulin, methyldopa, phenylbutazone, oxyphenbutazone, potassium chloride, sulfonamide, sodium warfarin, naproxen, guanidine, nitrofurantoin, clonidine, terbinafine, chlorhexidine, and doxycycline are additional medications known to expand the salivary glands. Additionally, sialorrhea-related bilateral salivary gland enlargement is caused by benzodiazepines. (9).

7. Mucous Membrane Pigmentation

In 10 to 20% of cases, acquired melanocytic pigmentations are brought on by drugs. The palate frequently exhibits this pigmentation, which can be localised, diffuse, or multifocal in the oral mucosa. There is no swelling or nodularity, and the lesions are flat. Most often, discoloration goes away a few months after stopping the medicine; nevertheless, pigmentation brought on by hormonal treatments may persist a lifetime. Melanogenesis can be induced by medicines or metabolites, while the exact mechanism is uncertain.

Temporary discoloration (yellow to brown) is typically caused by the consumption of certain foods and beverages (tea, coffee), or by engaging in certain behaviours (using betel, cocaine, or crack), as well as certain medications (iron, bismuth, chlorhexidine, and antibiotics), as well as psychoactive substances that cause xerostomia.

8. Drug Induced Gingival Enlargement

Indications of gingival enlargement include the excessive growth of connective and epithelial tissues, which appear between one and three months after taking a particular drug. Usually, it involves the interdental papilla and may completely or partially conceal the tooth. It typically affects anterior teeth and is generalised. It rarely hurts, however during function it could get traumatised and sore. The length of drug use, dosage, and patients' oral hygiene are all connected to the severity of the enlargement.

The following medicines are the most frequent ones to expand the gingiva: Diltiazem, amlodipine, verapamil, nifidipine, felodipine, nisoldipine, and other calcium channel blockers, as well as the anticonvulsants phenytoin, sodium valproate, phenobarbitone, vigabatrin, primidone, and ethosuximide, and immunosuppressants tacrolimus, sirolimus, and cyclosporine.

9. Dental Caries

Dental caries is a risk due to food choices, poor oral hygiene, and dry mouth. Children's syrups that contain sugar lower PH and cause tooth cavities. Antifungal (nystatin oral tablet) and antibacterial treatments increase the incidence of dental caries since they contain sugar up to 60%. Additionally, antileptic medications and psychoactive drugs including heroin, cocaine, methamphetamine, and cannabis can cause oral caries.

10. Dry socket

One of the most frequent side effects following the extraction of third molars is dry socket, also known as alveolar osteitis. This extremely painful condition usually appears one to three days after the tooth is removed. It happens when the clot inside the socket is removed. This phenomenon affects between 0.5 and 5% of people. OCPs may make dry socket more common. It might be connected to the OCP's fibrinolytic action, which disrupts coagulation. A local anesthetic's vasoconstrictor may be a factor in the development of a dry socket. The chance of developing dry socket is further increased by trauma, smoking, radiation, and bacteria.

11. Halitosis

After tooth decay and gum disease, malodor ranks third on the list of reasons why people seek dental care. Poor oral hygiene, dental caries, mouth infections, periodontal disease, systemic illnesses such as hepatic, renal, gastrointestinal, and upper airway infections, certain meals, or smoking can cause bad breath. However, additional medications including isosorbide dinitrate, cytotoxic agents, D-methyl sulfoxide, amyl-nitrate, disulfiram, paraldehyde, and chloral hydrate are the primary causes of halitosis. Halitosis can also be

associated to the indirect effects of pharmaceuticals that produce dry mouth. Halitosis can also be brought on by taking certain vitamins, like B6. Malodor and a hairy tongue are side effects of tetracycline. Penicillin, griseofulvin, lithium mineral, and medications containing iodine and bismuth are a few medications that might result in phantom or actual halitosis.

