Adverse Oral Effects of Systemic Drug Use

Douglas Galan and Ruby Grymonpre

ABSTRACT

Individuals may suffer from oral signs and symptoms as a result of systemic drug use. Such oral changes may be varied in their presentation. The pharmacist is in a position to assist the prescribing health professional in correlating drug use with oral complaints and in offering specialized knowledge which may be helpful in patient management. Drug-induced oral signs, symptoms, and their management are described.

Key words: *oral side effects, systemic drugs*

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RÉSUMÉ

L'usage d'un médicament systémique peut déclencher l'apparition de signes et de symptômes oraux chez le malade. Les changements oraux peuvent varier en apparence. Le pharmacien est en mesure d'aider le professionnel de la santé qui a prescrit le médicament à corréler l'usage du produit aux doléances du malade, et de lui proposer les connaissances spécialisées qui l'aideront à prendre en charge son patient. Suit une description des signes et des symptômes oraux induits par la pharmacothérapie et de la manière de les régler.

Mots-clés : *effets secondaires oraux, médicaments systémiques*

INTRODUCTION

The increasing use of medications in the prevention and control of disease raises the potential for unwanted side effects, which may present in the oral cavity. Oral side effects include a wide variety of morphological changes, such as ulcerations and swellings, or the production of oral dysfunctions, such as dry mouth (xerostomia), taste disorders (dysgeusia), and altered mouth movements (dyskinesia). When confronted with individuals experiencing an oral reaction, the pharmacist should not be expected to provide a definitive diagnosis but should attempt to correlate the oral complaints with a specific medication, and provide this information to the prescribing dentist or physician.

The purpose of this review is to provide information for pharmacists regarding potential adverse oral effects and the principles involved in their management. Drugs selected and included in this report are based on the frequency of occurrence of oral signs and symptoms, and the functional significance of these adverse reactions. This review is not intended to provide an all inclusive list of medications implicated in adverse oral effects. In addition, only the primary drug-induced oral side effects will be discussed.

Oral Ulcerations

Drug-induced oral ulcerations can arise from either topical applications or systemic use. Ulcerations may occur exclusively in the mouth or may present with multi-system involvement. In most cases, single intra-oral ulcers are due to mechanical irritation (e.g., chipped tooth), a local disease process (e.g., cancer), or a contact hypersensitivity (e.g., toothpaste hypersensitivity). A single oral ulcer secondary to drug use is usually due to topical application of an irritant drug such as acetylsalicylic acid.[1] Drugs commonly implicated as systemic ulcerogenic agents include anti-neoplastic drugs[2-5] and gold salts.[3,6] Patients presenting with oral ulcerations should be investigated by a dentist. A biopsy may be required if an ulcer does not resolve within two weeks after elimination of the suspected local etiologic factors.

Multiple ulcers or a generalized change of the oral cavity is more supportive of a drug reaction, with many of the lesions being due to a drug-induced leukopenia. If the ulcers create functional problems such as excessive drooling, pain, inability to wear dentures, or inability to eat, the patient's physician must be informed, and if necessary, the medication changed. Usually these lesions subside following drug discontinuation. Drug-induced erythema multiforme may produce ulceration as an oral manifestation. The oral mucosa shows reddened patches which may rapidly develop into bullae, erosions, or ulcers (Figure 1). If they occur, "target lesions" of the skin are helpful in supporting the diagnosis

