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REVIEW ARTICLE

A review and guide to drug-associated oral adverse effects - Oral mucosal and lichenoid reactions. Part 2.

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Abstract

Dental practitioners and other health professionals commonly encounter and manage adverse medicine effects that manifest in the orofacial region. Numerous medicines are associated with a variety of oral adverse effects. However, due to lack of awareness and training, these side effects are not always associated with medicine use and are underreported to pharmacovigilance agencies by dentists and other health professionals. This article aims to inform health professionals about the various oral adverse effects that can occur and the most commonly implicated drugs to improve the management, recognition and reporting of adverse drug effects. This article follows on from Part 1, however the focus here is on lichenoid reactions and oral mucosal disorders including oral aphthous-like ulceration, mucositis and bullous disorders such as drug-induced pemphigus, pemphigoid, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Introduction

A wide range of medications have been associated with causing adverse drug reactions (ADRs) in the oral cavity. However, due the limitations of standard clinical trials and a lack of oral health pharmacovigilance by medical researchers and patients themselves, oral ADRs are often missed during clinical trials. Short term and well-known symptoms such as dry mouth and taste disturbances may be reported, but more obscure diagnoses such as oral mucosal changes as well as long term oral effects such as osteonecrosis of the jaw are not usually identified as being drug-induced until a drug has been on the market for many years.[2, 3] This highlights the need for oral health practitioners to be aware of the limitations of oral ADR information with new drugs, and the importance of their involvement in post-marketing drug safety monitoring, as it may only be dental practitioners who will observe oral symptoms or are in a position to ask about ADRs that manifest in the mouth. Moreover, dentists need to be aware that oral ADRs need to be reported to pharmacovigilance agencies to be recognised and collated with data from other countries. The increasing diversity and complexity of medications being marketed today makes it even more important for oral health pharmacovigilance to become embedded in current dental practice.

To do this, dental practitioners require an understanding the range of oral ADRs that have been reported, and the medicines that they are associated. Thus, the aim of this review and guide is to summarise the commonly implicated drugs associated with orofacial adverse effects for health professionals to help with patient management in clinical practice. This review follows on from Part 1, with the focus here on the oral mucosal adverse effects including bullous disorders and lichenoid reactions. Since the authors of this review practice in Australia, only drugs that are currently marketed in Australia have been included in this review.

Drug-induced lichenoid reactions

Lichen planus is a chronic inflammatory disease that can affect the skin and any lining mucosa, including the oral, oesophageal and genital mucosa.[6] It is reported to affect approximately 2% of the population, with women more commonly affected than men.[6] Oral lichen planus typically occurs on the buccal mucosa, tongue and gingivae and can have a variety of clinical presentations, from a white striated reticular pattern to white and red confluent plaques, ulcerations or erosions.[7] While the aetiology is unclear, it is thought it be

an immunologically mediated reaction of the lymphocytes to the basal keratinocytes on the surface of the skin or mucosa.[8] Oral lichenoid reactions (OLR) refer to a lesion that clinically and histologically resembles lichen planus.[9] A wide range of drugs have been implicated in causing oral lichenoid reactions with conflicting presentations.[10] The ambiguity of these case reports arise from the lack of biopsy confirming the diagnosis, the use of imprecise terminology when establishing a full diagnosis, when the histological appearance is similar to but not consistent with classical lichen planus,[11] as well as the lack of the use of an adverse drug reaction validation protocol, such as the challenge–dechallenge-rechallenge (C-D-R) procedure or Naranjo algorithm.[10, 12]

While there are numerous case reports of medications associated with oral lichenoid reactions, a systematic review showed that most evidence for this rare adverse effect exists for a few drugs only.[10] Of the cardiac medications, most evidence exists for methyldopa, with one case of the reappearance of the oral lesions on rechallenge.[13] There are single case reports of other cardiac drugs, including oxprenolol,[14] atenolol,[15] captopril and enalapril[16] also demonstrating oral lichenoid lesions on both clinical and histological examination.