12. Xerostomia

The most frequent adverse drug-related effect in the mouth is xerostomia, or dry mouth. Xerostomia can have a variety of reasons. A frequent cause is pharmaceutical treatment. Antidepressants, antipsychotics, antihypertensives, antihistamines, anticholinergics, and decongestants are just a few of the more than 500 drugs that have been linked to xerostomia. In senior individuals who take many drugs (polypharmacy), the synergistic effects of pharmaceuticals have been acknowledged and are becoming more prevalent. Oral dryness or the sense of dryness may also be influenced by behaviours such as smoking, drinking alcohol, and even regular usage of caffeinated beverages. Clinical symptoms include speech and swallowing difficulties, trouble speaking, and a lack of saliva in the mouth, which could also be thick stringy saliva. (15).

13. Taste disorders

The loss of taste sharpness (hypogusia), loss of taste sensation (agusia), distortion of taste (dysgusia), and poor taste (paragusia) are all common taste abnormalities that are linked to several medicines. A strange, bitter, or metallic flavour may occasionally be present in the mouth as a result of a taste disturbance. Salivary excretion of medicines or their metabolites is one of the known methods, albeit the specific mechanism is yet unknown. Another explanation has to do with how medications affect taste receptors directly or indirectly through hyposalivation. It may have an impact on the patient's lifestyle or physical and mental health. The most often prescribed medications that cause taste disturbance include ACEI inhibitors, anti-thyroids, beta lactam, opiates and protease inhibitors, calcium channel blockers (nifidipin, diltiazem), chlorhexidine, anti-diabetic medicines (metformin), and antibiotics.

Management

The seriousness of a potential adverse medication reaction, such as anaphylactic shock, might often make quick intervention crucial. A cautious reintroduction of important medications should be taken into consideration when emergency treatment and the discontinuation of all medications are necessary. In any other case, one determines which medicine or medications should be removed as a trial using clinical benefit-risk judgment and support from investigations. If one or more of the medications are necessary for the patient, a problem occurs right away during withdrawal, the patient should be watched. Depending on the pathology and how quickly the medicine is eliminated from the body, different waiting periods will apply. For instance, permanent psoriatic skin reactions can take weeks to clear up once the medicine is removed, whereas urticaria typically goes away immediately. Alternative treatments for the underlying illness may be provided if necessary if the patient is visibly improving and improving in accordance with the prediction. The next most likely suspect should be taken into consideration, and the process should be repeated, if the patient is not doing well after stopping the first drug. The patient, on the other hand, might be experiencing pain as a result of the drug being withheld. (6)

Guidelines for treating cutaneous ADRs have been developed by the American Academy of Dermatology. In a drug eruption, there are five factors to take into account: (i) an evaluation of the eruption; (ii) the likelihood that the eruption and the drug are related; (iii) the potential seriousness of the eruption; (iv) management; and (v) prevention of recurrence. Finding out whether the oral manifestation began following the use of a certain medication is the first step, and it is then required to assess whether the illness may be caused by the medication. (4).

CONCLUSION

Reactions observed beyond 2 weeks are less likely to be brought on by medication use because the majority of drug reactions happen within 1 to 2 weeks of the start of therapy. Some reactions are dose- or cumulative toxicity-dependent. Most drug-induced oral responses are mild to moderate in intensity. Many oral lesions and drug reaction symptoms can mimic systemic disorders and can be treated locally or occasionally systemically. (78).

ADR risk is influenced by a variety of patient- and drug-related variables. Age (highest prevalence in the young and old), sex (more prevalent in women), genetics (differences in metabolising enzymes may explain response variability), underlying disease (more prevalent in patients with disease, which decreases the ability to metabolise and clear a drug), and prior drug reactions are all factors relating to the patient. (4). an issue emerges when a patient is declared allergic to a drug and is consequently prohibited from receiving that drug or that set of pharmaceuticals in the future. In normal practise, ADRs are frequently mild and self-limiting.