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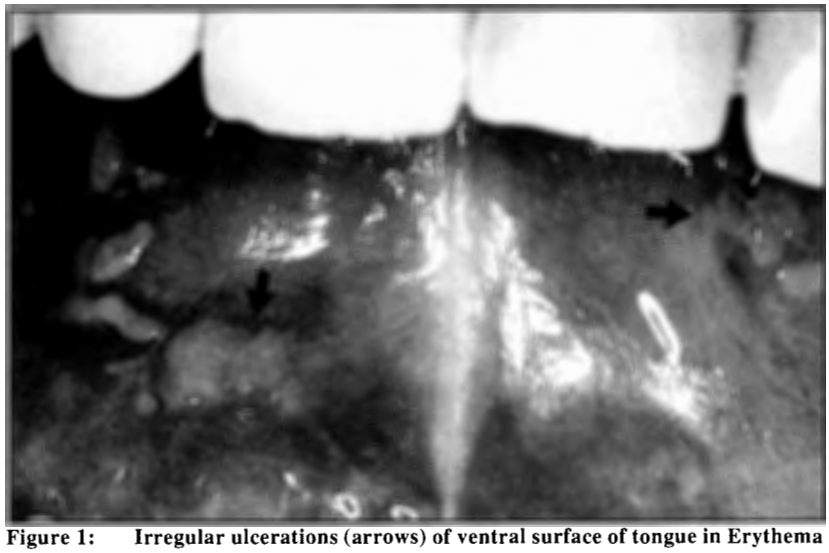

Figure 1: Irregular ulcerations (arrows) of ventral surface of tongue in Erythema Multiforme (courtesy Dr. J.B. Perry)

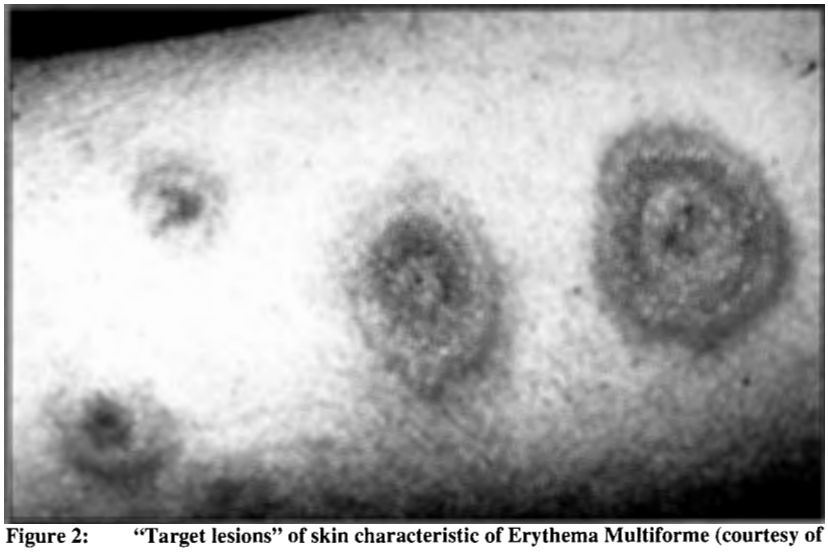

Figure 2: "Target lesions" of skin characteristic of Erythema Multiforme (courtesy of Dr. J.W.P. Toole).

(Figure 2). Although the majority of erythema multiforme cases are considered idiopathic in origin,[7] some have been associated with drug use (Table I).[8-14] Lesions produced are usually self-limiting and heal three to four weeks after drug withdrawal. A further exposure to the causative agent may cause lesion recurrence.

Lupus erythematosus (SLE) secondary to drug use, manifests itself as a cutaneous rash, with pulmonary, cardiac, muscular, and abdominal symptoms.[8] In conjunction with these symptoms, fever, weight loss and lymphadenopathy may occur.[8] The oral mucosa in 25% of cases have erythematous patches that subsequently break down to form painful ulcers, often with white peripheral striations (Figure 3).[3] Most of the drug-induced cases resolve upon removal of the causative agents. Drugs primarily associated with SLE include hydralazine and procainamide hydrochloride.[3,15,16] Other less prominent drugs include: ethosuximide, isoniazid, lithium carbonate, quinidine, thiouracil, and D-penicillamine.[16,17]

Table I: Drugs Associated With Erythema Multiforme Reactions[8-14]