The immunosuppressants imatinib, infliximab and interferon-alpha (IFN-alpha) appear to have substantial evidence to support their association with causing OLR.[10] Imatinib is a tyrosine kinase inhibitor, which inhibits the effect of specific tyrosine kinases that can be abnormally activated in certain cancers.[17] Each case report for imatinib describes the OLR appearing between 3-12 months after starting therapy.[18, 19] The oral lesions either resolved on withdrawal of imatinib or were treated, and one case also confirms the adverse effect by demonstrating the re-appearance of the oral lesions after the re-introduction of imatinib.[20]

Tumour necrosis factor-alpha (TNF-alpha) inhibitors infliximab and adalimumab are used as immunosuppressants for conditions such as rheumatoid arthritis and inflammatory bowel disease, including Crohn's disease and ulcerative colitis. TNF-alpha is a signaling molecule involved in the aetiopathogenesis of inflammatory and immune responses.[17] Several cutaneous and mucosal lesions have been described, with most case reports detailing OLR for infliximab developing between 3-8 weeks after commencement.[21, 22] Withdrawal of the drug resulted in either partial or complete resolution of the OLR. No rechallenges or adverse drug reaction validation protocol was undertaken or recorded in these cases. Two case reports have been described for adalimumab,[23] with one showing that rechallenge of the medication resulted in an OLR.[24]

IFN-alpha is an immunosuppressant drug that has multiple actions including suppression of cell proliferation and other immunomodulatory effects. It is mostly used in certain cancers including chronic myeloid leukaemia and renal cell cancer. Several case reports have detailed the adverse effect of OLR occurring between 10 days – 8 months after starting therapy, where the lesions resolved after discontinuation.[25, 26]

NSAIDs have been implicated in causing OLRs,[27] with naproxen having the most evidence for both skin and oral lesions.[28, 29] One retrospective study showed that the oral lesions developed between 2 weeks and 3 months, with lesion resolution on withdrawal.[29] However, the literature is contradictory regarding the link between NSAIDs and OLRs, with one prospective study not finding any association between oral keratoses (lichen planus and leukoplakia) and use of NSAIDs,[30] while in contrast, another retrospective study supported the association between beta-blockers and NSAIDs in the pathogenesis of OLRs.[31] Finally, one case report clearly detailed a strong association between the use of indomethacin provoking an OLR, which recurred on rechallenge.[32]

There is a long list of other drugs considered capable of causing OLRs, but many case reports lack detail in terms of confirmation of the diagnosis by histopathology, or absence of a definite diagnosis by use of imprecise terminology regarding histological findings.[10] Other medications that may be drugs associated with OLRs include: lithium carbonate,[33] hepatitis B vaccine,[34] clopidogrel,[35] ribavirin,[36] carbamazepine,[37] risperidone,[37] certolizumab,[38] glimepiride,[39] duloxetine[40] and secukinumab.[41] Most of these medications however have only single or a few case reports associating them with OLRs, although all have had a biopsy or immunofluorescence to determine the diagnosis of oral lichenoid lesion and some have shown that a rechallenge of the culprit medication has resulted in reappearance of the reaction. Drug-induced OLR are a rare adverse effect so it is important for health practitioners to be aware of this possibility, confirm the diagnosis by an adverse drug algorithm and report the case to their respective drug regulatory authority. In agreement with Fortuna et al[10] and Myers et al,[11] a universal protocol should be established to conclusively prove this association for each case. Table 1 details drugs associated with lichenoid-like reactions, and is adapted from Fortuna et al.[10]