REFERENCES

1. Zelickson BD, Rogers RS. Drug reactions involving the mouth. Clin Dermatol, 1986.4(1):98-109.
2. Boras VV, Andabak-Rogulj A, Brailo V, Simunkovic SK, Gabric D, Vrdoljak DV. Adverse Drug Reactions in The Oral Cavity. Acta Clin Croat, 2015. 54(2): 208-15.
3. Yuan A, Woo SB. Adverse drug events in the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol, 2015. 119(1): 35-47. Oral Surg Oral Med Oral Pathol Oral Radiol, 2015. 119(1):35-47. doi: 10.1016/j.oooo.2014.09.009.
4. Femiano F, Lanza A, Buonaiuto C, Gombos F, Rullo R, Festa V, et al. Oral manifestations of adverse drug reactions: guidelines. J Eur Acad Dermatol Venereol, 2008. 22(6): 681-91. doi: 10.1111/j.1468- 3083.2008.02637.x.
5. Abdollahi M, Rahimi R, Radfar M. Current opinion on drug-induced oral reactions: a comprehensive review. J Contemp Dent Pract, 2008. 9(3): 1-15.
6. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet, 2000. 356(9237): 1255-9. doi:10.1016/S0140-6736(00)02799-9.
7. Fortuna G, Aria M, Schiavo JH. Drug-induced oral lichenoid reactions: a real clinical entity? A systematic review. Eur J Clin Pharmacol, 2017. 73(12):1523-37. doi: 10.1007/s00228-017-2325-0.
8. Gaultier F, Rochefort J, Landru MM, Allanore L, Naveau A, Roujeau JC, et al. Severe and Unrecognized Dental Abnormalities After DrugInduced Epidermal Necrolysis. Arch Dermatol, 2009. 145(11):1332-3. doi: 10.1001/archdermatol.2009.233.
9. Abdollahi M, Radfar M. A review of drug-induced oral reactions. J Contemp Dent Pract, 2003. 4(1):10-31.
10. Baccaglini L, Brennan MT, Lockhart PB, Patton LL. World Workshop on Oral Medicine IV: Process and methodology for systematic review and developing management recommendations. Reference manual for management recommendations writing committees. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2007. 103 Suppl: S3.e1-19. doi: 10.1016/j.tripleo.2006.12.002
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg, 2010. 8(5): 336-41. doi: 10.1016/j.ijsu.2010.02.007.
12. Glick M. Burket's Oral Medicine. 12th ed., People Medical Publishing House-USA, Chapter 4, 2016.
13. Pedersen AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. Oral Dis, 2002. 8(3): 117-29.
14. Aliko A, Wolff A, Dawes C, Aframian D, Proctor G, Ekstrom J, et al. World Workshop on Oral Medicine VI: clinical implications of medication-induced salivary gland dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol, 2015. 120(2): 185-206. doi: 10.1016/j.oooo.2014.10.027.
15. Field EA, Longman LP, Bucknall R, Kaye SB, Higham SM, Edgar WM. The establishment of a xerostomia clinic: a prospective study. Br J Oral Maxillofac Surg, 1997. 35(2): 96-103.
16. de Matos LF, Pereira SM, Kaminagakura E, Marques LS, Pereira CV, van der Bilt A, et al. Relationships of beta-blockers and anxiolytics intake and salivary secretion, masticatory performance and taste perception. Arch Oral Biol, 2010. 55(2):164-9. doi: 10.1016/j.archoralbio.2009.11.011.
17. Kotecha D, Manzano L, Altman DG, Krum H, Erdem G, Williams N,et al. Individual patient data meta-analysis of beta-blockers in heart failure: rationale and design. Syst Rev, 2013. 18(1):2-7. doi: 10.1186/2046-4053-2-7.
18. Nonzee V, Manopatanakul S, Khovidhunkit SO. Xerostomia, hyposalivation and oral microbiota in patients using antihypertensive medications. J Med Assoc Thai, 2012. 95(1): 96-104.
19. Djukic LJ, Roganovic J, Brajovic MD, Bokonjic D, Stojic D. The effects of anti-hypertensives and type 2 diabetes on salivary flow and total antioxidant capacity. Oral Dis, 2015. 21(5): 619-25. doi: 10.1111/odi.12325.
20. Jinbo Y, Demitso T. Oral ulcerations due to drug medications. Jap Dent Sci Revi, 2014. 50(2): 40-6. https://doi.org/10.1016/j.jdsr.2013.12.001
21. Yousefi H, Yuan J, Keshavarz-Fathi M, Murphy JF, Rezaei N. Immunotherapy of cancers comes of age. Expert Rev Clin Immunol, 2017. 13(10):1001-15. doi:

