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REVIEW ARTICLE

A review and guide to drug-associated oral adverse effects - Dental, salivary and neurosensory reactions. Part 1.

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Abstract

Numerous adverse drug reactions manifest in the oral cavity and orofacial region. Dentists and other health professionals commonly encounter and manage these adverse effects however, due to lack of awareness and training, they are not always recognised as being drug-induced nor reported to pharmacovigilance agencies. The broad diversity and increasing number of medications for which dental pharmacovigilance is needed can be overwhelming for all health professionals. Thus, the aim of this review and guide is to outline the common medications associated with orofacial side effects so as to improve recognition, management and reporting of adverse drug reactions. Adverse effects discussed in Part 1 include drug-induced bruxism, tardive dyskinesia, hairy tongue, gingival enlargement, hypersalivation, xerostomia, tooth discolouration and taste disturbance.

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Introduction

Medicine use is common with 87.1% of Australians older than 50 years taking one or more medicines regularly, with polypharmacy occurring more frequently with increasing age.¹ An adverse drug reaction (ADR) is defined by the World Health Organisation as “*a response to a medicine which is noxious and unintended, and occurs at doses normally used in man*”.² The prevalence and severity of ADRs have been shown to occur via a meta-analysis in nearly 16% of patients during hospitalisation³ with substantial impact on public health.

Oral ADRs are common, with xerostomia alone being reported in association with approximately 80% of the 100-most frequently prescribed medications in the United States.⁴ ⁵ Dentists are in an ideal position to observe or ask about oral ADRs as taking a medication history and oral examination are integral to a dental consultation. Although ADRs are underreported throughout the health industry, the contribution by dentists is extremely limited with 47 cases of ADRs reported by dentists in the past decade to the Therapeutic Goods Administration (TGA) in Australia, and dentists have contributed merely 0.1% of ADR reports since voluntary recording began in 1971.⁶ Previous studies have also shown variable awareness and knowledge of ADR reporting by dentists.^{7, 8}

While some oral adverse effects such as xerostomia and dysgeusia are common, others such as lichenoid reactions are rare and not usually detected until the drug has been marketed for some years. By the time of licensing, most drugs have only been trialled in 1000-2000 subjects, and exposure to less than 5,000 human subjects allows only the more common ADRs to be detected, whereas at least 30,000 subjects are needed to ensure an ADR with an incidence of 1 in 10,000 subjects is detected.² Indeed, the adverse effect of bisphosphonate-induced osteonecrosis of the jaw was only identified through post-marketing ADR reporting that has subsequently influenced the dental management of patients on these medicines today. Drug surveillance during the post-marketing period is essential to allow the detection of unexpected, rare, and sometimes serious ADRs.⁵

The increased access to medications due to the Internet, wider prescribing rights and greater off-label uses, requires close monitoring of drug safety. It is hoped that this two-part series of articles on oral adverse effects will raise awareness of ADRs that manifest in the orofacial region and prompt dentists to report them. Thus, the aim of this review and guide is to outline the commonly implicated medications associated with orofacial ADRs to improve recognition, management and reporting of ADRs. Adverse effects discussed include bruxism,

tardive dyskinesia, hairy tongue, gingival enlargement, hypersalivation, xerostomia, tooth discolouration and taste disturbance. All oral mucosal and bullous disorders are discussed in Part 2 of this review. Since the authors of this review practice in Australia, only drugs that are currently marketed for use in Australia have been included in this review.