Drug-associated mucosal ulceration, mucositis and bullous disorders

Drug-associated aphthous-like ulceration

Recurrent aphthous ulceration (RAS) is defined as an "inflammatory condition of unknown aetiology characterised by painful recurrent, single or multiple ulcerations of the oral mucosa."[42] Medications have been associated with causing aphthous-like ulcerations, but this side effect is generally rare (Table 2).[42, 43] The oral lesions present as discrete, ovoid, well-demarcated, relatively shallow ulcers surrounded by a characteristic erythematous border.[44] Lisi et al[43] describes that the differentiation between RAS and oral ulceration due to drugs can be difficult, where drug stomatitis generally displays features such as the presence of numerous and simultaneous lesions of a similar size (generally 2-3mm), a tendency to coalesce into larger ulcers (0.5-2cm), cause severe pain with longer duration and their recurrence after intake of medicines.

Aphthous-like ulceration has been associated with the anti-anginal drug nicorandil, which has many confirmatory case reports.[17, 45] It is established that these large, painful ulcers mostly occur in the oral cavity, but can be in the perianal area, and fistulae can also develop in the gastro-intestinal and genital tracts, where healing occurs only after cessation of nicorandil.[17] There has been one case report of captopril causing aphthous-like ulcerations on the tongue and buccal mucosa,[42] and two case reports confirming the association of piroxicam with this adverse effect.[43, 46] A case-control study that assessed the role of drug-exposure in aphthous ulcer formation found an association between beta-blockers and NSAIDs.[47]

Many case reports have been published regarding the association between the oral bisphosphonate alendronate and oral ulceration.[48, 49] Oesophageal and gastrointestinal ulceration are well-established side effects of alendronate, but oral ulceration is less widely-known.[48] Many case reports attribute the development of oral ulceration with incorrect use of the medication, where the patient keeps the tablet in the mouth for a prolonged period instead of immediately swallowing it.[50] However, reports have surfaced in which the adverse reaction has occurred when alendronate has been administered appropriately.[49] While alendronate accounts for the majority of oral ulceration case reports, there have been cases involving the use of both etidronate and risedronate.[51] Published cases indicate that improvement occurs within weeks after ceasing the offending drug, but complete recovery can take several months.[51]

Aphthous-like ulceration has also been well documented with the mammalian target of rapamycin (mTOR) inhibitors used in cancer therapy, including sirolimus, everolimus, temsirolimus and ridaforolimus.[52-54] The median time to development of mucositis was found

to be a week to 10 days,[52, 53] and it has been reported to be the most frequent adverse effect of these medicines.[53] Oral mucosal injury has been reported to account for 27.3% of dose reductions and 13.1% of cases of discontinuations of therapy.[53] Presentation of the ulceration is described as being "aphthous-like" and is clinically distinct from classic chemotherapy-induced mucositis.[44, 53] The pathogenesis of how mTOR inhibitors activate the inflammatory cascade to cause the ulceration is unclear.[53]

Immunosuppressant-induced mucositis

Mucositis is a common, dose-limiting adverse effect associated with use of anti-neoplastic drugs for cancer chemotherapy, with an occurrence of about 40%.[55] With the myelosuppression that occurs with cancer treatment and concurrent ulcerative lesions providing access for microorganisms, mucositis is a significant source of systemic infection for these patients.[55] Unlike the discrete aphthous-like ulceration, Sonis et al[44] describe mucositis as appearing on movable mucosa and has a non-uniform shape, increased depth and the presence of a fibrinous pseudomembrane with cellular debris, and a lack of a peripheral erythematous border. Lesions tend to develop within 4-5 days after starting chemotherapy, peak between days 7-10,[44] and can induce such severe pain as to require dose de-escalation[55] and systemic analgesics.[44]