10.1080/1744666X.2017.1366315.
22. Kaste SC, Goodman P, Leisenring W, Stovall M, Hayashi RJ, Yeazel M, et al. Impact of radiation and chemotherapy on risk of dental abnormalities: a report from the Childhood Cancer Survivor Study. Cancer, 2009. 115(24):5817-27. doi: 10.1002/cncr.24670.
23. Ruocco V, Ruocco E, Lo Schiavo A, Brunetti G, Guerrera LP, Wolf R. Pemphigus: etiology, pathogenesis, and inducing or triggering factors: facts and controversies. Clin Dermatol, 2013. 31(4): 374-81. doi: 10.1016/j.clindermatol.2013.01.004.
24. Habbab KM, Moles DR, Porter SR. Potential oral manifestations of cardiovascular drugs. Oral Dis, 2010. 16(8): 769-73. doi: 10.1111/j.1601-0825.2010.01686.
25. Firouze Moqadam I, Najafi S, Mohammadzadeh M, Zare Bidoki A, Yousefi H, Farhadi E, et al. Lack of Association between Interleukin-12 Gene Polymorphisms and Recurrent Aphthous Stomatitis. Avicenna J Med Biotechnol, 2016. 8(4):200-201.
26. Najafi S, Yousefi H, Mohammadzadeh M, Bidoki AZ, Farhadi E, Rezaei N. Interleukin-2, Interferongamma Gene Polymorphisms in Recurrent Aphthous Stomatitis. Prague Med Rep, 2017. 118(2-3): 81-6. doi: 10.14712/23362936.2017.
27. Treister NS, Richardson P, Schlossman R, Miller K, Woo SB. Painful tongue ulcerations in patients with bisphosphonate-associated osteonecrosis of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2008. 105(6): 1-4. doi: 10.1016/j.tripleo.2008.02.010.
28. Kharazmi M, Sjoqvist K, Warfvinge G. Oral ulcers, a little known adverse effect of alendronate: review of the literature. J Oral Maxillofac Surg, 2012. 70(4): 830-6. doi: 10.1016/j.joms.2011.03.046.
29. Kharazmi M, Sjoqvist K, Rizk M, Warfvinge G. Oral ulcer associated with alendronate: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2010. 110(6): 11-3. doi: 10.1016/j.tripleo.2010.04.035.
30. Clayton R, Chaudhry S, Ali I, Cooper S, Hodgson T, Wojnarowska F. Mucosal (oral and vulval) lichen planus in women: are angiotensin-converting enzyme inhibitors protective, and beta-blockers and non-steroidal anti-inflammatory drugs associated with the condition? Clin Exp Dermatol, 2010. 35(4): 384-7. doi: 10.1111/j.1365-2230.2009.03581.
31. Hirota SK, Moreno RA, dos Santos CH, Seo J, Migliari DA. Analysis of a possible association between oral lichen planus and drug intake. A controlled study. Med Oral Patol Oral Cir Bucal, 2011. 16(6): 750-6.
32. Dafar A, Cevik-Aras H, Robledo-Sierra J, Mattsson U, Jontell M. Factors associated with geographic tongue and fissured tongue. Acta Odontol Scand, 2016. 74(3):210-6. doi: 10.3109/00016357.2015.1087046.
33. Jallouli M, Frances C, Piette JC, Huong du LT, Moguelet P, Factor C, et al. Hydroxychloroquineinduced pigmentation in patients with systemic lupus erythematosus: a case-control study. JAMA Dermatol, 2013. 149(8): 935-40. doi: 10.1001/jamadermatol.2013.709.
34. Tuccori M, Lapi F, Testi A, Ruggiero E, Moretti U, Vannacci A, et al. Drug-induced taste and smell alterations: a case/non-case evaluation of an italian database of spontaneous adverse drug reaction reporting. Drug Saf, 2011. 34(10):849-59. doi: 10.2165/11593120-000000000-00000.
