

ADVERSE DRUG REACTIONS IN THE OROFACIAL REGION

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ABSTRACT: A wide spectrum of drugs can sometimes give rise to numerous adverse orofacial manifestations, particularly dry mouth, taste disturbances, oral mucosal ulceration, and/or gingival swelling. There are few relevant randomized double-blind controlled studies in this field, and therefore this paper reviews the data from case reports, small series, and non-peer-reviewed reports of adverse drug reactions affecting the orofacial region (available from a MEDLINE search to April, 2003). The more common and significant adverse orofacial consequences of drug therapy are discussed.

Key words. Oral, drugs, adverse reactions, salivary, mucosa, ulcers, taste.

Introduction

A wide spectrum of drugs can sometimes give rise to numerous adverse oral manifestations, particularly dry mouth, taste disturbances, oral mucosal ulceration, and/or swelling. A review of the 200 most frequently prescribed drugs (in the USA in 1992) showed the most frequent oral adverse drug reactions (ADRs) to be dry mouth (80.5%), dysgeusia (47.5%), and stomatitis (33.9%) (Smith and Burtner, 1994). However, few randomized double-blind controlled studies have been conducted, and therefore most of the evidence available at the present time is of low level, originating only from case reports, small series, or non-peer-reviewed reports of adverse drug reactions.

This paper reviews the literature based on a MEDLINE search to April, 2003, and highlights the more common and significant adverse oral consequences of drug therapy. When relevant, it provides sources of other suitable reports: It does not include details on the oral side-effects of foodstuffs, tobacco, alcohol, or recreational drugs, or the adverse effects of drugs upon the dentition.

Drug-related Disorders of the Salivary Glands

(1) DRUG-RELATED XEROSTOMIA

Dry mouth has a variety of possible causes (Femiano *et al.*, 2003b)(AQ) (Table 1). Common habits such as tobacco smoking, alcohol use (including in mouthwashes), and the consumption of beverages containing caffeine (coffee, some soft drinks) can cause some oral dryness. Drugs are the most common cause of reduced salivation (Table 1, Fig. 1) (Scully, 2003). The drugs most commonly implicated include: alpha receptor antagonists for treatment of urinary retention; amphetamines; anticholinergics; antidepressants (serotonin agonists, or nor-adrenaline and/or serotonin re-uptake blockers); antihistamines; antihypertensive agents; antimigraine agents; anti-psychotics such as phenothiazines; appetite suppressants; atropinics; benzodiazepines, hypnotics, opioids, and drugs of

abuse; bronchodilators; cytokines; cytotoxics; decongestants and 'cold cures'; diuretics; histamine H2 antagonists and proton pump inhibitors; muscarinic receptor antagonists for the treatment of overactive bladder; opiates; protease inhibitors; radioiodine; retinoids; and skeletal muscle relaxants (Scully, 2003).

There appear to be multiple mechanisms whereby drugs can produce xerostomia (Madinier *et al.*, 1997). Although a wide range of drugs can give rise to oral dryness (Di Giovanni, 1990; Sreebny and Schwartz, 1997; Wynn and Meiller, 2001; Femiano *et al.*, 2003d), (AQ) the most dramatic effect is with radio-iodine (Mandel and Mandel, 2003).

Dry mouth is a common complaint in patients treated for hypertensive, psychiatric, or urinary problems (Streckfus, 1995) and in the elderly (Vissink *et al.*, 1992; Loesche *et al.*, 1995b), (AQ) mainly as a consequence of the large number of drugs used (Fox, 1998b; Närhi *et al.*, 1999) and polypharmacy (Loesche *et al.*, 1995a; Nederfors, 1996; Fox, 1998a). (AQ) For example, 63% of hospitalized patients and 57% of outpatients complained of dry mouth, and in all patients, the use of psychiatric drugs was the main cause (Pajukoski *et al.*, 2001).

Age and medication seem to play a more important role in individuals with objective evidence of hyposalivation, while female gender and psychological factors are important in individuals with subjective oral dryness (Bergdahl and Bergdahl, 2000).

Hypnotics are also commonly used by the elderly, and most users report ADRs, mainly dry mouth (30%) (Wishart *et al.*, 1981a; (AQ) Busto *et al.*, 2001). In the elderly using non-prescription products—most frequently, dimenhydrinate (21%), acetaminophen (paracetamol) (19%), diphenhydramine (15%), alcohol (13%), and herbal products (11%)—mild ADRs were reported by 75%, the most common complaint being dry mouth (Sproule *et al.*, 1999).

In a large survey of 3311 evaluable questionnaires, 21.3% of men and 27.3% of women reported dry mouth, with women statistically reporting higher prevalence of dry mouth than men (Nederfors, 1996). Dry mouth was significantly age-related, and

TABLE 1
Drug-related Xerostomia

Alfuzosin	Duloxetine	Mirtazapine	Sertraline
Amiloride	Ecstasy	Morphine	Sibutramine
Amitriptyline	Elliptinium	Moxonidine	Sucralfate
Amoxapine	Ephedrine	Nabilone	Tamsulosin
Benzhexol	Fenfluramine	Nefopam	Terazosin
Benzpropine	Fluoxetine	Nortriptyline	Thiabendazole
Biperiden	Fluoxetine	Olanzapine	Tiaprude
Bupropion	Furosemide	Omeprazole	Tiotropium
Buspirone	Guanfacine	Orphenadrine	Tizamidine
Cannabis	Hyoscine	Oxitropium	Tolterodine
Cetirizine	Imipramine	Oxybutynin	Tramadol
Chlormezanone	Indoramine	Paroxetine	Tranlycypromine
Chlorpromazine	Interferon alpha	Phenelzine	Trazodone
Citalopram	Interleukin-2	Pipamperone	Trepium chloride
Clemastine	Ipratropium	Pipenzolate	Triamterene
Clomipramine	Iprindole	Pirenzepine	Trimipramine
Clonidine	Isocarboxazid	Poldine	Trospium
Clozapine	Isotretinoin	Pratropium	Venlafaxine
Cyclizine	Ketorolac	Procyclidine	Viloxazine
Cyclobenzaprine	Ketotifen	Propafenone	Zopiclone
Desipramine	Lansoprazole	Propantheline	
Dexamphetamine	L-dopa	Propiverine	
Diazepam	Lithium	Pseudoephedrine	
Dicyclomine	Lofepramine	Quetiapine	
Dideoxyinosine	Lofexidine	Reboxetine	
Dihydrocodeine	Loratadine	Rilmenidine	
Disopyramide	Maprotiline	Risperidone	
Donopezil	Mepenzolate	Rizatriptan	
Dosulepine	Methylodopa	Selegiline	
Doxepin	Mianserine		

there was a strong co-morbidity between reported prevalence of dry mouth and ongoing pharmacotherapy. Unstimulated salivary flow rates were lower among older persons who were female or taking antidepressants, and higher among smokers or people who were taking hypolipidemic drugs (Thomson *et al.*, 2000). It is clear that medication is a better predictor of risk status for dry mouth than either age or gender (Field *et al.*, 2001).

Even in elderly patients with advanced cancer, dry mouth was the fourth most common symptom (78% of patients), but the usual cause was drug treatment, and there was an association with the number of drugs prescribed (Davies *et al.*, 2001). That is not to say that disease can always be excluded as a cause of dry mouth; for example, saliva secretion is more affect-

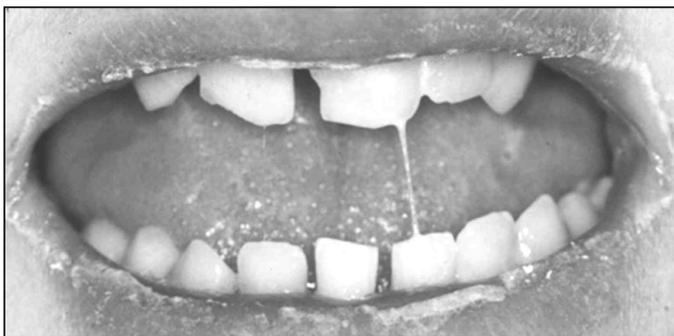


Figure 1. Drug-induced xerostomia.

ed by xerogenic drugs and autonomic nervous dysfunction in patients with non-insulin-dependent diabetes than in non-diabetic controls (Meurman *et al.*, 1998).

Furthermore, the cause for which the drug is being taken may also be important. For example, patients with anxiety or depressive conditions may complain of dry mouth even in the absence of drug therapy or evidence of reduced salivary flow. It is thus important to recognize that some patients complaining of a drug-related dry mouth have no evidence of a reduced salivary flow or a salivary disorder, and there may then be a psychogenic reason for the complaint.