Drug Group	Drug
Antibacterial agents	clindamycin tetracycline penicillins sulfonamides
Antitubercular agents	isoniazid rifampin
Anticonvulsants	barbiturates carbamazepine phenytoin
Antidiabetic agents	chlorpropamide
Antithyroid agents	propylthiouracil
Cardiovascular agents	minoxidil propranolol
Nonsteroidal antiinflammatory agents	phenylbutazone salicylates
Laxatives	phenolphthalein

Gingival Hyperplasia

Gingival hyperplasia (enlarged gums) (Figure 4) is principally associated with phenytoin,[18] although cyclosporine[19,20] and nifedipine[21,22] have also been implicated. The reported incidence of phenytoin hyperplasia varies from 3 to 62%, with the greater frequency seen in younger individuals.[23] Severity and onset of the hyperplasia is not necessarily related to drug dosage and it decreases with increasing age.[8,18] The hyperplasia is not well correlated with the presence or absence of local irritants.[23] Nevertheless, in most cases oral hygiene plays a role in treatment and prevention. Surgical reduction of gross tissue overgrowth is often necessary to provide a more cleansable environment. Topical daily treatments with 0.325% stannous fluoride or 0.12% chlorhexidine gluconate has also

Table II: Drugs Frequently Causing Xerostomia[8,25,26]

Drug Group	Drug
Anticholinergic agents	trihexyphenidyl procyclidine benztropine
Antidepressants	amitriptyline imipramine doxepin
Antiemetics	prochlorperazine
Antihistamines	diphenhydramine orphenadrine
Antipsychotics	thioridazine chlorpromazine
Cardiovascular agents	clonidine methyldopa prazosin disopyramide
CNS stimulants	mazindol fenfluramine diethylpropion
Muscle relaxants	cyclobenzaprine orphenadrine baclofen

been shown to be effective in reducing the severity of the hyperplastic response.[24]

Effects on Salivary Glands

Xerostomia

Xerostomia, or dryness of the mouth, is primarily caused by drugs that either stimulate sympathetic activity or depress parasympathetic activity. More than 300 medications are capable of producing xerostomia, but some medications are more commonly implicated (Table II).[8,25,26] Intraorally, the mucosa may appear atrophic, inflamed, fissured, or ulcerated. Often the lesions are associated with a burning sensation, a sore tongue or generalized mouth soreness.[27,28] Other clinical problems include decreased denture retention; increased prevalence of dental caries; inflammatory disorders of the periodontium and mucous membranes; difficulty with chewing, swallowing, and speech; and infections of the pharynx and salivary glands.[27,28]

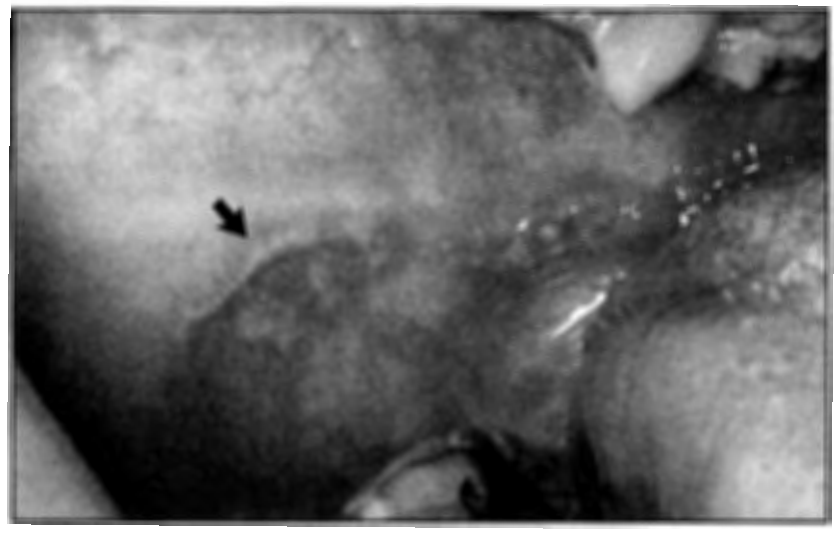

Figure 3: Ulcerations and erythematous plaque of buccal mucosa (arrow) with white peripheral striations in Lupus Erythematosus (courtesy Dr. S.I. Ahing).