Many anti-neoplastics and anti-metabolites are associated with oral mucositis as an adverse effect and are listed in Table 3.[17] The exact mechanism by which these drugs cause mucosal toxicity is largely unknown, but some authors indicate that the pathophysiology involves pro-inflammatory cytokines specific to each drug.[56] Others propose that this complex process has multiple aetiologies involving direct action of the drug on the epithelium, the bacterial flora and the immune status of the patient.[55] Oral mucositis is a well-documented side effect of the antimetabolites methotrexate and fluorouracil when used in high dose, and also mycophenolate and tacrolimus[57] that are used for immunosuppression after organ transplantation. It has also been proposed that sirolimus, used for kidney transplant recipients, has an antiproliferative effect responsible for the toxic action on the oral mucosa.[58]

Drug-associated lupus

Drug-induced lupus (DIL) is a rare, lupus-like autoimmune condition that usually occurs after long-term use, from one month to as long as over a decade,[59] of certain drugs with complete resolution after withdrawal of the offending medicine.[59, 60] While oral ulcerative lesions are common with systemic lupus erythematous,[61] they are rare in DIL.[62] The mechanism by which the medicines cause lupus-like syndrome is unknown, but is postulated to be linked to susceptibility of the adaptive immune system to descend into a state of auto-reactivity.[63] Procainamide, (no longer marketed for use in Australia) and hydralazine (used for moderate to severe hypertension) are both well-documented to have the highest risk for developing DIL of 15-20% and 7-13% risk respectively.[62] The yearly incidence of clinical DIL for hydralazine is 5-8% with standard doses.[62, 63] Penicillamine, methyldopa, sulfasalazine, chlorpromazine, carbamazepine, isoniazid, captopril, propylthiouracil and minocycline are considered to be of low risk.[63-65] There are many other drugs that have been associated with DIL, but the evidence for association is not strong and only a few case reports exist. More recently, there have been increasing case reports of proton-pump inhibitors being associated with DIL,[60, 66] and evidence for anti-TNF-alpha inhibitors including infliximab, etanercept and adalimumab being associated with DIL.[59, 62] The drugs listed in Table 4 are only the established high and low risk medicines associated with DIL.

Drug-associated pemphigoid

Drug-induced pemphigoid (DIP) is a variant of the autoimmune disease bullous pemphigoid, and is characterised by sub-epithelial blistering, intra-epidermal vesicles and ulceration following administration of the offending drug.[67] The clinical and histological presentation and immunopathologic characteristics are similar or identical to that of the acquired autoimmune disease.[68] In bullous pemphigoid, the autoantibodies are directed against the antigens located in the dermo-epidermal junction,[68] however in drug-induced pemphigoid, no specific antigens have been identified.[67]

DIP tends to occur in younger people than bullous pemphigoid, with generally mild and inconsistent mucosal involvement, and the bullae heal without scarring.[67, 69] A drug-induced bullous eruption can present up to 3 months after the ingestion of the offending medication.[67]

Table 5 lists the medicines that are reported to trigger DIP, grouped into their likelihood of association.[69] Many other drugs have been implicated, however these tend to report an association with no re-challenge for ethical reasons.[67-69] It is suspected that drugs act as triggers in genetically predisposed patients to either alter the immune response or modify the

antigenic characteristics of the epidermal basement membrane to cause the sub-epithelial blistering.[69] Loop diuretics were used significantly more frequently by patients with bullous pemphigoid in a recent case control study in the United Kingdom[70] and a retrospective study confirmed that people taking systemic medicines were more susceptible to the development of bullous pemphigoid, with patients who had pemphigoid more commonly taking angiotensin converting enzyme inhibitors (ACEIs), anticoagulants and diuretics.[71] It is postulated that the sulfhydryl chemical moiety in some drugs, including penicillamine, captopril and frusemide, facilitates the development of drug-induced pemphigoid, with the proposal that the free sulfhydryl group can combine with other substrates and result in autoantibody formation to the basement membrane proteins.[69]