Several different mechanisms account for drug-related dry mouth, but an anticholinergic action underlies many: The M3-muscarinic receptors (M3R) mediate parasympathetic cholinergic neurotransmission to salivary (and lacrimal) glands, but other receptors may also be involved (Kawaguchi and Yamagishi, 1995).

(a) Antidepressants

Early antidepressant medications such as tricyclic antidepressants (TCAs) unfortunately also blocked histaminic, cholinergic, and alpha1-adrenergic receptor sites, causing ADRs such as dry mouth. Men and women may differ in their pharmacokinetic responses to TCAs, in several autonomic indices, and in various adrenergic receptor-mediated responses. Emerging evidence also suggests that women, relative to men, may have a lower rate of brain serotonin synthesis and a greater sensitivity to the depressant effects of tryptophan depletion (Pomara *et al.*, 2001). Finally, the ultrarapid metabolizer phenotype of the enzyme cytochrome P4502D6 (Laine *et al.*, 2001a)(AQ) may be a cause of non-responsiveness to antidepressant drug therapy, and the subsequent prescribing of high doses of antidepressants to such patients leads to an increased risk for ADRs; however, normalization of the metabolic status of ultrarapid metabolizers by the inhibition of cytochrome activity, such as with paroxetine, could offer a solution (Laine *et al.*, 2001b)(AQ)

Newer antidepressants are essentially serotonin (5-hydroxytryptamine: 5HT) agonists, or block re-uptake of noradrenaline (norepinephrine) and/or serotonin. Members of the newer generation of antidepressants—including the selective serotonin re-uptake inhibitors (SSRIs) and multiple-receptor antidepressants (such as venlafaxine, mirtazapine, bupropion, trazodone, and nefazodone)—target one or more specific brain receptor sites without, in most cases, activating unwanted sites such as histamine and acetylcholine (Feighner, 1999; Feighner and Overo, 1999a)(AQ) The SSRI produce no significant changes in salivation (Hunter and Wilson, 1995a)(AQ) but dry mouth may still be seen (*e.g.*, fluoxetine) (Ellingrod and Perry, 1994; Shrivastava *et al.*, 1994; Hunter and Wilson, 1995b)(AQ) Davis and Faulds, 1996; Boyd *et al.*, 1997; Ravindran *et al.*, 1997a)(AQ) Trindade *et al.*, 1998). However, some SSRIs, such as paroxetine, appear to result in less dry mouth than seen with TCAs (Ravindran *et al.*, 1997b)(AQ) Citalopram, the most selective SSRI, is well-tolerated (Feighner and Overo, 1999b)(AQ) Venlafaxine, a mixed-re-uptake inhibitor, may produce dry mouth (Gelenberg *et al.*, 2000). The incidence of ADRs in recipients of venlafaxine XR is similar to that in patients receiving treatment with well-established SSRIs (Wellington and Perry, 2001). Duloxetine hydrochloride, a dual-re-uptake inhibitor of serotonin and norepinephrine, also can produce dry mouth (Detke *et al.*, 2002), as can mianserin, a mainly post-synaptic serotonin 2A agonist (Dolberg *et al.*, 2002).

Nefazodone, which has moderate serotonin selective re-uptake blocking properties and direct 5-HT₂ antagonism, can produce dry mouth in 19% vs. 13% in placebo (Lader, 1996). Reboxetine, a selective norepinephrine re-uptake inhibitor (selective NRI), causes less dry mouth than TCAs, though it produces dry mouth more frequently than placebo (36% vs. 16%) (Schatzberg, 2000; Versiani *et al.*, 2002). Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), can also induce dry mouth (Anttila and Leinonen, **AQ**) 2001).

Bupropion hydrochloride, originally developed as an antidepressant, is a selective re-uptake inhibitor of dopamine and norepinephrine which was found to reduce nicotine withdrawal symptoms and the urge to smoke, but commonly produces dry mouth (Zwar and Richmond, 2002). Dry mouth is positively associated with mean bupropion metabolite concentrations, and is inversely related to patient weight (Johnston *et al.*, 2001).

(b) Antipsychotics

Long-term drug treatment of schizophrenia with conventional phenothiazine antipsychotics such as fluphenazine is commonly associated with dry mouth (Adams and Eisenbruch, 2000).

However, newly developed antipsychotic drugs with more potent and selective antagonistic activity against the dopamine D(2) receptor may not necessarily be associated with a lower incidence of dry mouth. Olanzapine is an atypical antipsychotic which appears to produce dry mouth (Duggan *et al.*, 2000). Significant correlations have been found in *in vitro* affinities of antipsychotics toward dopamine or other neuronal receptor systems and ADRs: for example, between the K(i) values for dopamine D(1) receptor, alpha (1)-adrenoceptor and histamine H(1) receptor, and the incidence of dry mouth (Sekine *et al.*, 1999). Other atypical antipsychotics—including tiapride (Roger *et al.*, 1998), lithium (Christodoulou *et al.*, 1977; Chacko *et al.*, 1987; Friedlander and Birch, 1990; Tohen *et al.*, 2002), pipamperone dihydrochloride (Potgieter *et al.*, 2002), quetiapine and risperidone (Srisurapanont *et al.*, 2000; Mullen *et al.*, 2001)—may produce dry mouth.

(c) Antihistamines

The therapeutic effects of most of the older antihistamines were associated with sedating effects on the central nervous system (CNS) and antimuscarinic effects including dry mouth (Gwaltney *et al.*, 1996). Non-sedating antihistamines—most of which are histamine H₁ receptor antagonists, such as acrivastine, astemizole, cetirizine, ebastine, fexofenadine, loratadine, mizolastine, and terfenadine, however—are not entirely free from ADRs, though there may be less dry mouth (Mattila and Paakkari, 1999).

(d) Muscarinic receptor antagonists used to treat overactive bladder

Overactive bladder (OAB)—a chronic, distressing condition characterized by symptoms of urgency (sudden overwhelming urge to urinate) and frequency (urinating more than eight times daily), with or without urge urinary incontinence (sudden involuntary loss of urine)—is treated with muscarinic receptor antagonists, which can lead to troublesome dry mouth.

Dry mouth is a common side-effect seen with immediate-release oxybutynin (Hay-Smith *et al.*, 2002), but a significantly lower proportion of patients taking controlled-release oxybutynin have moderate to severe dry mouth or any dry mouth compared with those taking immediate-release oxybutynin (Versi *et al.*, 2000). Tolterodine, a competitive muscarinic recep-

tor antagonist, produces dry mouth (Jacquetin and Wyndaele, 2001; Layton *et al.*, 2001), though few patients (< 2%) experience severe dry mouth (Zinner *et al.*, 2002), and there is a 23% lower incidence of dry mouth reported with once-daily extended-release tolterodine capsules than with twice-daily immediate-release tablets (Clemett and Jarvis, 2001). Propiverine hydrochloride, a safe and effective antimuscarinic drug as effective as oxybutynin, has a lower severity and incidence of dry mouth (Noguchi *et al.*, 1998; Madersbacher *et al.*, 1999).

(e) Alpha receptor antagonists used to treat overactive bladder

Tamsulosin, a selective alpha 1A-adrenoreceptor antagonist, produces significantly less dry mouth than terazosin, a less selective alpha antagonist (Lee and Lee, 1997).

(f) Diuretics

Diuretic agents and psychotropics were the most commonly used xerostomic medications in one study of elderly patients, and were almost equally potent in reducing mean salivary flow rate (Persson *et al.*, 1991). Thiazides may cause dry mouth (McCarron, 1984), but there appear to be few reports showing a relationship between diuretic use and dry mouth. Subjectively, xerostomia was experienced 10 times more frequently after ingestion of furosemide than placebo (Atkinson *et al.*, 1989).

(g) Antihypertensives

The ganglion blockers and particularly the beta-blockers (beta-adrenoreceptor antagonists) may cause dry mouth (Nederfors, 1996) thought to be associated with activation of CNS and salivary gland alpha 2-adrenergic receptors. Such antihypertensive drugs, or sympatholytics (reserpine, methyldopa, and clonidine), are now little used because of such prominent ADRs as dry mouth.

Newer centrally acting antihypertensives, with selective agonist effects on the imidazoline I₁ brainstem-receptors in the rostral ventromedulla (RVLM), appear to modulate sympathetic activity and blood pressure without affecting salivary flow: Moxonidine and rilmenidine are examples of this new class.