Drug-induced bruxism

Bruxism is defined as “a repetitive jaw-muscle activity characterised by clenching or grinding of the 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).”⁹ The incidence of bruxism has been reported to range from 14-20% in children,¹⁰ with a systematic review reporting a prevalence of 18.6% in adults.¹¹ Consequences of bruxism include jaw-muscle hypertrophy, tooth wear, fracture or failure of teeth, restorations or implants, sensitivity or pain of teeth, muscles or joints and temporomandibular joint disc displacements.¹¹

A range of medications have been associated with causing bruxism. Both typical and atypical antipsychotic drugs have inhibitory effects on dopamine-2 receptors in the central nervous system (CNS) and thereby can cause extrapyramidal involuntary movements that often affect the orofacial region including bruxism, orofacial dystonia and oromandibular dyskinesia.^{12, 13} Selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline all commonly prescribed for anxiety and depression,^{12, 14, 15} and serotonin and noradrenaline reuptake inhibitors (SNRIs) atomoxetine, venlafaxine and duloxetine have also been associated with bruxism.^{14, 16, 17} A recent systematic review of the relationship between serotonergic antidepressants and bruxism showed that medicines most commonly reported with this effect were fluoxetine, venlafaxine and sertraline.¹⁴ The average time of onset was 3-4 weeks after starting the medication or with dose escalation as the effect appears to be dose-dependent.¹⁴ In addition, two case reports have been published associating bruxism with atomoxetine, a drug used for treatment of attention deficit hyperactivity disorder (ADHD).^{18, 19} Medication-induced bruxism is under-recognised in dentistry,¹⁴ and associated drugs are listed in Table 1.

Drug-induced tardive dyskinesia

Tardive dyskinesias (TDK) are persistent, involuntary abnormal movements that can involve the face, head, neck, limbs and trunk.²⁰⁻²² Orobuccofacial dyskinesias, which are dyskinesias involving the face, mandible, lips and tongue, are often the first manifestation of TDK and the most common form. They usually present as lip-smacking, grimacing, puckering, rapid eye blinking and dyskinetic tongue movements, such as protrusion and tongue-rolling.^{20, 22, 23} Tardive dyskinesias can be stigmatising for patients, and adversely affect medication adherence and quality of life,²⁴ sometimes persisting even after the medication is stopped.²⁵ It is believed that the pathophysiology of tardive dyskinesias arise from drugs that block central dopamine receptors, although other neurotransmitters may be involved.²⁴

Metoclopramide and prochlorperazine, dopamine receptor-2 antagonists indicated for treatment and prevention of nausea and vomiting, can cause a variety of extrapyramidal disorders, with tardive dyskinesia being most common.²⁵⁻²⁷ The risk for both drugs increases with the cumulative dose and length of treatment.²¹

TDK can appear after medium to long term treatment with antipsychotic medications,²¹ typically 1-2 years after commencing the offending medication.²² It is reported that TDK will occur in up to one third of people who have taken an older antipsychotic for 10 years or longer.²¹ First generation antipsychotics, haloperidol, fluphenazine and trifluoperazine are all associated with having the highest risk of TDK.²¹ Clozapine carries a lower risk of tardive dyskinesia.²¹ Newer antipsychotics such as olanzapine, quetiapine and risperidone have a reduced incidence of tardive dyskinesias compared with first generation antipsychotics as they have greater affinity for serotonin receptors than dopamine, but the risk is still substantial.^{24, 28} While these medications are classified as antipsychotics, their indications for use have expanded over the years to include conditions such as anxiety, mania, adjunct treatment of alcohol withdrawal, and behavioural disturbances in dementia and autism.^{21, 28} Dentists should be aware of the possible adverse effects from these medications as they are being prescribed more frequently and across a wider range of age groups.²⁸ Table 2 lists the medicines associated with TDK.

Drug-induced hairy tongue

Hairy tongue occurs when hypertrophied filiform papillae of the dorsal surface of the tongue become stained by epithelial cells, exogenous material and overgrowth of chromogenic organisms.^{29, 30} This benign, self-limiting disorder can have a black, brown, yellow or green

discolouration.³⁰ Several factors have been identified in the pathogenesis of hairy tongue, including tobacco use, alcohol and intravenous drug use, poor oral hygiene, xerostomia, recent radiation therapy, and antibiotics and other medicines.^{30, 31}

The mechanism for drug-induced hairy tongue is unknown.³⁰ Several case reports have associated linezolid,³²⁻³⁴ olanzapine,³⁵ chlorpromazine³¹ and long-term use of erythromycin³⁶ with hairy tongue. Antibiotic use in general predisposes to developing hairy tongue due to their ability to modify the local oral flora,³¹ with some penicillins,^{37, 38} doxycycline,³⁸ metronidazole³⁹ and the antifungal griseofulvin³⁹ implicated as listed in Table 3.