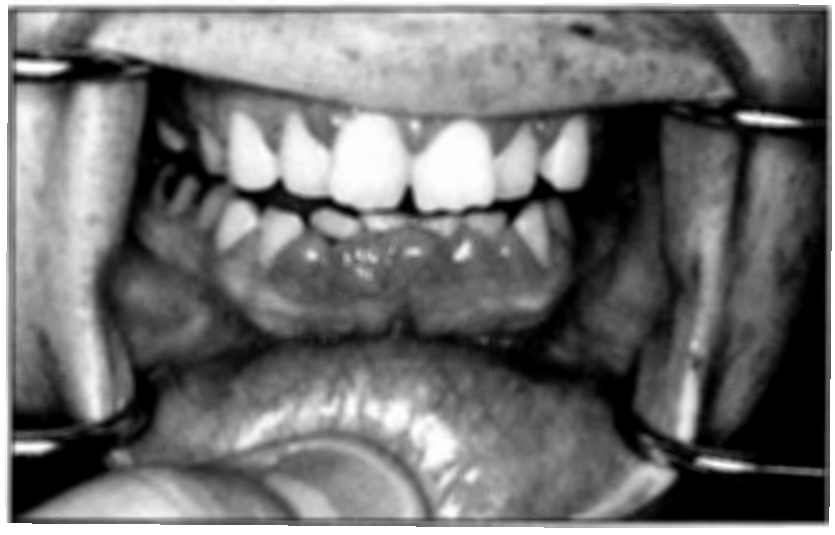

Figure 4: Enlarged gums (gingiva) secondary to phenytoin (Dilantin) therapy (courtesy of Dr. S.I. Ahing).

Symptomatic management is usually employed unless the responsible drug can be identified and substituted with one having fewer xerostomic side effects. A consultation with the patient's physician about the drug-induced xerostomia problem is suggested before any medication changes are made. Scrupulous oral hygiene is required in order to maintain the natural dentition. Effective brushing with a fluoridated dentifrice, regular flossing, fluoride (0.5%) and chlorhexidine gluconate (0.12%) oral rinses, and daily fluoride gel applications are needed. Since acidulated fluorides may aggravate the symptoms, neutral fluorides should be used whenever possible. Alcohol-based products, which can further exacerbate drying, retard healing, and induce erythema, should be avoided.

Saliva substitutes may aid in denture retention and facilitate

swallowing during meals. Water is a form of saliva substitute, but more sophisticated substitutes are available. These substitutes contain a carboxymethylcellulose compound to increase viscosity, a sugarless sweetening agent, electrolytes, and fluoride at a neutral pH.[28] For dentate individuals, a fluoridated substitute is useful. Some of the commercially available products include Saliment®, Glandosane®, and Moi-Stir® spray.

Sialagogues, agents that promote salivary flow, may be used for some patients.[28] The use of sugar containing candies is strongly discouraged because of the increased risk of dental caries and tooth erosion, although sugar-free candies are acceptable. Chewing gum, both sugar-free and low-sticking types, can be quite useful stimulants as the flavour in the gum and the action of chewing promote salivary flow. A secondary benefit of chewing forces saliva between the teeth, thereby raising the plaque pH and aiding in the prevention of caries formation. The muscarinic agent, pilocarpine, taken in four daily doses of between 1 and 10 mg can produce some therapeutic effects, but the effects vary with different individuals.[28,29] Some problems associated with pilocarpine include a risk of side effects and possible drug interactions.[29] Other parasympathomimetic drugs such as bethanechol, neostigmine, and pyridostigmine may be possible alternatives for pilocarpine, but more investigation is required regarding these agents.[28]