Moxonidine can produce dry mouth, more frequently than placebo (Dickstein *et al.*, 2000) but only in a minority (< 10%), and significantly less than with the older antihypertensives (Schachter, 1999). Rilmenidine produces little dry mouth (Reid, 2001).

ACE inhibitors, which block the ACE enzyme in the renin-angiotensin-aldosterone system, produce dry mouth in about 13% of patients (Mangrella *et al.*, 1998).

(h) Appetite suppressants

Several appetite suppressants can cause dry mouth, including sibutramine (Richter, 1999; Bray, 2001), fenfluramine plus phentermine (Weintraub *et al.*, 1992), and the herbal Ma Huang and Kola nut supplement (containing ephedrine alkaloids/caffeine) produce dry mouth (Boozer *et al.*, 2002).

(i) Decongestants and "cold cures"

Decongestants such as pseudoephedrine (Wellington and Jarvis, 2001) and loratadine plus pseudoephedrine sulphate can result in dry mouth (Kaiser *et al.*, 1998).

(j) Bronchodilators

Anti-asthma drugs can be associated with dry mouth (Thomson

et al., 2002). The most common reported ADR after use of the bronchodilator tiotropium is dry mouth (Casaburi *et al.*, 2000).

(k) Skeletal muscle relaxants

Tizanidine, an alpha 2-adrenoceptor agonist used for the relief of spasticity, can be associated with significant dry mouth (Taricco *et al.*, 2000).

(l) Antimigraine drugs

Rizatriptan, a serotonin agonist used for the treatment of migraine, can induce dry mouth (Winner *et al.*, 2002).

(m) Opioids, benzodiazepines, hypnotics, and drugs of abuse

Opioids are well-recognized causes of dry mouth (Bruera *et al.*, 1999b),(AQ) and atropine, hyoscine, and atropinics have long been used to reduce secretions pre-operatively. Dry mouth is the only significant side-effect of transdermal scopolamine (hyoscine) (Gordon *et al.*, 2001). Morphine (Bruera *et al.*, 1999a;(AQ) Zacny, 2001), dihydrocodeine (Freye *et al.*, 2001), and Tramadol (Scott and Perry, 2000) can produce dry mouth.

Benzodiazepines (such as diazepam) (Conti and Pinder, 1979; Elie and Lamontagne, 1984) and zopiclone, a cyclopyrrolone chemically unrelated to benzodiazepines (Wadworth(AQ) and McTavish, 1993), can produce dry mouth.

Cannabis (Consroe *et al.*, 1986; Grotenhermen, 1999) and Ecstasy ('XTC' or 'E': 3,4 methylenedioxy-methamphetamine; MDMA) (Peroutka *et al.*, 1988; Milosevic *et al.*, 1999) can produce dry mouth.

(n) H2 receptor antagonists and proton-pump inhibitors

H2-receptor antagonists produce dry mouth in 41% of recipients (Teare *et al.*, 1995; Kaviani *et al.*, 2001).

(o) Cytotoxic drugs

Dry mouth can be a consequence of exposure to agents used for chemotherapy of malignant neoplasms, such as retinol (Goodman *et al.*, 1983), or 5-fluorouracil (McCarthy *et al.*, 1998), but this is not invariable (Laine *et al.*, 1992a),(AQ) and there is a paucity of data in this area.

(p) Retinoids

Systemic retinoids such as etretinate (Wishart *et al.*, 1981b),(AQ) 13 cis-retinoic acid (Hennes *et al.*, 1984), and isotretinoin (Oikarinen *et al.*, 1995) can produce dry mouth.

(q) Anti-HIV drugs

Didanosine (Dodd *et al.*, 1992; Valentine *et al.*, 1992) and HIV protease inhibitors (Greenwood *et al.*, 1998) can cause dry mouth.

TABLE 2
Drug-related Salivary Gland Pain or Swelling

Bethanidine	Famotidine	Naproxen	Phenytoin
Bretylium	Guanethidine	Nicardipine	Ranitidine
Cimetidine	Insulin	Nifedipine	Ritodrine
Clonidine	Interferon	Nitrofurantoin	Trimepramine
Clozapine	Isoprenaline	Oxyphenbutazone	
Deoxycycline	Methyl dopa	Phenylbutazone	

(r) Cytokines

Alpha interferon therapy for the treatment of chronic hepatitis C infection (Cotler *et al.*, 2000) can cause significant dry mouth. Interleukin-2 (rIL-2), when used, for example, for control of nasopharyngeal carcinoma, can also impair salivation (Chi *et al.*, 2001), and major salivary gland dysfunction has been described in patients with hematological malignancies given interleukin-2-based immunotherapy after autologous stem cell transplantation (Nagler, 1998).

(2) DRUG-RELATED SALIVARY GLAND SWELLING

Some drugs have been related to salivary gland swelling (Table 2). Painless, usually bilateral, salivary gland enlargement (resembling sialosis) may be an occasional side-effect of phenylbutazone (Cohen and Banks, 1966; Murray-Bruce, 1966; Chimenes, 1971; Herman *et al.*, 1974; Kaufman *et al.*, 1977), oxphenbutazone(AQ) (Bosch *et al.*, 1985), or chlorhexidine (Rushton, 1977). The bilateral sialadenitis observed in one adult following naproxen therapy (Knulst *et al.*, 1995) was thought to be allergic in origin, since the affected patient also had a cutaneous rash. A similar mechanism has been proposed to underlie the salivary gland enlargement caused by intravenous radiological contrast media (Gattoni *et al.*, 1991; Ilia *et al.*, 1991). Clozapine, a novel antipsychotic agent, may cause transient salivary gland swelling (Vasile and Steingard, 1995) as well as sialorrhoea (see below).

(3) DRUG-RELATED SALIVARY GLAND PAIN

Antihypertensives, anti-thyroid agents, chlorhexidine, cytotoxics, ganglion-blocking agents, iodides, phenothiazines, and sulphonamides may cause salivary gland pain, as may drugs causing dry mouth (Glass, 1989). Salivary gland pain is rarely associated with guanethidine or guanacaine (Parker, 1975) therapy and can be a side-effect of several other drugs (Table 2).

(4) DRUG-RELATED HYPERSALIVATION

Anticholinesterases are the main cause of hypersalivation (Table 3). Clozapine, an atypical antipsychotic drug claimed to have superior efficacy and to cause fewer motor adverse effects than typical antipsychotics for people with treatment-resistant schizophrenic patients, can cause hypersalivation (Wahlbeck *et al.*, 2000). This may be ameliorated with atropine eye drops (Comley *et al.*, 2000).

(5) DISCOLORATION OF SALIVA

Discoloration of saliva (red or orange saliva) as well as other body fluids may be seen in patients treated with clofazimine,

TABLE 3
Drug-related Hypersalivation

Alprazolam	Guanethidine	Mefenamic acid	Tacrine
Amiodarone	Haloperidol	Mercurials	Tobramycin
Buprenorphine	Imipenem/cilastatin	Nicardipine	Triptorelin
Buspirone	Iodides	Niridazole	Venlafaxine
Clonazepam	Kanamycin	Pentoxifylline	Zaleplon
Diazoxide	Ketamine	Remoxipride	
Ethionamide	Lamotrigine	Risperidone	
Gentamicin	L-dopa	Rivastigmine	

levodopa, rifampicin, and rifabutin therapy (British National Formulary, 2002) (Table 4).

Drug-related Disorders of Taste

Drug-induced taste disorders are reviewed in detail elsewhere (Griffin, 1992; Henkin, 1994b)(AQ) but are reviewed and updated here (Table 5).

Drugs commonly impair taste. Drugs may cause a loss of taste acuity (hypogeusia), distortion of taste (dysgeusia), or loss of taste sense (ageusia), though this is rare (Ackerman and Kasbekar, 1997). Drugs act either by interfering with the chemical composition or flow of saliva, or by affecting taste receptor function or signal transduction (Femiano *et al.*, 2003f).(AQ)

ACE inhibitors, anti-thyroids, beta-lactam antibiotics, biguanides, chlorhexidine, opiates, and protease inhibitors are particularly implicated. Up to 4% of patients treated with ACE inhibitors may have dysgeusia, although this adverse effect is self-limiting and reversible within a few months, even with continued therapy (Henkin, 1994a).(AQ) Newer therapies—such as the anti-HIV protease inhibitors (Scully and Diz,(AQ) 2001b), therapy with tripotassium dicitrato bismuthate chelate, clarithromycin, and lansoprazole therapy for *H. pylori* infection (Scott, 1998), terbinafine (Stricker *et al.*, 1996), intravenous pentamidine (Glover *et al.*, 1995), and isotretinoin (Halpern *et al.*, 1996)—may cause some degree of loss of taste or altered taste.