Recently, there have been increasing case reports of other medicines being associated with bullous pemphigoid, reviewed in detail in Stavropoulos et al.[67] An increasing number of case reports have shown an association between drug-induced pemphigoid and TNF-alpha inhibitors,[67, 69] including etanercept[72] and adalimumab.[73] Various vaccines have also been associated with drug-induced pemphigoid, with mostly the influenza vaccine implicated.[74] Recent case reports have also emerged highlighting an association between drug-induced pemphigoid and the dipeptidyl peptidase-4 inhibitors, sitagliptin and vildagliptin, which are used in the management of type 2 diabetes.[75]

Drug-associated pemphigus

Pemphigus is a rare, autoimmune vesiculobullous disease that affects the skin and mucous membranes,[76] and for which drugs are the most common trigger.[77] Histologically, pemphigus is diagnosed as an intra-epithelial split due to loss of cohesion between the stratified squamous epithelial cells.[78, 79] There is also the presence of predominantly IgG autoantibodies directed against the epithelial cell surface, resulting in damage to the intercellular area between keratinocytes and subsequent acantholysis.[79] Oral lesions are usually present at an early stage and are mostly present on the buccal mucosa, palate, ventral tongue and lips.[79] They start as blisters and progress to chronic erosions and ulcers. In advanced disease severe desquamative or erosive gingivitis can also be present.[79]

There are three separate chemical moieties in drugs that have been associated with inducing pemphigus: drugs containing a sulfhydryl group; drugs containing a phenol group; and non-sulfhydryl, non-phenol drugs.[76, 77] These drugs are listed in Table 6.[77, 79, 80] Drugs that are

most frequently implicated in triggering pemphigus contain a sulfhydryl group including penicillamine, captopril, penicillin and piroxicam.[77] It has been shown that the incorporation of the sulfhydryl drugs into the keratinocyte can cause changes that result in the production of autoantibodies responsible for the immune-driven acantholysis in pemphigus.[77] It should be noted that the induction of this reaction by drugs is rare with the exception of penicillamine, where it is estimated that approximately 7% of patients taking penicillamine for at least 6 months develop pemphigus.[78]

Phenolic drugs reported to induce pemphigus include cephalosporins, aspirin, rifampicin, levodopa, heroin and phenobarbitone.[77] It is thought that the keratinocytes release specific cytokines on exposure to the phenol drugs that are involved in the acantholytic process in patients with an underlying genetic predisposition.[77] The mechanism by which other non-sulfhydryl, non-phenol drugs, such as ACEIs, NSAIDs and some calcium channel blockers may trigger pemphigus is thought to be due to overexpression of target antigens on the keratinocyte combined with an amplification of the immune response.[77]

Drug-associated erythema multiforme

Erythema multiforme (EM) is an acute, self-limiting, inflammatory disorder that is characterised by typical target skin lesions or mucosal ulcerations, or both.[81] There are several reports of EM confined to the oral cavity.[82] The frequency of mucosal involvement has been estimated to be between 25 to 60% in all cases of erythema multiforme,[83] often with the appearance of blood crusted lips.[84] Mucosal lesions start with erythematous macules, that develop into oedematous vesicles and subsequently rupture forming erosions with a fibrinous pseudomembrane.[83, 84] They generally heal within 6 weeks[83] without scarring.[84] Other mucosa involved can also include the eyes, pharyngeal, genital and respiratory tract, and is associated with significant morbidity.[83] When there is skin involvement by definition there is less than 10% of body surface area affected.[81, 85] While EM has a strong association with viruses, such as herpes simplex, and other infectious agents such as mycoplasma pneumoniae and candida, drugs are the second most common cause.[81]

Many individual case reports exist that implicate numerous drugs with EM. Drug-induced EM, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reviewed in detail by Lerch et al,[81, 86] but will be summarised here and in Tables 7 and 8. A large case control study (SCAR study) conducted between 1989 and 1995 quantified the

association of specific drugs with EM, SJS and TEN, and showed that the highly implicated drugs were oxicam-NSAIDs (piroxicam), phenobarbitone, phenytoin, anti-bacterial sulphonamides and allopurinol.[81, 85, 87] A population-based study found that allopurinol/diphenhydramine, amoxicillin, ampicillin, erythromycin, diphtheria-tetanus-pertussis vaccination, nitrofurantoin, tetracycline and valproic acid were all implicated.[81, 88] Sulfonamides have been reported in several studies, including the trimethoprim/sulfamethoxazole combination.[83]