Drug-associated gingival enlargement

Drug-induced gingival enlargement (DGE) is characterised by overgrowth of the gingiva accompanied by swelling, bleeding, and can cause problems with speech, function and aesthetics.⁴⁰ The swollen interdental papillae can have a nodular-like appearance, with the overgrowth most often affecting the anterior buccal marginal and attached gingiva.^{41, 42} While the enlarged tissue is often healthy, it impedes the patient's ability to maintain their oral hygiene, and plaque accumulation will lead to inflammatory changes including oedema and bleeding.⁴²

The mechanism by which drugs cause DGE is poorly understood.⁴³ While it seems a minimum threshold plasma level of the drug is required before overgrowth starts,^{42, 44} there is conflicting evidence regarding whether severity or incidence is related to dosage, duration of use or the pharmacodynamics of the causative medicines.^{41, 44}

It is well established that the anticonvulsant phenytoin is associated with DGE.⁴¹ While this drug is no longer frequently prescribed, in 2015 over 100,000 prescriptions were dispensed for phenytoin in Australia.⁴⁵ Reports associating phenytoin with gingival overgrowth appeared in the literature soon after its clinical introduction in the 1960s.^{41, 46} Prevalence has been reported between 13-50%,^{43, 47, 48} with a retrospective analysis of adverse drug reaction databases finding that DGE was observed around 1-3 months after starting phenytoin.⁴⁰ Case reports of other anticonvulsants associated with DGE include valproate,⁴⁹ vigabatrin⁵⁰ and phenobarbitone,⁵¹ but these reports are rare or less well documented.

Cyclosporin is an immunosuppressant used for the prevention of transplant rejection and management of autoimmune diseases.²¹ Case reports of cyclosporin being associated with

DGE appeared soon after its introduction into clinical use in the 1980s⁵² with prevalence estimated to be around 25-30% in adults and >70% in children⁴³ and time to onset 1-4 months.⁴⁰ Studies have indicated that there is a likely positive correlation between cyclosporin plasma levels and incidence of overgrowth.⁴⁴

Calcium channel blockers (CCBs) are indicated for management of hypertension, arrhythmias and angina²¹ and most have been associated with DGE, with the first case report of nifedipine being associated with gingival hyperplasia in 1984.⁵³ The median onset time to develop gingival overgrowth is reported to be between 2-14 months⁴⁰.

Drug-induced salivary secretory disorders

Salivary secretory disorders are common in the community, with drugs being one of several causes.⁵⁴

Hypersalivation and drooling

Sialorrhea or hypersalivation is the increased flow of saliva diagnosed by quantitative sialometry.⁵⁴ Drooling is not necessarily a consequence of hypersalivation, where flow and production of saliva can be normal but there is inadequate handling of the saliva.⁵⁴ Sialorrhea and drooling can be stigmatizing and embarrassing for patients, with potential consequences being sleep disturbance and social impairment.⁵⁵ In addition, long term hypersalivation can cause salivary gland swelling and inflammation, parotitis, skin irritation and aspiration pneumonia.^{21, 55}

The pathophysiology of drug-induced hypersalivation is unclear, but is thought to arise from increased cholinergic stimulation of salivary glands. The most common drug associated with hypersalivation is clozapine,⁵⁶ with sialorrhea being its second most common adverse effect.⁵⁵ Despite clozapine being useful for treatment-refractory schizophrenia,²¹ the high incidence of sialorrhea of around 31% can adversely affect treatment adherence.^{55, 57, 58}