There is preliminary evidence that alpha lipoic acid might improve dysgeusia, at least in idiopathic cases (Femiano *et al.*, 2002), but the condition is best improved by reducing use of the offending drug.

Drug-related Mucosal Disorders

(1) ORAL ULCERATION

A wide range of etiologies, from burns to vesiculobullous disorders of various kinds, can result in oral ulceration. Many reports of mouth ulceration following drug use have been from non-specialists, and therefore their description as 'aphthous'-like or other fairly specific entities can often be questioned, leading to some difficulty in accurately ascribing cause and effect.

(a) Drug-related oral burns

Oral desquamation or ulceration may follow burns from the accidental ingestion of caustics such as lime (Schier *et al.*, 2002), from the local application of aspirin or toothache preparations, potassium tablets, pancreatic supplements, and other agents such as trichloroacetic acid or hydrogen peroxide or from the use of various oral health care products (Kuttan *et al.*, 2001b).(AQ) Sodium lauryl sulfate, present in some oral health care products, particularly dentifrices, may cause mucosal irritation or ulceration (Herlofson and Barkvoll, 1994a;(AQ) Scully *et al.*, 1999; Kuttan *et al.*, 2001a).(AQ) Application of cocaine may produce similar lesions (Parry *et al.*, 1996).(AQ)

TABLE 4
Drug-related Discoloration of Saliva

Clofazimine	L-dopa	Rifabutin	Rifampin
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(b) Drug-related aphthous-like ulceration

Sodium lauryl sulfate may predispose to ulcers similar to aphthous ulceration (Herlofson and Barkvoll, 1994b).(AQ) There are also case reports of aphthous-like ulceration arising following the use of beta-blockers such as labetalol (Pradalier *et al.*, 1982), alendronate (Gonzalez-Moles and Bagan-Sebastian, 2000), captopril (Seedat, 1979; Nicholls *et al.*, 1981; Corone *et al.*, 1987; Montoner *et al.*, 1990), nicorandil (Boulinguez *et al.*, 1997; Reichart, 1997; Cribier *et al.*, 1998; Roussel *et al.*, 1998; Marquart-Elbaz *et al.*, 1999; Shotts *et al.*, 1999), some non-steroidal anti-inflammatory drugs (NSAIDs) (Siegel and Balciunas, 1991; Healy and Thornhill, 1995), mycophenolate or sirolimus (van Gelder *et al.*, 2003), protease inhibitors (Scully and Diz Dios, 2001),(AQ) tacrolimus (Hernandez *et al.*, 2001), and sulfonamides, though the exact pathogenic mechanisms are unclear in all of these.

A case-control study has now confirmed the associations of oral ulceration with NSAIDs and beta-blockers (Boulinguez *et al.*, 2000) (Fig. 2).

(c) Fixed drug eruptions

Fixed drug eruptions (contact stomatitis or stomatitis venenata) comprise repeated ulceration at the same site in response to a particular drug and may be caused by anesthetics, antibiotics, antiseptics, barbiturates, chewing gum, cosmetics, dental materials, dentifrices, mouthwashes, phenacetin, sulphonamides, or tetracyclines. The lesions may be localized to the mouth or can

TABLE 5
Drug-related Disturbed Taste

Acarbose	Cholestyramine	Hyoscyamine	Perindopril
Acetazolamide	Choline magnesium trisalicylate	Imipenem	Phenformin
Alcohol	Cilazapril	Indometacin	Phenindione
Allopurinol	Cisplatin	Interferon gamma	Phenylbutazone
Amiloride	Clarithromycin	Iodine	Phenytin
Amityptiline	Clidinium	Isotretinoin	Procaine penicillin
Amphetamines	Clofibrate	L-dopa	Propafenone
Amphotericin	Clomipramine	Levamisole	Propantheline
Amrinone	Cocaine	Levodopa	Propranolol
Aspirin	Diazoxide	Lincomycin	Propylthiouracil
Atorvastatin	Dicyclomine	Lisinopril	Quinapril
Auranofin	Diltiazem	Lithium	Ramipril
Aurothiomalate	Dipyridamole	Lomefloxacin	Rifabutin
Azathioprine	EDTA	Losartan	Rivastigmine
Azelastine	Enalapril	Lovastatin	Selegiline
Aztreonam	Ethambutol	Methimazole	Sodium lauryl sulphate
Baclofen	Ethionamide	Methotrexate	Spiroinolactone
Biguanides	Etidronate	Methyl methacrylate	Sulfasalazine
Bleomycin	Flunisolide	Methylthiouracil	Terbinafine
Bretylium	Fluoxetine	Metronidazole	Tetracycline
Calcitonin	Flurazepam	Nifedipine	Thiamazole
Captopril	5-fluorouracil	Niridazole	Tocainide
Carbamazepine	Fluvoxamine	Nitroglycerin	Topiramate
Carbimazole	Glycopyrrolate	Ofloxacin	Trandolapril
Carboplatin	Griseofulvin	Omeprazole	Triazolam
Ceftirizine	Hexetidine	Penicillamine	Venlafaxine
Cephazandole	Hydrochlorothiazide(AQ)	Pentamidine	Zopiclone
Chlormezanone	Hydrocortisone	Pergolide	



Figure 2. NSAID-induced ulceration.



Figure 3. Phenylbutazone-induced ulceration.

be associated with lesions at other mucocutaneous sites, and manifest as ulceration, bullae, erythematous patches, or superficial erosions. Initially, the lesions are solitary, but with repeated drug exposure, they may become multiple. A wide range of drugs may cause fixed drug eruption, particularly paracetamol, barbiturates, phenacetin, pyrazolone derivatives, sulphonamides, and tetracyclines (Abdollahi and Radfar, 2003), as may agents such as cinnamon (Miller *et al.*, 1992).

(d) Drug-related mucositis

Cytotoxic drugs are very commonly associated with mucositis and ulceration, which arises consistently with many chemotherapy regimens (Table 6), particularly those involving methotrexate, 5-fluorouracil, doxorubicine, melphelan, mercaptopurine, or bleomycin (Femiano *et al.*, 2003e).(AQ) Such reactions can be so severe as to be treatment-limiting on occasion (Bell *et al.*, 2001). Widespread sloughing and ulceration arise within days of commencement of therapy, the associated pain often requiring opioid therapy and/or alteration or cessation of chemotherapy. The ulceration may be a portal of entry for infection and hence a potential cause of septicemia. Drugs such as phenylbutazone that can cause agranulocytosis may also induce oral ulceration (Fig. 3).

Immunosuppressive agents may also cause ulceration. Ulcers in iatrogenically immunocompromised individuals may have a herpesvirus etiology, or occasionally other infective causes (Greenberg *et al.*, 1987; Schubert *et al.*, 1993). Opportunistic infection secondary to cytotoxic chemotherapy may cause oral

ulceration. In particular, herpes simplex virus 1, varicella zoster, and cytomegalovirus give rise to oral ulceration, while, less commonly, ulceration may be due to Gram-negative bacterial infections (*e.g.*, pseudomonas, klebsiella, *Escherichia coli*, enterobacter, or proteus) or to exogenous bacteria such as tuberculosis (Toren *et al.*, 1996), or to fungi such as mucormycosis (Femiano *et al.*, 2003c)(AQ) or even candidosis (see below).

(e) Drug-related neoplasms and potentially malignant lesions

There is an increased prevalence of dysplastic and malignant lip lesions in immunosuppressed renal-transplant recipients (King *et al.*, 1995b)(AQ) and liver transplant recipients (Haagsma *et al.*, 2001). Oral leukoplakia has progressed rapidly to squamous cell carcinoma in some immunosuppressed patients (Hernandez *et al.*, 2003), and oral squamous cell carcinoma has been reported in immunosuppressed patients without any recorded precursor lesion (Varga and Tyldesley, 1991a).(AQ)

Post-transplant lymphoproliferative disease (Raut *et al.*, 2000), non-Hodgkin's or MALT lymphoma (Hsi *et al.*, 2000), usually manifesting as ulceration of the gingivae, fauces, or palate (Bilinska-Pietraszek *et al.*, 2001; Mandel *et al.*, 2001), or, rarely, Kaposi's sarcoma (Meyers *et al.*, 1976; Qunibi *et al.*, 1988b)(AQ) may be complications of long-term immunosuppressive therapy, and there have even been reports of the resolution of malignancies where immunosuppression has been reduced (Keogh *et al.*, 2002).