Salivary Gland Enlargement

A condition resembling mumps is sometimes associated with the administration of iodides,[30-32] methyldopa,[30,33,34] phenylbutazone,[30,35,36] phenothiazines, sulfonamides, thiocyanates and thiouracil[30]. It is uncertain what mechanisms induce gland enlargement, but in the case of phenylbutazone it may be due to a hypersensitivity reaction.[3] The reactions usually subside once the offending drug is discontinued.[3,30] Salivary gland enlargement may occasionally be accompanied by xerostomia, or features of acute sialadentis including pain, low-grade fever, headache, and malaise.[27]

Salivary Gland Pain

Occasional parotid pain can be produced by bretylium,[37] clonidine hydrochloride,[38] guanethidine sulfate,[3] and methyldopa.[33] Although the exact mechanism is unclear, glandular vasoconstriction producing excessive hyperemia may be involved.[8] Upon discontinuing the drug therapy, the symptoms of pain subside.

Sialorrhea

Sialorrhea (excessive salivation) can be produced by cholinergic stimulation; by directly stimulating the parasympathetic receptors with agents such as pilocarpine; or by inhibiting the action of cholinesterase with agents such as neostigmine.[39] Other medications implicated include: iodides,[26] lithium carbonate,[40,41] nitrazepam,[42] loxapine,[43] and clozapine.[44] Sialorrhea is generally not regarded as a common problem, but in the absence of a primary salivary gland pathology, a possible drug reaction involving any of the listed drugs should be considered.[26]

Altered Taste Sensation

Most patients who complain about a loss of taste will be found to be suffering from a loss of smell, often interpreting their failure to appreciate "flavour" as a lack of taste. Recognition of this distinction is important from a diagnostic and therapeutic viewpoint.[45] Alterations in taste sensation (dysgeusia), a diminished taste perception (hypogeusia), or a complete loss of taste (ageusia) can be caused by a variety of drugs (Table III).[46] The mechanism causing the altered sensation is uncertain, but it may be mediated by a drug's action on trace metal ions such as nickel, zinc, and copper.[47,48] These ions modulate the interaction of the tastants with the membrane proteins of the taste pores.[48] There is usually no treatment for diminished taste acuity other than withdrawal of the causal medication following which resolution of symptoms may occur.[49] In certain clinical conditions (e.g., renal dialysis patients), zinc supplementation may produce some improvement,[50,51] while in other conditions the use of zinc has no effect.[52,53]

Oral Flora Changes

Changes to the normal oral flora can result from either a direct drug action on the oral flora or from an indirect effect on host defence mechanisms. Persons taking immunosuppressive drugs, such as azathioprine[8] and systemic corticosteroids,[54] frequently develop fungal and viral infections. These infections occur because the drugs diminish or impair the immune and inflammatory responses, permitting Candida albicans and Herpes simplex organisms to flourish.[8] However, any drug which irritates the skin may act as one of several non-specific activating factors for fungal and herpetic infections. Topical antifungal and antiviral agents