Recently, several case reports have emerged of EM being triggered by TNF-alpha inhibitors including adalimumab, infliximab and etanercept,[89] as well as alectinib.[90] In addition, a recent case report has identified the antineoplastic drugs nivolumab and vemurafenib causing EM.[81, 91]

Drug-associated Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and it's more severe variant, TEN are delayed T-cell mediated hypersensitivity reactions largely due to medications,[86, 92] characterised by blistering and erosion of the skin and mucous membranes.[93] The principal difference between SJS, SJS-TEN overlap and TEN is determined by the percentage of cutaneous involvement, with SJS having <10% of epidermal detachment, SJS-TEN overlap having between 10-30% and TEN is having >30% of skin detachment.[85, 86] While SJS and TEN are rare severe cutaneous adverse reactions with an estimated incidence of 2 cases/million population/year, they have a high morbidity and mortality.[93] The painful widespread oral mucositis causes dysphagia and odynophagia.[94] The mortality risk is high for TEN (>40%), and other complications such as ocular involvement are prominent in survivors (40-50%).[95]

Exposure to drugs are the leading cause of SJS and TEN, with a delay of 4-28 days in most cases between the onset of drug intake and commencement of symptoms, although there can be a delay of up to 30 weeks before symptoms develop for drugs not commonly associated with SJS/TEN.[86, 93] While there have been more than 100 drugs identified in case reports as causes of SJS/TEN, only a limited number are responsible for the majority of cases.[87] The SCAR study showed that trimethoprim/sulfamethoxazole, oxicam-NSAIDs (piroxicam), allopurinol, phenobarbitone, phenytoin and carbamazepine had substantial increased risk for causing SJS/TEN.[85, 87] A subsequent similar study, conducted through a hospital network in Europe from 1997 to 2001 (the EuroSCAR study) that assessed the risk of medicines for

inducing SJS/TEN showed that nevirapine, lamotrigine and meloxicam had increased risk, and weaker associations were shown for sertraline.[93] Valproic acid was considered a high risk drug in the original SCAR study,[85] but this risk was not confirmed in the EuroSCAR study.[93] The same study confirmed that allopurinol was the most frequently associated drug with SJS and TEN, with daily doses of more than 200mg being associated with increased risk.[86, 96] A pooled analysis assessing medications as risk factors for the development of SJS and TEN in children identified anti-infective sulphonamides, phenobarbitone, carbamazepine and lamotrigine as high risk drugs.[95] Recent literature has shown that the risk of SJS/TEN with carbamazepine treatment is strongly associated with people who have variant alleles of the human leukocyte antigen (HLA-B 1502 and HLA-A3101).[97] Current recommendations therefore include genetic testing for people in at-risk populations prior to commencing carbamazepine.[97] A retrospective analysis of drug-related hospitalisations in Portugal from 2009 to 2014 found that the most frequently associated drug classes with SJS/TEN included antibiotics, antivirals, anticonvulsants and uric acid metabolism drugs, and in particular allopurinol and lamotrigine.[98] A systematic review of drug-induced SJS and TEN in the Indian population showed carbamazepine, phenytoin, fluoroquinolones (gatifloxacin, ciprofloxacin, ofloxacin, and levofloxacin) and paracetamol as being strongly associated with SJS/TEN.[86, 99] Other studies[95] have also suspected paracetamol while others still have questioned its association due to confounding by indication or other concurrent medication.[93]