(f) Drug-related pemphigoid-like reactions and other bullous disorders

At least 30 drugs can give rise to conditions resembling bullous or mucous membrane pemphigoid (Vassileva, 1998) (Table 7).

TABLE 6
Drug-related Oral Ulceration

Alendronate	Emepromium	Molgramostim	Phenytoin
Allopurinol	Flunisolide	Naproxen	Potassium chloride
Aurothiomalate	Gold	Nicorandil	Proguanil
Aztreonam	Indometacin	NSAIDs	Sertraline
Captopril	Interferons	Olanzapine	Sulindac
Carbamazepine	Interleukin-2	Pancreatin	Vancomycin
Clarithromycin	Isoprenaline	Penicillamine	
Diclofenac	Ketorolac	Phenindione	
Dideoxycytidine	Losartan	Phenylbutazone	

TABLE 7
Drug-related Pemphigoid-like Reactions

Amoxicillin	Ibuprofen	Penicillin v	Salicylic acid
Azapropazone	Isoniazid	Penicillamine	Suphasalazine(AQ)
Clonidine	Mefenamic acid	Phenacetin	Sulphonamides
Furosemide	Nadolol	Practolol	

These drugs belong to a variety of pharmacological (thiol and non-thiol) and therapeutically targeted groups, including ACE inhibitors, furosemide, NSAIDs, penicillamine, psoralens, sulphonamides, cardioactive agents, and penicillin-related antibiotics. The oral mucosa is frequently affected in drug-induced pemphigoid, particularly penicillamine-induced disease, and can be the only affected mucosal surface, although patients often also have cutaneous lesions (Troy *et al.*, 1981; Shuttleworth *et al.*, 1985; Velthuis *et al.*, 1985; Gall *et al.*, 1986; Rasmussen *et al.*, 1989b). (AQ) Other than the high frequency of oral mucosal lesions, the only other clinically distinguishing features of drug-induced pemphigoid are the younger age of affected patients compared with idiopathic (autoimmune) pemphigoid, and the resolution of disease following withdrawal of the causative agent.

Drug-induced pemphigoid may be due to thiol-induced local epithelial damage, drugs acting as haptens, or drug-induced immunological dysfunction. Affected patients can have circulating antibodies to the same antigens as idiopathic pemphigoid, hence making diagnosis of drug-related disease so reliant upon the recording of an accurate drug history.

Linear IgA disease (LAD) can be drug-induced, and affected patients have IgA antibodies to bullous-pemphigoid-associated antigen 1 (BPAG or BP1) or other antigens (Palmer *et al.*, 2001). LAD is especially commonly induced by vancomycin (Kuehle *et al.*, 1994a). (AQ) but other drugs such as angiotensin-converting enzyme inhibitors may be involved (Femiano *et al.*, 2003a). (AQ)

(g) Drug-related pemphigus

Drug-induced pemphigus is not uncommon (Brenner *et al.*, 1997). Traditionally, drugs that are capable of inducing pemphigus are divided into two main groups according to their chemical structure—drugs containing a sulfhydryl radical (thiol drugs or SH drugs) and non-thiol or other drugs, the latter often sharing an active amide group in their molecules (Wolf and Brenner, 1994).

Pemphigus vulgaris may occasionally be associated with drugs with active thiol groups in the molecule (Scully and Challacombe, 2002). Drugs implicated include penicillamine (Wolf *et al.*, 1991; Laskaris and Satriano, 1993; Shapiro *et al.*, 2000), phenol drugs (Goldberg *et al.*, 1999), rifampicin (Gange *et al.*, 1976), diclofenac (Matz *et al.*, 1997), and, rarely, captopril (Korman *et al.*, 1991b). (AQ) other ACE-inhibitors (Kaplan *et al.*, 1992; Ong *et al.*, 2000), and other drugs (Table 8).

The clinical features of drug-induced pemphigus mimic those of pemphigus vulgaris or foliaceus, and affected individuals can have variable levels of circulating antibodies to epithelial components and to expected antigens (*e.g.*, desmoglein 1 and 3) (Kuehle *et al.*, 1994b). (AQ) Aside from epithelial damage being due to the action of these antibodies, some of the implicated drugs are thiols (Wolf and Ruocco, 1997) that may induce a fall in local levels of plasminogen activator inhibitor, leading to increased plasminogen activation and epithelial damage (Lombardi *et al.*, 1993). Thiols such as penicillamine may also interfere in cell membrane cysteine links, potentially leading to antibody generation and epithelial damage (Wolf *et al.*, 1991).

The role of diet in the etiology of pemphigus is

reviewed elsewhere (Brenner *et al.*, 1998; Tur and Brenner, 1998), but garlic in particular may cause occasional cases of pemphigus (Laskaris and Nicolis, 1980; Korman *et al.*, 1991a). (AQ) Ruocco *et al.*, 1996).

(h) Drug-related erythema multiforme

A wide range of drugs—especially barbiturates, cephalosporins, NSAIDs, estrogens, phenothiazines, progestogens, (AQ) protease inhibitors, sulphonamides, sulphonylurea derivatives, and tetracyclines—may give rise to erythema multiforme (Table 9), and it may be clinically impossible to distinguish drug-induced erythema multiforme from disease due to other causes (Roujeau, 1997; Ayangco and Rogers, 2003b). (AQ) The distinction of severe erythema multiforme from toxic epidermal necrolysis is quite unclear.

Lesions of erythema multiforme typically affect the oral mucosa, the lips, and bulbar conjunctivae. Initial bullae rupture to give rise to hemorrhagic pseudomembrane of the lips and widespread superficial oral ulceration. Other mucocutaneous surfaces less commonly affected include the nasopharyngeal, respiratory, and genital mucosae.

(i) Drug-related toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN; Lyell syndrome) is clinically characterized by extensive mucocutaneous epidermolysis preceded by a macular or maculopapular exanthema and enanthema (Lyell, 1979; Rasmussen *et al.*, 1989a). (AQ) Intra-orally, there is widespread painful blistering and ulceration of all mucosal surfaces. Toxic epidermolysis may be associated with

TABLE 8
Drug-related Pemphigus-like Reactions

Ampicillin	Cephalexin	Oxyphenbutazone	Probenecid
Arsenic	Diclofenac	Penicillamine	Procaine penicillin
Benzylpenicillin	Gold	Phenobarbital (AQ)	Rifampicin
Captopril	Interferon-beta	Phenylbutazone	
Cephadoxil	Interleukin-2	Piroxicam	

TABLE 9
Drug-related Erythema Multiforme (and Stevens-Johnson syndrome and toxic epidermal necrolysis)

Acetylsalicylic acid	Digitalis	Mesterolone	Streptomycin
Allopurinol	Diltiazem	Minoxidil	Sulindac
Amlodipine	Ethambutol	Nifedipine	Sulphasalazine
Arsenic	Ethyl alcohol	Omeprazole	Tenoxicam
Atropine	Fluconazole	Oxyphenbutazone	Tetracyclines
Busulphan	Fluorouracil	Penicillin derivatives	Theophylline
Carbamazepine	Furosemide	Phenolphthalein	Tocainide
Chloral hydrate	Gold	Phenylbutazone	Tolbutamide
Chloramphenicol	Griseofulvin	Phenytoin	Trimethadione
Chlorpropamide	Hydantoin	Piroxicam	Vancomycin
Clindamycin	Hydrochlorothiazide	Progesterone	Verapamil
Codeine	Indapamide	Pyrazolone derivatives	Zidovudine
Co-trimoxazole	Measles/mumps/ rubella vaccine	Quinine	
Diclofenac	Meclofenamic acid	Retinol	
Diflunisal	Mercury	Rifampicin	

antimicrobials (sulphonamides, thiacetazone), analgesics (phenazones), anti-epileptics, allopurinol, chlormezanone, rifampicin, fluconazole, and vancomycin (Ayangco and Rogers, 2003a). (AQ)

(j) Drug-related lupus-like disorders

Systemic lupus erythematosus (SLE) may be induced by a wide variety of different drugs. Indeed, over 70 agents have been implicated in causing drug-induced lupus (Rich, 1996) (Table 10). The most commonly implicated agents of drug-induced SLE are procainamide and hydralazine, although drugs less commonly associated include chlorpromazine, isoniazid, methylidopa, penicillamine, and quinine, as well as whole groups of drugs such as anticonvulsants, beta-blockers, sulphonamides, and others (Price and Venables, 1995).