35. Onder G, Pellicciotti F, Gambassi G, Bernabei R. NSAID-related psychiatric adverse events: who is at risk? Drugs,2004. 64: 2619-27. 36. Jarari N, Rao N, Peela JR, Ellafi KA, Shakila S, Said AR, et al. A review on prescribing patterns of antihypertensive drugs. Clin Hypertens, 2016. 27:22-7. doi: 10.1186/s40885-016-0042-0.
37. Wolff A, Zuk-Paz L, Kaplan I. Major salivary gland output differs between users and non-users of specific medication categories. Gerodontology, 2008. 25(4):210-6. doi: 10.1111/j.1741-2358.2008.00223.
38. de Almeida Pdel V, Gregio AM, Brancher JA, Ignacio SA, Machado MA, de Lima AA, et al. Effects of antidepressants and benzodiazepines on stimulated salivary flow rate and biochemistry composition of the saliva. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2008. 106(1): 58-65. doi: 10.1016/j.tripleo.2007.11.008.
39. Hasan SS, Keong SC, Choong CL, Ahmed SI, Ching TW, Anwar M, et al. Patient-reported adverse drug reactions and drug-drug interactions: a crosssectional study on Malaysian HIV/AIDS patients. Med Princ Pract, 2011. 20(3):265-70. doi: 10.1159/000321274.
40. Desoutter A, Soudain-Pineau M, Munsch F, Mauprivez C, Dufour T, Coeuriot JL. Xerostomia and medication: a cross-sectional study in long-term geriatric wards. J Nutr Health Aging, 2012. 16(6): 575-9.
41. Basso FG, Boer CC, Correa ME, Torrezan M, Cintra ML, de Magalhaes MH, et al. Skin and oral lesions associated to imatinib mesylate therapy. Support Care Cancer, 2009. 17(4): 465-8. doi: 10.1007/s00520-008-0536-8.
42. Hey J, Setz J, Gerlach R, Vordermark D, Gernhardt CR, Kuhnt T. Effect of Cisplatin on parotid gland function in concomitant radiochemotherapy. Int J Radiat Oncol Biol Phys, 2009. 75(5): 1475-80. doi: 10.1016/j.ijrobp.2008.12.071.
43. Lee WJ, Lee JL, Chang SE, Lee MW, Kang YK, Choi JH, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol, 2009. 161(5): 1045-51. doi: 10.1111/j.1365-2133.2009.09290.
44. Sonis S, Treister N, Chawla S, Demetri G, Haluska F. Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer, 2010. 116(1): 210-5. doi: 10.1002/cncr.24696.
45. Hsieh SG, Hibbert S, Shaw P, Ahern V, Arora M. Association of cyclophosphamide use with dental developmental defects and salivary gland dysfunction in recipients of childhood antineoplastic therapy. Cancer, 2011. 117(10):2219-27. doi: 10.1002/cncr.25704.
46. Gomez Fernandez C, Sendagorta Cudos E, Casado Verrier B, Feito Rodriguez M, Suarez Aguado J, Vidaurrazaga Diaz de Arcaya C. Oral lichenoid eruption associated with imatinib treatment. Eur J Dermatol, 2010. 20(1): 127-8. doi: 10.1684/ejd.2010.0818.
47. Nofal A, El-Din ES. Hydroxyurea-induced dermatomyositis: true amyopathic dermatomyositis or dermatomyositis-like eruption? Int J Dermatol, 2012. 51(5):535-41. doi: 10.1111/j.1365-4632.2011.05105.
48. Martins F, de Oliveira MA, Wang Q, Sonis S, Gallottini M, George S, et al. A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. Oral Oncol, 2013. 49(4): 293-8. doi: 10.1016/j.oraloncology. 2012.11.008.
49. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. Support Care Cancer, 2017. 25(5): 1713-39. doi: 10.1007/s00520-017-3629-4.
50. Jinbu Y, Obi Y, Kawa R, Ikeda K, Kusama M, Tsukinoki K. Oral ulcerations due to an antirheumatic drug (Methotrexate) : report of a case. Oral Med Pathol, 2008. 12:97-9
51. Gupta S, Gupta S, Mittal A, David S. Oral fixed drug eruption caused by gabapentin. J Eur Acad Dermatol Venereol, 2009. 23(10): 1207-8. doi: 10.1111/j.1468-3083.2009.03124.x.
52. Kikuchi K, Miyazaki Y, Tanaka A, Shigematu H, Kojima M, Sakashita H, et al. Methotrexate-related Epstein-Barr Virus (EBV)-associated lymphoproliferative disorder--so-called "Hodgkinlike lesion"--of the oral cavity in a patient with rheumatoid arthritis. Head Neck Pathol, 2010. 4(4): 305-11. doi: 10.1007/s12105-010-0202-6.
53. Pedrazas CH, Azevedo MN, Torres SR. Oral events related to low-dose methotrexate in rheumatoid arthritis patients. Braz Oral Res, 2010. 24(3): 368-73.
54. Mendonca R, Gueiros LA, Capellaro K, Pinheiro VR, Lopes MA. Oral lesions associated with hydroxyurea treatment. Indian J Dent Res, 2011. 22(6): 869-70. doi: 10.4103/0970-9290.94690.
55. Weng RR, Foster CE, Hsieh LL, Patel PR. Oral ulcers associated with mycophenolate mofetil use in a renal transplant recipient. Am J Health Syst Pharm, 2011. 68(7):585-8. doi: 10.2146/ajhp100276.
56. Lee HJ, Hong SK, Seo JK, Lee D, Sung HS. A Case of Cutaneous Side Effect of Methotrexate Mimicking Behcet's Disease. Ann Dermatol, 2011. 23(3): 412-4. doi: 10.5021/ad.2011.23.3.412.
57. Baricevic M, Mravak Stipetic M, Situm M, Marinovic B, Seiwerth S, Baricevic D, et al. Oral bullous eruption after taking lisinopril--case report and literature review. Wien Klin Wochenschr, 2013. 125(13-14): 408-11. doi: 10.1007/s00508-013-0382-7.
58. Troeltzsch M, von Blohn G, Kriegelstein S, Woodlock T, Gassling V, Berndt R, et al. Oral mucositis in patients receiving low-dose methotrexate therapy for rheumatoid arthritis: report of 2 cases and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol, 2013. 115(5): 28-33. doi: 10.1016/j.oooo.2012.12.008.
59. Hanakawa H, Orita Y, Sato Y, Uno K, Nishizaki K, Yoshino T. Large ulceration of the oropharynx induced by methotrexate-associated lymphoproliferative disorders. Acta Med Okayama, 2013. 67(4):265-9. doi: 10.18926/AMO/51072
60. Dervisoglou T MA. Oral Ulceration Due to Methotrexate Treatment: A Report of 3 Cases and Literature Review. Balk J dent Med, 2015. 19(1): 116-120. doi: https://doi.org/10.1515/bjdm-2015-0045
61. Sahraei Z, Mirabzadeh M, Eshraghi A. Erythema Multiforme Associated With Misoprostol: A Case Report. Am J Ther, 2016. 23(5): 1230-3. doi: 10.1097/MJT.0000000000000193.
62. Aleid W, Sidebottom A. Oral mucosal irritation with incorrect use of alendronate. Br J Oral Maxillofac Surg, 2009. 47(2): 170-1. doi: 10.1016/j.bjoms.2008.08.005.
63. Puri PK, Lountzis NI, Tyler W, Ferringer T. Hydroxychloroquine-induced hyperpigmentation: the staining pattern. J Cutan Pathol, 2008. 35(12): 1134-7. doi: 10.1111/j.1600-0560.2008.01004.