Conclusion

Oral ADRs are often a neglected area of pharmacovigilance by all health professionals. It is suspected that dentists tend not to report ADRs as they do not recognise it as their role, they may not realise the condition is drug-induced, may not know how to report an ADR, or are not confident that it should even be reported. In Australia, an ADR can be reported to the Therapeutic Goods Administration (https://www.tga.gov.au/publication/reporting-adverse-drug-reactions)

A systematic review of the determining factors towards under-reporting of adverse drug reactions listed ignorance (where clinicians had the impression that only “severe” ADRs needed reporting), diffidence, indifference and complacency as some personal reasons why clinicians chose not to report ADRs.[100] Knowledge and attitudes of clinicians have also been shown to be strongly associated with pharmacovigilance reporting.[100] It is not known which

factors are more specific to dentists, and as such further research investigating reasons for under-reporting is required so as to develop specific interventions targeting dental pharmacovigilance.

With rising numbers of medication use, expanded indications for current medications, increased access due to wider prescribing rights and greater access via the Internet, monitoring of drug safety is more important now than ever. 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 and other health professionals to report them. It is also recommended that pharmacovigilance agencies worldwide make greater efforts to include dentists and other oral health professionals in their activities.

Table 1. Drugs Associated with Lichenoid Reactions*

Drug Class	Drug
Antihypertensives	Atenolol
	Captopril
	Enalapril
	Oxprenolol
	Methyldopa
Immunosuppressants	Adalimumab
	Imatinib
	Infliximab
	Interferon-alpha
NSAIDs	Indomethacin
	Naproxen
Other	Carbamazepine
	Certolizumab
	Clopidogrel
	Duloxetine
	Glimepiride
	Hepatitis B vaccine
	Lithium carbonate
	Ribavirin
	Risperidone
	Secukinumab

*Adapted from Fortuna et al, 2017[10]

Table 2. Drugs Associated with Oral Aphthous-Like Ulceration

Drug Class	Drug
Antianginals	Nicorandil
Antihypertensives	Captopril
NSAIDs	Piroxicam
Bisphosphonates	Alendronate
	Etidronate
	Risedronate
mTOR inhibitors	Everolimus
	Ridaforolimus
	Sirolimus
	Temsirolimus

Table 3. Drugs Associated with Mucositis*

Drug class	Drug	Drug class	Drug
Alkylating agents	Bendamustine	Vinca alkaloids	Vinblastine
	Busulfan		Vincristine
	Chlorambucil		Vinflunine
	Lomustine		Vinorelbine
	Melphalan	Other cytotoxic	Bleomycin
	Procarbazine	antineoplastics	Dactinomycin
Anthracyclines	Daunorubicin		Eribulin
	Doxorubicin		Mitomycin
	Epirubicin		Romidepsin
	Idarubicin		Trastuzumab
	Mitozantrone	Antineoplastic	Bevacizumab
Antimetabolites	Azacitidine	antibodies	Cetuximab
	Capecitabine		Panitumumab
	Clofarabine		Pertuzumab
	Cytarabine	mTOR inhibitors	Everolimus
	Fludarabine		Sirolimus
	Fluorouracil		Temsirolimus
	Gemcitabine	Tyrosine kinase	Afatinib
	Hydroxyurea	inhibitors	Axitinib
	Mercaptopurine		Dasatinib
	Methotrexate		Erlotinib
	Pemetrexed		Gefitinib
	Raltitrexed		Lapatinib
	Thioguanine		Sorafenib
Platinum	Carboplatin		Sunitinib
compounds	Oxaliplatin	Other non-cytotoxic	Cobimetinib
Podophyllotoxins	Etopoxide	antibodies	Trametinib
	Teniposide		Tretinoin
Taxanes	Carbazitaxel	Calcineurin inhibitors	Tacrolimus
	Docetaxel	Other	Mycophenolate
	Paclitaxel	immunosuppressants	
Topoisomerase I inhibitors	Topotecan		