Other antipsychotic drugs including amisulpride, chlorpromazine, fluphenazine, haloperidol, olanzapine, risperidone, quetiapine and zuclopenthixol are also associated with drooling or sialorrhea.^{56, 59} This adverse effect is thought to occur due to a combination of at least three factors: dopamine receptor blockade causing bradykinesia and impaired swallowing; alpha-2 adrenergic receptor blockade leading to reduced sympathetic innervation of the salivary

glands; and stimulation of M3 muscarinic receptors increasing parasympathetic stimulation of salivary glands.⁵⁴

Drugs that inhibit the enzyme acetylcholinesterase are also associated with hypersalivation, most likely due to increased cholinergic stimulation of the salivary glands by acetylcholine.⁵⁴ The anticholinesterases used for Alzheimer's disease including donepezil, galantamine and rivastigmine have a weaker association with hypersalivation⁶⁰⁻⁶² than the anticholinesterase drug pyridostigmine,^{21, 54} for which it is well established. Interestingly, betel nut contains arecoline, which is a muscarinic agonist also associated with sialorrhea.⁵⁴

Xerostomia

Xerostomia refers to the subjective complaint of dry mouth that may or may not be associated with reduced salivary flow, whereas salivary gland hypofunction is an objective decrease in the quantity of saliva.²⁹ The prevalence of xerostomia has been estimated to be around 17-29% of patients.^{54, 63} A cross-sectional survey reported a xerostomia incidence of 20% with risk factors including older age, use of medication and polypharmacy.⁶⁴

It is established that xerostomia can reduce the quality of life, making individuals at greater risk of smooth surface dental caries, gingivitis, worsening of periodontitis, increased risk of oral candidosis, taste disturbance and dysphagia.^{29, 64} People can also experience difficulty swallowing dry foods, complain of halitosis and a burning sensation, and it makes the retention of dentures more difficult.^{29, 64}

Medications are reported as the most common cause of dry mouth,⁶⁵ with some authors⁶⁶ identifying more than 400 drugs associated with xerostomia or salivary gland hypofunction. The usefulness of such a long list is questionable as the inclusion of most drugs listed is based on expert opinion or case reports where other compounding factors are usually present.⁶⁵ In addition, polypharmacy is common in the older population⁵ so it is difficult to identify both the causative medication as well as the possibility that the dry mouth is caused by cumulative drug effects and comorbidities.⁶⁵ Medications listed in Table 6 and discussed below as associated with xerostomia were identified from a systematic review by Wolff et al,⁵⁹ which grouped medications according to their level of evidence.

There are various mechanisms by which drugs cause xerostomia, but some are often not well documented. Drugs that have anticholinergic or antimuscarinic action decrease parasympathetic innervation of the salivary gland and therefore cause reduced saliva

secretion.⁵⁴ This can be part of the drug's primary action, such as with oxybutynin, or a side effect such as the anticholinergic effects of antihistamines, antidepressants and antipsychotics.⁶³ Antidepressants that increase the effect of serotonin, such as fluoxetine, are also strongly associated with causing xerostomia.⁶⁷ Adrenergic or psychostimulant agents such as lisdexamfetamine and methylphenidate are agonists of the sympathetic nervous system and therefore also decrease secretion of saliva.⁵⁴

Drug-induced tooth and alveolar bone discolouration

Tooth discolouration can be either extrinsic, where the stain develops after tooth eruption, or intrinsic, where tooth discolouration occurs during tooth development.⁶⁸ Chlorhexidine is well established in causing extrinsic staining of teeth, restorative materials and dorsum of the tongue.⁶⁸ Orally administered iron salts in liquid form can cause greenish-black discolouration of the teeth and to avoid this effect it is recommended to drink iron liquid using a straw and follow with water.²¹ Several case reports have recently emerged of the antibiotic linezolid causing both extrinsic yellow tooth and tongue staining in children.^{33, 69}

Tetracycline antibiotics are a well-established cause of intrinsic tooth discolouration, with a prevalence of 3-4%.⁷⁰ The tetracycline chelates with calcium ions during tooth development and forms a tetracycline-calcium orthophosphate complex in teeth.^{70, 71} As the tetracycline layer inside the tooth is oxidised by light it forms visible discolouration.^{71, 72} The appearance of the yellow, grey or brown permanent discolouration tends to be on the cervical one third of the crowns,⁷² with the degree of staining being related to the duration and timing of drug administration.⁷⁰ Reports emerged in the 1960s of tooth discolouration caused by tetracycline,⁷³ leading to the avoidance of tetracyclines in the second and third trimester of pregnant women and children up to 8 years of age.