64. Woo V, Bonks J, Borukhova L, Zegarelli D. Oral lichenoid drug eruption: a report of a pediatric case and review of the literature. Pediatr Dermatol, 2009. 26(4):458-64. doi: 10.1111/j.1525-1470.2009.00953.
65. Asarch A, Gottlieb AB, Lee J, Masterpol KS, Scheinman PL, Stadecker MJ, et al. Lichen planuslike eruptions: an emerging side effect of tumor necrosis factor-alpha antagonists. J Am Acad Dermatol, 2009. 61(1): 104-11. doi: 10.1016/j.jaad.2008.09.032.
66. Kaomongkolgit R. Oral lichenoid drug reaction associated with antihypertensive and hypoglycemic drugs. J Drugs Dermatol, 2010. 9(1): 73-5.
67. Artico G, Bruno IS, Seo J, Hirota SK, Acay R, Migliari DA. Lichenoid reaction to carbamazepine in the oral mucosa: case report. An Bras Dermatol, 2011. 86(4 Suppl 1):S152-5.
68. Shino M, Takahashi K, Murata T, Iida H, Yasuoka Y, Furuya N. Angiotensin II receptor blockerinduced angioedema in the oral floor and epiglottis. Am J Otolaryngol, 2011. 32(6):624-6. doi: 10.1016/j.amjoto.2010.11.014.
69. Li CC, Malik SM, Blaeser BF, Dehni WJ, Kabani SP, Boyle N, et al. Mucosal pigmentation caused by imatinib: report of three cases. Head Neck Pathol, 2012. 6(2):290-5. doi: 10.1007/s12105-011-0325-4.
70. Fessa C, Lim P, Kossard S, Richards S, Penas PF. Lichen planus-like drug eruptions due to betablockers: a case report and literature review. Am J Clin Dermatol, 2012. 13(6):417-21. doi: 10.2165/11634590-000000000-00000.
71. Balaji G, Maharani B, Ravichandran V, Parthasarathi T. Linezolid induced black hairy tongue. Indian J Pharmacol, 2014. 46(6): 653-4. doi: 10.4103/0253-7613.144942.
72. Kumaraguru J, Flanagan SE, Greeley SA, Nuboer R, Stoy J, Philipson LH, et al. Tooth discoloration in patients with neonatal diabetes after transfer onto glibenclamide: a previously unreported side effect. Diabetes Care, 2009. 32(8):1428-30. doi: 10.2337/dc09-0280.
73. Petropoulou T, Lagona E, Syriopoulou V, Michos A. Teeth and tongue discoloration after linezolid treatment in children. Pediatr Infect Dis J, 2013. 32(11):1284-5. doi: 10.1097/INF.0b013e3182a5c42b.
74. Helenius-Hietala J, Ruokonen H, Gronroos L, Rissanen H, Vehkalahti MM, Suominen L, et al. Oral mucosal health in liver transplant recipients and controls. Liver Transpl, 2014. 20(1):72-80. doi: 10.1002/lt.23778.
75. Hellwig E, Lussi A. Oral hygiene products, medications and drugs - hidden aetiological factors for dental erosion. Monogr Oral Sci, 2014. 25: 155-62. doi: 10.1159/000359942.
76. Hu KF, Chou YH, Wen YH, Hsieh KP, Tsai JH, Yang P, et al. Antipsychotic medications and dental caries in newly diagnosed schizophrenia: Anationwide cohort study. Psychiatry Res, 2016. 245:45-50. doi: 10.1016/j.psychres.2016.07.047.
77. Pejcic A. Drug-Induced Oral Reactions [Internet]. Emerging Trends in Oral Health Sciences and Dentistry. InTech; 2015. Available from: http://dx.doi.org/10.5772/59261
78. Abdollahi M, Radfar M. A Review of Drug-Induced Oral Reactions. J Contemp Dent Pract 2003 February;(4)1:010-031.