The possible pathogenesis of drug-related SLE is reviewed in detail elsewhere, but it may have an immunogenetic basis, and affected patients have some of the immunological features of classic SLE (Burlingame and Rubin, 1996).

(2) DRUG-RELATED WHITE LESIONS

(a) Burns (see above)

(b) Lichenoid eruptions

Since the advent of antimalarial therapy, there have been an ever-increasing list and spectrum of drugs that may give rise to mucocutaneous lichen planus (LP)-like eruptions (lichenoid reactions) (McCartan and McCreary, 1997; Scully *et al.*, 1998). However, many of the reports claiming associations have been single case reports, and many of the drugs implicated in cutaneous lichenoid reactions have not been shown to be associat-

ed with oral lesions.

The possible association of drugs with lichenoid reactions was noted when quinacrine and mepacrine, used as antimalarials during World War II, were seen to cause lichenoid lesions. Apart from these drugs, gold was probably the most common agent recognized as initiating a lichenoid reaction (Penneys *et al.*, 1974). Gold salts can cause a range of mucocutaneous lesions (Hakala *et al.*, 1986) of which oral lichenoid lesions may be the first (Brown *et al.*, 1993; Laeijendecker and van Joost, 1994).

The drugs now most commonly implicated in lichenoid reactions are the non-steroidal anti-inflammatory drugs and the angiotensin-converting enzyme inhibitors (Potts *et al.*, 1987b; (AQ) Firth and Reade, 1989; Robertson and Wray, 1992; Van Dis and Parks, 1995). Lichenoid reactions also may follow the use of HIV protease inhibitors (Scully and Diz, 2001c), (AQ) antihypertensive agents, antimalarials, phenothiazines, sulphonamides, tetracyclines, thiazide diuretics, and many others (Table 11) (Dinsdale and Walker, 1966; Roberts and Marks, 1981; Chau *et al.*, 1984; Hogan *et al.*, 1985; Colvard *et al.*, 1986; Markitziu *et al.*, 1986; Torrello *et al.*, 1990), but the list of drugs implicated lengthens almost weekly and, interestingly, includes several agents which have also been used in the therapy of lichen planus, particularly dapsone (Downham, 1978), levamisole (Kirby *et al.*, 1980), tetracycline (Mahboob and Haroon, 1998), and interferon (see below). Occasionally, there are lichenoid reactions to multiple drugs (Wiesenfeld *et al.*, 1982).

Several questions remain regarding drugs as causal agents of these reactions. For example, why can the same drug bring about different clinical manifestations? How can quite different chemical structures coincide in the clinical expression of their side-effects? and How can some drugs belonging to the same family (such as antimalarials) both produce a lichenoid reaction and at the same time find some use in the treatment of oral lichen planus (LP)? (Eisen, 1993).

The exact pathogenic mechanism by which drugs may cause LP-like disease are not known. Some of the agents implicated (*e.g.*, penicillamine, captopril, and gold sodium thionalate) are thiol-like and hence implicated in pemphigus-like disease (see below). However, in LP, quite different immunological mechanisms are involved. It is likely that Grinspan's syndrome simply represents a drug-induced disorder (Lamey *et al.*, 1990), and drug therapy may occasionally account for the co-occurrence of LP with lupus erythematosus or bullous-like disease (Flageul *et al.*, 1986). (AQ) Clinical identification of lichenoid drug reactions has been based largely on subjective criteria: There does seem to be sometimes a tendency for these oral lesions to be unilateral (Lamey *et al.*, 1995a) and erosive (Potts *et al.*, 1987a), (AQ) but these features are by no means invariable. Histology may help; lichenoid lesions may have a more diffuse lymphocytic infiltrate and contain eosinophils and plasma cells, and there may be more colloid bodies than in classic LP, but there are no specific features (Van *et al.*, 1989), and immunostaining is usually non-contributory, though basal cell cytoplasmic antibodies may be found (Lamey *et al.*, 1995b), but this has not been confirmed (Ingafou *et al.*, 1997) and surely occurs less reliably than in cutaneous drug reactions (van Joost, 1974; McQueen and Behan, 1982; Gibson *et al.*, 1986).

TABLE 10
Drug-related Lupoid Reactions

Ethosuximide	Isoniazid	Phenytoin	Sulphonamides
Gold	Methylidopa	Phenothiazines	Tetracyclines
Griseofulvin	Para-aminosalicylate	Procainamide	
Hydralazine	Penicillin	Streptomycin	

TABLE 11
Drug-related Lichenoid Reactions

Allopurinol	Dipyridamole	Mepacrine	Piroxicam
Amiphenazole	Ethionamide	Mercury (amalgam)	Practolol
Barbiturate	Flunarizine	Metformin	Prazosin
BCG vaccine	Gaunoclor	Methylidopa	Procainamide
Captopril	Gold	Metronidazole	Propranolol
Carbamazepine	Griseofulvin	Niridazole	Propylthiouracil
Carbimazole	Hepatitis B vaccine	Oral contraceptives	Prothionamide
Chloral hydrate	Hydroxychloroquine	Oxprenolol (AQ)	Quinidine
Chloroquine	Interferon-alpha	Para-aminosalicylate	Quinine
Chlorpropamide	Ketoconazole	Penicillamine	Rifampicin
Cholera vaccine	Labetalol	Penicillins	Streptomycin
Cinnarizine	Levamisole	Phenindione	Tetracycline
Clofibrate	Lincomycin	Phenothiazines	Tocainide
Colchicine	Lithium	Phenylbutazone	Tolbutamide
Dapsone	Lorazepam	Phenytoin	Triprolidine

The most reliable means to diagnose lichenoid reactions is if the reaction remits with drug withdrawal and returns on rechallenge, but frequently this is not possible because of the need to ensure patient safety.

Dental restorative materials may also be associated with lichenoid lesions. Most patients with OLP have no evidence of any association with dental restorative materials (Hietanen *et al.*, 1987b). However, contact with or proximity to restorations involving amalgams or other materials causes some lichenoid reactions—that is, lesions that clinically and histologically resemble LP closely, but have an identifiable etiology (Lind *et al.*, 1986a; Bolewska *et al.*, 1990a). These reactions are presumably due to allergic or toxic reactions to compounds released or generated, the Koebner phenomenon, or possibly due to plaque accumulated on the surfaces of the restorations (Holmstrup, 1991).

Some of these oral lesions may improve after substitution of the amalgam by other materials (Finne *et al.*, 1982c; Jolly *et al.*, 1986; Lind *et al.*, 1986b; Bolewska *et al.*, 1990b; Jameson *et al.*, 1990; Skoglund and Egelrud, 1991b; Laine *et al.*, 1992b; Bircher *et al.*, 1993; Ostman *et al.*, 1994d; Henriksson *et al.*, 1995b; Smart *et al.*, 1995b; Bratel *et al.*, 1996; Ibbotson *et al.*, 1996b), though this is often not the case with gingival lesions (Henriksson *et al.*, 1995a).

Significant reactions to mercuric salts on skin-testing may be seen in some patients with OLP (Finne *et al.*, 1982d; Eversole and Ringer, 1984; Mobacken *et al.*, 1984; James *et al.*, 1987; Ostman *et al.*, 1994c), though others have not found this (Hietanen *et al.*, 1987a). Finne *et al.* (1982b) demonstrated mercury sensitivity by patch-testing in 62% of 29 patients with OLP and only 3.2% of a control group, and in a few patients their oral lesions regressed on removal of the amalgams (Finne *et al.*, 1982a). Reactions to mercuric chloride have been reported (Skoglund and Egelrud, 1991a; Smart *et al.*, 1995a). These findings have been supported, and recently in studies by Skoglund and co-workers (Ostman *et al.*, 1994b), a patch-test positivity against mercury was found in 39.6% of 48 patients. Of those who had a positive patch test to mercury, 94.7% showed regression of lesions after removal of amalgams, but even 82.6% of those who showed *no* reaction to mercury on patch-testing also showed regression after removal of amalgams. Epicutaneous patch tests are of little prognostic value (Ostman *et al.*, 1994a; Ibbotson *et al.*, 1996a). Oral mucosal lesions of lichenoid character might not be associated with allergy to mercury, but with mechanical or galvanic insults; their interpretation calls for intra-oral patch-testing (Axéll *et al.*, 1986).