Table III: Drugs Commonly Producing Taste Changes*

Drug Group	Drug	Symptom
Antibacterial agents	cefamandole	"bad taste"
	lincomycin	taste disorder
	procaine penicillin	metallic taste
	metronidazole	metallic taste
	sulphasalazine	taste disorder
	chlorhexidine rinse	metallic taste
	pentamidine	taste perversion
Antifungal agents	amphotericin B	taste disturbance
	griseofulvin	taste disturbance
	terbinafine	loss of taste
Antitubercular	ethambutol	metallic taste
Anticonvulsants	carbamazepine	taste disorder
Antidiabetic agents	biguanides	metallic taste
Antineoplastics	adriamycin	altered taste
	azathioprine	taste disturbance
	bleomycin	taste loss
	cisplatin	taste loss
	methotrexate	metallic taste
	5-fluorouracil	altered bitter & sour taste sensitivity increased sweet appreciation
Antiparkinsonian agents	levodopa	taste disturbance
Antipsychotic	lithium	metallic taste
Antithyroid agents	methimazole	taste and smell loss
	methylthiouracil	taste and smell loss
Antimigraine	sumatriptan	"bad taste" or bitter taste
Cardiovascular agents	amiloride	decreased taste for salt
	amrinone	hypogeusia
	bretylium	enhanced salt taste
	captopril	altered taste
	diltiazem	hypogeusia
	enalapril	altered taste, metallic taste
	nifedipine	altered taste and smell
	nitroglycerin	loss of taste
	propafenone	metallic taste
	spironolactone	loss of taste
Hypnotic agents	zopiclone	taste perversion
	flurazepam	metallic taste
Nonsteroidal antiinflammatory agents	acetylsalicylic acid	taste disorder
	phenylbutazone	taste loss
	ibuprofen	taste complaint
Other antirheumatoids	allopurinol	metallic taste
	auranofin	metallic taste
Miscellaneous	acetazolamide	acidic taste-bitter dysgeusia
	deferoxamine	"bad taste"
	dipyridamole	metallic taste
	isotretinoin	disturbed taste and smell
	levamisole	metallic taste
	omega fatty acids	fishy taste

* Adapted from Griffin JP.[46]

are useful in managing these infections, but the immunocompromised patient may require higher than average doses and/or treatment for longer periods.

All types of antibiotics have the potential to alter the oral flora, but only broad spectrum agents or combination therapies cause clinically apparent candidiasis in otherwise healthy individuals.[54] In debilitated persons, the role of antibiotics in predisposing these individuals to candidiasis is often complicated by multiple disease states and concomitant medications.[8] Nystatin oral suspension may be used to treat oral candidiasis.

Drug-Induced Blood Disorders

Abnormal bleeding tendencies associated with drug therapy are usually due to defects in coagulation, platelet function, or vascular integrity. Clinical conditions such as bone marrow aplasia, agranulocytosis, thrombocytopenia, hemorrhage, or anemia, can be induced by drug therapy (Table IV).[55,56] These disorders may be produced by different methods including a direct toxic effect or by an unpredictable immunologic effect on the bone marrow. Oral signs and symptoms include unresponsive infections, unexplained hemorrhage, pale mucosa, oral ulceration, atrophy of the lingual papillae, and soreness of the tongue, mucosa or throat.[55,57] Should a patient present with these signs and symptoms, especially bleeding gingiva, petechiae (pin-point bleeds) or purpura (larger bleeds), a hematologic and dental assessment would be indicated.

Neurological Disorders

Extrapyramidal syndromes may occur extra-orally secondary to drug therapy. Drugs usually

Table IV: Drugs Causing Blood Disorders*

Drug Group	Aplastic Anemia	Agranulocytosis	Thrombocytopenia
Antibacterial agents			
cloramphenicol	+	+	+
streptomycin	+	+	+
sulfonamides	+	+	+
vancomycin	–	–	+
Anticoagulants			
heparin	–	–	+
Anticonvulsants			
carbamazepine	+	+	+
ethosuximide	+	+	+
hydantoin derivatives	+	+	+
primidone	+	+	+
valproic acid	–	–	+
Antimalarials			
chloroquine	–	–	+
pyrimethamine	+	–	–
Antirheumatic agents			
acetylsalicylic acid	+	–	+
gold salts	+	+	+
indomethacin	+	+	+
phenylbutazone	+	+	+
Antithyroid agents			
propylthiouracil	+	+	+
methimazole	+	+	+
Antiarrhythmics agents			
quinidine	–	–	+
procainamide	+	+	–
Diuretics			
hydrochlorothiazide	–	+	+
acetazolamide	+	+	+
Psychotropics			
clozapine	–	+	–
phenothiazine derivatives	+	+	+
antidepressants	+	+	+
meprobamate	+	–	+
Antidiabetic Agents			
tolbutamide	+	–	+
chlorpropamide	+	–	+

