FACT SHEET

FOR NON-ORAL HEALTH PROFESSIONALS

Oral Adverse Drug Reactions

Background

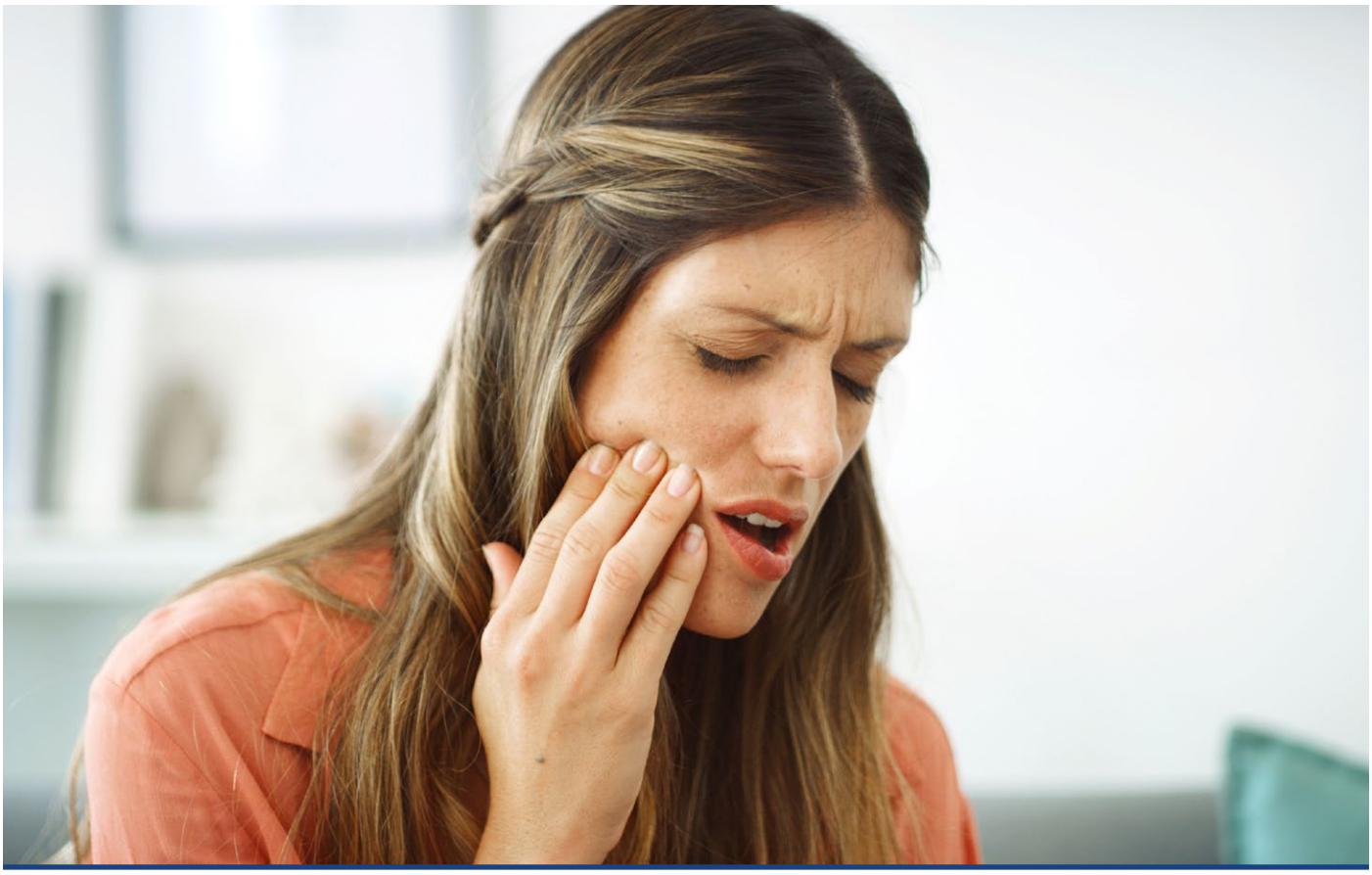
An adverse drug reaction (ADR) is defined as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen or withdrawal of the product.[1]' Oral ADRs are common and manifest in the orofacial region. They have varied presentation and are associated with 43 of the 100 most frequently dispensed drugs in Australia in 2018[2]. Most of these reactions are reversible and subside when the use of the implicated medication is stopped.