Minocycline, a derivative of tetracycline commonly used for the management of acne,^{21, 71} not only causes tooth discolouration but also gum and alveolar bone pigmentation.^{71, 74} While tetracycline staining affects the developing dentition, minocycline can also cause staining in fully erupted teeth, after the period of odontogenesis.⁷⁵ Minocycline staining tends to take on a blue-grey hue, mostly at the incisal and middle thirds of the crown.^{70, 72, 74} The prevalence of minocycline staining has been reported to be between 3-6%,⁷⁴⁻⁷⁶ and while various theories exist, the mechanism by which the staining occurs is unknown. The stain can also occur on the roots of teeth, causing a "black" or "green" discolouration which has been noted after

extractions.^{70, 74, 75} Minocycline can cause pigmentation in other tissues, including alveolar bone, producing a “black bone” appearance.^{75, 77} Eisen⁷⁸ reported that alveolar bone pigmentation is most clinically noticeable beneath the semitranslucent maxillary and mandibular anterior alveolar mucosa, followed by the mandibular posterior lingual mucosa and the hard palate, and that the incidence of minocycline-induced bone pigmentation is estimated to be around 10% after 1 year in patients taking at least 100mg of minocycline daily, with the incidence increasing to 20% after 4 years, and is thought not to be reversible.⁷⁸

It should also be noted that there are case reports of doxycycline being associated with discolouration of the erupted dentition,^{74, 79} while ciprofloxacin has also been associated with causing an intrinsic green stain on teeth when used in infants.⁷⁴

Drug-induced taste disturbance

Many drugs can interfere with the perception of taste, and this has been reviewed in detail by Henkin et al,⁸⁰ Ackerman et al⁸¹ and Naik et al.⁸² Dysgeusia, the experience of distortion or misinterpretation of taste, is the most common taste disorder caused by drugs.⁸² Other categories include ageusia (the absence of one or more of the basic taste sensations of sweet, salty, sour or bitter), hypogeusia (the decrease in taste sensitivity) and parageusia (the perception of a spoiled taste).^{81, 82} Various studies have estimated the prevalence between 3-11%,⁸² but difficulty arises in determining true incidence due to the subjective interpretation of the disorder.⁸² Onset of most taste disturbances occur early in treatment even from the first dose and usually persists for several weeks after the drug has been ceased.

An extensive number of drugs have been associated with causing taste disorders^{80, 81} however those listed here have been previously reported by Naik et al⁸² and are in agreement with those specifically identified in the monographs for each drug in the Australian Medicines Handbook.²¹ It is thought that drugs can alter taste sensation by affecting ion channel receptors of taste buds or their second messenger systems that relay the sensation of taste via cranial nerves to the brainstem.^{81, 82} Several anti-hypertensive medicines can cause dysgeusia, including captopril, which is associated with a metallic or bitter taste.^{81, 82} Calcium channel blockers, including nifedipine and diltiazem are associated with dysgeusia.⁸¹ Acetazolamide, used for glaucoma can cause a bitter or metallic taste, possibly secondary to acidosis caused by its effect as a carbonic anhydrase inhibitor.^{81, 83} Metronidazole, the second most commonly prescribed antibiotic in dentistry,⁸⁴ frequently causes a metallic taste as a

side effect.²¹ The oral antifungal medicines griseofulvin and terbinafine can cause taste disturbances,²¹ with terbinafine also being associated with ageusia.⁸¹ Several anti-inflammatory drugs, immunosuppressants and anti-neoplastics have been reported to be associated with one or more of the different taste disorders as listed in Table 8.