There may also be occasional reactions to gold restorations (Conklin and Blasberg, 1987), although this has not been substantiated. There is also a report of OLP in relation to cobalt in a restoration (Torresani *et al.*, 1994).

Composite restorations have also been implicated in oral lichenoid reactions (Lind and Hurlen, 1988), and so the wholesale replacement of amalgams as a possible treatment is not necessarily warranted.

(c) Lupoid reactions (see above)

(d) Candidosis

Pseudomembranous candidosis arises secondary to therapy with broad-spectrum antibiotics (Scully *et al.*, 1994), corticosteroids (both systemic and inhaler preparations), and other

immunosuppressive regimens (*e.g.*, ciclosporin)(AQ) and cytotoxic therapies (Table 12). More rarely, mucormycosis and aspergillosis may cause thrush-like areas or other lesions in patients on long-term immunosuppressive therapies (Dreizen *et al.*, 1992; Scully, 1992; Seymour *et al.*, 1997c).(AQ)

(e) Papillomas

Human papillomavirus infection manifesting as warty-like growths may arise in patients on long-term immunosuppressive therapy (Schubert, 1991).

(f) Hairy leukoplakia

Oral hairy leukoplakia, usually affecting the dorsum and lateral borders of the tongue and floor of mouth, may be a consequence of Epstein-Barr virus infection, associated with therapy with corticosteroids (topical and systemic), ciclosporin, or other long-term immunosuppressive regimens (Triantos *et al.*, 1997).

(g) Leukoplakia

Tobacco and alcohol use are important risk factors for leukoplakia (Pindborg *et al.*, 1980; Sciubba, 1995) and oral epithelial dysplasia (Jaber *et al.*, 1998). An increased frequency of lesions with epithelial dysplasia of the lips (but not oral mucosa) has been observed in some but not all iatrogenically immunosuppressed patients (King *et al.*, 1995a; Seymour *et al.*, 1997a).(AQ)

Sanguinarine, the principal alkaloid of the bloodroot plant (*Sanguinaria canadensis*), which is used in some mouthwashes and dentifrices for its anti-plaque activity, may be associated with the development of oral leukoplakia (Damm *et al.*, 1999; Allen *et al.*, 2001; Mascarenhas *et al.*, 2001, 2002).

Drug-related Mucosal Pigmentation

(1) DRUG-RELATED SUPERFICIAL TRANSIENT DISCOLORATION

Superficial transient discoloration of the dorsum of the tongue and other soft tissues and teeth may be of various colors, typically yellowish or brown, and may be caused by some foods and beverages (such as coffee and tea), some habits (such as tobacco, betel, and crack cocaine use) (Mirbod and Ahing, 2000), and some drugs (such as iron salts, bismuth, chlorhexidine, or antibiotics), especially if these also induce xerostomia (such as psychotropic agents) (Ramadan, 1969; Suzuki *et al.*, 1983; Ogunwande, 1989; Heymann, 2000) (Table 13). When such discoloration noticeably affects the posterior dorsum of the tongue, and the filiform papillae are excessively long and stained dark brown or black, the term 'black hairy tongue' is used, but this is less common than other superficial discolorations.

Stomatitis has been reported after the use of proton pump inhibitors (PPIs) such as lansoprazole with amoxicillin (Hatlebakk *et al.*, 1995), and discolored tongue or glossitis has been recorded after the use of lansoprazole plus antibiotics

TABLE 12
Drug-related Oral Candidosis

Broad-spectrum antimicrobials	Corticosteroids
Drugs causing xerostomia	Immunosuppressives

such as clarithromycin with or without amoxicillin (Greco *et al.*, 1997) or lansoprazole alone (Scully and Diz, 2001a).**(AQ)**

(2) DRUG-RELATED INTRINSIC PIGMENTATION

Localized areas of pigmentation of the mucosa may be due to amalgam, while gingival pigmentation can arise secondary to the gold or metal alloys of crowns (Kedici *et al.*, 1995). Heavy metal salts were previously reported to cause pigmentation, particularly of the gingival margin (Tables 13, 14).

Blue, blue-grey, or brown mucosal pigmentation can be an adverse effect of antimalarials, phenothiazines, and phenytoin (Giansanti *et al.*, 1971; Watson and MacDonald, 1974; Manor *et al.*, 1981; McAllan and Adkins, 1986). Amiodarone may cause a grey orofacial and oral mucosal pigmentation (Bucknall *et al.*, 1986).

Minocycline has increasingly been reported to cause widespread blue, blue-grey, or brown pigmentation of the gingivae and mucosae. While much of this pigmentation may reflect discoloration of the underlying bone and roots of teeth, there is also inherent pigmentation of the oral mucosa, includ-

TABLE 13
Drug-related Oral Mucosal Pigmentation

ACTH	Chlorhexidine	Iron	Phenothiazines
Amodiaquine	Chloroquine	Lead	Quinacrine
Anticonvulsants	Clofazimine	Manganese	Quinidine
Arsenic	Copper	Mepacrine	Silver
Betel	Cyclophosphamide	Methyldopa	Thallium
Bismuth	Doxorubicin (AQ)	Minocycline	Tin
Bromine	Gold	Oral contraceptives	Vanadium
Busulphan	Heroin	Phenolphthalein	Zidovudine

TABLE 14
Drug-related Oral Mucosal Pigmentation; Different Colors

Blue	Brown (hypermelanosis)	Black	Grey	Green
Amiodarone	Aminophenazone	Amiodiaquine	Amiodiaquine	Copper
Antimalarials	Betel nut	Betel nut	Chloroquine	
Bismuth	Bismuth	Bismuth	Fluoxetine	
Mepacrine	Busulphan	Methyldopa	Hydroxychloroquinine	
Minocycline	Clofazimine	Minocycline	Lead	
Phenazopyridine	Contraceptives		Silver	
Quinidine	Cyclophosphamide		Tin/zinc	
Silver	Diethylstilbestrol			
Sulphasalazine	Doxorubicin			
	Doxycycline			
	Fluorouracil			
	Heroin			
	Hormone-replacement therapy			
	Ketoconazole			
	Menthol			
	Methaqualone			
	Minocycline			
	Phenolphthalein			
	Propranolol			
	Smoking			
	Zidovudine			

ing the tongue (Meyerson *et al.*, 1995; Westbury and Najera, 1997).

Oral contraceptives may, albeit rarely, cause melanotic pigmentation (Hertz *et al.*, 1980), as can cyclophosphamide, busulphan, and ACTH (Scully and Porter, 1997). In HIV disease, drug-induced melanotic pigmentation may arise following therapy with clofazimine zidovudine and/or ketoconazole, the pigmentation being variably diffuse or macular-like (Ficarra *et al.*, 1990; Porter *et al.*, 1990).

Kaposi's sarcoma of the mouth is a rare complication of immunosuppression, manifesting as a blue, red, or purple macule, papule, nodule, or area of ulceration, typically on the palate or gingivae, but able to affect other oral mucosal sites (see above).

Drug-related Swellings

(1) DRUG-RELATED GINGIVAL ENLARGEMENT

Gingival enlargement is a well-described oral side-effect of drug therapy (Marshall and Bartold, 1998) (Table 15). The drugs most commonly implicated in causing this enlargement are phenytoin (Seymour and Jacobs, 1992b),**(AQ)** ciclosporin (Seymour and Jacobs, 1992a), and the calcium-channel-blockers nifedipine (Fattore *et al.*, 1991), diltiazem (Bowman *et al.*, 1988), verapamil (Pernu *et al.*, 1989), and amlodipine (Ellis *et al.*, 1993). Patients receiving therapy with both ciclosporin and calcium-channel-blockers (*e.g.*, post-cardiac or -renal allograft recipients) may be sometimes, but not always, particularly liable to drug-induced gingival enlargement.

In general, the gingival enlargement develops within a few months of the commencement of drug therapy, is usually generalized, is only partly associated with poor oral hygiene and local plaque accumulation, and responds variably to improved plaque control and/or withdrawal or reduction of drug therapy (Cebeci *et al.*, 1996; Thomason *et al.*, 1996; Jackson and Babich, 1997).

Rarely, Kaposi's sarcoma (Qunibi *et al.*, 1988a)**(AQ)** or squamous cell carcinoma (Varga and Tyldesley, 1991b)**(AQ)** may arise within areas of ciclosporin-induced gingival enlargement.