*From the Australian Medicines Handbook, 2017[17]

Table 4. Drugs Associated with Lupus*

Drug Class	Drug
High-risk	Hydralazine
Low-risk	Captopril
	Carbamazepine
	Chlorpromazine
	Isoniazid
	Methyldopa
	Minocycline
	Penicillamine
	Propylthiouracil
	Sulfasalazine
	TNF-alpha inhibitors

*Adapted from Rubin et al, 2015[63]

Table 5. Drugs Associated with Bullous Pemphigoid*

Likely association[a]	Enalapril
	Frusemide
	Ibuprofen
	Influenza vaccine
Probable association[b]	Ampicillin
	Bumetanide
	Cephalexin
	Fluoxetine
	Penicillamine
	Penicillin
	Spironolactone
Questionable association[c]	Amiodarone
	Captopril
	Chloroquine
	Interleukin-2
	Omeprazole
	Risperidone
	Sulfonamides
	Tetanus toxoid
	Topical fluorouracil

a Rechallenge evidence supports association
b Young age group with bullous pemphigoid and temporarily associated medication, or spontaneous resolution of bullous pemphigoid after drug withdrawal alone
c Elderly age group and temporarily associated medication

*Reproduced from Lo Schiavo et al, 2013[69]

Table 6. Drugs Associated with Inducing Pemphigus*

Drugs containing a sulfhydryl group	Penicillamine
	Captopril
	Penicillin
	Cephalosporins†
	Piroxicam
Drugs containing a phenol ring	Cephalosporins†
	Aspirin
	Rifampicin
	Levodopa
	Heroin
	Phenobarbitone
Non-thiol non-phenol drugs	Diclofenac
	Enalapril
	Fosinopril
	Interferon-alpha
	Interferon-beta
	Isotretinoin
	Nifedipine
	Norfloxacin
	Progesterone
	Propanolol
	Ramipril

†Some cephalosporins contain a sulfhydryl group or a phenol ring

*From Ruocco et al 2001,[80] Ruocco et al 2013,[77] Scully and Mignogna 2008[79]

Table 7. Drugs Associated with Erythema Multiforme

Drug class	Drug
Antibacterials	Amoxicillin
	Ampicillin
	Erythromycin
	Nitrofurantoin
	Sulfonamides
	Tetracycline
	Trimethoprim/sulfamethoxazole
Anticonvulsants	Carbemazepine
	Phenobarbitone
	Phenytoin
	Valproic acid
Antineoplastics	Alectinib
	Nivolumab
	Vemurafenib
Oxicam-NSAIDs	Piroxicam
TNF-alpha inhibitors	Adalimumab
	Etanercept
	Infliximab
Other	Allopurinol
	Diptheria-tetanus-pertussis vaccination

*Adapted from Lerch et al, 2018[81]

Table 8. Drugs Associated with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis*

	Drug class	Drug
High-risk	Antibacterials	Trimethoprim/sulfamethoxazole
	Sulfonamide antibiotics	Sulfasalazine
		Sulfadiazine
	Anticonvulsants	Carbemazepine
		Lamotrigine
		Phenytoin
		Phenobarbital
	Oxicam-NSAIDs	Piroxicam
		Meloxicam
	Other	Allopurinol
		Nevirapine
Significant but lower risk	Acetic acid NSAIDs	Diclofenac
		Indomethacin
		Sulindac
		Ketorolac
	Macrolides	Azithromycin
		Clarithromycin
		Erythromycin
		Roxithromycin
	Quinolones	Ciprofloxacin
		Levofloxacin
		Norfloxacin
		Ofloxacin
	Cephalosporins	Cephalexin
		Ceftriaxone
		Cefuroxime
	Tetracyclines	Doxycycline
		Minocycline
	Penicillins	Amoxicillin

*Adapted from Ronjeau et al 1995,[87] Mockenhaupt et al 2008,[93] Patel et al 2013[99]

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