Medication-related osteonecrosis of the jaw

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but serious adverse effect that causes substantial morbidity for patients. Since the first published report of MRONJ by Marx in 2003,⁸⁵ there have been many case reports and a plethora of literature on this relatively recently recognised condition. The list of drugs implicated in triggering MRONJ has grown since the early days when bisphosphonates were considered the main cause, to now including many types of drugs.⁸⁶ MRONJ is defined by the following three characteristics:^{86, 87}

1. Current or previous treatment with antiresorptive or antiangiogenic agents
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

Risk factors for MRONJ include dentoalveolar surgery, with tooth extraction most commonly reported as the precipitating event in 73% of cases in an Australian study,⁸⁸ and the American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper on MRONJ reports tooth extraction as the predisposing event in 52-61% of patients.⁸⁶ They also report other invasive dental procedures as risk factors, including dental implant placement, periapical surgery and periodontal surgery involving osseous injury.⁸⁹ Twice as many cases of MRONJ have been reported in the mandible compared to the maxilla,⁸⁷⁻⁸⁹ and an increased risk is shown with the concurrent use of systemic corticosteroids.⁸⁶

While it is well established that bisphosphonates (BPs) carry an increased risk of causing MRONJ, the exact pathogenesis is unknown.⁸⁶ Various theories exist for both BPs and the antiangiogenic drugs, mostly involving altered bone remodelling, suppression of bone resorption and inhibition of new blood vessel formation.⁸⁶ More potent IV nitrogen-containing BPs carry a greater risk, with pamidronate and zoledronic acid (the latter being 100,000 times more potent than etidronate)⁹⁰ having a greater risk for MRONJ than the oral

BP alendronate.^{88, 90} A recent systematic review and meta-analysis has shown that the risk of MRONJ is also greater in oncology patients who are exposed to antiresorptive drugs than those who are treated for osteoporosis.⁸⁷ The Australian survey-based study by Mavrokokki et al reports a risk of 0.09-0.34% for patients who are taking BPs for osteoporosis and have had a tooth extraction, and a subsequent greater risk of 6.67-9.1% in oncology patients undergoing an extraction.⁸⁸ Increased duration of treatment and exposure to these medicines also correlates with higher risk of developing MRONJ.^{87, 89}

Denosumab reduces bone resorption by binding to the receptor activator of nuclear factor-kappa B ligand (RANKL), which causes decreased formation and activity of osteoclasts,²¹ and its association with MRONJ is well established.^{91, 92} Longer treatment duration and higher doses are correlated with an increased risk for MRONJ. An international, randomised double-blinded phase 3 study using high dose denosumab for patients with multiple myeloma showed that the incidence of MRONJ in the denosumab group was 2.0% during the first year of treatment, 5.0% in the second year and 4.5% per year thereafter.^{91, 93} The AAMOS reported the risk of developing MRONJ for oncology patients exposed to denosumab to be between 0.7-1.9%, proportionate to the risk by zoledronic acid.⁸⁶

Anti-angiogenic therapies, including sunitinib, sorafenib, bevacizumab and sirolimus, have had increasing case reports regarding their association with MRONJ.^{86, 94, 95} A pooled analysis from two randomised prospective trials showed that the risk of developing MRONJ in an oncology patient exposed to bevacizumab is 0.2%.^{86, 96} There is also a case report of aflibercept, in combination with fluorouracil and irinotecan being associated with this condition, highlighting the association between anti-angiogenic therapies and MRONJ.⁹⁷

Furthermore, there are case reports of methotrexate its association with MRONJ, possibly due to its inhibitory effects on osteoclasts and impairment of wound healing.⁹⁸ Some TNF-alpha inhibitors, adalimumab and etanercept are also implicated, as well as the antineoplastic antibody, rituximab.⁹⁹ These recent reports accentuate the growing number of drugs from different drug classes associated with MRONJ.