Why do non-oral health professionals need to know how to identify oral adverse drug reactions?

Non-oral health professionals are well-positioned to observe changes in their patients and should be aware that new symptoms affecting the oral cavity may not always stem or originate from the primary disease but could result from an ADR.

The following aspects of Oral ADRs should be noted:

1. They are common and can be serious, affecting a patient's quality of life by negatively, impacting food intake, speech, the ability to swallow and a person's appearance.
2. They can be a symptom of an underlying systemic condition or disease.



Some examples of common oral adverse drug reactions are summarized below.

Xerostomia

Definition and incidence

Xerostomia is defined as the subjective sensation of dry mouth, which may or may not be associated with hyposalivation (a reduction in salivary flow). It is very common, with 20% of patients self-reporting xerostomia in a cross-sectional study[3]. Xerostomia is most commonly a side-effect of medication.

Clinical effects

- Xerostomia is associated with increased risk of dental caries (tooth decay) and worsening of non-carious tooth wear, such as erosion.
- Lack of saliva is also associated with increased risk of oral infection, i.e. oral candidiasis.
- Patients can experience difficulties with denture retention, while the lack of lubrication of their mouth can lead to challenges with eating, swallowing and talking.

Associated drugs

A wide range of drugs[4] are associated with xerostomia:

- Drugs with anticholinergic or antimuscarinic effects are associated due to negative cholinergic inhibition of the salivary glands.
- Drugs that stimulate the sympathetic nervous system causing inhibition of saliva production are also associated[5].
- Many drugs, e.g. opioids and benzodiazepines, cause xerostomia by inhibiting salivary gland function in ways that are not fully understood[4,6].

Bruxism

Definition and incidence

Bruxism is defined as 'a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or bracing of teeth and/or bracing or thrusting of the mandible. Bruxism has two distinct circadian manifestations: it can occur during sleep (indicated as sleep bruxism) or during wakefulness (indicated as awake bruxism)[7]. The incidence of bruxism is 8% in adults[8].

Clinical effects

- The repetitive movement of tooth grinding can lead to wear of the teeth, cracks and fractures of teeth and loss of tooth fillings.
- Patients can also experience tooth and jaw joint pain and headaches.

Drugs associated

- Antidepressant drugs, e.g. selective serotonin re-uptake inhibitors (SSRIs) and serotonin and noradrenaline re-uptake inhibitors (SNRIs), are associated with bruxism[9]. This is thought to be due to their effects on the neurotransmitters dopamine, serotonin and noradrenaline.
- Some of the typical antipsychotics, such as chlorpromazine or haloperidol, are also associated with bruxism, due to their modulation of dopamine in the central nervous system[10].

Oral mucositis

Definition and incidence

Oral mucositis is inflammation of the oral mucosa. This typically occurs when patients have received cytotoxic chemotherapy agents and occurs in up to 40% of patients receiving these drugs[11].

Clinical effects

- Ulcerations will manifest on all parts of the oral mucosa, mostly the cheeks and tongue. Typically, they are large and have irregular borders.
- These large ulcerations that breach the oral mucosa can also be portals of entry for microorganisms and increase the risk of infection[11].
- Oral mucositis associated with pain, sometimes requires dose reduction of the causative chemotherapy agents and analgesics[11].
- Patients typically have trouble with eating and swallowing and generalized pain from these lesions.

Drugs associated

- Most cytotoxic chemotherapy agents are associated with oral mucositis as well as several antimetabolites.

Gingival overgrowth

Definition and incidence

Drug-induced gingival overgrowth is the enlargement of the gingival and periodontal tissues due to an increase in extra-cellular tissue volume. The incidence varies depending on the drug that is prescribed. The most common drugs causing gingival overgrowth are anticonvulsants, immunosuppressants and calcium channel blockers.

Clinical effects

- Enlarged, swollen gingiva, mostly at the front of the mouth, cause difficulties with eating and talking.
- Enlarged gingiva can also make oral hygiene challenging; the presence of dental plaque worsens the swelling by causing inflammation and bleeding.