Other drugs that have been occasionally reported to cause gingival enlargement include erythromycin (Valsecchi and Cainelli, 1992), sodium valproate (Syrjanen and Syrjanen, 1979), phe-

TABLE 15
Drug-related Gingival Swelling

Drugs Most Commonly Implicated	Drugs Occasionally Implicated	
Amlodipine	Co-trimoxazole	Nitrendipine
Ciclosporin	Erythromycin	Norethisterone
Diltiazem	Diphenoxylate	+ mestranol
Felodipine	Ethosuximide	Phenobarbitone
Lacidipine	Interferon-alpha	Primidone
Nifedipine	Ketoconazole	Sertraline
Oral contraceptives	Lamotrigine	Topiramate
Phenytoin	Lithium	Valproate
Verapamil	Mephenytoin	Vigabatrin

TABLE 16
Drug-related Angio-edema

Asparaginase	Disulphite sodium	Ketoconazole	Penicillin derivatives
Captopril	Droperidol	Mianserin	Pyrazolone derivatives
Carbamazepine	Enalapril	Miconazole	Quinine
Clindamycin	Epoetin alpha	Naproxen	Streptomycin
Clonidine	Ibuprofen	Nitrofurantoin	Sulphonamides
Co-trimoxazole	Indometacin	Penicillamine	Thiouracil

nobarbitone (Gregoriou *et al.*, 1996), and vigabatrin (Katz *et al.*, 1997), but these have all been isolated reports.

(2) DRUG-RELATED LIP AND MUCOSAL SWELLING

Drug-induced mucosal swelling predominantly affects the lips and tongue (although rare isolated swelling of the uvula [Quinke's(AQ) disease] can occur [Mattingly *et al.*, 1993]), and is typically due to type I hypersensitivity reactions. The oral and dental aspects of hypersensitivity are reviewed elsewhere (Rees and Gibson, 1997), but a range of drugs—particularly penicillins, local anesthetic agents, cephalosporin derivatives, angiotensin-converting enzyme inhibitors, aspirin, and barbiturates—may give rise to angio-edema (Table 16). Hypersensitivity to latex is an increasing problem in oral health care and may cause rapid-onset angio-edema in susceptible patients.

Non-allergic oral swelling can also arise in response to angiotensin-converting enzyme (ACE) inhibitor therapy. This adverse effect occurs in 0.1 to 0.7% of patients, typically arising in the early weeks of therapy, although it may occur within a few hours of commencement of treatment, or after long-term therapy. The swelling usually affects the lips, although it can be localized to the tongue, and is occasionally fatal. Black Americans may be at particular risk (Ulmer and Garvey, 1992; Gabb *et al.*, 1996; Sabroe and Black, 1997; Lapostolle *et al.*, 1998; Vleeming *et al.*, 1998). The tissue swelling associated with ACE inhibitor therapy may be due to a rise in levels of bradykinins and/or altered levels or function of C1 esterase inhibitor (Ebo and Stevens, 1997; Seymour *et al.*, 1997b).(AQ)

Plasmacytosis due to 'tartar control' toothpastes gives rise to localized enlargements of the gingivae, tongue, and other oral mucosae. This disorder is histopathologically characterized by a polyclonal plasmacytic infiltrate of the upper lamina

TABLE 18
Drug-related Trigeminal Paresthesia or Hypo-esthesia

Acetazolamide	Interferon alpha	Nitrofurantoin	Streptomycin
Amitriptyline	Isoniazid	Pentamidine	Sulphonylureas
Articaine	Labetalol	Phenytoin	Sulthiame
Chlorpropamide	Mefloquine	Prilocaine	Tolbutamide
Colistin	Methysergide(AQ)	Propofol	Tricyclics
Ergotamine	Monoamine oxidase inhibitors	Propranolol	Trilostane
Gonadotropin-releasing hormone analogues	Nalidixic acid	Prothionamide	Vincristine
Hydralazine	Nicotinic acid	Stilbamidine	Streptomycin

TABLE 17
Drug-related Cheilitis

Actinomycin	Cyancobalamin	Isotretinoin	Streptomycin
Atorvastatin	Ethyl alcohol	Lithium	Sulphasalazine
Busulphan	Etretinate	Menthol	Tetracycline
Busulphan	Gold	Methyldopa	Vitamin A
Clofazimine	Indinavir	Penicillamine	
Clomipramine	Isoniazid	Selegiline	

propria and may rarely affect other mucosal surfaces, such as the larynx and anogenital surfaces (White *et al.*, 1986; Timms *et al.*, 1988).

Drug-related Cheilitis

Cheilitis is commonly caused by contact reactions to cosmetics or foods, but drugs may also be implicated, particularly cytotoxic agents, phenothiazines, protease inhibitors, psoralens, and retinoids (Scully *et al.*, 2000) (Table 17).

Drug-related Neuropathies

(1) DRUG-RELATED TRIGEMINAL NEUROPATHIES

Trigeminal paresthesia, hypoesthesia, or anesthesia can arise following the use of interferon alpha (Read *et al.*, 1995), acetazolamide, labetalol, sulthiame, vincristine (McCarthy and Skillings, 1992), mefloquine (Watt-Smith *et al.*, 2001), and, occasionally, with other agents—most recently by hepatitis B vaccination (Maillefert *et al.*, 1997) and some of the protease inhibitors (Scully and Diz, 2001d)(AQ) (Table 18). Local anesthetics such as articaine and prilocaine may exhibit a small degree of neurotoxicity (Haas and Lennon, 1995).(AQ)

(2) DRUG-RELATED INVOLUNTARY FACIAL MOVEMENTS

Butyrophenones, phenothiazines, tricyclic antidepressants, and other drugs can occasionally produce several different drug-induced movements which can affect the mouth and face (Jimenez-Jimenez *et al.*, 1997), particularly tardive dyskinesia secondary to antipsychotics (Hansen *et al.*, 1997; Diederich and Goetz, 1998) and dystonias with metoclopramide (Table 19). Although these disorders principally affect the face, there can be abnormal movements restricted to the tongue—for example, the dystonia secondary to carbamazepine therapy.

(3) DRUG-RELATED OROFACIAL PAIN AND ORAL DYSESTHESIA

Several drugs, especially the vinca alkaloids such as vincristine, can cause orofacial pain (Table 20) (McCarthy and Skillings, 1991, 1992). Enalapril (Guasti *et al.*, 1998) and sometimes other angiotensin-converting enzyme inhibitors, such as captopril

TABLE 19
Drug-related Involuntary Facial Movements

Carbamazepine	Methyldopa	Phenytoin
L-dopa	Metoclopramide	Tetrabenazine
Lithium	Metirosine	Trifluoroperazine

TABLE 20**Drug-related Orofacial Pain**

Benztropine	Lithium	Stilbamidine
Biperidin	Penicillins	Ticarcillin
Griseofulvin	Phenothiazines	Vitamin A

TABLE 21**Drug-related Halitosis**

Dimethyl sulphoxide (DMSO)	Disulfiram	Isorbide dinitrate
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Table 22**Drug-related Tooth Discoloration**

Enalapril	Pentamidine	Ramipril
Etidronate	Perindopril	Terbinafine
Fosinopril	Propafenone	Trandolopril
Lisinopril	Quinapril	Zopiclone

and lisinopril, may rarely cause a scalded-type sensation of the mouth (Vlasses *et al.*, 1982; Savino and Haushalter, 1992). Orofacial pain may also be a rare consequence of drug-induced tardive dyskinesia (Ford *et al.*, 1994).

Drug-related Oral Malodor (Halitosis)

Oral malodor may be related to drugs causing xerostomia, which may indirectly cause or aggravate this problem, but other drugs, such as isosorbide dinitrate, dimethyl sulphoxide, or disulfiram, can be directly responsible for malodor (Table 21).

Drug-related Tooth Discoloration

Chlorhexidine, fluorides, iron, and habits such as tobacco and betel use are well-recorded as causing superficial tooth discoloration, but some other drugs such as antibiotics and essential oils may also be causal. Intrinsic discoloration is prominent when tetracyclines are given to children under 12 years, but other drugs, especially ACE inhibitors, are also able to produce alterations in the color of the teeth (Table 22).

Summary

A wide spectrum of drugs can give rise to numerous adverse orofacial manifestations. The most common reactions are dry mouth, taste disturbances, and gingival swelling. Drug-induced oral mucosal ulceration is also not uncommon, particularly in cancer chemotherapy. There are many other occasional reactions.

There are few relevant randomized double-blind controlled studies in this field, and the only data available are from case reports, small series, and non-peer-reviewed reports of adverse drug reactions.

The clinician should take a careful drug history and always exclude drugs as a cause of oral and peri-oral symptoms and signs.

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