Other considerations

Oral ADRs are often a neglected area of pharmacovigilance. In Australia, an ADR can be reported to the Therapeutic Goods Administration (<https://www.tga.gov.au/publication/reporting-adverse-drug-reactions>)

A survey of dentists in the UK revealed that one reason for the lack of reporting of ADRs by dentists was the rarity of oral adverse effects.⁷ Previous suggestions to improve ADR reporting include collaboration between dental and pharmacy industries to target recognition of oral ADRs⁷ and the incorporation of pharmacovigilance education into undergraduate dental training.¹⁰⁰ It is also recommended to list oral ADRs separately in the registered product information so they are easily found, as the current convention is to list them in the “gastrointestinal” section. Not only does this obscure useful information for dentists as they can be easily overlooked in a section assumed to be about the stomach and bowel, but implies they are not important enough to list separately or that they do not exist.

Other recommendations include a focus on pharmacovigilance as part of dental continuing education programs, or as suggested by Patel et al,⁸ considering changing voluntary ADR reporting in Australia to a compulsory system, similar to some European countries. These concepts, as well as other oral adverse effects including lichenoid reactions and drug-induced oral mucosal lesions, will be further discussed in Part 2 of this series.

In summary, there is an increasing array of drugs available in health care today, with increasing availability, wider variety of prescribers and broadening range of uses. As it is likely that the incidence of oral adverse effects will increase, it behoves dental professionals to consider drug-induced oral adverse effects. The importance of establishing a correct diagnosis, using an adverse drug validation algorithm to confirm the reaction if possible and reporting of adverse reactions to drug regulatory agencies cannot be underestimated.

Table 1. Drugs Associated with Bruxism*

Drug class	Drug	
Antidepressants	Citalopram	Paroxetine
	Escitalopram	Sertraline
	Duloxetine	Venlafaxine
	Fluoxetine	
	Fluvoxamine	
Antipsychotics	Chlorpromazine	
	Fluphenazine	
	Haloperidol	
Drugs for ADHD	Atomoxetine	

*Adapted from Garrett and Hawley, 2018¹⁴ and Fratto and Manzon, 2014¹³

Table 2. Drugs Associated with Tardive Dyskinesia

Drug class	Drug	
Antipsychotics	Amisulpride	Olanzapine
	Aripiprazole	Paliperidone
	Chlorpromazine	Pericyazine
	Clozapine	Quetiapine
	Droperidol	Risperidone
	Flupenthixol	Trifluoperazine
	Fluphenazine	Ziprasidone
	Haloperidol	Zuclopenthixol
	Lurasidone	
Dopamine antagonists	Metoclopramide	
	Prochlorperazine	

Table 3. Drugs Associated with Hairy Tongue

Drug class	Drug	
Antibiotics	Penicillins	Amoxicillin
		Amoxicillin/clavulanic acid
		Ampicillin
		Phenoxymethylpenicillin
	Macrolides	Erythromycin
	Nitroimidazoles	Metronidazole
	Oxazolidinones	Linezolid
Antifungals	Tetracyclines	Doxycycline
		Griseofulvin
Antipsychotics		Olanzapine
		Chlorpromazine

Table 4. Drugs Associated with Gingival Enlargement

Drug class		Drug
Anticonvulsants		Phenytoin
Calcium channel blockers	Dihydropyridines	Amlodipine
		Nifedipine
		Felodipine
	Non-dihydropyridines	Diltiazem
		Verapamil
Immunosuppressants		Cyclosporin

Table 5. Drugs Associated with Hypersalivation

Drug class	Drug	
Acetylcholinesterase inhibitors	Donepezil	
	Galantamine	
	Pyridostigmine	
	Rivastigmine	
Antipsychotics	Haloperidol	Olanzapine
	Amisulpride	Quetiapine
	Chlorpromazine	Risperidone
	Clozapine	Zuclopenthixol
	Fluphenazine	
Other	Betel nut	