Drugs associated

- The anticonvulsant phenytoin has an association with gingival overgrowth, with a prevalence of 13-50%[12,13]. Other anticonvulsants, such as valproic acid, are also associated with gingival overgrowth, although this is rare[14,16].
- The immunosuppressant cyclosporin is associated with gingival overgrowth, with a prevalence of 25-30% in adults, but a higher prevalence in children of >70%[13].
- Calcium channel blockers, e.g. nifedipine and diltiazem, are also associated, with varying prevalence[13].

Drug-induced oral lichenoid reactions

Lichen planus is an immunologically mediated disease of both the skin and mucosa and can also present on its own in the oral cavity. The incidence is approximately 1%, and it is more common in women over the age of 50 years[18]. Medication can cause an oral lichenoid reaction with similar clinical and histological features to lichen planus.

Clinical effects

- Drug-induced oral lichenoid reactions (DIOLRs) can affect any oral mucosal surface, including the buccal mucosa, tongue and gingiva[17].
- These reactions can have a variety of clinical presentations, including white striated lesions, erythematous confluent plaques, erosions and ulcerations[17,18].

Drugs associated

- Many drugs are associated with adverse effects and ADR protocols exist. Since protocols for drugs associated with OLRs have often not been validated, there is evidence for a handful of drugs only[19].
- Association of drugs is mostly through case reports due to the rarity of the adverse effect18.
- Some cardiac medications, including methyldopa, oxprenolol, atenolol, captopril and enalapril, as well as immunosuppressants imatinib, infliximab and interferon-alpha, have been associated with OLRs[17,19].
- Other drugs, such as lithium, carbamazepine and duloxetine are associated with drug-induced lichenoid reactions, although only through a single or a few case reports[17,19].

Summary

- Oral ADRs are common and associated with frequently prescribed medicines, especially in older people having co-morbidities, who may be prescribed several medications.
- There are many different types of oral ADRs that can negatively affect the patient's quality of life.
- Most oral ADRs are reversible and will subside with the cessation of the causative drug.
- Recognition of these effects are an important part of managing the oral health of patients.

Oral healthcare delivery framework

Ask

- Obtain a comprehensive medical history, including all medications, whether prescription, over the counter or herbal medications.
- Ask about oral symptoms such as dryness, pain, ulcers, bleeding gums, or difficulty eating and speaking.
- Enquire about the duration and onset of symptoms in relation to medication use.
- Assess for other risk factors, including systemic conditions, smoking, alcohol use, and oral hygiene habits.

Look

- Conduct a basic oral examination, checking for:
  - dryness or lack of saliva flow;
  - ulcerations, erosions, or white patches on the oral mucosa;
  - gingival swelling or overgrowth;
  - tooth wear, fractures, or increased dental plaque due to reduced saliva;
  - signs of infection, such as oral candidiasis or secondary bacterial involvement.
- Check for any other systemic signs that may suggest an underlying condition contributing to oral symptoms.

Decide

- Identify oral adverse drug reactions that require urgent attention, such as severe oral mucositis, painful ulcerations, or extensive gingival overgrowth affecting function.
- Consider whether the symptoms warrant a medication review or dose modification in consultation with the prescribing physician.
- Determine if lifestyle modifications, such as improving hydration or oral hygiene, could help alleviate symptoms.
- Decide if referral to a dental or medical specialist is necessary for further evaluation and treatment.

Act

- Identify the medication causing an oral ADR and discontinue use.
- Provide initial symptom management, such as recommending saliva substitutes or encouraging chewing to stimulate saliva production.
- Encourage patients to maintain good oral care practices, including use of fluoride toothpaste, avoiding dehydrating/acidic foods/drinks, regular hydration and avoidance of irritants like alcohol-based mouthwashes.
- Facilitate referrals for oral health assessment, particularly in cases of progressive or severe oral reactions requiring specialized care.

Document

- Record the patient's symptoms, possible association with their medications and any interventions or referrals made.
- Include details of any oral care recommendations and patient education provided to ensure continuity of care.
- Report any suspected ADRs to the relevant pharmacovigilance agency or service, for example to the Therapeutic Goods Administration (TGA) in Australia or the Food and Drug Administration (FDA) in the US.