* Adapted from Horler AR.[55]

associated with extrapyramidal syndromes include: levodopa,[58] antipsychotics, and phenothiazines such as haloperidol and prochlorperazine,[59-63] reserpine,[64] methyldopa,[65] and metoclopramide.[66] Extrapyramidal syndromes have also been reported with the use of anticonvulsants and diazoxide.[8] The orofacial musculature often exhibits abnormal lip and jaw movements. Tongue protrusion, bruxism (tooth grinding), trismus (limited mouth opening), dysphagia (swallowing difficulty), salivation and dislocations of the mandibular condyles may be possible consequences.[60,62] Most of these symptoms will usually resolve upon drug withdrawal.[8]

Tardive dyskinesia is characterized by repetitive, involuntary movements of the mouth and tongue. Movements such as tongue protrusion, licking and smacking of the lips, sucking and chewing movements, along with grimacing are usually seen.[64,67,68] This is usually an irreversible side effect of long-term drug therapy. Should tardive dyskinesia be observed in a patient, a consultation with the patient's physician is required. Management involves elimination or reducing the dosage of the causative medication to the lowest possible level. The dyskinesia can be voluntarily suppressed in the early stages.[69] The pharmacist could observe these movements through surreptitious patient observation and by questioning the family members about the symptoms.

Approximately 20% of all patients taking neuroleptic medications regularly for more than one year will develop tardive dyskinesia.[70] If these patients are over 50, the prevalence rises to 40-60%.[70-2] Females may also be at a higher risk and may have a poorer prognosis.[73] As a result, these individuals may experience difficulty in eating, communicating, and using dentures.

Lichenoid Eruptions

Although the exact etiology for lichenoid eruptions is unknown, certain drugs can produce oral lesions indistinguishable from classical lichen planus (Table V).[3,26,74-7] Oral manifestations include white or erythematous plaques (patches), erosions, or painful ulcerations with peripheral white striations (Figure 5).[8] The buccal mucosa and the lateral borders of the tongue are most often affected. With drug-induced lesions, resolution occurs once the drug therapy is discontinued, although taking a biopsy is often helpful for diagnostic purposes.

Table V: Drugs Associated With Lichenoid Reactions[3,26,74-7]

Drug Group	Drug
Antidiabetic agents	chlorpropamide
Antihistamines	triprolidine hydrochloride
Antimalarial agents	chloroquine hydroxychloroquine
Antirheumatoid agents	allopurinol gold salts - auranofin penicillamine
Cardiovascular agents	beta-blockers - oxprenolol - labetolol captopril thiazide diuretics methyldopa quinidine

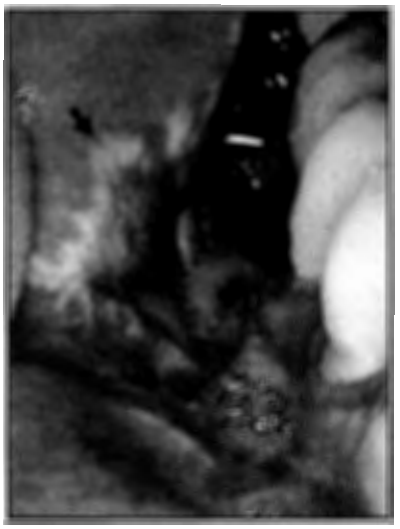

Figure 5: Ulcerations of buccal vestibule exhibiting white peripheral striations (arrow) in a Lichenoid eruption (courtesy of Dr. J.B. Perry).

DISCUSSION

Drug-induced oral problems may not be easily identified unless suspected and actively investigated. A number of steps are involved in determining the link between an adverse drug reaction involving the oral cavity and a particular drug. The first step is to obtain a complete medication history, including all prescription, over-the-counter (OTC), and recreational drugs. This history will also identify the dosages, dosing schedules, duration of drug use, and purpose for which the drugs were given. Pharmacists can assist dentists or physicians by providing current information regarding all the medications that an individual may be taking.