Table 6. Drugs Associated with Xerostomia or Salivary Gland Hypofunction*

	Medications with a higher level of evidence		Medications with a moderate level of evidence	Medications with a weaker level of evidence
Anticholinergic/antimuscarinic medicines	Atropine Oxybutynin Propantheline Scopolamine Solifenacin Tolterodine		Darifenacin Hyoscine	Ipratropium
Anticonvulsants	Gabapentin		Pregabalin Sodium valproate	
Antidepressants	Amitriptyline Citalopram Duloxetine Escitalopram Fluoxetine Imipramine	Nortriptyline Paroxetine Reboxetine Sertraline Venlafaxine Vortioxetine	Desvenlafaxine Dothiepin Doxepin	Clomipramine Mirtazapine Moclobemide Phenelzine
Antihistamines	Doxylamine		Azelastine Cetirizine Desloratadine	Chlorpheniramine Dimenhydrinate Diphenhydramine Pheniramine
Antihypertensives	Clonidine Verapamil		Atenolol Enalapril Lisinopril Methyldopa Metoprolol Terazosin	Diltiazem Perindopril
Antipsychotics	Aripiprazole Chlorpromazine Olanzapine Paliperidone Quetiapine Risperidone	Ziprasidone	Amisulpride Asenapine Haloperidol Lurasidone	
Antivirals			Didanosine Etravirine Lamivudine Maraviroc Nevirapine Raltegravir Saquinavir	
Diuretics	Furosemide		Tolvaptan	Amiloride
Muscle relaxants	Baclofen			
Opioid analgesics	Buprenorphine		Dihydrocodeine Fentanyl Morphine Tapentadol Tramadol	Pethidine
Sedatives and hypnotics	Zolpidem		Zopiclone	
Other medicines	Alendronate Bevacizumab Brimonidine Bupropion Lisdexamfetamine Lithium Methylphenidate Phentermine Rotigotine Timolol Tiotropium		Dexmedetomidine Naltrexone Nicotine Orlistat	Apraclonidine Atomoxetine Cisplatin Disopyramide Granisetron Levomopromazine Modafinil Moxifloxacin Pseudoephedrine Selegiline

*Adapted from Wolff et al, 2017,⁵⁹ classifications of drugs are from AMH²¹

Table 7. Drug-Associated Tooth Discolouration*

	Drug class	Drug
Tooth discolouration (extrinsic)		Chlorhexidine
		Linezolid
		Oral liquid iron
Tooth discolouration (intrinsic)	Fluoroquinolones	Ciprofloxacin
	Tetracyclines	Doxycycline
		Minocycline
		Tetracycline

*Adapted from Tredwin et al, 2005⁶⁸

Table 8. Some Drugs Associated with Taste Disturbance*

Drug Class	Drug
Anticonvulsants	Topiramate
Antifungals	Griseofulvin
	Terbinafine
Antibacterials	Metronidazole
Antihypertensives and other cardiac medicines	Amiodarone
	Captopril
	Nifedipine
	Diltiazem
	Losartan
	Candesartan
Anti-inflammatory and immunosuppressants	Auranofin
	Aurothiomalate
	Penicillamine
	Interferon alfa
Anti-neoplastics	Carboplatin
	Cyclophosphamide
Antipsychotics	Lithium
Drugs for glaucoma	Acetazolamide
Hypnotics	Zopiclone
	Zolpidem

*Adapted from Naik et al, 2017⁸² and Australian Medicines Handbook²¹

Table 9. Medication-Related Osteonecrosis of the Jaw*

Drug class	Drug
Bisphosphonates	Alendronate
	Clodronate
	Ibandronic acid
	Pamidronate
	Risedronate
	Zoledronic acid
Human monoclonal antibody	Denosumab
Mammalian target of rapamycin inhibitor	Sirolimus
VEGF antineoplastic antibody	Bevacizumab
Tyrosine kinase inhibitor	Sorafenib
	Sunitinib

*Adapted from Ruggiero et al, 2014⁸⁶

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