References

1. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356(9237): 1255-1259. Available from: doi.org/10.1016/s0140-6736(00)02799-9
2. Teoh L, Stewart K, Moses G. Where are oral and dental adverse drug effects in product information? Int J Pharm Pract. 2020; Available from: doi.org/10.1111/ijpp.12650
3. Villa A, Abati S. Risk factors and symptoms associated with xerostomia: a cross-sectional study. Aust Dent J. 2011; 56(3): 290-295. Available from: doi: 10.1111/j.1834-7819.2011.01347.x
4. Wolff A, Joshi RK, Ekstrom J, et al. A Guide to Medications Inducing Salivary Gland Dysfunction, Xerostomia, and Subjective Sialorrhea: A systematic review sponsored by the world workshop on oral medicine VI. Drugs R D. 2017; 17(1): 1-28. Available from: doi:10.1007/s40268-016-0153-9.
5. Miranda-Rius J, Brunet-Llobet L, Lahor-Soler E, Farre M. Salivary Secretory Disorders, Inducing Drugs, and Clinical Management. Int J Med Sci. 2015; 12(10): 811-824. Available from: doi: 10.7150/ijms.12912
6. Expert Advisory Committee. Australian Medicines Handbook. 2019. Australian Medicines Handbook Pty Limited. 978-0-9943262-9-4 https://shop.amh.net.au
7. Lobbezoo F, Ahlberg J, Glaros AG, et al. Bruxism defined and graded: an international consensus. J Oral Rehabil. 2013; 40(1): 2-4. Available from: doi: 10.1111/joor.12011.
8. Feu D, Catharino F, Quintao CC, Almeida MA. A systematic review of etiological and risk factors associated with bruxism. J Orthod. 2013; 40(2): 163-71. Available from: doi: 10.1179/1465313312Y.0000000021.
9. Garrett AR, Hawley JS. SSRI-associated bruxism: A systematic review of published case reports. Neurol Clin Pract. 2018; 8(2): 135-141. Available from: doi: 10.1212/CPJ.0000000000000433.
10. Clark GT, Ram S. Four oral motor disorders: bruxism, dystonia, dyskinesia and drug-induced dystonic extrapyramidal reactions. Dent Clin North Am. 2007; 51(1): 225-243, viii-ix. Available from: doi: 10.1016/j.cden.2006.09.002.
11. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. Oral Oncol. 1998; 34(1): 39-43. Available from: doi: 10.1016/s1368-8375(97)00053-5.
12. Thomason JM, Seymour RA, Rawlins MD. Incidence and severity of phenytoin-induced gingival overgrowth in epileptic patients in general medical practice. Community Dent Oral Epidemiol. 1992; 20(5): 288-291. Available from: doi: 10.1111/j.1600-0528.1992.tb01701.x
13. Dongari-Bagtzoglou A. Drug Associated Gingival Enlargement. J Periodontol. 2004; 75(10): 1424-31. Available from: doi: 10.1902/jop.2004.75.10.1424.
14. Behari M. Gingival hyperplasia due to sodium valproate. J Neurol Neurosurg Psychiatry. 1991; 54(3): 279-80. Available from: doi: 10.1136/jnnp.54.3.279-a.
15. Mesa FL, Lopez C, Gonzalez MA, Del-Moral R, FJ OV. Clinical and histopathological description of a new case of vigabatrin-induced gingival overgrowth. Med Oral. 2000; 5(2): 133-137.
16. Hatahira H, Abe J, Hane Y, et al. Drug-induced gingival hyperplasia: a retrospective study using spontaneous reporting system databases. J Pharm Health Care Sci. 2017; 3: 19. Available from: doi: 10.1186/s40780-017-0088-5.
17. Teoh L, Moses G, McCullough MJ. A review and guide to drug-associated oral adverse effects-Oral mucosal and lichenoid reactions. Part 2. J Oral Pathol Med. 2019; 48(7): 637-46. Available from: https://doi.org/10.1111/jop.12910
18. 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- 1537. Available from: doi: 10.1007/s00228-017-2325-0.
19. Serrano-Sanchez P, Bagán J, Jimenez- Soriano Y, Sarrion G. Drug- induced oral lichenoid reactions. A literature review. J Clin Exp Dent. 2010;2(2):71- 75

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