Secondly, it is necessary to establish a temporal relationship between initial drug use and the onset of oral changes. Intra-oral reactions may occur immediately after administration of an offending drug, may appear as the treatment progresses, or may develop and/or persist for variable periods after the offending medication has been discontinued. Consulting relevant primary literature to determine the usual temporal relationship will help determine if the suspected agent is likely causative. Some drug reactions may take months to resolve.

A third step is to evaluate all current medications for their potential to produce an oral lesion. Because multiple drug regimens can complicate the identification of a single etiologic agent, it may be necessary to work with the dentist and the physician to serially eliminate drugs until the responsible one is identified. Following identification, it may be possible to replace the offending drug with one that has the same therapeutic effect, but without the same side effects. Occasionally, the offending medication is found to be unnecessary and can be discontinued completely. In other cases a medication change may not be possible, resulting in the need to provide supportive and palliative care.

Circumstances may arise where the pharmacist is asked to suggest an OTC preparation to relieve the oral problem. Should an OTC preparation be used in an attempt to provide relief, some caution should be exercised because an alteration of the oral signs or symptoms may occur, making the diagnosis of an intra-oral lesion more difficult.

Following an assessment of the medication history and an evaluation of the signs and symptoms, other investigative methods may have to be used (Table VI). After a relationship between the oral manifestation and drug use has been established, it would be beneficial to determine if it was a toxic or allergic reaction. The clinical significance of differentiating between the two is that in the former, the pathophysiology would dictate dose alteration or formulation substitution, whereas the latter implies that the drug cannot be used at all. This would subsequently influence the prescribing pattern of dentists and physicians for that particular patient possibly necessitating alterations in medications or in choosing between surgery or pharmacologic management.

When confronted with a possible drug-induced intra-oral reaction, the pharmacist should be aware that: 1) oral manifestations of drug reactions are not uncommon; 2) some patterns of oral reactions are predictable and patients should be directed to the appropriate prescribing clinician;

Table VI: Major Investigative Methods for Drug-induced Intraoral Lesions

Reaction	Major Investigative Method
Allergic reaction	Mucocutaneous challenge tests (patch, injection)
Toxic reaction	Dose alteration
Oral ulceration	Biopsy / drug withdrawal
Gingival hyperplasia	Drug withdrawal / altered dose +/- biopsy
Xerostomia	Drug withdrawal / altered dose
Salivary gland enlargement	Drug withdrawal / altered dose +/- biopsy
Salivary gland pain	Drug withdrawal / altered dose
Taste changes	Drug withdrawal
Changes in flora	Cultures / cytologic smears
Blood dyscrasias	Complete blood cell count
Neurological disorders	Drug withdrawal / altered dose and neurologic exam
Lichenoid eruptions	Biopsy / drug withdrawal

(Table courtesy of Dr. S.I. Ahing)

3) disease states may mimic drug reactions (e.g., lupus erythematosus), and vice versa; and 4) polypharmacy, including OTC preparation use, may complicate the diagnostic investigation. The pharmacist's specialized knowledge may be helpful for patient management in: 1) knowing the pathophysiologic mechanism for the adverse reaction (e.g., toxic or allergic effect); 2) knowing the available drug substitutes and suggesting a replacement for the offending drug; 3) understanding the complete medication record (e.g., identifying duplicate drugs); 4) providing supportive treatment when drugs cannot be changed (e.g., saliva substitutes); and 5) counselling patients to prevent adverse reactions between prescribed medications and OTC drugs (e.g., antihistamines and xerostomic drugs). When adverse effects involve the oral cavity, the pharmacist should attempt to correlate the oral complaints with a specific medication, and then suggest a consultation with the prescribing dentist or physician for diagnosis and management. Overall, the patient, dentist, physician, and pharmacist have specialized and significant roles to play in the successful management and alleviation of oral side effects.

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